

Liver Transplantation

Liver Trans

Liver Transplantation

Author

Dilip Chakravarty K

Division of HPB Surgery and Liver Transplantation
Department of General Surgery
Chang Gung Memorial Hospital (Linkou)
Taipei, Taiwan (ROC)

Co-authors

WC Lee

Professor and Chief
Department of Liver and Transplantation Surgery
Chang Gung Transplantation Institute (Linkou)
Chang Gung University
Taipei, Taiwan (ROC)

YY Jan

Professor and Chairman
Department of General Surgery
Chang Gung Memorial Hospital (Linkou)
Chang Gung University
Taipei, Taiwan (ROC)

YC Chen

Department of Nephrology
Chang Gung Memorial Hospital (Linkou)
Chang Gung University
Taipei, Taiwan (ROC)

Po-Huang Lee

Professor of Surgery and Chairman
Department of Surgery and
Liver Transplantation Program
National Taiwan University Hospital
Taipei, Taiwan (ROC)

Foreword

Sir Roy Calne



JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD

St Louis (USA) • Panama City (Panama) • New Delhi • Ahmedabad • Bengaluru • Chennai
Hyderabad • Kochi • Kolkata • Lucknow • Mumbai • Nagpur

Published by

Jitendar P Vij

Jaypee Brothers Medical Publishers (P) Ltd

Corporate Office

4838/24 Ansari Road, Daryaganj, **New Delhi** 110 002, India

Phone: +91-11-43574357, Fax: +91-11-43574314

Registered Office

B-3 EMCA House, 23/23B Ansari Road, Daryaganj, **New Delhi** 110 002, India

Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021,

+91-11-23245672, Rel: +91-11-32558559 Fax: +91-11-23276490, +91-11-23245683

e-mail: jaypee@jaypeebrothers.com, Website: www.jaypeebrothers.com

Branches

- ❑ 2/B, Akruti Society, Jodhpur Gam Road Satellite, **Ahmedabad** 380 015
Phones: +91-79-26926233, Rel: +91-79-32988717, Fax: +91-79-26927094
e-mail: ahmedabad@jaypeebrothers.com
- ❑ 202 Batavia Chambers, 8 Kumara Krupa Road, Kumara Park East, **Bengaluru** 560 001
Phones: +91-80-22285971, +91-80-22382956, +91-80-22372664, Rel: +91-80-32714073
Fax: +91-80-22281761 e-mail: bangalore@jaypeebrothers.com
- ❑ 282 IIIrd Floor, Khaleel Shirazi Estate, Fountain Plaza, Pantheon Road, **Chennai** 600 008
Phones: +91-44-28193265, +91-44-28194897, Rel: +91-44-32972089
Fax: +91-44-28193231 e-mail: chennai@jaypeebrothers.com
- ❑ 4-2-1067/1-3, 1st Floor, Balaji Building, Ramkote Cross Road, **Hyderabad** 500 095
Phones: +91-40-66610020, +91-40-24758498, Rel: +91-40-32940929, Fax: +91-40-24758499
e-mail: hyderabad@jaypeebrothers.com
- ❑ No. 41/3098, B and B1, Kuruvi Building, St. Vincent Road, **Kochi** 682 018, Kerala
Phones: +91-484-4036109, +91-484-2395739, +91-484-2395740
e-mail: kochi@jaypeebrothers.com
- ❑ 1-A Indian Mirror Street, Wellington Square, **Kolkata** 700 013
Phones: +91-33-22651926, +91-33-22276404, +91-33-22276415
Fax: +91-33-22656075, e-mail: kolkata@jaypeebrothers.com
- ❑ Lekhraj Market III, B-2, Sector-4, Faizabad Road, Indira Nagar, **Lucknow** 226 016
Phones: +91-522-3040553, +91-522-3040554, e-mail: lucknow@jaypeebrothers.com
- ❑ 106 Amit Industrial Estate, 61 Dr SS Rao Road, Near MGM Hospital, Parel, **Mumbai** 400012
Phones: +91-22-24124863, +91-22-24104532, Rel: +91-22-32926896 Fax: +91-22-24160828
e-mail: mumbai@jaypeebrothers.com
- ❑ "KAMALPUSHPA" 38, Reshimbag, Opp. Mohota Science College, Umred Road, **Nagpur** 440 009 (MS)
Phone: Rel: +91-712-3245220, Fax: +91-712-2704275 e-mail: nagpur@jaypeebrothers.com

North America Office

1745, Pheasant Run Drive, Maryland Heights (Missouri), MO 63043, USA

Ph: 001-636-6279734, e-mail: jaypee@jaypeebrothers.com, anjulav@jaypeebrothers.com

Central America Office

Jaypee-Highlights Medical Publishers Inc., City of Knowledge, Bld. 237, Clayton,

Panama City, Panama, Ph: (507)317-0160

Liver Transplantation

© 2010, Jaypee Brothers Medical Publishers

All rights reserved. No part of this publication should be reproduced, stored in a retrieval system, or transmitted in any form or by any means: electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the authors and the publisher.

This book has been published in good faith that the material provided by contributors is original. Every effort is made to ensure accuracy of material, but the publisher, printer and authors will not be held responsible for any inadvertent error(s). In case of any dispute, all legal matters are to be settled under Delhi jurisdiction only.

First Edition: 2010

ISBN: 978-81-8448-770-1

Typeset at JPBMP typesetting unit

Printed at

“History tells us that procedures that were inconceivable yesterday, and are barely achievable today, often become the routine of tomorrow.”

—Thomas E Starzl



Contributors

Sir Roy Yorke Calne FRS

Emeritus Professor of Surgery
University of Cambridge and
National University of Singapore
Cambridge, United Kingdom

Masatoshi Makuuchi MD PhD
President, Japanese Red Cross Medical
Center, 4-1-22 Hiro-o, Shibuya-ku
Tokyo 150-8935, Japan

Burckhardt Ringe

Department of Surgery
Center for Liver, Biliary and
Pancreas Diseases
Drexel University College of Medicine
Philadelphia, Pennsylvania

Sung Gyu Lee

Department of Surgery
Asan Medical Center, Ulsan University
388-1 Poong-Nap Dong
Song-Pa Ku, Seoul 138-736, Korea

Hiroto Egawa MD

Organ Transplant Unit
Kyoto University Hospital
54 Kawara-cho, Sakyo-ku
Kyoto-606-8507, Japan

Hiroshi Imamura MD

Department of Hepatobiliary
Pancreatic Surgery
Juntendo School of Medicine
2-1-1, Hongo, Bunkyo-ku
Tokyo 113-8421, Japan

Seiji Kawasaki MD

Department of Hepatobiliary-
Pancreatic Surgery, Juntendo
University, 2-1-1
Hongo Bunkyo-ku, Tokyo 113-8421
Japan

Miin-Fu Chen MD

Professor of Surgery and
Superintendent, Chang Gung
Memorial Hospital (Linkou)
Chang Gung University
Taipei, Taiwan (ROC)

Chao-Long Chen MD

Superintendent and Chief
Department of Liver transplantation
Chang Gung Memorial Hospital
Kaohsiung Medical Center
Kaohsiung, Taiwan (ROC)

Hironori Haga MD

Associate Professor
Department of Surgical Pathology
Hokkaido University Hospital
North 14, West 5, Kita-ku
Sapporo, 060-8648, Japan

Jordi Bruix

Barcelona Clinic Liver Cancer Group
Liver Unit, Hospital Clinic
CIBERehd, Institute for Biomedical
Investigations, August Pi Sunyer
Villarroel 170, 08036, Barcelona
Catalonia, Spain

Nai-Jen Liu MD

Chief
Division of Therapeutic Endoscopy
Department of Hepatogastroenterology
Chang Gung Memorial Hospital
Taipei, Taiwan

Christian S Kuhr MD FACS

Director of Transplantation
Virginia Mason Medical Center
Seattle, Washington, USA

Arianeb Mehrabi

Department of General, Visceral
and Transplantation Surgery
University of Heidelberg, Im
Neuenheimer Feld 110, 69120
Heidelberg, Germany

Carl-Gustav Groth MD

Professor Emeritus
Transplantation Surgery
Karolinska Institute
Fogdevreten 2A SE- 171 77
Stockholm, Sweden

Constantino Fondevila

Assistant Professor of Surgery
Liver Surgery and Liver Transplant
Unit, Institute of Digestive Diseases
Pav. 4, 3rd floor, office 19
Hospital Clinic, University of
Barcelona, Villarroel 170
Barcelona 08036, Spain

Laura Llado

Department of Surgery and
Gastroenterology
Liver Transplant Unit, Hospital U.
Bellvitge, University of Barcelona,
Barcelona, Spain
C/Feixa Llarga s/n, 08907 Hospitalet
LL, Barcelona, Spain

Jia Fan MD PhD FACS

Liver Cancer Institute
Zhongshan Hospital, Fudan
University
180 Feng Lin Road, Shanghai, 200032
China

James Neuberger

Liver Unit
Queen Elizabeth Hospital
Birmingham B15 2TH
United Kingdom

Sergio Mies MD PhD

Associate Professor of Surgery
Sao Paulo Medical School - USP
Liver Unit, Instituto Dante Pazzanese
de Cardiologia, São Paulo - SP
Brazil

Nicolas Jabbour MD FACS

Director
Nazih Zuhdi Transplant Institute
INTEGRIS Baptist Medical Center
3300 NW Expressway, 100-3444
Oklahoma City, OK 73112-4481
USA

Jaime Bosch MD PhD

Liver Unit
Institut d'Investigacions Biomediques
August Pi i Sunyer (IDIBAPS)
University of Barcelona
Hospital Clínic, C.Villarroel 170,
08036, Barcelona, Spain

H Ramesh MS MCh FACS FRCS

Director of Surgical Gastroenterology
and Liver Transplantation Surgery
Lakeshore Hospital and Research
Center, Nettoor, Cochin 682304,
Kerala, India

Kyu-Bo Sung MD

Department of Radiology
Asan Medical Center
University of Ulsan College of
Medicine, 388-1, Pungnap-2dong,
Songpa-gu, Seoul 138-736
Republic of Korea

Pere Ginès MD

Liver Unit, 7-3
Institut de Malalties Digestives
Hospital Clinic, IDIBAPS
University of Barcelona
Villarroel 170, 08036
Barcelona, Spain

Yuji Soejima

Assistant Professor
Department of Surgery and Science
Kyushu University, 3-1-1 Maidashi
Higashi-Ku, Fukuoka 812-8582
Japan

Ta Sen Yeh MD PhD.

Professor of surgery
Chang Gung Memorial Hospital
Director of Surgical Laboratory
Chang Gung University
Taipei, Taiwan

Chun-Yen Lin MD DPhil (Oxon)

Associate Professor
Department of Gastroenterology
Chang-Gung Memorial Hospital and
College of Medicine
Chang-Gung University
Taipei, Taiwan

Chih Chung Lin MD

Division of Liver transplantation
Anesthesia
Department of Anesthesia
Chang Gung Memorial Hospital
Chang Gung University
Linkou, Taoyuan Taiwan

Ching Sung Lee MD

Division of Therapeutic Endoscopy
Department of Hepatogastroenterology
Chang Gung Memorial Hospital
Chang Gung University
Taipei, Taiwan

Tsann Long Hwang MD

Vice President and Dean
Department of General Surgery
Chang Gung Memorial Hospital
and School of Medicine
Chang Gung University
Taipei, Taiwan

Hirota Tashiro MD

Hiroshima University
1-2-3 Kasumi, Minami-ku
Hiroshima 734-8551, Japan

Rey Hung Hu MD PhD

Associate Professor
Division of Hepatobiliary Surgery
and Transplantation Surgery
Department of Surgery
National Taiwan University Hospital
Taipei, Taiwan

Rei Ping Tang MD

Chief of Division of Colorectal
Surgery, Department of Surgery
Chang Gung Memorial Hospital
Chang Gung University
Taipei, Taiwan

Yao-Ming Wu MD

Assistant Professor
Division of Hepatobiliary surgery
and Transplantation surgery
Department of Surgery
National Taiwan University Hospital
Taipei, Taiwan

Chun Nan Yeh MD

Assistant Professor
Department of General Surgery
Chang Gung Memorial Hospital
Chang Gung University
Linkou, Taoyuan, Taiwan

Sung-Yu Chu MD

Department of Medical Imaging and
Interventional Radiology
Chang Gung memorial hospital
Linkou, Taoyuan, Taiwan

Akshay Kumar Mishra MD

Deputy Director
(Monitoring and Evaluation/
Surveillance)
AP State AIDS Control Society,
DM and HS Campus
Hyderabad-500095, India

SP Samantaray MS

Department of Cardiothoracic and
Vascular Surgery, MKCG Medical
College, Berhampur, India

Chin Hsin Chen

Department of Proctology
Chang Gung Memorial Hospital
Taoyuan, Taiwan

Piyush Joshi MD

Surgeon Commander
Classified Specialist Radiology
Command Hospital
Pune, India

Baiju Senadhipan MS Mch
Chief of Gastrointestinal Surgery
Holicross Hospital, Kottiyam,
Kollam, Kerala, India

Santosh K Shau MS
Surgeon Commander
Classified Specialist Surgery
INHS Jeevanti, Vasco-Da-Gama
Goa, India

Chai Chiah Yang MD
Department of Surgery
Taipei Medical University Hospital
Taipei, Taiwan

Aratatan Nahak MS Mch
Consultant Cadiothoracic surgeon
Fortis Hospital, Mohali, Chandigarh
India

Ramendrapati Pandey
Institute of Biomedical Science
Chang Gung University
Taipei, Taiwan

M Jayashri PhD
Department of Molecular Virology
Chung Gung University
Taipei, Taiwan

Manesh Senan MS MCh MNAMS FRCS
Consultant Plastic Surgeon
KIMS Hospital , Anamugham PO,
Anayara, Trivandrum, India

Chih-chi Wang MD
Director
Department of General Surgery
Chang Gung Memorial Hospital
Kaohsiung Medical Center
Kaohsiung, Taiwan (ROC)

Vani Chakravarty MS MRCOG
Consultant Gynecologist
Bangalore, India



The book *Liver Transplantation* is the result of an enormous amount of work and scholarship, and to put so many different aspects of liver transplantation into one volume is a significant achievement.

Dr Dilip and his colleagues have produced a comprehensive text on liver transplantation covering all aspects of this very complicated subject, starting with the history, the relevant anatomy of the liver, clinical and ethical aspects of liver transplantation with particular emphasis on the ethics of adult liver donors. The text is well illustrated with particularly good photographs and details of surgical techniques. The complications and short- and long-term results are discussed, including the morbidity and mortality of living donation. The medical and anesthetic aspects of liver transplantation and pediatric liver transplantation are also described and the individual details of special diseases.



As liver transplantation has no geographical boundaries, the book will be welcomed by the transplant units. It provides a very fulsome handbook of the subject, suitable for surgeons and physicians and especially young surgeons in training, to give them a readily available and practical "hands-on" account of liver transplantation.

The authors are to be congratulated on this up-to-date and authoritative review of liver transplantation, which should be available in all medical libraries and the offices of doctors, nurses and other health care personnel involved in the complicated aspects of liver transplantation.

Sir Roy Calne FRS

Emeritus Professor of Surgery; University of Cambridge
Visiting Professor to Department of Surgery;
National University of Singapore
Cambridge, United Kingdom



Preface

Hepatitis B virus is the most common cause of cirrhosis and hepatocellular carcinoma since many decades in Taiwan and rest of Asia, whereas hepatitis C virus is the leading cause in the Western countries. In Taiwan even though the first hepatic surgery program was started in 1954 by Dr TY Lin, and first experimental auxiliary liver transplantation was attempted by Dr CJ Lee in 1960; clinically first successful deceased donor liver transplantation was performed by Dr CL Chen in 1984. In present transplantation scenario, very good results can be achieved after liver transplantation due to the advances in surgical techniques and better postoperative care. Evolution of living donor liver transplantation has reduced the number of patients on waiting list and increased the number of transplants all over the world.



This book “Liver Transplantation” is a complete book on liver transplantation which comprehensively describes almost every aspect of the liver transplantation including donor selection, surgical techniques practised in different types of transplantation, postoperative management, long-term complications and the management of complications of end stage liver disease. I believe this book is very helpful for the fellows who visit any liver transplantation unit. Most authors write their own experience and protocols followed at their transplant units. But this book includes not only our experience but also describes an overall comprehensive review of transplantation techniques and principles practiced in both east and west.

The book is completed by the contribution of professionals from three different medical universities in Taiwan and many pioneers from across the world. We are very thankful to all the contributors for making this project successful. I appreciate the initiative taken by Dr Dilip and his interest and motivation in involving Chang Gung Memorial Hospital (Linkou and Kaohsiung branches) and National Taiwan University Hospital together along with many professionals from across the world to complete this project.

李伯皇

Prof Po-Huang Lee MD, PhD
Professor of Surgery and Chairman
Department of Surgery and
Liver Transplantation Program
National Taiwan University Hospital
Taipei, Taiwan (ROC)



Acknowledgments

Liver transplantation as a whole is a challenging procedure in the field of surgery. Even though four decades have passed ever since the first successful liver transplantation, new innovative techniques are emerging each and every day. Evolution of living donor liver transplantation has changed the concept of liver transplantation. Keeping in view of changing trends in approach to the management of a patient with end stage liver disease and recent advances in the field of liver transplantation, it is essential to have a book which narrates everything about liver transplantation starting from the management of complications in a cirrhosis patient to long-term outcomes in liver transplantation. Every new fellow who enters a liver transplantation unit finds it difficult to understand the principles and techniques of liver transplantation. Each center designs its own protocols based on available resources. It takes time for a new comer to get acquainted with the transplantation procedures, postoperative management, immunosuppression and management of early and late complications of liver transplantation. The purpose of writing the book is to give information briefly and lucidly about the various surgical techniques followed at different institutions with a comparative analysis of the long-term results. This book describes different types of liver transplantations including their technical aspects, pre- and postoperative management, early and late complications and long-term outcome both in the Eastern and Western countries. We tried to narrate all the recent innovations in surgical techniques and management in the field of liver transplantation in depth.

I am extremely obliged to chief editors of all the journals we referred, all the contributors across the globe who cooperated in contributing material in the form of script, illustrations and tables, and made this one and half year long project successful. My sincere thanks to liver transplant teams of CGMH (Linkou), CGMH-Kaohsiung Medical Center and National Taiwan University Hospital. I am thankful to Prof. Miin-Fu Chen, Prof. Yi-Yin Jan, Prof. Chao-Long Chen, Prof. Po-Huang Lee, Prof. Wei-Chen Lee, Prof. Tsann-Long Hwang, Prof. Rei-Ping Tang, Prof. Ta-Sen Yeh and Dr. Yung-Chang Chen for their motivation, support and contribution to this project. I am very grateful to Sir Roy Calne for his timely guidance and suggestions in improving the quality of this book to meet the international standards.

My wholehearted thanks to Ariel for her continuous selfless support and cooperation during the entire course of this project. She is closely involved in every aspect of this book starting from manuscript writing, to the final editing process. Such a challenging project would not have been possible without her cooperation.

The people who made this book reader friendly and attractive by their graphic designing skills and hard work are Shu Fang Huang, Stone, Yueh Chia He, Stacey Hsu, Ming yu Lin and Ivy Cheng. I personally remain indebted to them. My sincere thanks to Dr. Hitesh Gopalan for his inspiration and timely suggestions. The people behind my success are my parents, my family Dr Vani, Navisha and Anushka. My sincere thanks to Shri Jitendar P Vij (Chairman and Managing Director), Mr Tarun Duneja (Director-Publishing) and Staff of Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India, who made my dreams, come true.

Dilip Chakravarty K

Division of HPB Surgery and Liver Transplantation
Department of General Surgery
Chang Gung Memorial Hospital (Linkou)
Taipei, Taiwan (ROC)



Contents

<i>Abbreviations</i>	<i>xix</i>
1. History of Liver Transplantation	1
2. Anatomy of Liver	8
3. UNOS, Organ Allocation Policy and MELD Score	24
4. Indications and Contraindications of Liver Transplantation	32
5. Liver Transplantation Team	39
6. Evaluation of Live Donor	41
7. Graft Volume Estimation and Donor with Fatty Liver	54
8. Liver Donation after Brain Death and Cardiac Death	58
(A) Heart-beating Donors/Donation After Brain Death	
(B) Donation after Cardiac Death (DCD)	
9. Marginal Donor and Donor Risk Index	67
10. Donor Surgery	70
(A) Right Lobe Graft	
(B) Left Lateral Segment	
(C) Right Posterior Segment or Right Lateral Sector Graft	
(D) Left Lobes Graft	
(E) Deceased Donor Hepatectomy	
11. Graft Preservation and Bench Procedure	90
12. Recipient Surgery	97
(A) Live Donor Liver Transplantation: Recipient Hepatectomy	
(B) Right Lobe Graft	
(C) Left Lobe Graft	
(D) Left Lateral Segment Graft	
(E) Recipient Surgery for Deceased Donor Liver Transplantation	
13. Reperfusion Syndrome and Preservation Injury	118
14. Technical Modifications in Recipient Surgery	120
15. Small for Size Syndrome	127
16. Split Liver Transplantation	131
17. Dual Grafts	140
18. Auxiliary Partial Orthotopic Liver Transplantation (APOLT)	144
19. Domino Liver Transplantation	149
20. Postoperative Care and Immunosuppression	155
21. Immunosuppression Drugs	166

22. Hepatic Hemodynamics and Role of Doppler Ultrasonography	181
(A) Hepatic Hemodynamics	
(B) Doppler Ultrasonography in Liver Transplantation	
23. ABO-Incompatible Liver Transplantation	191
24. Electrolyte Abnormalities in ESLD	197
25. Immunology of Transplantation	204
26. Early Complications of Liver Transplantation	213
(A) Primary Nonfunction	
(B) Allograft Rejection	
(C) Biliary Complications	
(D) Vascular Complications	
(E) Post-transplant Infections	
27. Role of Liver Biopsy in Transplantation	275
28. Renal Dysfunction in Liver Transplantation	282
29. Long-term Care of Recipient.....	288
30. Pregnancy after Liver Transplantation	298
31. Recurrent Diseases after Liver Transplantation	301
32. Retransplantation	310
33. Pediatric Liver Transplantation	312
34. Anesthesia in Liver Transplantation	320
35. Extracorporeal Liver Supporting Systems	329
36. Health-related Quality of Life	335
37. Liver Transplantation in Asia and Western Countries	340
38. Hepatocellular Carcinoma and Liver Transplantation	347
39. Hepatitis B Virus and Liver Transplantation	358
40. Hepatitis C Virus and Liver Transplantation.....	370
41. Alcoholism and Liver Transplantation	378
42. Autoimmune Liver Diseases	383
43. Acute Liver Failure	388
44. Metabolic Liver Diseases	397
45. Non-alcoholic Fatty Liver Disease	402
46. Wilson's Disease	407
47. Budd-Chiari Syndrome	411
48. Recent Advances in Liver Transplantation	415
(A) Hepatocyte Transplantation	
(B) Xenotransplantation	
(C) Stem Cell Transplantation	
49. Complications of ESLD	429
(A) Ascites	
(B) Portal Hypertension and Variceal Bleeding	
(C) Hepatorenal Syndrome	
(D) Hepatic Encephalopathy	
(E) Hepatopulmonary Syndrome	
(F) Spontaneous Bacterial Peritonitis	
(G) Hyponatremia	

<i>Index</i>	465



Abbreviations

A

ABO-I	ABO-Incompatibility
ACR	Acute cellular rejection
AD/ADV	Adefovir dipivoxil
AFP	Alfa-fetoprotein
ALDLT	Adult living donor liver transplantation
ALT	Alanine aminotransferase
AMR	Antibody mediated rejection
APOLT	Auxiliary partial orthotopic liver transplantation
AZA	Azathioprine
APTT	Activated partial thromboplastin time
AS	Anastomotic stricture
AST	Aspartate amino transferase
AVT	Antiviral therapy

B

BD	Bile duct
BMI	Body mass index

C

CAH	Chronic active hepatitis
CBD	Common bile duct
CBF	Cerebral blood flow
CC	Choledocho-choledochostomy
CCO	Continuous cardiac output
CHA	Common hepatic artery
CHB	Chronic hepatitis B
CIN/CNI	Calcineurin inhibitor
CIT	Cold ischemic time
CMV	Cytomegalovirus
CPHT	Cavoportal hemitransposition
CPP	Cerebral perfusion pressure
CR	Chronic rejection
Cs A	Cyclosporine A
CT Scan	Computerized tomography scan
CTP	Child-Turcotte-Pugh score
CVVHD	Continuous venovenous hemodialysis

D

DDLT	Deceased donor liver transplantation
DRI	Donor risk index
DUS	Doppler ultrasonography

E

EBV	Epstein-Barr virus

ECG Electrocardiogram

EDV End diastolic volume

EHBA Extrahepatic biliary atresia

ELTR European liver transplant registry

ENBD Endoscopic nasobiliary drainage

ERCP Endoscopic retrograde cholangiopancreatography

ESLV Estimated standard liver volume

ESLD End stage liver disease

ESRD End stage renal disease

EVR Early viral response

F

FFP Fresh frozen plasma

FHF Fulminant hepatic failure

G

GDA Gastroduodenal artery

GFR Glomerular filtration rate

GRWR Graft recipient weight ratio

GV Graft volume

GGT γ -Glutamyl transpeptidase

H

HAART Highly active antiretroviral therapy

HAF Hepatic arterial flow

HA Hepatic artery

HAI Hepatic artery infusion

HAT Hepatic artery thrombosis

HAV Hepatitis A virus

HBV Hepatitis B virus

HCC Hepatocellular carcinoma

HCV Hepatitis C virus

HDV Hepatitis D virus

HIDA scan Hepato-iminodiacetic acid scan

HLT Heterotopic liver transplantation

HPCS Hemiportocaval shunt

HRQL Health-related quality of life

HRS Hepatorenal syndrome

HSV Herpes simplex virus

HTK Histidine-Tryptophan-Ketoglutarate

I

IJV Internal jugular vein

IL Interleukin

IMV Inferior mesenteric vein

INR International normalized ratio
IRHV Inferior right hepatic vein
IUGR Intrauterine growth retardation
ICP Intracranial pressure
IVC Inferior vena cava
IVIG Intravenous immunoglobulin

L

LAM Lamivudine
LDLT Living donor liver transplantation
LGA Left gastric artery
LHA Left hepatic artery
LHV Left hepatic vein
LLG Left lobe graft
LPV Left portal vein
LT/LTX Liver transplantation

M

MARS Molecular adsorbent recirculating system
MDCT Multi-detector computer tomography
MELD Model for end-stage liver disease
MHA Middle hepatic artery
MHV Middle hepatic vein
MMF Mycophenolate mofetil
MPA Mycophenolic acid
MPV Main portal vein
MRCP Magnetic resonance cholangiopancreatography
MRHV Middle right hepatic vein
MRI Magnetic resonance imaging

N

NAS Non-anastomotic stricture
NASH Nonalcoholic steatohepatitis

O

OLT Orthotopic liver transplantation
OPO Organ procurement organization
OPTN Organ procurement transplant network

P

PAH Pulmonary arterial hypertension
PAP Pulmonary arterial pressure
PBC Primary biliary cirrhosis
PCP Pneumocystis Carinii pneumonia
PCR Polymerase chain reaction
PE Plasma exchange or plasmapheresis
PELD Pediatric end stage liver disease
PGB Piggyback
PI Pulsatility index
PNF Primary nonfunction
PPH Portopulmonary hypertension
PSC Primary sclerosing cholangitis
PSV Peak systolic velocity
PT Prothrombin time

PTCD Percutaneous transhepatic cholangiographic drainage
PTLD Post-transplant lymphoproliferative disease
PT Prothrombin time
PTT Partial thromboplastin time
PVBF Portal vein blood flow
PVF Portal vein flow
PVI Portal vein infusion
PVP Portal venous pressure
PV Portal vein
PVT Portal vein thrombosis

R

RHA Right hepatic artery
RHV Right hepatic vein
RI Resistive index
RLG Right lobe graft
RLV Residual liver volume
RPA Renoportal anastomosis
RPV Right portal vein
RRT Renal replacement therapy
RVR Rapid viral response

S

SAL Splenic artery ligation
SAT Systolic acceleration time
SBP Subacute bacterial peritonitis
SFSG Small for size graft
SFSS Small for size syndrome
SI Situs inversus
SLT Split liver transplantation
SMA Superior mesenteric artery
SMV Superior mesenteric vein
SPSS Splenic artery steal syndrome
SRR Steroid resistant rejection
SVR Sustained viral response
SVR Systemic vascular resistance

T

TACE Transarterial catheter embolisation
TNF Tumor necrotic factor
TPA/tPA Tissue plasminogen activator
TTFM Transient time flow meter

U

ULN Upper normal limit
UNOS United Network for Organ Sharing
USG/US Ultrasonography
UW University of Wisconsin

V

VB Venovenous bypass
VZV Varicella zoster virus

W

WIT Warm ischemia time

History of Liver Transplantation

INTRODUCTION

Translations in Sanskrit written in 12th century BC reveal a legend about a Hindu God who transplanted the head of an elephant (xenograft) onto a boy whom the God had wrongly beheaded.¹ However, this was lacking an immunological explanation for xenotransplantation. The earliest reports on transplantation related to allotransplantation were experimental. In 600 BC, an Indian surgeon, Sushruta, supposedly used skin flaps to replace cut-off noses (the nose was often cut-off as a punishment).² In 255 BC, a famous Chinese surgeon, Pien Ch'iao, successfully exchanged the hearts of 2 soldiers Ying and Yang. This was considered to be first reference of general anesthesia; to perform surgery.³

In the 2nd century AD the concept of transplantation was first evoked by a Chinese surgeon, Hua-To, who replaced sick organs by healthy organs while making it clear that his purpose was to cure patients.⁴ In the 3rd century AD, in Rome, Italy, two Syrian doctors, Cosmas and Damian amputated the cancerous leg of a sacristan suffering from gas gangrene and replaced it with the leg of a dead black man.^{5,6} In the 16th century, an Italian surgeon, Gaspare Tagliacozzi, took up and improved the nose graft techniques of Susrata.⁷ He noted the difficulties associated with transplantation.

In 1902, Emerich Ullmann performed the first experimental kidney transplantation in dogs in Vienna. A few years later, in 1906, Mathieu Jaboulay, professor of surgery in Lyon, France, connected the renal vessels of a sheep and a pig kidney, respectively, to the brachial vessels of two patients who were dying of renal failure. Both kidneys failed to work. But these were the first transplants, albeit xenografts, that had been placed in humans. The first cadaveric kidney transplant was performed in 1936 in an attempt to treat renal failure after mercury poisoning, but the patient died after 2 days.⁸ Later on 23rd Dec 1954, first successful kidney

transplantation was performed between 2 identical twins, who was dying of renal disease. The surgery was performed at the Peter Bent Brigham Hospital in Boston by Joseph Murray, John Merrill, Hartwell Harrison and their team. The operation was successful and renal function was restored in the recipient, and the donor suffered no adverse effects. This was the first successful transplantation, performed against a background of failure.^{9,10}

HISTORY OF LIVER TRANSPLANTATION

Liver transplantation was first attempted in dogs by Welch in Albany in 1955 and Cannon in California in 1956. In the late 1950s and early 1960s two centers, Starzl working in Denver¹¹ and Moore in Boston were interested in the technique of transplanting the liver, which was clearly going to be a formidable undertaking. Both had realized that dogs would not tolerate clamping of the vena cava and portal vein that is necessary to take out and transplant the liver.¹² On 1st March, 1963, Thomas E Starzl (**Figure 1.1**) in Denver, University of Colorado Health Sciences Center (UCHSC), USA had performed the first human liver transplantation in the world in a 3 years old child with biliary atresia and received the liver from another child who died from brain tumor. But they could not complete the surgery and patient died due to uncontrolled hemorrhage.¹³ The second liver transplantation in man was performed on 5th May, 1963. Patient died on the 22nd postoperative day due to pulmonary embolism but with a normal liver. Starzl therefore decided to have a moratorium on clinical application of liver transplantation that lasted until 1967 when he started his main program. The first long term survival was achieved in 1967 by Starzl in Denver, Colorado, USA.^{14,15} Despite the developments in surgical techniques, liver transplantation remained experimental till 1970 with 1 yr patient survival rate around 25%.



Figure 1.1: Prof Thomas E Starzl (World's 1st Liver transplantation)
[Contributed and reproduced with permission of Terry Mangan, UPMC, USA]

By the end of summer 1967, the Denver experience included 11 liver transplantations. Eight of the patients had undergone orthotopic liver transplantation, and three had been provided with an auxiliary liver. Early immunosuppressive therapy consisted of azathioprine and prednisolone, but rejection was usually rapid. None of these patients had recovered their health; the longest survival was 34 days. In the same year, a chamber for

the preservation of the liver was developed in Denver. The system included perfusion of the liver with diluted blood under hypothermia and hyperbaric oxygenation. When dog livers were placed in the chamber, it was found that the livers could be preserved for 8 hours.¹⁶ At the same time, Denver group set out to prepare antihuman anti-lymphocyte globulin (ALG).

In July 1967, a 2½ yrs old child underwent orthotopic liver transplantation on (23rd July, 1967). The donor liver had been maintained for 3 hours in the preservation chamber. The early postoperative function was satisfactory. Postoperatively, antilymphocyte globulin (ALG) was given for several months in combination with azathioprine, and prednisolone. During the following 2 months, two more infants, both suffering from biliary atresia, underwent orthotopic liver transplantation. The protocol was the same as that for the first child. These three children were the first to achieve extended survival after liver transplantation.¹⁷ In 1969, Starzl published a monograph on liver transplantation, and by that time 25 patients had been treated in Denver and a number of the patients had survived for more than 1 year.¹⁸

Thomas E Starzl's pioneering efforts in organ transplantation for four decades have resulted in clinically proven treatments for patients with end-staged organ failure, who were previously doomed to death. His contributions to immunosuppression, organ procurement, organ preservation, tissue matching, surgical transplant technology, and the team approach to organ transplantation paved the way for the acceptance

TABLE 1.1: Historical milestones of liver transplantation^{15,23-27,66,69}

Year	Type of liver transplantation	Surgeon and Country
1963	1st Liver transplantation (biliary atresia)	Starzl TE, Denver, Colorado, USA
1964	1st Liver transplantation in Asia from non-heartbeating donor (biliary atresia)	Nakayama, Chiba Univ., Japan
1967	1st Successful liver transplantation	Starzl TE Denver, Colorado, USA
1968	1st Long-term survival (1 yr) of child	Denver, Colorado, USA
1968	1st Liver transplantation in Europe	Roy Y Calne, Cambridge, Europe
1983	NIH Consensus Conference declares liver transplantation is justified in the treatment of ESLD	
1984	1st Reduced-size liver transplantation	Bismuth H, Univ Paris Sud, France
1987	1st LDLT in a child	Raia S, Univ. of São Paulo Brazil
1987	Introduction of University of Wisconsin Solution	
1988	1st Split Liver transplantation (2nd Feb.)	Pichlmayr R, Germany
1989	1st Successful LDLT in child	Strong RW, Brisbane, Australia
1989	1st LDLT in Asia (Biliary atresia)	Nagasue, Japan
1993	1st Adult to adult LDLT	Makuuchi, Tokyo Univ., Japan
1997	1st Split Liver transplantation in Asia	Chen CL, Chang Gung Univ, Taiwan
2000	1st Dual graft transplantation	Lee SG, Ulsan Univ., Korea
2001	UNOS/OPTN Board of Directors approve MELD and PELD scoring system for organ allocation in liver transplantation	
2002	MELD and PELD Scoring system becomes effective	
2007	1st Dual graft transplantation in Europe	Broering DC, H-E Univ, Germany

TABLE 1.2: Details of the initial 7 orthotopic liver transplants in the world^{13,15,18-21,23,70}

No	Survival (Days)	Cause of death	Center
1.	0	Uncontrolled hemorrhage	Denver
2.	22	Sepsis and pulmonary embolism	Denver
3.	7.5	Sepsis and pulmonary embolism	Denver
4.	6.5	Pulm. edema, hepatic failure, and pulm. embolism	Denver
5.	11	Hepatic failure, pneumonitis, and liver abscess	Boston
6.	23	Peritonitis, sepsis, and hepatic failure	Denver
7.	0	Hemorrhage	Paris

of heart, lung, pancreas, intestinal, liver, and kidney transplantation. Starzl combined the marginally effective drugs, azathioprine and prednisolone, in a strategy (1962-63) that made kidney transplantation a viable option for treatment of end-stage renal disease.

Dr Starzl introduced the first major innovation in hypothermia, when canine liver allografts were cooled by infusion of chilled fluids into the vascular bed of hepatic allografts via the portal vein.²¹ In the initial stages of liver transplantation, 1-year survival rates were below 30% due to various limitations related to surgical technique, ineffective immunosuppression, and inadequate postoperative care. But results later improved drastically.

Till now, 8 patients have survived for more than 30 years after liver transplantation worldwide and 6 of them are from the Denver series.²² The longest survivor has had her new liver for 38 years. This patient was only 3 years old at the time of transplantation. Carl Groth reported that a total of 8 patients transplanted with livers from nonheart-beating donors have by now survived for more than 20 years in Stockholm.²³

One of Starzl's early experimental animals survived for many years after the immunosuppressant had been stopped.²⁸ In Cambridge, Roy Y Calne (**Figure 1.2**) and team were fascinated with the immunological studies of orthotopic liver transplantation and decided to follow Starzl with clinical application in April 1968.²⁹ Calne performed 1st OLT on May 2, 1968, in Addenbrookes Hospital, Europe. In any immunosuppressed patient with an organ graft, there is a danger of sepsis, or infection, and this was in fact the cause of failure in many of the early cases performed in Cambridge.

Starzl wrote in **Annals of Surgery** (1994):³⁰ Once a seam is opened in the fabric of the finished transplant product by rejection or by the drugs used to control it—whether this be in the graft vasculature, drainage system or any other components of the operation—the deadly handmaid of sepsis.....is close by.



Figure 1.2: Sir Roy Yorke Calne (Introduced cyclosporine, 1st liver transplantation in Europe, and World's 1st combined heart, lung and liver transplantation) (Reproduced with permission from Sir Roy Y Calne)

CONCEPT OF LIVING DONOR LIVER TRANSPLANTATION (LDLT)

Silvano Raia (**Figure 1.3**) in San Paolo, Brazil, introduced the concept of a living donor transplant to a child.³¹ The first attempt was performed in December, 1988 without success (the child died on the 6th postoperative day during hemodialysis). The second one was performed in July, 21st, 1989 and the girl survived for 4.5 months and died probably due to CMV infection. His efforts were not successful but were followed up shortly afterward by cases done in Brisbane, Australia by Russell Strong with success.³² This provided an opportunity to develop liver transplantation in Japan by Makuuchi M and Tanaka K³³



Figure 1.3: Prof Silvano Raia. Professor emeritus at the Faculty of Medicine of the University of San Paulo, San Paulo, Brazil (World's first Living Donor Liver Transplantation in a child) (Contributed and reproduced with permission of Dr. Sergio Mies, Sao Paulo Medical School - USP, Liver Unit, Instituto Dante Pazzanese de Cardiologia, São Paulo-SP, Brazil)

that previously had been impossible due to the law on organ donation and reluctance of the public to donate organs. However, parents would frequently offer a lobe of a liver for their child. The Japanese became the most experienced and skillful exponents of this technique in the world, although there was also enthusiasm for it in other centers particularly in the United States.

As results improved and FK506 (tacrolimus) became available as another calcineurin inhibitor like cyclosporine, but with certain advantages in therapeutic index for liver transplants, the criteria of selection for living donors widened to people who are not necessarily parents of a child, but more distant relatives or even friends. Then, adult-to-adult living donation was popularized in Hong Kong by ST Fan whose excellent techniques showed that good results could be obtained either using the right or left lobe, depending on the size of the donor and recipient.³⁴ In Taiwan, first successful deceased donor liver transplantation was performed in March 1984 by CL Chen and his team.

ADULT-TO-ADULT LDLT

Initially adult-to-adult liver transplantation was considered as hazardous to the donor. The exact mortality is not known but it has been calculated to be around 0.1-1% either due to complications or inappropriate donor selection with small residual volume or a fatty liver leading to hepatic failure after surgery. But the techniques of LDLT are refined with gaining experience the morbidity and mortality rates are less and risk of the donor can be balanced against the benefits of the recipient.

SPLIT LIVER

First split liver transplantation was done on 2nd Feb. 1988 by Rudolf Pichlmayr (**Figure 1.4**), Germany, later many studies have been reported and is an option to increase the donor pool in carefully selected deceased donor. In Asia, Chen CL from Taiwan performed the first split liver transplantation in May 1997, followed by KC Tan in July 1997 in Singapore.⁶⁵ Initially, split liver was used for one adult and one pediatric patient, but in the present transplantation scenario, split liver for 2 adults is the subject of interest.



Figure 1.4: Prof Rudolf Pichlmayr (1932-1997) (First split liver transplantation) (Contributed and reproduced with permission of S. Karger AG, Medical and Scientific Publishers, Allschwilerstrasse, Basel, Switzerland)

DOMINOS

1st domino transplantation was introduced in 1997 to increase the donor pool. But this is popular in few countries—Portugal, Japan, and in Sweden, where metabolic diseases like Familial amyloid polyneuropathy was seen. Few cases were also done in Spain, UK and USA.

ABO-INCOMPATIBLE (ABO-I) LDLT⁷¹

The first ABO-I LDLT was performed in November 1991 in Japan to overcome the organ shortage. As per the data of National Registry of the Japan Study Group for ABO-incompatible, 291 (155 children and 136 adults) ABO-I LDLTs have been performed till March 2006 in Japan from 28 institutions. ABO-incompatible LDLT is a standard practice in children (< 2 years), and plasmapheresis, local infusion and rituximab prophylaxis are promising in adults. In adult LDLT, it is exceptionally performed only as a rescue option in an emergent situation where suitable donor is not available.

DUAL GRAFTS

First Dual grafts reported by Lee SG and team from Korea in 2000.⁶⁶ Several reports suggesting excellent results of this procedure have already been published.⁶⁷⁻⁶⁹

HISTORICAL REVIEW OF IMMUNOSUPPRESSION

IMMUNOSUPPRESSION DURING EARLIER TIMES

In 1944, Medawar reported that rejection is an immunological event; suppression of the immune system was shown to prolong skin and renal graft survival in animals.⁴⁰

Immunosuppression in the early 1960s was first performed with total body irradiation,⁹ corticosteroid therapy,^{41,42} and later 6-mercaptopurine and its derivative azathioprine.⁴³⁻⁴⁵ In animal experiments and clinical trials, no single modality or combination provided complete control of rejection without lethal side effects.⁴⁶⁻⁵⁰ In 1963, Starzl discovered that azathioprine and prednisone had a synergistic effect in animals.⁵¹ When these two drugs were immediately applied in human kidney transplant recipients,^{52,53} the result was a revolution in clinical transplantation. Rejection could usually be reversed with prednisone, and the amount of drugs required could often be reduced with time.⁵⁴

In 1967, at the University of Colorado, first clinical trials were performed with an antilymphocyte globulin prepared from sensitized horses⁶⁵ and used as a supplement to azathioprine and prednisone. Most attempts at liver transplantation in 1967 and 1968 at the

TABLE 1.3: Historical review of rejection and immunosuppression^{35-39, 55-57}

Year	Events
1900	ABO blood grouping defined
1916	Immune properties of lymphocytes discovered
1944	Immunological basis of rejection discovered by Medawar
1948	Histocompatibility gene identified in the mice
1950	Histocompatibility complex identified in humans
1951	Lymphocyte sensitivity to radiation discovered
1952	Organic compounds used to prevent rejection
1959	Total body irradiation used to prevent rejection, survival of allografts used linked to HLA typing
1962	Clinical trials on Azathioprine
1964	Experimental transplantation between baboons and humans
1966	Animal experiments with antilymphocyte serum
1967	Antilymphocyte globulins used clinically in heart transplantation
1972	Immune properties of cyclosporine discovered
1972	Immune properties of cyclosporine discovered
1976	T cell inhibition of cyclosporine discovered
1978	Calne first introduced cyclosporine A in renal allografts
1979	FDA approves cyclosporine A for clinical use
1980	Combined cyclosporine and steroids used
1981	Klintmalm reported the nephrotoxicity of Cs A
1984	Immune properties of Tacrolimus discovered
1989	Tacrolimus introduced into clinical trials
1990	1st reports of MMF use in rejection
1993	OKT3 used for induction therapy Chimerism in organ transplantation discovered.
1996	Interleukin expression discovered
1998	Interleukin pathway blocked to prevent rejection
1999	Donor specific tolerance experiments.

University of Colorado were initially successful, but all recipients eventually died. The first long-term survivor died of recurrent cancer at 400 days post-transplant.^{66,67} During the next 12 years, however, the one-year mortality rate never fell below 50%. In the meantime, other researchers around the world were also initiating attempts to transplant livers. At Cambridge University in England, Roy Calne began clinical trials in 1967.⁵⁸ Rudolf Pichlmayr started a program in Hanover in 1972, and Henri Bismuth started in Paris in 1974. Nevertheless, liver transplantation remained an impractical procedure because of the high mortality rate.

CYCLOSPORINE ERA

Jean Borel in 1977 showed that the cyclic peptide cyclosporine A prolonged skin graft survival and inhibited immune reactions. Clinical trials with cyclosporine were conducted in cadaveric renal transplantation by Calne.⁵⁹ The combination of cyclosporine with steroids was used in liver transplant trials by Starzl.⁶⁰

The greatly improved results reported with cyclosporine A from 1981 to 1982 led to the historic NIH Consensus Development Conference in 1983,⁶¹ at which the world's four largest transplant centers presented their results. The conclusion, that liver transplantation was no longer to be considered an experimental procedure, was followed over the next few years by phenomenal increase in the number of liver transplants, transplant centers, and liver transplant candidates. In 1988, when Starzl reported the Pittsburgh experience with 1000 liver transplants with cyclosporine,⁶² the one-year patient survival rate had risen from 27% with azathioprine to 74% with cyclosporine.

TACROLIMUS ERA

In 1989, tacrolimus, another potent calcineurin inhibitor, was introduced in clinical practice in Pittsburgh.^{63,64} Tacrolimus was found to be effective in reducing the frequency of acute and chronic rejection in liver transplantation. Later these two calcineurin inhibitors, cyclosporine and tacrolimus, have become the primary immunosuppressive agents for transplantation of not only the liver but also other organs.

Recently, additional immunosuppressive agents with different mechanisms of action have become available such mycophenolate mofetil, sirolimus, etc. These agents are usually used in combination with lowered doses of a calcineurin inhibitor, to boost immunosuppression with additive or synergistic effects and to reduce the adverse effects of calcineurin inhibitors.

REFERENCES

- O' Flaherty WD. Hindu myths translated. London, England: Penguin Books Ltd 1975:261.
- Ray P, Gupta HN, Roy M. *Susruta Samhita*. A Scientific Synopsis. New Delhi: Indian National Science Academy, 1980.
- Kahan BD. Pien Ch'iao, the legendary exchange of hearts, traditional Chinese medicine, and the modern era of cyclosporine. *Transplant Proc* 1988;20:2.
- Kuss R, Bourget P. Une histoire illustre' e de la greffe d'organes. La grande aventure du sie" cle. [An illustrated history of organ transplantation: The great adventure of the century]. Rueil-Malmaison, France: Laboratoires Sandoz, 1992.
- Kahan BD. Cosmas and Damian revisited. *Transplant Proc* 1983;15:2211.
- Rinaldi E. The first homoplastic limb transplant according to the legend of Saint Cosmas and Saint Damian. *Ital J Orthop Traumatol* 1987;13:393.
- Zimblar MS. Gaspare Tagliacozzi (1545-1599): Renaissance surgeon. *Arch Facial Plast Surg* 2001;3:283.
- Hamilton DN, Reid WA, Yu Yu. Voronoy and the first human kidney allograft. *Surg Gynecol Obstet* 1984;159:289-94.
- Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins *JAMA* 1956;160:277-82.
- Tilney NL. *Transplant: from myth to reality*. New Haven, Conn: Yale University Press 2003.
- Starzl TE, Kaupp HA Jr., Brock DR, et al. Reconstructive problems in canine liver homotransplantations with special reference to the postoperative role of hepatic venous flow. *Surg Gynecol Obstet* 1960;111:733-43.
- Moore FD, Wheelers HB, Demissianos HV, et al. Experimental whole organ transplantation of the liver and of the spleen. *Ann Surg* 1960;142:374-87.
- Starzl TE, Marchioro TL, Von Kaulla KN, Hermann G, Brittain RS, Waddel WR. Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963;117:659-76.
- Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ. The use of heterologous antilymphoid agents in canine renal and liver homotransplantations and in human renal homotransplantations. *Surg Gynecol Obstet* 1967;124:301-18.
- Starzl TE, Groth CG, Brettschneider L, et al. Extended survival in 3 cases of orthotopic homotransplantation of the human liver *Surgery* 1968;63:549.
- Brettschneider L, Daloze PM, Huguet C, et al. The use of combined preservation techniques for extended storage of orthotopic liver homografts. *Surg Gynecol Obstet* 1968;126:263.
- Starzl TE, Groth CG, Brettschneider L, et al. Extended survival in 3 cases of orthotopic homotransplantation of the human liver *Surgery* 1968;63:549.
- Starzl TE. *Experience in Hepatic Transplantation*. Philadelphia: Saunders 1969.
- Moore FD, Birtch AG, Dagher F, et al. Immunosuppression and vascular insufficiency in liver transplantation. *Ann NY Acad Sci* 1964;102:729.
- Demirleau, Noureddine, Vignes, et al. Tentative d'homographe hepaticque (attempted hepatic homograft). *Men Acad Chir (Paris)* 1964;90:177.
- Starzl TE: *Experience in hepatic transplantation*. W.B. Saunders Company. Philadelphia 1969.
- World Transplant Records. Liver. In Cecka JM, Terasaki PJ, (eds): *Clinical Transplants 2005*. Los Angeles: Immunogenetics Center, UCLA 2006.
- CG Groth. Forty years of liver transplantation. *Personal recollections. Transplantation Proceedings* 2008;40:1127-29.
- Raia S, Nery J, Mies S. *Lancet* 1989;2:497.
- Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990;322:1505-07.
- Shimada M, Fuji M, Morine Y, et al. Living donor liver transplantation, present status and future prospective. *Journal of medical investigations* 2005;52:22-32.
- National Institute of Health. *Hepatology* 1984;4:107 S-110 S.
- Starzl TE. *Experience in Hepatic Transplantation*. Philadelphia: WB Saunders 1969:45-48.
- Calne RY, Williams R. Liver transplantation in man. Observations on technique and organization in five cases. *BMJ* 1968;4:535-50.
- Todo S, Fung JJ, Starzl TE, Tzakis A, et al. Single center experience with primary orthotopic liver transplantation under FK506 immunosuppression. *Ann Surg* 1994;220:297-309.
- Raia S, Nery JR, Mies S. Liver transplantation from live donors. *Lancet* 1988;ii:497.
- Strong RW, Lynch SV, Ong TN, et al. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990;322:1505-07.

33. Tanaka K, Uemoto S, Tokunaga Y, et al. Surgical techniques and innovations in living related liver transplantation. *Ann Surg* 1993;217:82-91.
34. Lo CM, Fan ST, Liu CL, et al. Adult-to-adult living donor transplantation using extended right lobe grafts. *Ann Surg* 1997;226:261.
35. A De Vitto Dabbs, JH Dauber, LA Hoffman. Rejection after organ transplantation. A historical review. *American journal of critical care* 2000;10:419-29.
36. Calne RY, White DJ, Thiru S, et al. *Lancet* 1978;2:1323.
37. Klintmalm GB, Iwatsuki S, Starzl TE. Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. *Lancet* 1981; 1:470.
38. Klupp J, Bechstein WO, Platz KP, et al. Mycophenolate mofetil added to immunosuppression after liver transplantation—first results. *Transpl Int* 1997;10:223.
39. Fisher RA, Ham JM, Marcos A, et al. A prospective randomized trial of mycophenolate mofetil with neoral or tacrolimus after orthotopic liver transplantation. *Transplantation* 1998;66:1616.
40. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits *J Anat* 1944;78:176.
41. Dempster WJ, Lennox B, Boag JW. Prolongation of survival of skin homotransplants in the rabbit by irradiation of the host. *Br J Exp Pathol* 1950;31:670.
42. Morgan JA. The influence of cortisone on the survival of homografts of skin in the rabbit. *Surgery* 1951;30:505.
43. Meeker WR, Condie R, Weiner D, et al. Prolongation of skin homograft survival in rabbits by 6-mercaptopurine. *Proc Soc Exp Biol Med* 1959;102:459.
44. Calne RY. The rejection of renal homografts: Inhibition in dogs by 6-mercaptopurine. *Lancet* 1960;1:417.
45. Calne RY, Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-332. *Surg Forum* 1961;12:118.
46. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. *Ann Surg* 1962;156:337.
47. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy *N Engl J Med* 1963;268:1315.
48. Woodruff MFA, Robson JS, Nolan B, et al. Homotransplantation of kidney in patients treated with preoperative administration of antimetabolite (Imuran). *Lancet* 1963;2:675.
49. Groth CG. Landmarks in clinical renal transplantation. *Surg Gynecol Obstet* 1972;134:323.
50. Hamburger J, Vaysse J, Crosnier J, et al. Renal homotransplantation in man after radiation of the recipient. *Am J Med* 1962;32:854.
51. Marchioro TL, Axtell HK, LaVia MF, et al. The role of adrenocortical steroids in reversing established homograft rejection. *Surgery* 1964;55:412.
52. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection human renal homografts with subsequent development of homograft tolerance. *Surg Gynecol Obstet* 1963;117:385.
53. Starzl TE. *Experience in Renal Transplantation*. Philadelphia: WB Saunders 1964.
54. Starzl TE, Schroter GJP, Hartmann HM, et al. Long term (25 year) survival after renal homotransplantation—the world experience. *Transplant Proc* 1990;22:2361.
55. Starzl TE, Marchioro TL, Porter KA, et al. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. *Surg Gynecol Obstet* 1971;133:981.
56. Starzl TE, Groth CG, Bretschneider F, et al. Orthotopic homotransplantation of the human liver. *Ann Surg* 1968; 168:392.
57. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. *Hepatology* 1982;2:614.
58. Calne RY, Williams R. Liver transplantation in man. I. Observations on technique and organization in five cases. *Br Med J* 1968;4:535.
59. Calne RY, Rolles K, White DJG, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979; 2:1033.
60. Starzl TE, Klintmalm GBG, Porter KA, et al. Liver transplantation with the use of cyclosporin A and prednisone. *N Engl J Med* 1981;305:266.
61. National Institutes of Health Consensus Development Conference Statement. Liver transplantation—June 20–23, 1983. *Hepatology* 1984;4:S107.
62. Iwatsuki S, Starzl TE, Todo S, et al. Experience in 1,000 liver transplants under cyclosporine steroid therapy: a survival report. *Transplant Proc* 1998;20:498.
63. Starzl TE, Todo S, Fung J, et al. FK506 for liver, kidney, and pancreas transplantation. *Lancet* 1989;2:1000.
64. Todo S, Fung J, Starzl TE, et al. Liver, kidney, and thoracic organ transplantation under FK506. *Ann Surg* 1990;212:295.
65. VH de Villa, CL Chen, YS Chen, et al. Split Liver Transplantation in Asia. *Transplantation Proceedings* 2001; 33:1502-03.
66. Lee S, Hwang S, Park K, et al. An adult-to-adult living donor liver transplant using dual left lobe grafts. *Surgery* 2001;129:647-50.
67. Lee SG, Hwang S, Park KM et al. Seventeen adult-to-adult living donor liver transplantations using dual grafts. *Transplant Proc* 2001;33:3461-63.
68. Hwang S, Lee SG, Lee YJ et al. Lessons learned from 1,000 living donor liver transplantations in a single center: How to make living donations safe. *Liver Transpl* 2006;12:920-27.
69. Broering DC, Walter J, Rogiers X. The first two cases of living donor liver transplantation using dual grafts in Europe. *Liver Transpl* 2007;13:149-53.
70. Starzl TE. History of Liver and Other Splanchnic Organ Transplantation. In: Busutill RW, Klintmalm GB, eds. *Transplantation of the Liver*. Philadelphia, Pa:Saunders; 1996:3-22 and www.emedicine.com
71. Hiroto E, Satoshi T, Hironori H, et al. Present Status of ABO-Incompatible Living Donor Liver Transplantation in Japan. *Hepatology* 2008; 47(1):143-52.

CHAPTER 2

Anatomy of Liver

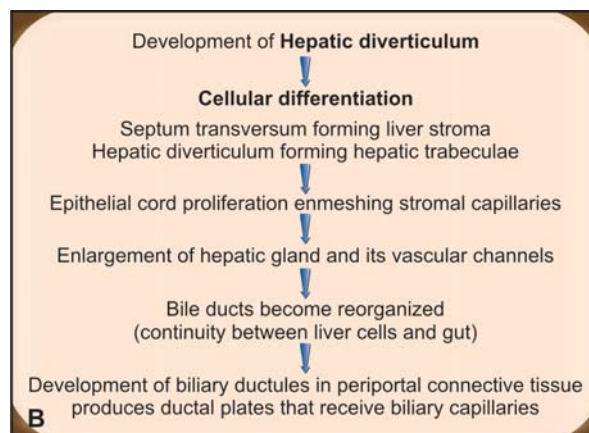
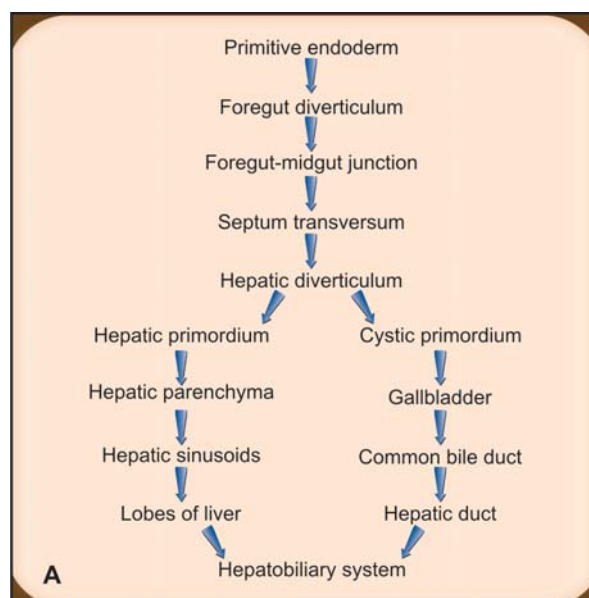
INTRODUCTION

Liver accounts for approximately 2 to 3% of the total body weight of an adult and weighs approximately 1400-1600 gm. Understanding of segmental and lobar anatomy of liver is very important before proceeding for any hepatic resections or liver transplantation. The ability to regenerate after resection or trauma is unique characteristic of liver, which allows a surgeon to perform major resections.

EMBRYOLOGY

The liver is one of the first organs to develop in the embryo, and it rapidly becomes one of the largest organs in the fetus.¹ The development of the liver parenchyma, biliary system, and vascular supply reflects the anatomical relationships of these structures in the adult organ. The transverse septum (septum transversum) arises at an embryonic junctional site. The junctional region externally is where the ectoderm of the amnion meets the endoderm of the yolk sac. The junctional region internally is where the foregut meets the midgut. The mesenchymal structure of the transverse septum provides a support within which both blood vessels and the liver begin to form. This structure grows rapidly. The transverse septum then differentiates to form the hepatic diverticulum and the hepatic primordium; these two structures together will go on to form different components of the mature liver and gall bladder.

In fetal life, organization of the hepatic epithelial cords occurs around the developing portal vein, which itself arises from the vitelline and umbilical veins.² The development of the hepatic artery closely parallels the development of the bile ducts.^{3,4} The arterial and biliary systems are immature at birth. Development of arterial vessels and peri-biliary plexuses begins at the hilum and spreads to the periphery mimicking the development of



Flow charts 2.1A and B: Sequence of events in the development of liver

ducts in that order. The hepatic arterial system in humans continues to proliferate and grows to reach an adult form only at 15 years of age, suggesting that, unlike the portal supply, the arterial supply is not crucial to lobular architecture.^{4,5}

LIGAMENTS OF LIVER (FIGURE 2.1)

The liver is covered by a Glisson capsule. It envelops all the 3 structures such as hepatic artery, portal vein, and bile duct at the hilum of the liver.

Ligaments of liver are composed of regular connective tissue^{6,7} which support the liver. The ligaments are:

- Round ligament (Ligamentum teres)
- Falciform ligament
- Coronary ligament
- Right and left triangular
- Ligamentum venosum

where the bare area of the liver connects to the diaphragm, the liver is suspended mostly by the ligaments and hepatic veins.⁸ The 2 layers of parietal peritoneum continue as falciform ligament and surround the liver except in the bare area, where the two layers separate to form the coronary ligament and the left triangular ligament. The left layer of the falciform ligament becomes the superior layer of the left coronary ligament. The right layer becomes the upper layer of the coronary ligament, which meets the lower layer to form the right triangular ligament.

The lower layer of the coronary ligament continues on the posterior surface of the liver and can reflect on the upper part of the right kidney to form the hepatorenal ligament. Then it passes in front of the groove for the inferior vena cava (IVC), and, after a semicircular course in front of the caudate lobe, it meets the right leaf of the

lesser omentum. The leaf of the lesser omentum continues in the posterior leaf of the left triangular ligament.⁵⁶

LOBAR AND SEGMENTAL ANATOMY OF LIVER

Anatomically liver has 4 lobes such as right, left, quadrate, and caudate.¹² Right and left lobes are separated by the falciform ligament on the anterosuperior surface (portoumbilical fissure). On the visceral surface of the liver, ligamentum teres and the fissures for the ligamentum venosum separate both the lobes. The quadrate lobe is demarcated in the visceral surface of the liver by the gallbladder fossa, porta hepatis, and the portoumbilical fissure. The caudate lobe is demarcated by the groove for the IVC and the fissure of the venous ligament. The right portion of the caudate lobe is continuous with the right lobe by the caudate process.⁵⁶

FUNCTIONAL/SURGICAL LOBES OF LIVER

Rex et al in 1988 showed the plane of division is not through the falciform ligament but through a plane passing through the gallbladder bed and the notch of the IVC⁹, later in 1897 Cantle described the Cantle's line dividing the surgical/ functional right and left lobes.¹⁰

SEGMENTAL ANATOMY OF LIVER

The liver is divided into segments based on inflow, outflow and biliary drainage. Most widely accepted segmental anatomy of liver was reported by Couinaud in 1954,^{11,12} later Bismuth in 1982, also presented his report about segmental anatomy.¹³

COUINAUD'S SEGMENTAL ANATOMY (FIGURE 2.2)

This anatomy is based on portal and hepatic venous distribution¹⁴ and shows a special consideration to caudate lobe. Fissures of the three hepatic veins (portal scissurae) divide the liver into four sectors (segments), lateral and paramedian, on the right and left sides, respectively. The planes containing portal pedicles are called hepatic scissurae.⁵⁶

8 segments of liver:

Segment I	Right lobe	Left lobe
Caudate lobe	Segment V	Segment II
	Segment VI	Segment III
	Segment VII	Segment IV
	Segment VIII	

Couinaud et al¹² and Filipponi et al¹⁵ also used the term segment IX for an area of the dorsal sector of the liver close to the IVC. In 2002, however, Abdalla et al¹⁶ reported that there are no separate veins, arteries, or ducts

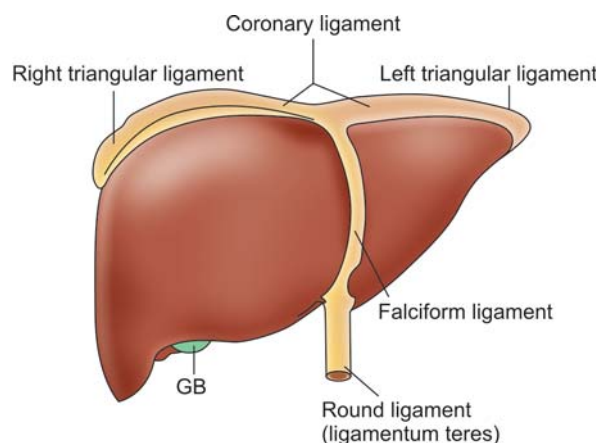


Figure 2.1: Ligaments of liver

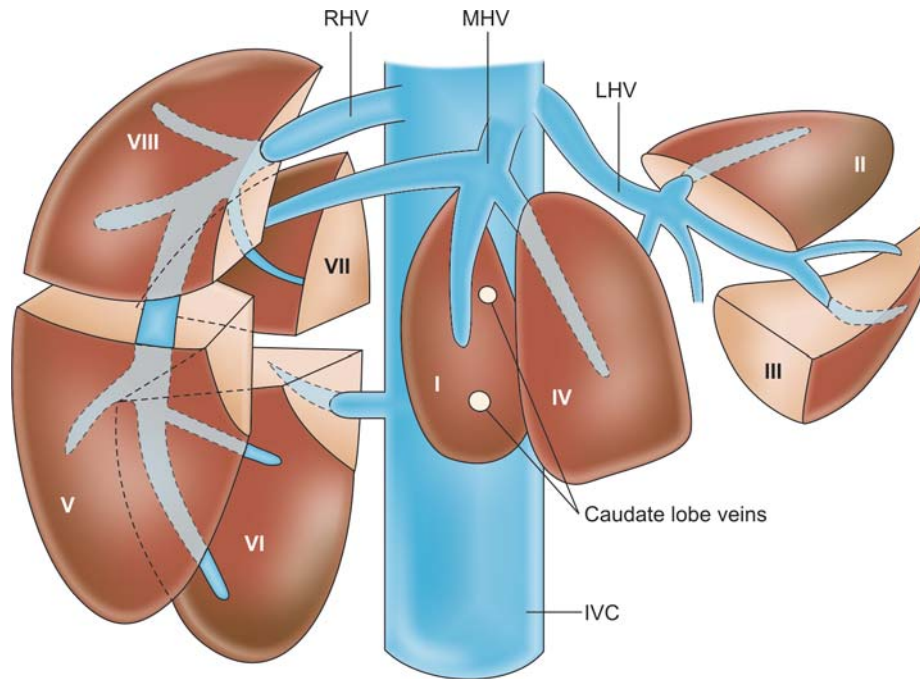


Figure 2.2: Schematic representation of anatomical segments of liver (RHV: Right hepatic vein, LHV: Left hepatic vein, MHV: Middle hepatic vein, IVC: Inferior vena cava)

that can be defined for the right paracaval portion of the posterior liver and because pedicles cross the proposed division between the right and left caudate, the concept of segment IX is abandoned.”

BISMUTH'S SEGMENTAL ANATOMY¹³

He used the three fissures (scissurae) hosting the hepatic veins and a transverse fissure passing through the right and left portal branches. Bismuth described a right and left hemiliver divided by the median fissure, with each hemiliver having anterior (topographically medial) and posterior (topographically lateral) sectors (segments). He took into specific consideration the caudate lobe (segment I). The left lobe is thus divided into three segments: II (left lateral superior subsegment), III (left lateral inferior subsegment), and IV (left medial subsegment). The right lobe has four segments: V (right anterior inferior subsegment), VI (right anterior superior subsegment), VII (right posterior inferior subsegment), and VIII (right posterior superior subsegment).⁵⁶

SEGMENT I

Caudate lobe needs special consideration, relating to the portal and biliary drainage. The number of portal branches of segment I varies from 1 to 6 (average 3).⁵⁰

Segment I has its own biliary drainage.²⁶ The left hepatic duct receives one (or more) duct of segment 4 and one or two ducts of segment I. The right duct receives one duct of segment I. Biliary drainage of segment I goes to both hepatic ducts (80%). In 15% cases bile drainage is only to the left hepatic duct and in 5% to the right, always close to the biliary confluence at a variable location.²⁶ The segment I ducts are posterior, running above the portal branch and joining the corresponding bile duct on its posterior margin.

ANATOMICAL RELATIONS AROUND THE HILUM

A precise understanding of general hilar anatomy is the key correctly dissecting and dividing the hilar structures. The technical difficulty in LDLT is the division of the hilar structures outside the liver.¹⁷ The most common anatomical variants of hilar structures are shown in the **Figure 2.4**. The hepatic hilum and the hepatoduodenal ligament are composed of three layers¹⁸:

- Portal vein located in the most dorsal aspect
- Hepatic artery located in the middle
- Bile duct located in its most ventral aspect

PORTAL VEIN

Portal venous anatomy is usually very regular and divides on the right side of the hepatic hilum. The left portal vein consists of a transverse portion that runs from

the bifurcation of the main portal vein to the ligamentum venosum and an umbilical portion that runs upward in the umbilical fissure.¹⁹ The portal vein is 7 and 10 cm long and 0.8 and 1.4 cm in diameter and is without valves. It is formed by the union of superior mesenteric vein and the splenic vein behind the neck of the pancreas. At the porta hepatis, the portal vein bifurcates into right and left branches before entering the liver (**Figure 2.3**). Usually portal veins are found posterior to hepatic arteries and the bile ducts in their lobar and segmental distribution.

The right branch of the portal vein is located anterior to the caudate process and is shorter than the left branch. Near its origin it gives off a branch for the caudate lobe. It follows the distribution of the right hepatic artery and duct and bifurcates into anterior and posterior segmental branches as soon as it enters the hepatic parenchyma. Each segmental branch further divides into inferior and superior subsegmental branches for its respective parenchymal subsegments. Left portal vein has a long extrahepatic course. It has two parts, transverse and umbilical. It begins in the porta hepatis as the transverse part²¹, which gives off a caudate branch, and travels to the left.

At the level of the umbilical fissure, the umbilical part turns sharply. It courses anteriorly in the direction of the round ligament and terminates in a cul-de sac proximally to the inferior border of the liver.²⁰ Here it is joined anteriorly by the round ligament (ligamentum teres hepatis).⁸ The left portal vein divides into medial and lateral segmental branches, each with superior and inferior subsegmental branches. The umbilical part provides the superior and inferior subsegmental veins for the lateral segment and also provides the medial segmental veins from its right side.²¹

HEPATIC ARTERY

Common hepatic artery takes origin from the celiac trunk (86%); other sources are the superior mesenteric artery (2.9%), the aorta (1.1%), and, very rarely, the left gastric artery.²² The common hepatic artery then runs horizontally along the upper border of the head of the pancreas covered by the peritoneum of the posterior wall of the omental bursa. The gastroduodenal artery branches off the common hepatic artery posterior and superior to the duodenum. The common hepatic artery continues as the proper hepatic artery and turns upward to ascend in the lesser omentum, enveloped by the hepato-duodenal ligament, in front of the epiploic (Winslow's) foramen. Within the hepato-duodenal ligament, the proper hepatic artery lies to the left of the common bile duct and anterior to the portal vein. The portal vein, however, is located posteriorly or deeper to the proper hepatic artery and the common bile duct.

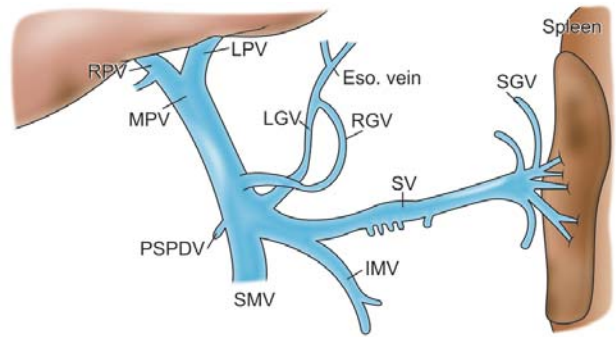


Figure 2.3: Formation of portal vein and its branches (SMV: Superior mesenteric vein, IMV: Inferior mesenteric vein, SV: Splenic vein, LGV: Left gastric vein, RGV: Right gastric vein, MPV: Main portal vein, RPV: Right portal vein, LPV: Left portal vein, PSPDV: Posterior superior pancreaticoduodenal artery, SGV: Short gastric vein, Eso. vein: esophageal vein)

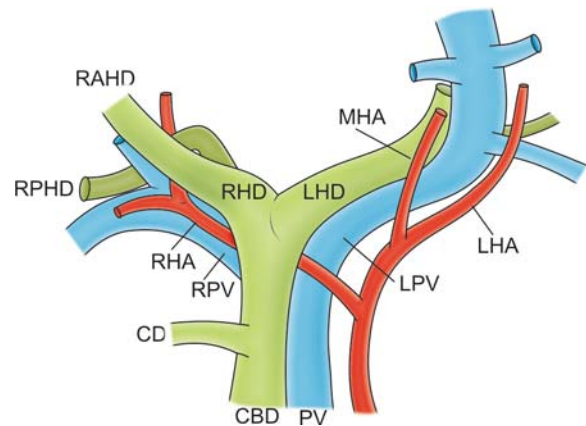


Figure 2.4: Course and relations of structures around hepatic hilum. (RHA: Right hepatic artery, LHA: Left hepatic artery, LPV: Left portal vein, RPV: Right portal vein, CBD: Common bile duct, CD: Cystic duct, RHD: Right hepatic duct, LHD: Left hepatic duct, RAHD: Right anterior hepatic duct, RPHD: Right posterior hepatic duct) (Modified and redrawn with permission of H. Imamura)

Within the ligament the proper hepatic artery divides into a large right branch, smaller left and middle branches more proximally in the hepatoduodenal ligament than the divisions of the bile duct or portal vein. Both right and left branches have a relatively long extrahepatic course that of other hilar structures. The right hepatic artery is usually larger and passes behind the bile duct immediately after branching off the proper hepatic artery. The left and middle hepatic arteries travel along the left side of the hepatoduodenal ligament, with no relationship to the bile duct until the end of the transverse portion. Hepatic artery is also subjected to more anatomical variations.⁵⁶

BILE DUCT

It normally follows an extrahepatic course very similar to that of the portal vein. Its bifurcation is located more cranially than that of the portal vein or hepatic artery. Immediately after bifurcating, its right and left branches run ventrally to portal vein, but they pass to the dorsal aspect of the right and left portal branches more cranially. Anatomical variations are much more common in bile duct than the portal vein.²³

Blood Supply of the Bile Duct

The hilar duct receives a copious supply of arterial blood from its surroundings, forming a rich arterial plexus on the surface of the duct in continuity with the vessels around the supraduodenal duct. A communicating arcade between the right and left arterial system is located within the hilar plate, and originated from the segment 4 arteries and the right branch of the middle hepatic artery.³⁰

Bile duct anatomy and its blood supply requires attention in living donor liver transplantation (LDLT). The blood supply for biliary anastomosis is a major concern in LDLT. 60% of the arterial supply of bile duct comes from the caudal side through preduodenal arteries. Blood vessels are located at 3 and 9 o'clock positions in the CBD and retro-portal arteries give rise to multiple arteriolar branches, which form a free anastomosis within the wall of the bile duct.²⁴

CBD is supplied by Epicholedochal plexus receives blood supply from 3 arterial branches²⁵ (shown in **Figures 2.5 and 2.6**):

- Branch from posterior superior pancreaticoduodenal artery (PSPDA).
- Branch from right hepatic artery arising at the point where it passes behind the CBD.
- Branch running caudally from the arteries of hepatic hilum.

All these branches communicate with each other, but the division of any one of them occasionally results in biliary ischemia. RHA courses parallel to the right bile duct branch towards the liver on its dorsal aspect. Dissection of dorsal aspect of right bile duct should be avoided when harvesting the right lobe graft in LDLT, in order to avoid devascularization of this branch. RHA should be divided to the right of CBD during donor hepatectomy.

INTRAHEPATIC BILIARY ANATOMY (FIGURE 2.7)

Intrahepatic bile duct anatomy is very important in LDLT during donor hepatectomy. Anomalies of the bile ducts are much more common than those of the portal vein.^{26,27} Intraoperative cholangiography is essential to visualize the biliary anatomy and identifying the precise site of

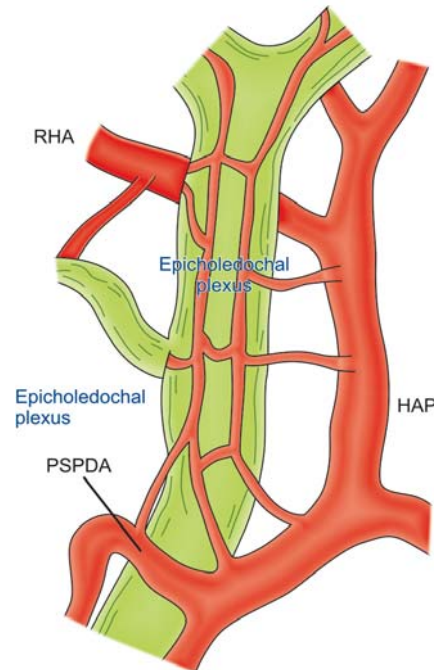


Figure 2.5: Blood supply of extrahepatic bile duct and Epicholedochal plexus. (Anterior view) (HAP: Hepatic artery proper; PSPDA: Posterior superior pancreaticoduodenal artery; RHA: Right hepatic artery) (Modified and redrawn with permission of H Imamura²⁵)

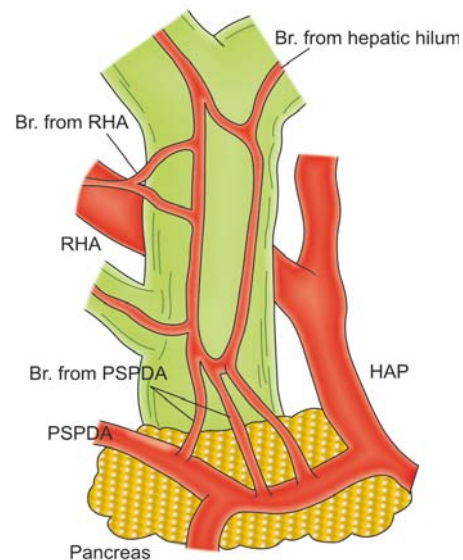


Figure 2.6: Normal blood supply of bile duct. (HAP: Hepatic artery proper; PSPDA: Posterior superior pancreaticoduodenal artery; RHA: Right hepatic artery) (Modified and redrawn with permission of H Imamura²⁵) (Lateral view of blood supply to extrahepatic bile duct: Arterial supply from PSPDA, arterial supply from the RHA arising at the point where it passes posterior to the common bile duct, and arteries running caudally from the hepatic hilum)

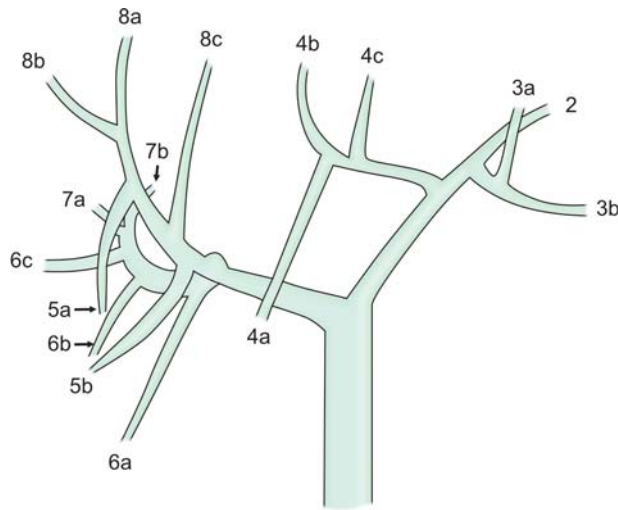


Figure 2.7: Normal intrahepatic biliary anatomy

division.^{28,29} Bile canaliculi are formed by parts of the membrane of adjacent parenchymal cells, and they are isolated from the perisinusoidal space by junctions. Bile flows from the canaliculi through ductules (canals of Hering) into the interlobular bile ducts found in portal pedicles.

RIGHT HEPATIC DUCT

The right hepatic duct has an average length of 0.9 cm and is formed by the union of the anterior and posterior sectorial branches close to the porta hepatis.

Anterior branch: Drains segment V (Va and Vb) and VIII (VIIIa and VIIIb).

Posterior branch: Drains segment VI (VIa, VIb and VIc) and VII (VIIa and VIIb).

This is the usual pattern, present in 72% of specimens examined by Healey and Schroy.²⁶

LEFT HEPATIC DUCT

Medial and lateral branches converge to form the left hepatic duct, which has an average length of 1.7 cm. Medial branch drains segment IV (IVa, IVb and IVc) (left medial subsegment) and lateral branch drains segment II (left lateral superior subsegment) and III (IIIa and IIIb) (left lateral inferior subsegment). Segment IV is drained by mediosuperior and medioinferior branches. This typical pattern was met in 67% of Healey and Schroy's specimens.³⁰

CAUDATE LOBE

The biliary drainage of the caudate lobe (segment I) enters both the right and the left hepatic duct systems in 80% of individuals.³¹ In 15% of cases the caudate lobe drains only into the left hepatic duct system, and in 5% it drains only in the right system.³¹

ANATOMICAL VARIATIONS IN INTRAHEPATIC BILIARY TRACT

Intrahepatic biliary tract variations can present in 6 different types (Figures 2.8A to F):

Type A: Right anterior and right posterior sectorial ducts joint to form RHD.

Type B: The right hepatic duct is absent. The right anterior and posterior sectorial ducts join directly to the confluence with the left hepatic duct to form the CHD

Type C: Right anterior sectorial duct opens directly into the LHD

Type D: Right posterior sectorial duct opens directly into the LHD

Type E: The right anterior sectorial duct opens directly into the CHD

Type F: Right posterior sectorial duct opens directly into the CHD

CONFLUENCE PATTERNS OF THE RIGHT INTRAHEPATIC BILE DUCTS AND ITS RELATION TO THE PORTAL VEIN

Confluence pattern of the right intrahepatic bile ducts can be classified into 3 types according to the anatomic relation between the right posterior bile duct and the portal vein.

Supraportal pattern

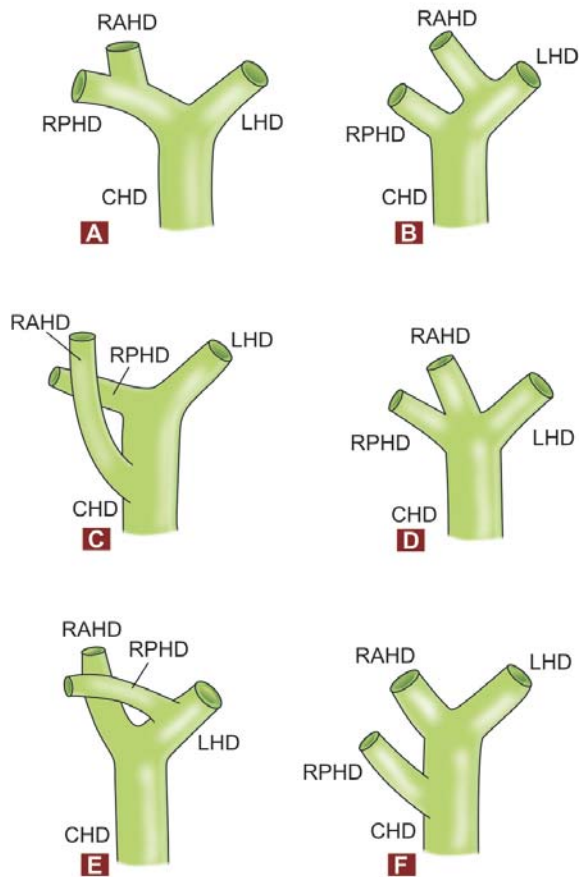
The right posterior bile duct runs dorsally and cranially to the right or to the right of anterior portal vein to join with the right anterior bile duct to form right hepatic duct.

Infraportal pattern

The right posterior bile duct runs ventrally and caudally to the right or the right anterior portal vein to join with the right anterior bile duct to form right hepatic duct.

Combined pattern

Branch of the right posterior bile duct enters supraportally and the other branch of right posterior bile duct runs infraportally to join the right anterior bile duct to form the right hepatic duct.



Figures 2.8A to F: Variations in the biliary anatomy at hilum³² (CHD: Common hepatic duct; LHD: Left hepatic duct; RHD: Right hepatic duct; RAHD: Right anterior sectorial hepatic duct; RPHD: Right posterior sectorial hepatic duct)³²

VARIOUS PATTERNS OF THE RIGHT INTRAHEPATIC BILE DUCTS BASED ON SUPRA- AND INFRA-PORTAL PATTERN

Supraportal pattern

Type I: Posterior sectorial duct joins the anterior sectorial duct to form RHD

Type II: Posterior sectorial duct drains into the confluence of anterior sectorial duct and LHD

Type III: Posterior sectorial duct enters LHD

Infraportal pattern

Type IV: Posterior sectorial duct joins anterior sectorial duct infraportally to form RHD.

Type V: Posterior sectorial duct enters the CHD

Combined pattern

Type VI: Some elements of the posterior sectional bile duct (P1. Br.) enter anterior sectorial duct infraportally and the remaining portion (P2. Br.) join supraportally

Type VII: P1 Br. joins the CHD infraportally and P2. Br. joins LHD supraportally

CONFLUENCE PATTERNS OF THE LEFT INTRAHEPATIC BILE DUCTS

Type A: Left medial sectional duct (Seg. 4) enters the left lateral sectional bile duct to form LHD

Type B: Segment 4 duct enters the confluence of the left lateral anterior (Seg. 3) and posterior (Seg. 2) sectorial ducts

Type C: Segment 4 duct joins seg. 3 duct

Type D: Segment 3 duct runs caudally to the umbilical portion of the left portal vein

Segment 4 duct unites with segment 3 duct

Type E: Segment 4 duct enters the confluence of right and left hepatic ducts

55% of the population have conventional anatomy where the common hepatic artery, a branch of the celiac trunk, supplies the liver through its right and left hepatic branches. The information provided by preoperative angiography is essential to surgical planning and donor safety in LDLT. Variant hepatic arteries that are not peripheral hepatic branches of the celiac axis are referred to as "aberrant" hepatic arteries. These vessels may be "accessory", occurring in addition to the normal arterial supply, or "replaced", representing the primary arterial supply to the hemiliver.³⁴

ANATOMICAL VARIATIONS OF THE HEPATIC ARTERIAL SUPPLY

Anatomical variations of the hepatic arterial supply (HA) can be classified into six different types as shown in Figure 2.9.

Type I: The common hepatic artery arises from the celiac axis, after a common section divides into the gastroduodenal artery and proper hepatic artery. The proper HA runs into the hilum for a variable length and then divides into left and right hepatic arteries, which supply arterial blood to corresponding hemilivers. Then the right HA runs into the right lobe and divides into right anterior and right posterior branches. This is the most common form of arterial supply to the liver.

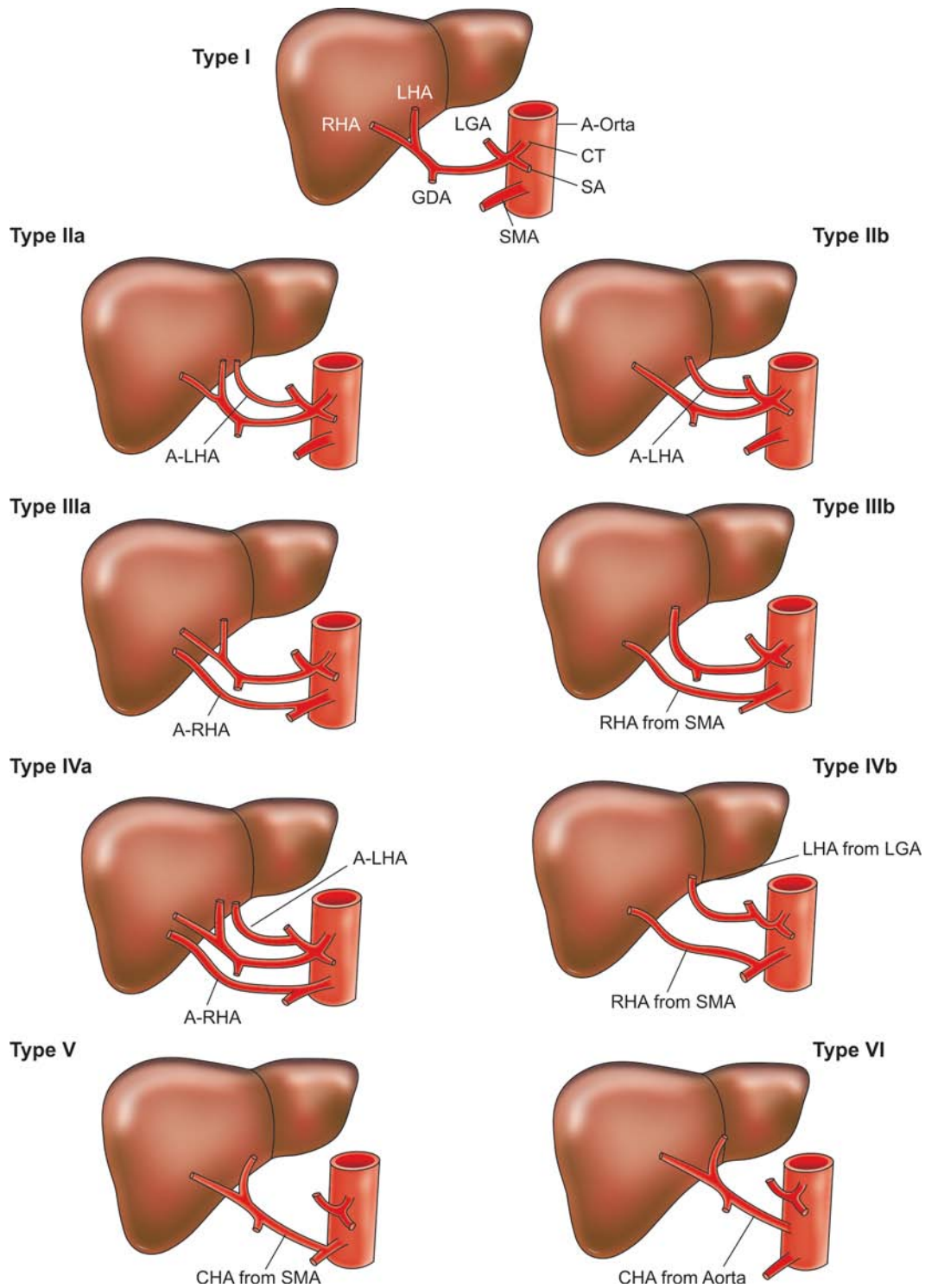


Figure 2.9: Variations in origin of hepatic artery and its branches (RHA and LHA) (CT: Celiac trunk; CHA: Common hepatic artery; GDA: Gastroduodenal artery; LGA: Left gastric artery; PHA: Proper hepatic artery; RHA: Right hepatic artery; A-RHA: Accessory RHA; LHA: Left hepatic artery; A-LHA, Accessory LHA; SMA: Superior mesenteric artery)³²

Type II: The left HA arises directly from the left gastric artery; it can be an accessory vessel, when it is present in addition to a normal left HA (Type IIa), or a complete replacement vessel, when it represents the unique arterial supply to the left liver (Type IIb).

Type III: The right HA arises directly from the superior mesenteric artery (SMA), as an accessory artery, when present in addition to a normal right HA (Type IIIa), or as a complete replacement, when it represents the unique arterial supply to the right liver (Type IIIb).

Type IV: Presence of a double accessory (Type IVa) or double replacement (Type IVb); the left HA arises from the left gastric artery and the right HA arises from the SMA.

Type V: The common HA arises from the SMA. Vascular obstruction, defined as reduction or cessation of flow, is a major complication of liver transplantation.

Type VI: Common hepatic artery arising from the aorta directly

Reported anatomic variations of the hepatic artery^{32,36-40}

Type (%)	Giovanni	Hiatt	Gruttadauria	Soin	Makisalo	Hardy
Type I	70.8	75.7	57.8	69.0	76.0	61.5
Type II	12.5	9.7	11.5	14.3	4.0	7.1
Type III	13.5	10.6	15.0	8.3	7.0	10.0
Type IV	2.1	2.3	7.4	1.0	2.0	7.1
Type V	1.0	1.5	0.9	2.3	3.0	4.2
Others	0.0	0.2	7.4	6.0	8.0	10.0

In LDLT, when the graft contains multiple hepatic arterial branches, there is controversy as to whether all of them should be reconstructed.^{41,42} Tanaka et al reported that reconstruction of all arterial branches, claiming that they are basically end arteries.⁴²

When there are accessory hepatic arteries, they usually communicate with the original lobar arteries in the hepatic hilum, even though such collaterals are not demonstrated on angiograms.⁴³ Ikegami et al,⁴¹ reported that in the majority of cases, it is unnecessary to anastomose all the hepatic arteries supplying the graft. Advantages of reconstruction of a single arterial branch:

- Technically simple
- Entire arterial blood supply of the graft passes through the single reconstructed artery
- High flow rate and blood volume in the reconstructed artery, and consequently increase in size, and this may probably reduce the incidence of arterial thrombosis.⁴¹

Adequate arterial flow to the smaller non-anastomosed arterial branches via hilar communications can be confirmed by different methods such as:

- Examining for pulsatile back-bleeding from the stumps of the branches when the smaller branches of hepatic artery are cut.
- During graft perfusion on the back table, if perfusion fluid flushed through the largest artery flows out of the smaller arterial branches.
- During the recipient operation, the presence of pulsatile back-bleeding from the stump of the other graft arteries after reconstruction of the largest artery.
- Doppler ultrasound detects the pulsatile intrahepatic arterial flow in every segment of the graft

In deceased donor liver transplantation (DDLT), accessory donor hepatic arteries are often reconstructed by re-implantation at the insertion of the splenic or gastroduodenal artery on the back-table. There does not appear to be an increase in the complication rate (occlusions, stenosis of the hepatic artery) following this reconstruction. The success of the reconstructed artery depends not only on the quality of the arterial anastomosis but also on the inflow in the pre-anastomotic arterial segment. It has been reported that in about 12% of adults and 50% of children the common hepatic artery is not suitable for anastomosis due either to hypersplenism or stenosis of the celiac artery (often due to compression of the celiac trunk by the median arcade ligament).

Arterial conduits using donor iliac artery have provided an effective and reliable method of revascularization in patients at higher risk of arterial thrombosis, particularly small children, and those undergoing retransplantation for hepatic artery thrombosis. Their use is indicated whenever there is:

- Doubt about the quality of the inflow provided by the native hepatic artery due to celiac artery stenosis or hypersplenism
- Small, multiple, or anomalous recipient hepatic arteries
- Friable or attenuated native hepatic arteries such as during retransplantation
- Small recipients in whom the recipient artery is < 3 mm in diameter
- For more complex procedures including living related, reduced, split, or auxiliary liver transplantation.

ANATOMICAL VARIATIONS IN THE PORTAL VEIN

Portal vein anatomy was classified according to Nakamura⁴⁴ as shown in the box below

Anatomical variations of portal vein^{44,45} (Nakamura et al)

Type A: The most common type; bifurcation type

Type B: The trifurcation pattern without the trunk of a right branch of the portal vein

Type C and D: In Types C and D, a right anterior/paramedian sector branch or a right posterior/lateral sector branch bifurcates separately from the LPV

Type C: The right anterior/paramedian sector branch originated from the proximal/extra parenchymal part of the LPV

Type D: The right anterior /paramedian sector branch originates from a distal/intra parenchymal part of LPV

Type E: The portal vein branches of segment V and VIII originate separately from the LPV.

(LPV—left portal vein)

The frequency of PV anomalies from A to E are 91%, 6%, 2%, 1% and 0% respectively as per the published data from Koshi et al, form a series of 261 cases of living donor liver transplantation.

PORTAL VEIN IN A LIVE DONOR

The left portal vein has a long extrahepatic course of several centimeters, making it easier to obtain a longer extrahepatic portion of the portal vein in grafts from the left side than in right hemiliver grafts. Despite this, the portal vein branch attached to the graft is often insufficiently long, because the portal vein must be divided so as to leave an adequate length for closure without encroaching on the donor portal vein of the remnant liver. One key to obtaining sufficient length and mobility of the graft portal vein is to divide portal tributaries to the caudate lobe (Segment I). Generally, speaking, portal vein anomalies do not have any impact on donor hepatectomy. Some workers have reported that portal branches to segment IV originating from the right portal trunk are not uncommon, and have insisted that care be taken to preserve the viability of segment IV during donor hepatectomy.²

Classification of portal vein variations by Imamura, et al³⁵

Anatomical variations of portal vein³⁵ (Figure 2.10A)

Type I: The right anterior branch and posterior branch from a short right common neck—most common type.

Type II: Early division of anterior and posterior sectoral branches; trifurcation (Figure 2.10B)

Type III: Independent posterior sectoral branching from the main trunk

Type IV: Anterior sectoral branching from the umbilical portion of the left portal vein and unclassified types. Extrahepatic location of the anterior portal branch in type III differentiates it from the type IV variant.

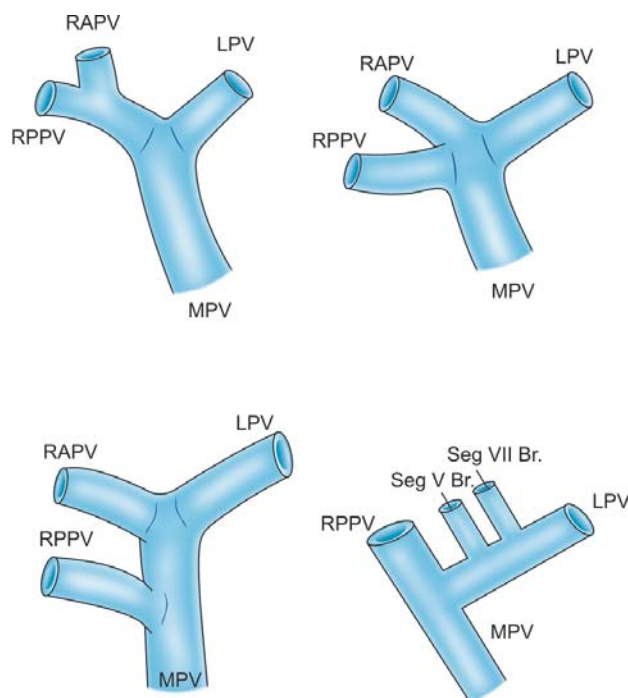


Figure 2.10A: The common variations in portal vein branching pattern. (1) Normal anatomy of PV (Type A). (2) Trifurcation (Type B). (3) Right anterior/paramedian portal vein branch opening into LPV (Type C and D). (4) Portal vein branches of segment V and VIII originate separately from the LPV. (RAPV: Right anterior/paramedian portal vein branch; RPPV: Right posterior/lateral portal vein branch; LPV: Left portal vein; MPV: Main portal vein) (Modified and redrawn with permission of H Imamura)²⁵

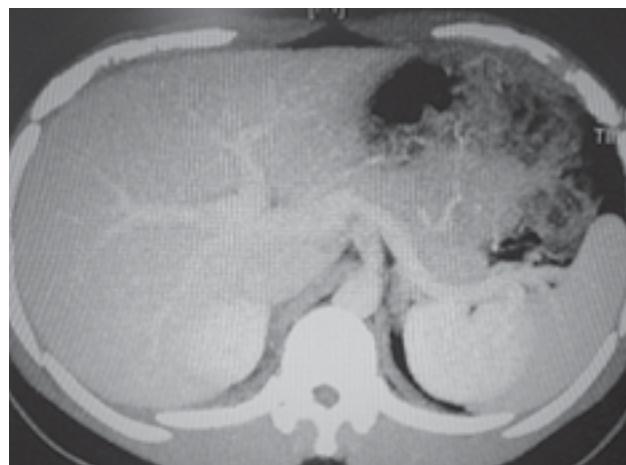


Figure 2.10B: CT angiography image showing trifurcation of portal vein

Modifications required for PV reconstruction in LDLT according to anatomical variations:^{57,58}

Type I/Type A/Bifurcation type

- End-to-end single anastomosis or
- End-to-end single anastomosis to variceal lateral vein

Type II/Type B/Trifurcation

The presence of a trifurcation means that the graft portal vein will consist of two branches when a right hemiliver graft is taken. There are two solutions:

- Venoplasty of the graft portal vein on the back table so that the anterior and posterior portal branches from a single lumen at the site of the anastomosis.
- Anastomose these branches separately, and grafting the posterior branch to the recipient right portal vein and the anterior branch to the recipient left portal vein.

Type III

- End-to-end double anastomosis
- U-graft interposition anastomosis: When both the branches are short and far apart then a U-shaped vein graft interposition technique can be used.⁵⁷

ANATOMY OF HEPATIC VEINS

There are two issues related to the anatomy of hepatic veins that need to be considered while performing LDLT.²⁵ The anatomy of the junction of the hepatic veins with the IVC is an important issue in regard to outflow reconstruction of the graft. The intrahepatic drainage territory of the individual hepatic veins and tributaries is important because attention must be paid to maintaining the venous drainage system of both the graft and the remnant donor liver during LDLT.

The liver is drained by a series of dorsal hepatic veins (**Figure 2.11**) also called as upper hilum.⁴⁷ Three major right, middle, left and 10 and 50 smaller veins open into the IVC.⁴⁸ The length of three major veins, which drain the adjacent segments and subsegments, varies from 0.5 to 1.5 cm. These veins are found intrahepatically within the (intrahepatic) planes separating lobes and segments (intersegmental) (**Figure 2.12**).

RIGHT HEPATIC VEIN (RHV)

It is the largest hepatic vein located in the right fissure. It drains segment V, VI, VII, and part of VIII. The extrahepatic portion of the RHV is anatomically separate and readily isolated from the MHV and LHV (**Figure 2.14**).⁴⁹

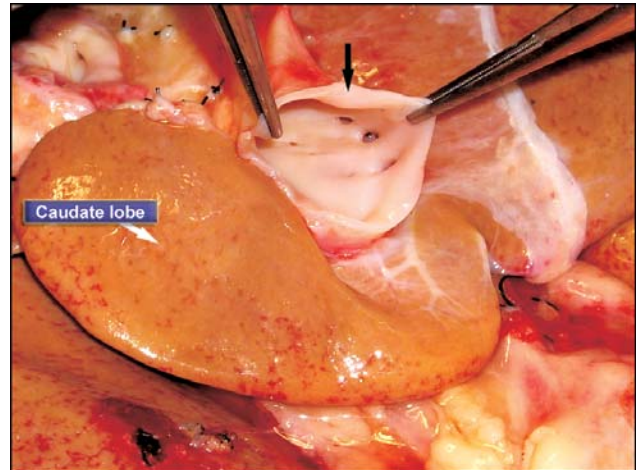


Figure 2.11: Small, multiple hepatic veins draining into IVC (short black arrow)

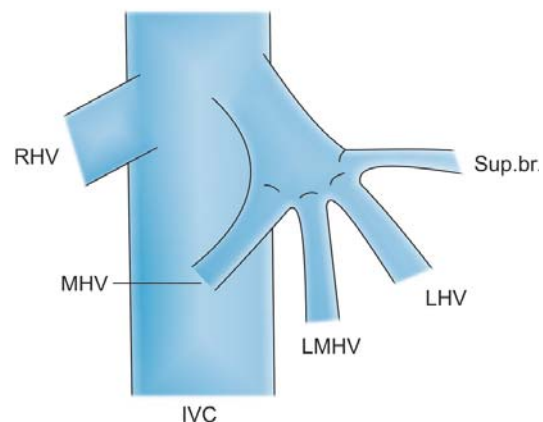


Figure 2.12: Relationships between the right, the middle, and the left hepatic veins. (IVC: Inferior hepatic vein, RHV: Right hepatic vein, MHV: Middle hepatic vein, LHV: Left hepatic vein, LMHV: Left medial hepatic vein, Sup Br: Superficial branch of the left hepatic vein) (Redrawn with permission of H Imamura²⁵)

MIDDLE HEPATIC VEIN

Middle hepatic vein (MHV) lies in the median fissure and drains part of segments IV, V and VIII.²⁰ This vein mainly serves the left liver, together with the left hepatic vein.²⁰

LEFT HEPATIC VEIN

Left hepatic vein (LHV) lies in the upper part of the left fissure and it drains segment II, III and IV. In about 60% of individuals, the LHV and MHV unite to form a common channel before entering the IVC.⁵¹

SUPERFICIAL BRANCH OF RHV (FIGURE 2.13)

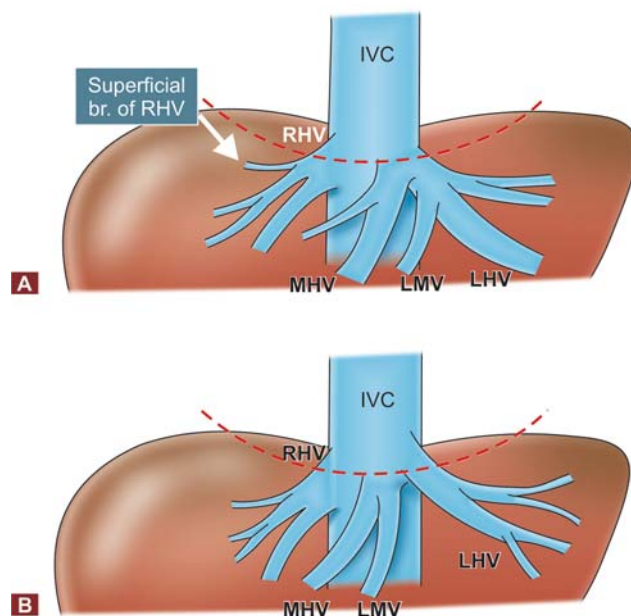
This is a tributary of RHV that drains the superficial area of the right lateral sector. The junction of this tributary with the RHV is located more distally than the junction between the superficial left hepatic vein and the left hepatic vein.²⁵ The venoplasty technique involving the superficial branch is usually not necessary for right hemiliver grafts when the right hepatic veins of both recipient and donor are anastomosed in an end-to-end manner. This tributary flows directly into the IVC in 4-6% of individuals⁴⁹, and when a right hemiliver graft is taken from such donors, it is advisable to reconstruct the outflow of this tributary separately from that of the RHV to avoid partial congestion of the graft.²⁵

LEFT MEDIAL HEPATIC VEIN

Two different patterns of branching of left medial hepatic vein are usually seen (Figure 2.13):²⁵

- **A** Left medial hepatic vein flows into the left hepatic vein
- **B** Left medial hepatic vein flows into the middle hepatic vein.

when left-sided grafts are used, venous supply to segment IV requires attention when the MHV is retained in the donor. This situation occurs when extended lateral segment grafts are used.⁵² In most cases, the hepatic vein tributaries draining the left portion of segment IV (left



Figures 2.13A and B: Branching pattern of left medial hepatic vein opening into the LHV and MHV (Redrawn with permission of H Imamura)²⁵

medial hepatic vein) flow into the LHV close to its junction with the MHV. But sometimes flow into the MHV close to this junction.⁵² This branch should be included in the graft in order to secure an adequate outflow of segment IV. When the left medial hepatic vein flows into the MHV, venoplasty is usually necessary to create a common trunk as the drainage vein of the graft.⁵²

Mehran et al⁵³ emphasized the value of the anatomy of minor hepatic veins. They proposed a four-part classification into veins of segments I (caudate lobe and caudate process), VI, VII, and IX. The area that they allotted to discredited segment IX describes the territory situated immediately anterior to the retrohepatic IVC.

MRHV AND IRHV

In 20-25% of the cases, one or two short hepatic veins are large enough to serve as major draining veins of segment VI and/or VII.⁴⁹ These veins are called the middle right hepatic vein (MRHV) and inferior right hepatic vein (IRHV or Makuuchi vein (Figure 2.14)).⁵⁴ It is always advisable to preserve the outflow from these veins, if they are significant size, by directly anastomosing them to the IVC in the recipient.²

If the preoperative CT and USG examination of the donor shows that the RHV is relatively small and short, then the MRHV, IRHV, or the branches from MHV become the major venous drainage of the right hemiliver. It is essential to preserve the outflow through these branches during graft implantation.⁴⁷ So precise preoperative radiological evaluation of the venous drainage pattern in each donor is essential part of LDLT.²⁵

Variations in the intrahepatic anatomy of outflow veins such as IRHV, veins draining segment 5 and 8 (V5 and

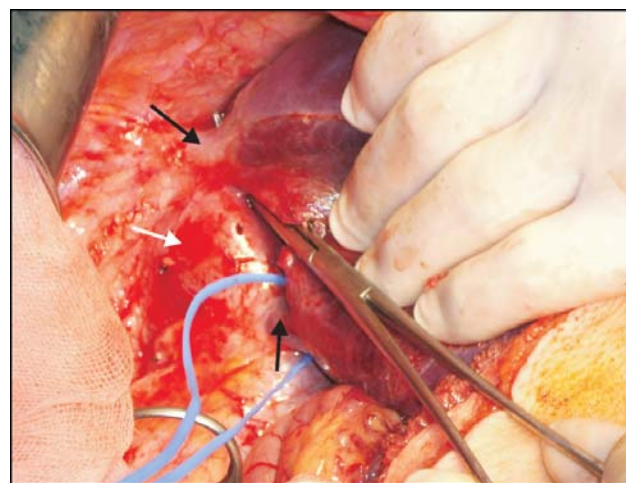


Figure 2.14: LDLT, Right lobe mobilization showing RHV covered by IVC ligament (long black arrow) and inferior right hepatic vein/ Makuuchi vein (IRHV) (short black arrow) IVC shown by white arrow

V8) are shown in **Figure 2.15**. Understanding of this anatomy is important in right lobe LDLT.

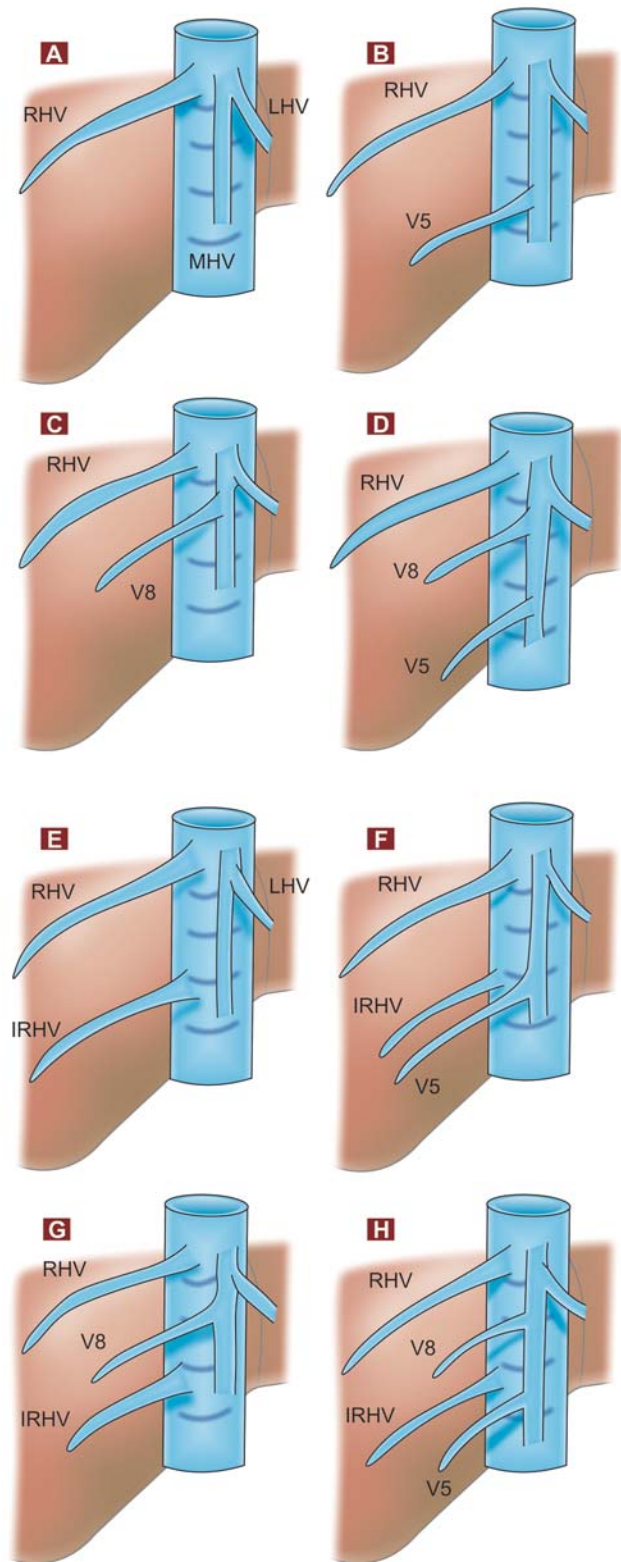
During mobilization of liver, freeing the liver from the retrohepatic IVC is completed by dividing the short hepatic veins and the IVC ligament, also called the “Makuuchi ligament”.⁵⁴ The RHV can be easily isolated extrahepatically,⁵⁴ whereas, division of the LHV during left lateral segmentectomy is performed at the end of the liver parenchymal dissection by resecting the side wall of the common trunk and the MHV. During an extended right hemiliver graft using both RHV and MHVs, requires division of the MHV by dissecting the side wall of the common trunk after the parenchymal dissection. CUSA can be a useful tool in dissecting around the trunk, because it dissects parenchyma of uniform thickness, making it easier to expose the common trunk.

INFERIOR PHRENIC VEINS

Both the right and left inferior phrenic veins flow into the RHV and the common trunk of LHV and MHV at their most cranial points, respectively. The division of these veins and subsequent dissection of the more proximal connective tissue becomes an important procedure during complete exposure of RHV or common trunk and facilitating extensive clamping of these veins for harvesting.⁵⁵ This procedure becomes particularly important for left-sided grafts, because the extrahepatic portion of the hepatic vein is shorter than in right hemiliver grafts.

LYMPHATICS

The hepatic lymphatic network, superficial and deep, does not follow the functional vasculobiliary organization. The superficial lymphatic system, located within the Glissonian sheath, travels toward the thorax and the abdominal regional lymph nodes. Lymph vessels pass the diaphragm mainly in the bare area or through Morgagni’s foramen to reach anterior or lateral phrenic nodes. These trunks join the internal thoracic artery lymph pathway as well as anterior and posterior mediastinal lymphatics.¹⁴



Figures 2.15A to H: Variations in the hepatic veins and their branches (IRHV, V5 and V8) (IVC: Inferior vena cava, LHV: Left hepatic vein, MHV: Middle hepatic vein, RHV: Right hepatic vein, IRHV: Inferior right hepatic vein) (Modified and Redrawn)³²

The posterior surface of the liver is drained toward the paracardial nodes (left lateral segment) or celiac nodes (right lobe). Most of the superficial stream, however, escapes the liver through hilar nodes to follow the proper hepatic artery and follows the classic path toward aortic nodes. The deep system is the system of greater lymphatic outflow. It drains toward the lateral phrenic nerve nodes through the caval hiatus following hepatic veins or to nodes of the liver hilum following portal vein branches.⁵⁶

LYMPHATIC DRAINAGE OF BILE DUCT

The lymphatic drainage of bile duct is distributed into two pathways:

- One superiorly with lymph nodes along the cystic duct, hepatic artery, and celiac axis
- One inferiorly with lymph nodes along the cystic duct, the anterolateral aspect of the portal vein, the posterior pancreas, and between the aorta and vena cava.⁵⁷

LIVER TRANSPLANTATION IN SITUS INVERSUS (SI)

Raynor et al reported the first OLT in SI in 1988.⁵⁹ The incidence is estimated to be between 0.0025% and 0.025%.⁶⁰

Situs inversus is a rare congenital anomaly, characterized by a mirror image orientation of the abdominal and thoracic viscera relative to the midline. Abdominal SI is usually associated with different disorders such as polysplenia syndrome, absence of the suprarenal inferior vena cava, midgut malrotation, preduodenal portal vein, aberrant hepatic arterial anatomy, and portal vein hypoplasia.^{61,62} LTX in SI is technically difficult due to its anatomic variations,

especially vascular anomalies. The donor liver may be placed orthotopically or a rotation of 45° to 90° is acceptable.⁷¹

There are other ways to place the graft:

- Split and reduced graft to fit in the abdomen^{61,63}
- Placement upside down, which may cause acute kinking of the vessels⁵⁹
- Assisted liver transplantation in the right abdominal cavity⁶⁴

The technique of rotation of the graft in patients with SI has several advantages:⁷¹

- Stomach is not compromised by the donor right lobe
- There is no need for a cut down of the donor liver, which is associated with risks
- There is no risk of kinking of the venous outflow, of blood clot formation, or of embolisation
- Hepatic hilum is aligned, which renders it easy to anastomose the portal vein, hepatic artery, and bile duct
- End-to-side anastomosis of the IVC can be performed to reduce the risk of graft congestion.

Provide effective graft support and reduce the risk of outflow obstruction, the following steps should be taken into consideration:⁶⁹

- Plication of the diaphragm combined with mobilization of the colon
- Fixation of the donor remnant falciform ligament to the recipient's diaphragmatic surface
- An innovative and simple technique, a Sengstaken-Blakemore tube.

If size discrepancy is a problem following implantation, the abdomen should be closed in stages with polypropylene mesh to cover any deficit.

Liver Transplantation in situs Inversus (Adults)⁶⁵⁻⁷¹

Author	Technique	Anastomosis			
		IVC	Hepatic artery	Bile duct	Year
Barone	Orthotopic	piggy-back	hepatic artery end-to-end	duct-to-duct	1992
Klintmalm	90° rotation	end-to-side	hepatic artery end-to-end	duct-to-duct	1993
Watson	Orthotopic	piggy-back	celiac patch to hepatic bifurcation	duct-to-duct	1995
Heimbach	LDLT	end-to-end	hepatic artery end-to-end	Roux-Y	2005
Tucker	Orthotopic	piggy-back	hepatic artery end-to-end	duct-to-duct	2006
Wente	Orthotopic	piggy-back	hepatic to gastroduodenal artery	duct-to-duct	2006
Tang	45° rotation	end-to-side	celiac patch to hepatic bifurcation	duct-to-duct	2008

REFERENCES

1. Zaret KS. Embryonic development of the liver. In: Arias IM, editor. *The liver—biology and pathobiology*. 4th edition. Philadelphia: Lippincott Williams and Wilkins; 2001.
2. Marks C. Developmental basis of the portal venous system. *Am J Surg* 1969;117:671-81.
3. Haratake J, Hisaoka M, Furuta A, et al. A scanning electron microscopic study of development of rat peribiliary plexus. *Hepatology* 1991;14:1196-200.
4. Terada T, Nakanuma Y. Development of peribiliary capillary plexus: A lectin-histochemical and immunohistochemical study. *Hepatology* 1993;18:529-36.
5. Godlewski G, Gaubert-Cristol R, Rouy S, et al. Liver development in the rat and in man during the embryonic period. *Microsc Res Tech* 1997;39(4):314-27.
6. Mirilas P, Skandalakis JE. Benign anatomical mistakes: Right and left coronary ligaments. *Am Surg* 2002;68:832-5.
7. Williams PL, Bannister LH, Berry MM, et al, editors. *Gray's anatomy of the human body*. 38th edition. Edinburgh (UK): Churchill Livingstone 1995;90.
8. Ger R. Surgical anatomy of the liver. *Surg Clin N Am* 1989;69:179-93.
9. Rex H. Beitrage sur Morphologie der Saugerleber. *Morphol Jahrb* 1888;14:517.
10. Cantlie J. On a new arrangement of the right and left lobes of the liver. *J Anat* 1987;32:4.
11. Couinaud C. Lobes et segments hepatiques: Note sur l'architecture anatomique et chirurgicale du foie. *Presse Med* 1954;62:709.
12. Couinaud C. Surgical approach to the dorsal section of the liver. *Chirurgie* 1993-1994;119:485-8.
13. Bismuth H. Surgical anatomy and anatomical surgery of the liver. *World J Surg* 1982;6:3-9.
14. Champetier J Le Foie. In: Chevrel JP, editor. *Anatomie clinique*, vol. 2: Le tronc. Paris: Springer-Verlag France 1994;389-406.
15. Filippini F, Romagnoli P, Mosca F, et al. The dorsal sector of human liver: embryological, anatomical and clinical relevance. *Hepatogastroenterology* 2000;47:1726-31.
16. Abdalla EK, Vauthey JN, Couinaud C. The caudate lobe of the liver: implications of embryology and anatomy for surgery. *Surg Oncol Clin N Am* 2002;11:835-48.
17. Rat P, Paris P, Favre JP. One liver for two: Partition of the portal elements. *World J Surg* 1992;16:1167-70.
18. Marcos A. Right lobe living donor liver transplantation: A review. *Liver Transplantation* 2000;6:3-20.
19. Kawasaki S, Makuuchi M, Miyagawa S, et al. Extended lateral segmentectomy using intraoperative ultrasound to obtain a partial liver graft. *Am J Surg* 1996;171:286-88.
20. Champetier J Le Foie. In: Chevrel JP, editor. *Anatomie clinique*, vol. 2: Le tronc. Paris: Springer-Verlag France; 1994;389-406.
21. Twelfth International Congress of Anatomists [London, 1985]. *Nomina anatomica*. 3rd edition. Edinburgh (UK): Churchill Livingstone; 1989;55, 87, 88, 98.
22. Van Damme JJP, Bonte J. The branches of the celiac trunk. *Acta Anat* 1985;122:110-4.
23. Takayama T, Makuuchi M, Kawasaki S, et al. Outflow Y-reconstruction for living related partial hepatic transplantation. *J Am Coll Surg* 1994;179:227-29.
24. Northover JM, Terblanche J. A new look at the arterial supply of the bile duct in man and its surgical implications. *Br J Surg* 1979;66:379-84.
25. Imamura H, Makuuchi M, Sakamoto Y, et al. Anatomical keys and pitfalls in living donor liver transplantation. *J Hepatobiliary Pancreat Surg* 2000;7:380-94.
26. Healey JE, Schroy PC. Anatomy of the biliary ducts within the human liver: analysis of the prevailing pattern of branchings and the major variations of the biliary ducts. *Arch Surg* 1953;66:599-616.
27. Huang TL, Cheng YF, Chen CL, et al. Variants of the bile ducts: clinical application in the potential donor of living-related hepatic transplantation. *Transplant Proc* 1996;28:1669-70.
28. Makuuchi M, Kawasaki S, Noguchi T, et al. Donor hepatectomy for living related partial liver transplantation. *Surgery* 1993;113: 395-402.
29. Takayama T, Makuuchi M, Kawarasaki H, et al. Hepatic transplantation using living donors with aberrant hepatic artery. *J Am Coll Surg* 1997;184:525-28.
30. Gunji H, et al. The blood supply of the hilar bile duct and its relationship to the communicating arcade located between the right and the left artery. *Am J Surg* 2006;192:276-80.
31. Meyers WC, Ricciardi R, Chiari RS. Liver. Anatomy and development. In: Townsend CM, editor. *Sabiston textbook of surgery*. 16th edition. Philadelphia: WB Saunders; 2001;997-1034.
32. Giovanni V, Gabriel EG, Sukru E, et al. Anatomic Variations in Right Liver Living Donors *J Am Coll Surg* 2004;198(4):577-82.
33. M Ohkubo, M Nagino, Nimura Y, et al. Asurgical anatomy of the bile ducts at the hilum as applied to living donor liver transplantation. *Ann Surg* 2004;239(1):82-86.
34. Hiatt JR, Gabbay J, Ronald W, Busuttil MD. Surgical anatomy of the hepatic arteries in 1000 cases. *Ann Surg* 1994;220:50-52.
35. Cheng YF, Huang TL, Lee TY, et al. Variation of the intrahepatic portal vein; angiographic demonstration and application in living-related hepatic transplantation. *Transplant Proc* 1996;28:1667.
36. Hiatt RJ, Gabbay J, Busuttil RW. Surgical anatomy of the hepatic arteries in 1000 cases. *Ann Surg* 1994;220:50-52.
37. Gruttadauria S, Scotti Foglieni C, Doria C, et al. The hepatic artery in liver transplantation and surgery: vascular anomalies in 701 cases. *Clin Transplant* 2001;15:359-63.
38. Soin AS, Friend PJ, Rasmussen A, et al. Donor arterial variations in liver transplantation: Management and outcome of 527 consecutive grafts. *Br J Surg* 1996;83:637-41.
39. Makisalo H, Chaib E, Krokos N, Calne SR. Hepatic arterial variations and liver related diseases of 100 consecutive donors. *Transpl Int* 1993;6:325-29.
40. Hardy KJ, Jones RM. Hepatic artery anatomy in relation to reconstruction in liver transplantation: some unusual variations. *Aust NZ J Surg* 1994;64:437-40.
41. Ikegami T, Kawasaki S, Matsunami H, Hashikura Y, Nakazawa Y, Miyagawa S, Furuta S, Iwanaka T, Makuuchi M. Should all hepatic arterial branches be reconstructed in living related liver transplantation? *Surgery* 1996;119:431-36.
42. Tanaka K, Uemoto S, Tokunaga Y, et al. Surgical techniques and innovations in living-related liver transplantation. *Ann Surg* 1993;217:82-91.
43. Redman HC, Reuter SR. Arterial collaterals in the liver hilum. *Radiology* 1970;94:575-79.
44. Nakamura T, Tanaka K, Kiuchi T, et al. Transplantation 2002;73:1896.

45. Y Kishi, Y Sugawara, M Makuuchi Y, et al. Classification of Portal Vein Anatomy for Partial Liver Transplantation. *J Hepatobiliary Pancreat Surg* 2000;7:380-94.
46. Marcos A. Right lobe living donor liver transplantation: a review. *Liver Transplantation* 2000;6:3-20.
47. McGregor AL, Du Plessis DJ. A synopsis of surgical anatomy. 10th edition. Baltimore (MD): Williams and Wilkins; 1969.
48. Nakamura S, Tsuzuki T. Surgical anatomy of the hepatic veins and the inferior vena cava. *Surg Gynecol Obstet* 1981;152:43-50.
49. Nakamura S, Tsuzuki T. Surgical anatomy of the hepatic veins and the inferior vena cava. *Surg Gynecol Obstet* 1981;152:43-50.
50. Kogure K, et al. Relation among portal segmentation, proper hepatic vein and external notch of the caudate lobe in human liver. *Ann Surg* 2000;231:223-28.
51. Healey JE Jr, Schwartz SI. Surgical anatomy. In: Schwartz SI, editor. *Diseases of the liver*. New York: McGraw-Hill; 1964.
52. Kawasaki S, Makuuchi M, Miyagawa S, et al. Extended lateral segmentectomy using intraoperative ultrasound to obtain a partial liver graft. *Am J Surg* 1996;171:286-288.
53. Mehran R, Schneider R, Franchebois P. The minor hepatic veins: anatomy and classification *Clin Anat* 2000;13:416-21.
54. Makuuchi M, Yamamoto J, Takayama T, Kosuge T, Gunven P, Yamazaki S, Hasegawa H. Extrahepatic division of the right hepatic vein in hepatectomy. *Hepatogastroenterology* 1991;38:176-79.
55. Kubota K, Makuuchi M, Takayama T, et al. Successful hepatic vein reconstruction in 42 consecutive living related liver transplantations. *Surgery* 2000;128:48-53.
56. JE Skandalakis, LJ Skandalakis, PN Skandalakis, et al. Hepatic surgical anatomy. *Surg Clin N Am* 2004;84:413-35.
57. Lee SG, Hwang S, Kim KH, et al. Approach to anatomic variations of the graft portal vein in right lobe living-donor liver transplantation. *Transplantation* 2003;75(3):S28.
58. Denis casting. Surgical anatomy of the biliary tract. *HPB* 2008;10:72-76.
59. Raynor SC, Wood RP, Spanta AD, et al. Liver transplantation in a patient with abdominal situs inversus. *Transplantation* 1988;45:661.
60. Sugawara Y, Makuuchi M, Takayama T, et al. Liver transplantation from situs inversus to situs inversus. *Liver Transpl* 2001;7:829.
61. Falchetti D, de Carvalho FB, Clapuyt P, et al. Liver transplantation in children with biliary atresia and polysplenia syndrome. *J Pediatr Surg* 1991;26:528.
62. Hoffman MA, Celli S, Ninkov P, et al. Orthotopic transplantation of the liver in children with biliary atresia and polysplenia syndrome: report of two cases. *J Pediatr Surg* 1989;24:1020.
63. Kawamoto S, Strong RW, Lynch SV, et al. Liver transplantation in the presence of situs inversus totalis: application of reduced-size graft. *Liver Transpl Surg* 1995;1:23.
64. Todo S, Hall R, Tzakis A, et al. Liver transplantation in patients with situs inversus. *Clin Transpl* 1990;4:5.
65. Barone GW, Henry ML, Elkhammas EA, et al. Orthotopic liver transplantation with abdominal situs inversus and dextrocardia. *Am Surg* 1992;58:651.
66. Klintmalm GB, Bell MS, Husberg BS, et al. Liver transplant in complete situs inversus: a case report. *Surgery* 1993;114:102.
67. Watson CJ, Rasmussen A, Jamieson NV, et al. Liver transplantation in patients with situs inversus. *Br J Surg* 1995;82:242.
68. Heimbach JK, Menon KV, Ishitani MB, et al. Living donor liver transplantation using a right lobe graft in an adult with situs inversus. *Liver Transplant* 2005;11:111.
69. Tucker O, Prachalias A, Kane P, et al. Graft position at liver transplantation in situs inversus. *Liver Transplant* 2006;12:1720.
70. Wente MN, Thorn M, Radeleff B, et al. A routine liver transplantation in a patient with situs inversus: a case report and an overview of the literature. *Clin Transpl* 2006;20:151.
71. DN Tang, JM Wei, YN Liu, et al. Liver Transplantation in an Adult Patient with Situs Inversus: A Case Report and Overview of the Literature *Transplantation Proceedings* 2008;40:1792-95.

CHAPTER 3

UNOS, Organ Allocation Policy and MELD Score

INTRODUCTION

In 1983 the National Institute of Health (NIH), consensus development conference concluded that liver transplantation was not an experimental procedure but an effective therapy that deserved broader application.¹ In 1986-UNOS receives the initial federal contract to operate the OPTN (organ procurement and transplantation network). Before implementation of the current allocation system, the waiting time for a liver transplant grew constantly from an average of 225 days in 1994 to 1811 days in 1999. Adding patients early on to the transplant list based on the necessity to accrue waiting time, rather than on medical urgency, was one of the main reasons behind the continuous growth of the waiting lists. The new system drastically de-emphasizes the importance of waiting time and imposes minimal criteria for transplantation, leading to a significant reduction in overall waiting time.

PROPOSED PROGNOSTIC MODELS FOR ESTIMATING PROGNOSIS IN LIVER DISEASE

NON-DISEASE-SPECIFIC CRITERIA

The Child-Turcotte-Pugh Classification

In 1964, a classification depending on the severity of "hepatic functional reserve" was proposed to predict survival among cirrhotic patients undergoing portosystemic shunts.² It had 3 groups such as class A (low risk), class B (intermediate risk) and class C (high risk) basing on ascites, encephalopathy, albumin, bilirubin, and nutritional status. Pugh et al in 1973³ modified this classification. He included prothrombin time for nutrition and a scoring system was added to it, ranging from 1 to 3 for each variable. So Child-Turcotte-Pugh (CTP) classes A, B, and C were calculated by totaling the sum

of individual scores. CTP score became the preferred method for estimating the severity risk in cirrhotic patients. CTP Scoring system is a useful guide for separating patients into broad categories depending on the severity of hepatic decompensation⁴² (Table 3.1).

TABLE 3.1: Child-Turcotte-Pugh score⁴²

Points	1	2	3
Encephalopathy	None	1 and 2	3 and 4
Ascites	Absent or minimal	Moderate or controlled by diuretics	Large
Bilirubin (mg/dL)	1–2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Modification of bilirubin levels in patients with PBC or PSC:			
Bilirubin	1–4	4–10	> 10
Total Score:			
Child	A. 1–6	B. 7–9	C. 10–15

INR: International normalized ratio

However, when UNOS adopted a system of minimal criteria for entry to the waiting list and stratification of urgency of patients on the list based on CTP, it became necessary to apply CTP scores with attention to small differences.⁴ This led to a pressure within transplant centers to inflate the significance of the components of the CTP in individual candidates for transplantation, and it eventually led to the call from the DHHS for priority rankings through objective and measurable medical criteria discussed earlier.

Drawbacks of CTP scoring system:⁴²

- This scoring system is restricted to patients with advanced cirrhosis and portal hypertension and it can't be applied to other groups of diseases requiring transplantation, such as HCC, FHF etc.

- Ceiling effect: Patient with 3.0 mg/dL of bilirubin and others with 15 mg/dL or more is categorized within the same degree of severity. Similarly it happens with albumin levels, and INR level <2.8 and >2.3

Because the CTP classification provides 3 strata only, waiting time became a second criterion to distinguish two potential candidates with the same CTP class. As a result, waiting time, and therefore getting onto the waiting list early look on an inordinate significance. Therefore, it became important to define minimal criteria for entry on the list.

Non disease specific minimal criteria⁴²

- Immediate requirement for liver transplantation
- Child-Pugh score >7 (B or C)
- Estimated 1 year survival <90%
- Portal hypertensive bleeding or a single episode of spontaneous bacterial peritonitis irrespective of CTP scores.⁴

Drawbacks of minimal criteria⁴²

- It is more liberal
- Increase in number of waiting list patients as more stable cirrhotic patients were added to the waiting list
- Increase in mortality of waiting list

Hence UNOS Liver and Intestinal Committee continued its search for a new simplified and effective allocation scheme.

Evolution of MELD Scoring System

MELD: Model for end-stage liver disease

In 1999, a Liver Disease Severity Score (LDSS) Committee was formed within the Organ Procurement and Transplantation Network (OPTN), an institution administered by the United Network for Organ Sharing (UNOS). This committee was assigned the task to define a model that would accurately predict mortality on the waiting list. The DHHS (Department of Health and Human Services) (USA) reaffirmed that urgency should take priority over usefulness (the so-called "sickest first" policy), and it requested from UNOS policies governing allocation of donor livers that set "priority rankings through objective and measurable medical criteria for patients or categories of patients who are medically suitable transplant candidates." In response, UNOS has adopted a new allocation scheme, in which the majority of donor livers are allocated using a recently devised prognostic instrument called MELD (model for end-stage liver disease) for adults with cirrhosis. MELD scoring system was introduced in 1999 (Malinchoc et al) to quantify the 3-month prognosis of cirrhotic patients after a transjugular intrahepatic portosystemic shunt (TIPS).

Because of the imbalance between organ donors and patients on the waiting list, the MELD was adopted by the United States in 27th February 2002 to allocate liver grafts for transplantation. Preliminary results have indicated a reduction in waiting list deaths and an increase in transplantation rates for candidates. The MELD score is currently considered to be the most accurate predictor of 90-day mortality risk for patients on the liver transplant waiting list. Before being validated and introduced in practice, the score was found to accurately predict mortality in several cohorts of patients with various disease etiologies.²⁵⁻²⁷

The initial MELD included the four clinical parameters

- Serum creatinine
- Bilirubin
- International normalized ratio (INR)
- Underlying diagnosis.

Due to public criticism, UNOS chose to omit diagnosis as a parameter in the MELD formula. UNOS proposed a modified version of the same model that could be applied as a prognostic indicator to allocate donor allografts to cirrhotic adults. At the same time, a complex system of provisions for exceptions was made. The main exception concerns patients with hepatocellular carcinoma.

MELD Equation

$$[0.957 \times \text{Log}_e (\text{Creatinine mg/dL})] + [0.378 \times \text{Log}_e (\text{Bilirubin mg/dL})] + [1.120 \times \text{Log}_e (\text{INR})] + 0.643$$

MELD scoring system is a good predictor of short and medium-term survival before liver transplantation and could be used to rank the urgency of patients waiting for transplantation. Advantages of MELD score is neither the complications of portal hypertension nor the etiology of liver disease influenced the accuracy of the MELD model.⁵ Ferraz et al reported that MELD score at the time of admission to the waiting list was higher among those patients who died either while awaiting transplantation or after OLT compared with those who survived after OLT or those who are still awaiting OLT.³⁸

MELD Score in HCC Patients

Patients who have HCC are assigned a higher MELD score based on tumor staging. Patients who had a T1 lesion initially were registered at a MELD score equivalent to a 15% 3-month mortality risk before transplantation (i.e., a score of 24), which was revised in April 2003 to an 8% mortality risk, a score of 20. Patients who had a

T2 lesion initially were listed at a MELD score of 29, which was equivalent to 30% 3-month mortality, later revised to a score of 24, or a 15% mortality risk. Patients who have HCC receive a 10% mortality bonus every 3 months while continuing on the waiting list until they are transplanted, die, or become no longer suitable for transplantation.²⁶ Later, in November 2003, priority for patients who have a T1 lesion was eliminated. The Regional Review Boards of UNOS handle any special cases not addressed by the MELD system, such as hepatopulmonary syndrome or familial amyloidosis. An individual patient's MELD score is updated regularly. The first year after implementation of MELD there were fewer registrations for transplantation and improved transplantation rates without increased mortality.⁴⁰

PELD Scoring System

PELD: Pediatric end stage liver disease

PELD equation is the best model for severity of liver disease in pediatric patients and comprises of serum albumin level, total serum bilirubin level, INR and growth failure. It includes corrections for growth failure (if growth is < 2 SD than age equivalent growth parameters) and for age less than 1 year. Albumin, as marker of hepatic malfunction, has replaced creatinine from the adult equivalent.

PELD Equation

$[0.436 (\text{Age} < 1 \text{ year})] - [0.687 \times \text{Log}_e (\text{albumin g/dL})] + [0.480 \times \text{Log}_e (\text{total bilirubin mg/dL})] + [1.857 \times \text{Log}_e (\text{INR})] + [0.667 (\text{Growth failure}) (< 2 \text{ Std. Deviations present})]$.

DISEASE-SPECIFIC CRITERIA

Mayo clinic models in primary biliary cirrhosis and primary sclerosing cholangitis.

Primary Biliary Cirrhosis (PBC)

It is characterized by the progressive destruction of interlobular and septal bile ducts leading insidiously to cholestasis, inflammation, fibrosis, and cirrhosis.⁶

In contrast to other parenchymal liver diseases, where progression is rapid and with significant variation over the years, PBC has a more gradual and consistent pattern of progression. Interval from the first sign of disease until hepatic failure may be as long as 20 years,⁷ and many patients may remain asymptomatic for several years.^{8,10} Ursodeoxycholic acid (UDCA) is an effective treatment for PBC, has recently changed the survival rates of PBC.

- It lowers serum bilirubin, alkaline phosphatase, and aminotransferase despite markers of synthetic function may not change significantly.¹¹⁻¹⁴
- It prolongs survival¹³ and delays the need for liver transplantation.

In Mayo clinic, Dickson et al¹⁵ developed a survival models for PBC, called Mayo clinic model. This model however, had been the most extensively applied and validated, not least because it does not require a biopsy, and therefore can be applied easily.¹⁵ It describes 5 independent prognostic variables: age, serum bilirubin, serum albumin, prothrombin time, and severity of edema.

Mayo Clinic Model for PBC

$R = [0.871 \log_e (\text{Bilirubin mg/dL}) \pm 2.38 \log_e (\text{Albumin g/dL}) + 0.0039 \text{ age in years} + 2.38 \log_e (\text{Prothrombin time in seconds}) + 0.895 \text{ Edema}]$

2 studies confirmed that the predictive ability of Mayo clinic model score in PBC is not affected either at entry or at 6 months by the UDCA.^{16,17}

Drawbacks of Mayo Clinic Model for PBC

- This model was developed basing on clinical data available at the time of referral and can't be used with certainty on multiple future occasions.
- Serum albumin and prothrombin time can have substantial variability between different centers and different methods used.¹⁸
- Age factor included in the model tends to overestimate disease mortality for older patients in a stable condition.

Primary Sclerosing Cholangitis (PSC)

It is a chronic progressive cholestatic disease of unknown etiology characterized by chronic inflammatory and fibrotic changes of the intra-and extrahepatic bile ducts.¹⁹ Severe form of this disease causes bile duct obliteration, portal and periportal fibrosis, biliary cirrhosis, and hepatic failure.^{20,21} Course is unpredictable and is frequently aggravated by dominant recurrent cholangitis, biliary tract strictures,²² and cholangiocarcinoma.²³ D-penicillamine for treatment of PSC, a drug that was found to have no effects on the natural history of the disease.²⁴ Wiesner et al reported that 5 variables are associated with disease progression from which a risk score could be calculated and translated into a survival curve. The variables are age, serum bilirubin, albumin, alanine aminotransferase (AST), and a history of variceal bleeding.²⁴

Mayo Clinic Model for PBC

$R = [(0.535 \times \log_e \text{Bilirubin mg/dL}) + (0.486 \times \text{histological stage}) + (0.041 \times \text{age in years}) + (0.705 \times \text{presence of splenomegaly})]$

ORGAN ALLOCATION SYSTEM IN USA AND LIVER TRANSPLANTATION

Different terms and definitions related to liver transplants

ORGAN ALLOCATION POLICY

It is the policy of prioritization of patients on the transplant waiting list. Donor organ allocation requires estimation of prognosis of potential recipients.

UNOS (UNITED NETWORK FOR ORGAN SHARING)

Organ Procurement and Transplant Network (OPTN)

The solid organ identification, retrieval, and distribution network. It is managed under contract by UNOS.

Organ Procurement Organization (OPO)

The local organizations that identify solid organ donors, and manage organ retrieval and distribution within the locality. There is no fixed size for an OPO, and they vary in geographic territory, number of potential donor livers available and number of transplant centers serviced.

DISTRIBUTION OF TRANSPLANT CENTERS IN USA

Prioritization of liver transplant centers in relation to the location of the cadaveric donor. It is usually characterized as a debate whether donor organs should be allocated to transplant centers in the locality or region from which they were derived.

Minimal Listing Criteria⁵

Predetermined thresholds of estimated severity of disease necessary to be placed on the transplant waiting list. Minimal criteria require some standardized prognostic estimation of patients when evaluated, similar to the allocation scheme.

Urgency

Risk that a candidate for transplantation will die if not transplanted.

Utility

Chances that a candidate will survive after transplantation.

UNOS AND ITS TERRITORY

UNOS: It is a private, nonprofit organization that was contracted by the US Government to regulate and manage solid organ identification, retrieval, distribution, data management and organ allocation system in the USA. The territory of the United States is divided into 11 UNOS regions. Within each region, there are several organ procurement agencies (OPO). Each OPO serves several transplant centers within their territory. The OPO centralizes the patients from the waiting lists of all centers within its territory and grants them priority by MELD score, so that available organs will first be allocated to the patients in descending order of MELD score within each specific OPO. Organ prioritization is denominated as “local” (within the OPO), “regional” (within a UNOS region), and “national.”

Functioning of UNOS

At each level of distribution, adult livers (i.e., greater than or equal to 18 years old) will be considered for transplantation depending on the degree of medical urgency and adult candidate status.

Degree of Medical Urgency

Each candidate is assigned a status code or mortality risk score (probability of candidate death) which corresponds to how medically urgent it is that the candidate receives a transplant.

Adult Candidate Status

Medical urgency is assigned to an adult liver transplant candidate (>18 years of age) based on either the criteria defined below for Status 1A, or the candidate's MELD Score.

Patients are prioritized on the waiting list within each blood type group by descending MELD score. This implies that the organs are basically allocated to the waitlisted patients with the highest mortality risk at the given time. Within each MELD score, livers are first allocated to identical blood type patients. To prevent inequitable distribution of organs, blood type O livers may only be attributed to blood type O recipients. The system allows patients with special situations (like very small size adult patients or AB type patients) to be listed for more than one blood type and thus be granted a higher chance of receiving a transplant. MELD scores have to be updated periodically (every 7 days for Status 1 patients and patients with MELD higher than 25). The UNOS algorithm for liver allocation is shown in the **Table 3.2**.

TABLE 3.2: Adult donor liver allocation policy in USA

1. Local Status 1 patients in descending point order
2. Regional Status 1 patients in descending point order
3. Local patients with MELD/PELD Scores >15 in descending order of mortality risk scores (probability of candidate death)
4. Regional patients with MELD/PELD Scores >15 in descending order of mortality risk scores (probability of candidate death)
5. Local patients with MELD/PELD Scores < 15 in descending order of mortality risk scores (probability of candidate death)
6. Regional patients with MELD/PELD Scores <15 in descending order of mortality risk scores (probability of candidate death)
7. National Status 1 patients in descending point order

(Source: www.unos.org)

The organ allocation is first directed to local recipients (listed at centers within the OPO). Should there be no adequate recipient within the OPO; the offer is directed regionally and, ultimately, nationally. The impact of this policy is that cold ischemia time is reduced by shipping the organs within a limited territory. By reducing the cold ischemia time, and thus improving the quality of the transplanted organs, and by lowering the logistical and transportation expenses, the global costs of the procedure are also reduced. Attributing organs to regional patients with MELD >15 before local patients with lower MELD is a measure that attempts to remove the inequity of sicker patients waiting longer, while patients with questionable transplant benefit are transplanted. Even so, differences and inequalities between regions and between OPOs cannot be totally removed. The number, experience, and volume of transplant centers within OPOs, as well as the experience and efficacy of the OPOs themselves, differ within large ranges, resulting in differences of average transplantation MELD scores among OPOs and among regions.

Status of the Patient on Waiting List

All the patients on waiting list are given different status depending on the clinical and laboratory reports such as 1A, 1B, 2A, 2B, 3 and 7.

Status 7: A candidate listed as Status 7 is temporarily inactive. Candidates who are considered to be temporarily unsuitable transplant candidates are listed as Status 7.

Status 1: Adult Status 1 patients may also be allocated pediatric livers; however, pediatric Status 1 patients have priority. Candidates who are listed as a Status 1A automatically revert back to their most recent MELD Score after 7 days unless these candidates are relisted as Status 1A by an attending physician. Adult Status 1 patients are those patients who fulfill 1 of the following criteria:

Status 1

- FHF with a life expectancy less than 7 days without a liver transplant
- PNF of a transplanted liver within 7 days of implantation
- HAT in a transplanted liver within 7 days of implantation
- Acute decompensated Wilson's disease.

FHF-Fulminant hepatic failure, PNF-Primary non-function, HAT-Hepatic artery thrombosis (Source: www.unos.org)

Fulminant Hepatic Failure

Fulminant hepatic failure defined as the onset of hepatic encephalopathy within 8 weeks of the first symptoms of liver disease. The absence of pre-existing liver disease is critical to the diagnosis. One of three criteria below must be met to list an adult candidate, who must be in the ICU, with fulminant liver failure: (1) ventilator dependence (2) requiring dialysis or continuous veno-venous hemofiltration (CVVH) or continuous veno-venous hemodialysis (CVVH) or (3) INR > 2.0.

Primary Non-function

Primary non-function of a transplanted liver within 7 days of implantation is defined by (a) or (b):

(a) AST = 3,000 and one or both of the following:

- INR = 2.5
- Acidosis (Arterial pH = 7.30 or venous pH of 7.25 and/or Lactate = 4 mmol/L)

(b) Anhepatic candidate

Hepatic Artery Thrombosis

Hepatic artery thrombosis in a transplanted liver within 7 days of implantation, with evidence of severe liver injury as mentioned in PNF. Candidates with HAT in a transplanted liver within 14 days of implantation not meeting the above criteria will be listed at a MELD of 40.

HIGH RISK PATIENTS AND ORGAN ALLOCATION

One of the problems that have been raised is the balance between allocating the organs to the sickest patients (with the drawback of poorer posttransplantation outcome) versus allocating them to patients who would benefit most from transplantation by having the best survival rates. The interest of a liver transplant candidate is best served when the expected survival is higher than that without transplantation. It has been shown that among patients with MELD scores under 15, the mortality risk

Adult candidate reassessment and recertification schedule

Status 1A	Status recertification every 7 days	Laboratory values must be no older than 48 hours.
MELD Score > 25	Status recertification every 7 days	Laboratory values must be no older than 48 hours.
Score >18 to < 24	Status recertification every 1 month	Laboratory values must be no older than 7 days.
Score > 11 to < 18	Status recertification every 3 months	Laboratory values must be no older than 14 days
Score > 0 to < 10	Status recertification every 12 months	Laboratory values must be no older than 30 days

(Source: www.unos.org)

with transplantation is higher than the mortality risk without transplantation.^{28,29} There is, however, a certain death rate on the waiting list among these patients: 53 deaths per 1000 patient years.

Recent UNOS policies have required a minimal transplant score of 15. Exceptions can be granted in selected cases (eg, for AB blood type or direct donation). At the other end of the disease spectrum, there are patients who are too sick to withstand liver transplantation. Allocating organs to these patients may not benefit them and may also be a waste of valuable organ resources. To limit this, 2 measures have been implemented.

- **Serum creatinine** value has been capped at 4 mg/dL. For patients with values above 4 mg/dL, as well as those undergoing hemodialysis, this maximal value is used in the calculation, and thus, their MELD score cannot further be increased.
- **Maximal MELD score >40:** Maximal MELD score that can be attributed to a patient is 40. Patients with >40 score, while not receiving any extra priority, can still be transplanted if deemed reasonable by the transplant center.

EXCEPTIONS TO MELD SCORE

It is recognized that there are categories of patients whose MELD scores do not reflect the true urgency of their need for transplantation. Several categories of patients qualify under current regulations for various degrees of upgrading of their MELD scores to values that would allow them to undergo transplantation within a predictable time frame. Examples of exceptions are patients with

- Hepatocellular carcinoma (HCC)
- Biliary strictures
- Recurrent biliary sepsis

- Refractory upper GI and variceal bleeding requiring transfusions and/or emergency intervention.
- Refractory ascites and/or pleural effusions when TIPS is contraindicated
- Hepatopulmonary syndrome
- Metabolic diseases
- Severe polycystic liver disease
- Pulmonary hypertension.

HCC AND LIVER TRANSPLANTATION

Prioritization of patients with HCC is one of the most debated topics. Under the previous organ allocation system, yearly dropout rates due to tumor progression were 25%.³⁰ Still, putting these patients at advantage may diminish the chances of otherwise sicker candidates to receive an organ in time. Currently, T2 tumors (namely, 1 nodule 2.0 to 5.0 cm: 2 or 3 nodules, all <3.0 cm as defined by the American Liver Tumor Study Group Modified Tumor-Node-Metastasis Staging Classification) are allocated 24 MELD points. Considering that T1 patients are at a relatively low risk of being removed from the list because of tumor progression, since April 2004, T1 patients do not receive extra MELD points.¹¹ Based on data reporting good outcomes among patients transplanted with tumors larger than 5 cm,¹² the review boards can accept well-documented lesions beyond T2 criteria to be granted 24 MELD points.

HYPONATREMIA AND MELD SCORE

Several factors have been studied as potential elements to improve the estimation of pretransplantation mortality. Change in MELD or PELD scores over short periods may be associated with higher mortality risk on the waiting list.^{33,34} Serum sodium (Na⁺) seems to be a reliable surrogate for ascites. In one single-center study, hyponatremia correlated well with the presence of ascites and was a predictor of 3-month mortality.³⁵ Adding serum sodium to MELD may improve the predictive value of the score. Ascites, encephalopathy, and variceal bleeding do not add significant improvement to the statistical performance of MELD.

RETRANSPLANTATION AND ORGAN ALLOCATION

Retransplanted patients tend to have a poorer outcome than patients undergoing a first liver transplantation. Reported studies showed that the MELD scores of retransplanted patients were higher than those of first-transplant patients. Also, in patients with MELD scores higher than 20, the relative risk of death on the waiting list was higher for relisted patients at similar MELD scores.^{31,32} These patients seem to have a greater risk of dying than that

reflected by the MELD score, and the accuracy of MELD as a predictor of waitlist mortality is thus somewhat lower in relisted patients.

TRANSPLANTATION STATISTICS

MELD score was confirmed as an excellent predictor of waitlist mortality, but its relationship with posttransplantation outcome was less consistent. The 2004 OPTN/SRTR Annual Report showed that slight lower rates of patient (at 3-month and 1-yr) and graft survival for patients with MELD > 30, while it was fairly equal among patients with lower MELD score.³⁶ An overall increased rate of DDLT was observed after implementation of the new allocation policy; in the context of a better rate of usage of cadaveric donors (**Table 3.3**). The increased rate of transplanted livers after 2002 cannot simply be attributed to a steadily increasing trend of the transplantation rate. Other factors that need to be taken into account to explain this growth include the higher rate of organ donor referrals and consent to donation. These increased by almost 10% and 5%, respectively, from 2002 to 2003.

TABLE 3.3: DDLT and LDLT statistics in USA

Year	DDLT	Increase from previous Year (%) (DDLT)	LDLT
2000	4595	2.1	5919
2001	4672	1.6	6586
2002	4969	6.3	6618
2003	5351	7.7	6814
2004	5847	9.3	6991
2005	6120	4.7	6901
2006	6362	3.8	6730
2007	6227	Decrease	6310

Source: UNOS/OPTN data, 29 Aug. 2008 (reproduced with permission)

FUTURE TRENDS IN ORGAN ALLOCATION

The ultimate goal of organ allocation would be to allocate organs to patients who would have the best posttransplantation outcome, while at the same time reducing as much as possible the removal rate due to death or severity of sickness from the waiting list. MELD alone does not serve both these goals, and is especially vulnerable in the prediction of posttransplantation outcome. Improving this aspect would require adding donor- and center-dependent factors to the allocation algorithm, but further data are necessary to sustain such a change. Future developments may also be directed toward attempting

to match donor organs and recipients through an elaborate information network. Such attempts have already been made at the University of Birmingham.³⁷

MELD score has proved to be effective as a predictor of pretransplantation mortality. It is currently the most reliable criterion to select waitlisted patients for liver transplantation. The applicability of MELD exceptions adds versatility and flexibility to the allocation algorithm. As time passes, further efforts to monitor the weaknesses and the strengths of this promising system must be undertaken.³⁹

MELD SCORE AND LDLT

The waiting-list mortality increases in patients with advanced liver disease and patients with an MELD score of 25 have 20% 3-month mortality.⁴¹ In general, it is uncommon to proceed with LDLT in patients with MELD scores >25. Thus, depending on the region of the country and the average MELD score at the time of transplant within the area served by the organ procurement organization, LDLT might offer patients transplantation before they die waiting for a deceased donor liver. The lower MELD score limit with LDLT is more controversial and varies from center to center. Russo and Brown⁴³ commented that they did not proceed with LDLT in candidates with MELD scores <11.

REFERENCES

1. Consensus Panel. National Institutes of Health consensus development conference statement: liver transplantation June 20-23, 1983. *Hepatology* 1984;4(Suppl):S107-10.
2. Child III CG, Turcotte JG. Surgery and portal hypertension. In: Child III CG, editor. *The Liver and Portal Hypertension*. Philadelphia: W.B. Saunders Co; 1964;50-6.
3. Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the esophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-9.
4. Albers I, Hartmann H, Bircher J, et al. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. *Scand J Gastroenterol* 1989;24:269-76.
5. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the study of liver diseases. *Liver Transplantation and Surgery* 1997;3:628-37.
6. Wiesner RH, McDiarmid SV, Kamath P, et al. MELD and PELD: Application of Survival Models to Liver Allocation. *Liver Transplantation* 2001;7:567-80.
7. Kaplan MM. Primary biliary cirrhosis. *N Engl J Med* 1996;335:1570-80.
8. Mahl TC, Shockcor W, Boyer JL. Primary biliary cirrhosis: Survival of a large cohort of symptomatic and asymptomatic patients followed for 24 years. *J Hepatol* 1994;20:707-13.

9. Nyberg A, Loof L. Primary biliary cirrhosis: clinical features and outcome, with special references to asymptomatic disease. *Scand J Gastroenterol* 1989;24:57-64.
10. Roll J, Boyer JL, Barry D, et al. The prognostic importance of clinical and histologic features in asymptomatic and symptomatic primary biliary cirrhosis. *N Engl J Med* 1983;308:1-7.
11. Mitchinson HC, Lucey MR, Kelly PJ, et al. Symptom development and prognosis in primary biliary cirrhosis: A study in two centers. *Gastroenterology* 1990;99:778-84.
12. Lindor KD, Dickson ER, Baldus WP, et al. Ursodesoxicolic acid in the treatment of primary biliary cirrhosis. *Gastroenterology* 1994;106:1284-90.
13. Poupon RE, Poupon R, Balkau B. Ursodiol for the long-term treatment of primary biliary cirrhosis. *N Engl J Med* 1994;330:134-27.
14. Lindor KD, Therneau TM, Jorgensen RA, et al. Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. *Gastroenterology* 1996;110:1515-9.
15. Heathcote EJ, Lindor KD, Poupon R, et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology* 1997;113:884-90.
16. Dickson ER, Grambsch PM, Fleming TR, et al. Prognosis in primary biliary cirrhosis: model of decision making. *Hepatology* 1989;10:1-7.
17. Grambsch PM, Dickson ER, Kaplan M, et al. Extramural cross-validation of the Mayo primary biliary cirrhosis survival model establishes its generalizability. *Hepatology* 1989;10:846-50.
18. Kilmurry MR, Heathcote EJ, Cauch-Dudek K, et al. Is the Mayo Model for predicting survival useful after the introduction of ursodeoxycholic acid treatment for primary biliary cirrhosis? *Hepatology* 1996;223:1148-53.
19. Robert A, Chazouilleres O. Prothrombin time in liver failure: Time, Ratio, Activity Percentage, or International Normalized Ratio? *Hepatology* 1996;24:1392-4.
20. Chapman RWG, Marborough BA, Rhodes JM, et al. Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. *Gut* 1980;21:870-7.
21. Ludwig J. Surgical Pathology of the syndrome of primary sclerosing cholangitis. *Mayo Clin Proc* 1994;69:969-82.
22. MacCarty RL, LaRusso NF, Wiesner RH, et al. Primary Sclerosing Cholangitis: findings on cholangiography and pancreatography. *Radiology* 1983;149:39-44.
23. Rosen CB, Nagomey DM. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:26-30.
24. Wiesner RH, Grambsch PM, Dickson ER, et al. Primary sclerosing cholangitis natural history, prognostic factors and survival analysis. *Hepatology* 1989;10:430-6.
25. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29.
26. Wiesner RH, McDiarmid SV, Kamath PS, et al: MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001;7:567.
27. Kamath PS, Wiesner RH, Malinchoc M, et al: A model to predict survival in patients with end stage liver disease. *Hepatology* 2001;33:464.
28. Merion RM, Schaubel DE, Dykstra DM, et al: The survival benefit of liver transplantation. *Am J Transplant* 2005;5:307.
29. Hanto DW, Fishbein TM, Wright Pinson C, et al: Liver and intestine transplantation: summary analysis 1994-2003. *Am J Transplant* 2005;5:916.
30. Yao FY, Bass NM, Nikolai B, et al: Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 2002;8:873.
31. Merion RM, Wolfe RA, Schaubel D, et al: Final analysis for SRTR data requests from the OPTN Liver Intestine Transplantation Committee Meeting of May 14-15, 2003.
32. Onaca N, Levy MF, Ueno T, et al: An outcome comparison between primary liver transplantation and retransplantation based on the pretransplant MELD score. *Transpl Int* 2006;19:282.
33. Merion RM, Wolfe RA, Dykstra DM, et al: Longitudinal assessment of mortality risk among candidates for liver transplantation. *Liver Transpl* 2003;9:12.
34. Report of the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee to the Board of Directors, June 26-27, 2003.
35. Ruf AD, Yanrorno SE, Descalzi VI, et al: Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. A single center experience. *Am J Transplant* 2004;4:438.
36. Annual Report of the U.S. OPTN and the Scientific Registry of Transplant Recipients 2005: Transplant Data 1994-2004. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, Md; United Network for Organ Sharing, Richmond, Va; University Renal Research and Education Association, Ann Arbor, Mich.
37. Lucey M: How will patients be selected for transplantation in the future? *Liver Transpl* 2004;10:S90.
38. BH Ferraz-Neto, R Hidalgo, T Thomé, et al. Analysis of Model for End-Stage Liver Disease (MELD) Score in a Liver Transplantation Waiting List. *Transplantation Proceedings* 2007;39:2511-13.
39. AP Martin, M Bartels, J Hauss, et al. Overview of the MELD Score and the UNOS Adult Liver Allocation System. *Transplantation Proceedings* 2007;39:3169-74.
40. Freeman RB, Wiesner RH, Harper EE, et al. Results of the first year of the new liver allocation plan. *Liver Transpl* 2004;10:7-15.
41. Wiesner R, Edwards E, Freeman R et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003;124:91-6.
42. RC Botero, MR Lucey. Organ allocation: model for end-stage liver disease, Child-Turcotte-Pugh, Mayo risk score, or something else. *Clin Liver Dis* 2003;7:715-27.
43. Russo MW, Brown RS Jr. Adult living donor liver transplantation. *Am J Transplant* 2004;4:458-65.

Indications and Contraindications of Liver Transplantation

INTRODUCTION

Liver transplantation is a lifesaving procedure for patients of end stage liver disease (ESLD).¹⁻³ The two major goals of liver transplantation are to prolong survival and to improve quality of life. Starzl performed the first three human liver transplantations at the University of Colorado in 1963, but did not achieve 1-year survival until 1967. One year survival rate was only 30% until the late 1970s and early 1980s when the implementation of cyclosporine-based immunosuppression led to doubling of the 1-year survival rate.¹ This improved outcomes in early 1980s, led to the decision at a National Institutes of Health Consensus Development Conference that liver transplantation was no longer experimental and deserved broader application in clinical practice.⁴ In USA, current 1-year patient and graft survival rates are 87.6% and 82.4% respectively.⁵

In the current environment of organ shortage, every effort should be made to avoid deviation from strict criteria for liver transplant evaluation and listing. The success of liver transplantation as treatment for most types of acute and chronic liver failure has led to increased referrals for transplantation in the setting of a relatively fixed supply of cadaver donor organs. These events have resulted in a marked lengthening of the waiting time for liver transplantation, resulting in increased deaths of those on the waiting list and sicker patients coming to transplantation. In USA, 6444 liver transplantations were performed in 2005, of which 6121 were DDLT and 323 were LDLT. This number of transplantations was somewhat greater than in the prior 5 years from 2000 to 2004, when 4995, 5190, 5331, 5672, and 6169 transplants, respectively, were performed.⁵ In the 6 years, around 2000 deaths/year in patients listed for liver transplantation. The persistent shortage of donor organs is obviously insufficient to meet the growing demand for liver

transplantation, and organ donation has increased only slightly in recent years. Faced with this shortage, indications should be based as much as possible on precise natural history data and expected post-transplantation survival rates for specific diseases leading to transplantation.³

Data from the United Network for Organ Sharing (UNOS) on 24,900 adult patients undergoing liver transplantation from October 1987 to September 1998 showed that 1-year, 4-year, and 10-year patient survival rates were 85%, 76%, and 61%, respectively, confirming that liver transplantation results in prolongation of life.⁶ 1-year survival has improved over time from 74.8% in 1990 to 86.2% in 1996.⁷ The best survival has been shown to occur among patients who undergo liver transplantation for chronic cholestatic liver diseases, including PBC and PSC; the worst survival seen in patients of hepatic malignancies undergoing transplantation.⁶

EVALUATION OF THE RECIPIENT AT THE TRANSPLANTATION CENTER (TABLE 4.1)

A patient referred to transplant center as potential candidate for transplantation by the physician, a thorough evaluation takes place at the transplantation center. Patients considered for transplantation should undergo all forms of therapy that might reverse or delay the need for transplantation.^{1,2} The patients who have a projected survival of less than 2 years due to their ESLD should be considered for transplantation, as liver transplantation has 10 to 15% mortality rate in the 1st year. Evaluation includes assessment of the present status of liver disease and associated co-morbidity that may influence the survival after transplant operation. The evaluation and selection process involves thorough assessment by

TABLE 4.1: Pre-transplantation evaluation of the recipient

1. Haemogram, liver chemistry, renal function tests, coagulation profile (PT, PTT, INR)
2. Viral assay
 - HBV: HBsAg, HBeAg, Anti HBs Ab, Anti HBc, Anti HBc IgM, Anti HBe, HBV DNA, Mutations in HBV
 - HCV: HCV RNA, Genotyping
 - HAV: Anti HAV IgM and HDV serology
 - CMV screening:
 - Age > 1 year: IgG and IgM titers
 - Age < 1 year: Urine CMV shell viral culture
 - EBV screening: IgG and IgM titers
 - Varicella zoster: IgG and IgM
 - Rubella—IgG and Ig M
 - Toxoplasma: IgG titer
 - Syphilis: Rapid plasma reagin (RPR) test (VDRL)
 - Screening for HIV 1 and 2 (HTLV III)
3. Autoimmune diseases:
 - Antinuclear antibody, IgG
 - Antismooth muscle antibody
 - Liver kidney microsomal antibody
 - Anti-neutrophil cytoplasmic antibody
4. Tumor markers: Alpha-fetoprotein
Carcinoembryonic antigen
CA-19-9
5. Hemochromatosis: Serum Ferritin, Transferrin
Salivary gland biopsy (selected cases)
Transferrin
6. Wilson's disease: Serum ceruloplasmin level
24-hr urinary copper
7. Alfa 1-antitrypsin phenotyping
8. Other standard tests:
 - Abdominal ultrasound with Doppler
 - ECG, Chest radiograph,
 - Pulmonary function tests
 - Endoscopic evaluations
 - Purified protein derivative skin tests
9. Standard consultations: Dietary
Psychosocial
10. Female recipient:
 - Pap smear and Mammogram (women over 35 years)
11. CT Scan and MRI scan of abdomen
12. HCC patients: CT of Brain and Chest and Bone Scan
13. Other optional tests:
 - Angiography (If vascular abnormalities suspected)
 - Doppler study (Older or Cardiovascular patients)
 - Contrast echocardiography (suspected hepatopulmonary syndrome)
 - Coronary angiography (suspected Coronary artery disease)
 - Colonoscopy done in high risk patients such as:
 - Family history of colon cancer or polyps
 - Primary sclerosing cholangitis
 - Fecal occult blood test +ve
 - Inflammatory bowel disease
 - ERCP (in Primary sclerosing cholangitis)
 - Liver biopsy (to rule out fatty liver and NASH—in selected cases)
 - Fungal serology (Endemic areas for dimorphic fungi)
14. Pre-transplantation vaccines (if indicated)
Hepatitis A and B, Tetanus booster, Pneumococcal and Influenza vaccine.

transplant hepatologist and surgeon, consultations with other specialty physicians as required, assessment by the social worker and often the psychiatrist, and final review and decision on candidacy by a multidisciplinary liver transplantation selection committee.

INDICATIONS FOR LIVER TRANSPLANTATION (TABLE 4.2)

Important indications for liver transplantation are shown in the Table 4.2.⁸ Patients who have ALF can recover spontaneously, but those who have subfulminant hepatic failure have 100% mortality without transplantation.^{1,8} It is recommended that patients who have ALF who fail to meet the king's college criteria still be considered for liver transplantation, because spontaneous recovery is not always possible. Timely referral for liver transplantation is the most important factor.^{1,2,8}

TABLE 4.2: Liver transplantation indications^{52,53}

1. Acute liver failure
 - Acute hepatitis HAV, HBV and HEV (less common)
2. Hepatotoxic Drugs/toxins
 - Acetaminophen
 - Amanita phylloides
 - Halothane
3. Chronic liver disease with cirrhosis
 - Chronic HBV/HCV/HDV
 - Alcoholic liver disease
 - Autoimmune hepatitis
 - Primary biliary cirrhosis
 - Primary sclerosing cholangitis
 - Cryptogenic liver disease
 - Secondary biliary cirrhosis
4. Metabolic disorders
 - Wilson's disease
 - Alpha-1 antitrypsin deficiency
 - Hereditary hemochromatosis
 - Glycogen-storage disorders
 - Familial Hypercholesterolemia
 - Familial amyloidotic polyneuropathy
 - Hereditary hemochromatosis
 - Primary Hyperoxaluria (type I)
 - Tyrosinemia
 - Crigler-Najjar disease type I
 - Protoporphyrria
5. Malignancy
 - Primary malignancy
 - Hepatocellular carcinoma
 - Cholangiocarcinoma
 - Secondary malignancy
 - Islet cell tumors
 - Carcinoids
 - Gastrinoma
6. Vascular
 - Budd-Chiari syndrome
7. Miscellaneous
 - Polycystic liver disease
 - Trauma

TRAUMA AS AN INDICATION FOR LIVER TRANSPLANTATION

Liver injury is the main cause of death following major blunt abdominal trauma with a mortality rate of 10 to 58%.³⁸⁻⁴³ Any injury to the main hepatic veins or retrohepatic cava is associated with mortality rates of 50 to 100%.⁴⁴⁻⁴⁶ Significant blunt liver trauma is associated with other intra-abdominal and/or extra-abdominal injuries in 69 to 90% of cases, which may be important in determining the outcome.^{38-40,47} Isolated penetrating liver injury is becoming more prevalent and is the commonest mode of injury.^{46,48} Prompt assessment and treatment following major blunt or penetrating abdominal injury are key to determining the outcome. Few reports are available in literature about trauma as an indication for liver transplantation.

Recently Tucker et al⁵³ reported 2 cases of liver trauma who underwent successful emergency liver transplantation. Approximately 85% of patients with blunt liver injury are stable at presentation, and non-operative management is associated with reduced transfusion requirements, ICU stay, intra-abdominal infections, and length of hospital stay.⁴⁹

LT is indicated only in:^{50,51,53}

- Progressive ALF after grade IV-V hepatic trauma
- Uncontrollable hemorrhage
- Life-threatening postreperfusion injury.

CONTRAINDICATIONS TO LIVER TRANSPLANTATION (TABLE 4.3)

Contraindications to liver transplantation include poor compliance, lack of an adequate support system, and clinical conditions associated with poor post-transplantation outcome are shown in the Table 4.3. Some contraindications are absolute and others are relative. Indications and contraindications vary from one center to another.

EXTRAHEPATIC MALIGNANCY

Liver transplantation is contraindicated due to poor survival rate. Exceptions to this are the patients with liver metastases from carcinoid tumors and neuroendocrine tumors including gastrinoma, insulinomas, glucagonomas, somatostatinomas.⁹

INFECTIONS

Spontaneous bacterial peritonitis (SBP), sepsis and pneumonia are absolute contraindications. SBP should be treated at least 48 hrs with documented eradication of infection on follow-up paracentesis before transplantation.^{1,2,10}

ACTIVE ALCOHOL OR DRUG ABUSE

This is an absolute contraindication to liver transplantation. Patients with a history of alcohol and/or drug abuse must complete a period of at least 6 months of abstinence and rehabilitation successfully and provide proof of compliance, as outlined by the local liver transplantation selection committee before undergoing transplantation.¹¹⁻¹³ Some patients can improve their liver function by abstinence to such an extent that liver transplantation can be deferred or avoided. 20-26% patients return to alcohol use in 4-5 years after transplantation.¹³ Guidelines for tobacco use are individualized and program specific.

CARDIOVASCULAR DISEASE (TABLE 4.4)

Liver transplantation surgery may be complicated by coronary artery disease like myocardial infarction and have an overall mortality rate of 50%.^{14,15} Dobutamine stress echocardiogram is the ideal screening test. Coronary angiography is done selectively for diabetics, chronic smokers, and patients with a positive stress test.^{16,17} Patients who have coronary artery disease can

TABLE 4.3: Contraindications to liver transplantation⁵²

<i>Absolute contraindications</i>	<i>Relative contraindications</i>
Brain dead recipient	Advanced age(>70 years)
Extrahepatic malignancy	Cholangiocarcinoma
Active uncontrolled infection/sepsis	HIV infection
Active alcohol or drug abuse	PV thrombosis, Grade IV
Severe cardiopulmonary disease	Psychologic instability
AIDS	Renal failure
Noncompliance	Pulmonary hypertension
Anatomic abnormalities precluding LTX	(Mean PA pr.>35 mm of Hg)
Compensated cirrhosis without any complications	Severe hypoxemia secondary to Rt. to Lt.
(Child score 5-6)	intrapulmonary shunts (PO ₂ < 50 mm Hg)
Lack of psychosocial and family support	Uncontrolled psychiatric disorder
Life-threatening systemic disease	

TABLE 4.4: Absolute cardiovascular contraindications^{1,2,16}

- Coronary artery disease
- Severe ventricular dysfunction
- Severe cardiomyopathy
- Severe pulmonary arterial hypertension
- Severe valvular heart disease
- Aortic stenosis with significant pressure gradient and poor ventricular function

be listed for liver transplantation after revascularization with angioplasty or bypass surgery.^{16,17}

PULMONARY CONDITIONS (TABLE 4.5)

Pulmonary Tuberculosis

Recipients with active tuberculosis should start therapy before transplantation and must continue treatment for at least 1 year after transplantation.¹⁰ Patients who have a positive purified protein derivative (PPD) test during pretransplantation evaluation should undergo prophylaxis with isoniazid and pyridoxine or ofloxacin for 6 months.

Portopulmonary Hypertension

Portopulmonary hypertension with ESLD should undergo risk stratification to assess their candidacy for liver transplantation.¹⁸ They are evaluated by right-sided cardiac catheterization.¹⁹

Pulmonary Hypertension

Severe pulmonary hypertension is defined as mean pulmonary artery pressure (PAP) of 50 mm Hg or above, is an absolute contraindication for liver transplantation and is associated with 100% risk of surgical mortality. Moderate pulmonary hypertension is defined as a mean PAP between 35 and 50 mm Hg, have a 50% risk of mortality after transplantation. Mild pulmonary hypertension is defined as mean PAP of less than 35 mm Hg, remain suitable candidates for liver transplantation.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome occurs in the setting of portal hypertension and leads to intrapulmonary vascular dilatation (with right-to-left shunting) and arterial

TABLE 4.5: Absolute pulmonary contraindications¹⁰

Severe pulmonary hypertension
Oxygen-dependent COPD
Advanced pulmonary fibrosis

(COPD—Chronic obstructive pulmonary disease)

hypoxemia.²⁰ The severity of pretransplantation hypoxemia determines the post-transplantation mortality rate.²¹ The mortality rate increases from less than 5 to 30% if the pretransplantation PaO₂ is lower than 50 mm Hg.²¹ The poor prognostic indicators for post-transplantation outcome include refractory hypoxemia with multiorgan shock, intracerebral hemorrhage, sepsis, and portal vein thrombosis.²²

ANATOMIC ABNORMALITIES

Portal vein thrombosis is a relative contraindication and a poor prognostic indicator for postoperative graft dysfunction. Grade IV portal vein thrombosis has a significant lower survival rate after transplantation.²³ Imaging studies during the pretransplantation evaluation should document portal vein patency. Patients who have portal vein thrombosis can be considered for thrombectomy or jump grafts.

PREVIOUS ABDOMINAL SURGERY

Abdominal adhesions due to previous surgery can lead to prolonged surgery, increased blood loss, and higher risk of complications. With careful surgical approach and planning, comparable results can be achieved to those previously unoperated patients.²⁴

HIV INFECTION

Introduction of highly active antiretroviral therapy (HAART) has changed the natural course and history of HIV infection from a fatal disease to a chronic disease. As a result, patients who have HIV are living longer and are usually dying of other co-morbidities like chronic hepatitis C and cirrhosis. Earlier reports in HIV positive patients with liver transplantation have shown an increased risk of progression to AIDS was due to the immunosuppression after transplantation.²⁵ Thus, the majority of liver transplant centers in the United States still consider HIV infection a contraindication for liver transplantation. Recent outcome after liver transplantation in HIV positive patients has improved significantly due to the efficacy of HAART in controlling the virus and survival rates are comparable to that of patients who do not have HIV and who have the same indications for liver transplantation.²⁶ Evaluation of such patients requires a collaborative approach by the liver transplantation and infectious disease teams.

PSYCHOSOCIAL SUPPORT

Patients undergoing evaluation for liver transplantation must demonstrate the existence of an adequate support

system. Lack of adequate support can lead to disqualification or deferral. Patients must undergo comprehensive psychosocial evaluation as part of the evaluation. Patients who have psychiatric disorders also are required to undergo psychiatric evaluation.⁵²

AGE

Reported 1-year and 5-year post-transplantation survival rates of patients over the age of 65 years is less than in a younger group of patients.²⁷ Elderly patients must undergo extensive diagnostic tests to rule out comorbid conditions. Increased age has been demonstrated to be an independent risk factor for mortality after liver transplantation.⁶ Malignancy is a major cause of late mortality in the elderly and in young patients, infection is a major cause of post-transplantation mortality.⁵²

CHOLANGIOCARCINOMA

In the absence of primary sclerosing cholangitis, curative surgical resection has a 5-year survival rate of 2 to 43%.²⁸ Patients who have unresectable cholangiocarcinoma or pre-existing primary sclerosing cholangitis should be considered for liver transplantation. Comprehensive staging is required before liver transplantation, including CT scan of abdomen and chest, bone scan, and exploratory laparotomy to rule out metastases. Early cholangiocarcinoma (stage I and II) can be considered for transplantation with protocols using adjuvant chemotherapy and radiotherapy and advanced cholangiocarcinoma is an absolute contraindication for liver transplantation.²⁸ Stage of cholangiocarcinoma determines the outcome after transplantation. Post-transplantation 5-yr. survival rate is 70% in patients with stage I and II tumors and 30% in advanced cholangiocarcinoma.²⁹

OBESITY

Obesity is on the rise in the USA and other developed countries. It is associated with increased peri- and post-transplantation morbidity and mortality due to its association with coronary artery disease, diabetes mellitus, hyperlipidemia, and restrictive pulmonary disease.³⁰ 5-year mortality rate after transplantation is significantly higher due to cardiovascular complications in morbidly obese patients (BMI > 40 kg/m²) than for non-obese patients (BMI < 25 kg/m²).³¹ Patients who have a BMI of 30 to 35 kg/m² have survival rates comparable to that of non-obese patients. Hence it is recommended that patients who have BMI > 35 kg/m² be considered for liver transplantation on case-to-case basis. Transplantation is deferred based on center-specific policies. Morbidly obese patients who are deferred need

to work with dietician with individualized recommendations and goals to achieve desired weight loss.

RENAL FAILURE

In cirrhotic patients, sodium retention with impaired water excretion, decreased renal perfusion and GFR are common renal abnormalities.⁴³ Pre-existing renal insufficiency reduces the survival rates and a higher likelihood of needing dialysis after transplantation.^{32,33}

Hepatorenal Syndrome

It is a late complication of cirrhosis with ascites. It is characterized by the following criteria (**Table 4.6**):

TABLE 4.6: Hepatorenal syndrome³⁴

Presence of liver failure
Serum creatinine level > 1.5 mg/dL
GFR < 40 mL/min
Proteinuria <500 mg/dL
Normal renal ultrasound
No improvement after saline challenge or diuretics
Absence of other causes of renal failure

Patients who have intrinsic renal disease may need evaluation for combined liver-kidney transplantation. National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database has indicated that renal insufficiency in ALF, in patients receiving dialysis or after combined liver and kidney transplantation, results in reduced patient and graft survival rates, prolonged ICU admission, and higher costs.³²

PREVIOUS NONHEPATIC MALIGNANCY

It is not an absolute contraindication for transplantation.³⁵ A mandatory tumor free period of 2 to 5 years after curative cancer treatment is required before liver transplantation. At least 5 years of tumor free survival period is required for patients who have malignancies such as malignant melanomas and breast and colon carcinomas.⁵²

RETRANSPLANTATION

Diseases which are likely to recur after transplantation:⁵²

- Hepatitis B and C
- Hepatocellular carcinoma
- Cholestatic liver disease
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis (NASH)
- Alcoholic liver disease

Recurrent disease, especially in chronic hepatitis C, may cause late morbidity and mortality and raise the need for retransplantation.³⁶ Recurrent HCV infection is an independent predictor of poor outcome after transplantation.^{37,38} The survival rate is less than 50% at 12 months in patients undergoing retransplantation for recurrent HCV infection. Progressive hyperbilirubinemia and renal failure are independent predictors of poor outcome after retransplantation in the setting of recurrent HCV infection.³⁸

REFERENCES

1. Yu AS, Keeffe EB. Liver transplantation. In: Zakim D, Boyer TD, editors. *Hepatology: A textbook of liver disease*. 4th edition. Philadelphia: Elsevier 2003;1617-56.
2. Murray KR, Carithers RL Jr. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 2005;41:1407-32.
3. Consensus Conference. Indications for liver transplantation, January 19 and 20, 2005, Lyon-Palais Des Congrès. Text of recommendations (long version). *Liver Transpl* 2006;12:988-1011.
4. National Institutes of Health Consensus Development Conference Statement: Liver transplantation June 20-23, 1983. *Hepatology* 1984;4(Suppl):107S-10S.
5. US Scientific Registry (UNOS). Richmond (VA). United Network for Organ Sharing. Available at: www.unos.org. Accessed February 12, 2006.
6. Seaberg EC, Belle SH, Beringer KC, et al. Liver transplantation in the United States from 1987-1998: Updated results from the Pitt-UNOS liver transplant registry. In: Cecka JM, Terasaki PI, editors. *Clinical transplants 1998*. Los Angeles (CA): UCLA Tissue Typing Laboratory 1999:17-37.
7. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database. *Liver Transpl* 2004;10:886-97.
8. Lee WM. Acute liver failure. *N Engl J Med* 1993;329:1862-72.
9. Pichlmayr R, Weimann A, Oldhafer KJ, et al. Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 1995;19:807-13.
10. Rosen HR, Martin P. Liver transplantation. In: Schiff ER, Sorrell MF, Maddrey WC, editors. *Schiff's diseases of the liver*. 8th edition. Philadelphia: Lippincott-Raven Publishers 1999:1589-615.
11. Lim JK, Keeffe EB. Liver transplantation for alcoholic liver disease: current concepts and length of sobriety. *Liver Transpl* 2004;10:S31-8.
12. Osorio RW, Ascher NL, Avery M, et al. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. *Hepatology* 1994;20:105-10.
13. DiMartini A, Day N, Dew MA, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl* 2006;12:813-20.
14. Plotkin JS, Scott VL, Pinna A, et al. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996;2:426-30.
15. Keeffe EB. Comorbidities of alcoholic liver disease that affect outcome of orthotopic liver transplantation. *Liver Transpl Surg* 1997;3:251-7.
16. Plotkin JS, Johnson LB, Rustgi V, et al. Coronary artery disease and liver transplantation: The state of the art. *Liver Transpl* 2000;6(Suppl 1):S53-6.
17. Keeffe BG, Valentine H, Keeffe EB. Detection and treatment of coronary artery disease in liver transplant recipients. *Liver Transpl* 2001;7:755-61.
18. Ramsay MA, Simpson BR, Nguyen AT, et al. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg* 1997;3:494-500.
19. Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl* 2000;6(4):443-50.
20. Krowka MJ. Hepatopulmonary syndrome: Recent literature (1997 to 1999) and implications for liver transplantation. *Liver Transpl* 2000;6(Suppl 1):S31-5.
21. Krowka MJ, Porayko MK, Plevak DJ, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: Case reports and literature review. *Mayo Clin Proc* 1997;72:44-53.
22. Egawa H, Kasahara M, Inomata Y, et al. Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. *Transplantation* 1999;67:712-7.
23. Manzanet G, Sanjuan F, Orbis P, et al. Liver transplantation in patients with portal vein thrombosis. *Liver Transpl* 2001;7:125-31.
24. Shaked A, Colonna JO, Goldstein L, et al. The interrelation between sclerosing cholangitis and ulcerative colitis in patients undergoing liver transplantation. *Ann Surg* 1992;215:598-603.
25. Dummer JS, Erb S, Breinig MK, et al. Infection with human immunodeficiency virus in the Pittsburgh transplant population. A study of 583 donors and 1043 recipients, 1981-1986. *Transplantation* 1989;47:134-40.
26. Neff GW, Bonham A, Tzakis AG, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003;9:239-47.
27. Keswani RN, Ahmed A, Keeffe EB. Older age and liver transplantation: a review. *Liver Transpl* 2004;10:957-67.
28. Malhi H, Gores GJ. Review article: The modern diagnosis and therapy of cholangiocarcinoma. *Aliment Pharmacol Ther* 2006;23:1287-96.
29. Iwatsuki S, Todo S, Marsh JW, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg* 1998;87:358-64.
30. Nair S, Cohen DB, Cohen MP, et al. Postoperative morbidity, mortality, costs, and longterm survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 2001;96:842-5.
31. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002;35:105-9.
32. Brown RS Jr, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. *Transplantation* 1996;62:1788-93.
33. Lafayette RA, Pare G, Schmid CH, et al. Pretransplant renal dysfunction predicts poorer outcome in liver transplantation. *Clin Nephrol* 1997;48:159-64.

34. Arroyo V, Guevara M, Gines P. Hepatorenal syndrome in cirrhosis: Pathogenesis and treatment. *Gastroenterology* 2002;122:1658-76.
35. Saigal S, Norris S, Srinivasan P, et al. Successful outcome of orthotopic liver transplantation in patients with pre-existing malignant states. *Liver Transpl* 2001;7:11-5.
36. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. *Am J Gastroenterol* 2006;101:1370-8.
37. Berenguer M, Lopez-Labrador FX, Greenberg HB, et al. Hepatitis C virus and the host: An imbalance induced by immunosuppression? *Hepatology* 2000;32:433-5.
38. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. *Transplantation* 1998;66:1612-16.
39. Cox EF, Flancbaum L, Dauterive AH, Paulson RL. Blunt trauma to the liver. Analysis of management and mortality in 323 consecutive patients. *Ann Surg* 1988;207:126-34.
40. Malhotra AK, Fabian TC, Croce MA, et al. Blunt hepatic injury: A paradigm shift from operative to nonoperative management in the 1990s. *Ann Surg* 2000;231:804-13.
41. Gao JM, Du DY, Zhao XJ, et al. Liver trauma: Experience in 348 cases. *World J Surg* 2003; 27:703-708.
42. Scollay JM, Beard D, Smith R, et al. Eleven years of liver trauma: The Scottish experience. *World J Surg* 2005;29:744-49.
43. Asensio JA, Roldan G, Petrone P, et al. Operative management and outcomes in 103 AAST-OIS grades IV and V complex hepatic injuries: Trauma surgeons still need to operate, but angioembolization helps. *J Trauma* 2003;54:647-53.
44. Caruso DM, Battistella FD, Owings JT, Lee SL, Samaco RC. Perihepatic packing of major liver injuries: Complications and mortality. *Arch Surg* 1999;134:958-62.
45. Menegaux F, Langlois P, Chigot JP. Severe blunt trauma of the liver: Study of mortality factors. *J Trauma* 1993;35:865-69.
46. Chen RJ, Fang JF, Chen MF. Factors determining operative mortality of grade V blunt hepatic trauma. *J Trauma* 2000;49:886-91.
47. Cogbill TH, Moore EE, Jurkovich GJ, Feliciano DV, Morris JA, Mucha P. Severe hepatic trauma: A multi-center experience with 1,335 liver injuries. *J Trauma* 1988;28:1433-38.
48. Brammer RD, Bramhall SR, Mirza DF, et al. A 10-year experience of complex liver trauma. *Br J Surg* 2002;89:1532-37.
49. Brown CV, Velmahos GC, Neville AL, et al. Hemodynamically "stable" patients with peritonitis after penetrating abdominal trauma: Identifying those who are bleeding. *Arch Surg* 2005;140:767-72.
50. Ringe B, Pichlmayr R. Total hepatectomy and liver transplantation: A life-saving procedure in patients with severe hepatic trauma. *Br J Surg* 1995;82:837-39.
51. Veroux M, Cillo U, Brolese A, et al. Blunt liver injury: From non-operative management to liver transplantation. *Injury* 2003;34:181-86.
52. A Ahmed, EB Keeffe. Current Indications and Contraindications for Liver Transplantation *Clin Liver Dis* 2007;11:227-47.
53. ON Tucker, P Marriott, M Rela, et al. Emergency Liver Transplantation Following Severe Liver Trauma. *Liver transplantation* 2008;14:1204-10.

Liver Transplantation Team

INTRODUCTION

Goals of successful liver transplantation assessment include establishing a relationship of trust between patients and the transplant team, including understanding the difficulties of transplant operations, realistic expectations from the procedure, and the overall outcome. In this respect, the transplant surgeon, hepatologist, nurse coordinator and social worker can play a pivotal role in explaining the system of organ allocation, quality of the donor organs, type of transplant (DDLT, LDLT, Split liver), surgical procedure, potential complications, immuno-suppressive medications and their adverse effects, short and long-term outcomes.

THE TEAM

A liver transplant team constitutes the followings

- Hepatologist/Transplant Physician
- Transplant surgeon
- Anesthesiologist trained in liver transplantation
- Radiologist trained in liver transplantation related radiology
- Nurse coordinator/Transplant coordinator
- Social worker
- Financial coordinator
- Pharmacist
- Nutritionist

HEPATOLOGIST/TRANSPLANT PHYSICIAN

The role of hepatologist is important. He is the first physician who sees the patient. The hepatologist decides which patients are appropriate candidates for liver transplant and will initiate the evaluation and refer to transplant surgeon for work up and is involved with the patient after transplantation and to advise the medical aspects of early and late transplant related complications.

SURGEON

He is the key person who is continuously involved from the time the patient comes to the transplant OPD work up and long as the patient survives after transplantation. He performs the surgery and monitors postoperative liver function, rejection, surgical complications and medication in collaboration with transplant physician. After discharge the recipient is on regular life-long follow-up.

ANESTHESIOLOGIST

Transplantation anesthesia is different from the routine cases. His key role intraoperatively is to maintaining suitable hemodynamic status, avoid abnormalities in coagulation profiles, hypothermia, metabolic complications, provide smooth post-operative weaning. His role is also vital in providing suitable postoperative analgesia to both liver related donor and recipient.

RADIOLOGIST

The role of radiologist is important in liver donor evaluation. Important aspects of live donor such as the estimation of graft volume, degree of fatty change and proper evaluation of biliary, vascular anatomy and their variations are studied in detail before final selection of liver donor. His role is also important during intraoperative and postoperative assessment of hepatic hemodynamics by Doppler ultrasound.

PATHOLOGIST

The role of transplant pathologist is crucial in live donor evaluation such as evaluation of fatty change, diagnosis of rejection, recurrent diseases, infections and management of long-term complications. Histopathological report of liver biopsy guides in diagnosis and management of short and long-term complications of transplant patients.

NURSE COORDINATOR / TRANSPLANT COORDINATOR

Transplant coordinator is a registered nurse with several responsibilities. Role of nurse coordinator starts from the time the patient is referred to transplant OPD and he/she helps the patients and family for evaluation of live donor and recipient.

The nurse coordinator will also schedule tests, monitor lab results, coordinate clinic visits and communicate any concerns to any of your health care providers. The coordinator's role is to educate, encourage and assist the patient and the family, both before and after transplantation.

He or she will coordinate all the events leading up to and following surgery. They include scheduling pretransplant testing, work up for the live donor; locating donor liver in cadaver transplants, testing for donor compatibility, contacting the recipient once a cadaveric liver is available, and making sure that the patient has proper follow-up care.

The coordinator will explain the patient how to take care of himself before and after transplantation, including how to take medication and when to return to the transplant center for follow-up visits. He or she can put the patient in touch with community services that will make life easier for the patient and family.

FINANCIAL COORDINATOR

Financial coordinator will explain the financial dealings like the cost of transplantation and post-transplant medication. He/She also explains the options regarding other financial assistance resources that are possible, if needed.

SOCIAL WORKER

Transplant social workers can provide counseling and support to the patient and family. They will help the patient in understanding about transplantation and cope with the condition, and will help to identify any emotional or family issues. The social workers will determine whether the patient has an appropriate caretaker and family support. They can also provide information about community resources such as support groups, transportation and lodging. Social worker also plays an important role in cadaveric liver transplantation in motivating the donor family for multiorgan donation when the patient is declared brain dead.

PHARMACIST

Pharmacists are a medical professionals licensed to dispense prescription drugs. He or she will instruct the patient and his family about the importance of medication and their adverse effects used before and after liver transplantation.

NUTRITIONIST

Nutritionist is a qualified health specialist who guides about the food and nutritional science, preventive nutrition, diseases related to nutrient deficiencies, and the use of nutrient manipulation to enhance the clinical response before and after transplantation. Special attention to address nutritional issues, growth and development, especially neurologic development, are areas that need special consideration in pediatric patients.

Evaluation of Live Donor

INTRODUCTION

First successful LDLT was reported in 1990.¹ Most cases of LDLT are reported from Asia. But the recent reports from UNOS and ELTR show that increased rate of LDLT is in Europe and other countries.² Living liver donation has a surgical risk with donor mortality and morbidity rates is 1-1.0% and 15-25%, respectively. A living donor is a normal individual who is mentally, physically and psychologically healthy. Subjecting a healthy individual to high risk surgery was a matter of debate in the initial stage of LDLT. But keeping the benefit of recipient and balanced selection of donor to avoid complications has evoked a revolution in the modern era of LDLT all over the world.

Aim of donor evaluation

- To find out whether donor is suitable for donation or not
- Detect hidden medical diseases in donor
- Detailed anatomical evaluation of liver, related to segmental anatomy, vascular anatomy and flow (anatomy of HA, PV and HV) and bile duct anatomy and drainage
- Estimate the required graft volume
- To avoid unnecessary morbidity and mortality
- Evaluate psychological status, motivation for donation and legal requirement

Ideal Donor

- Mentally, physically and psychologically fit
- Volunteer for donation
- No financial or any other benefits from donation
- Without any pressure or compulsion from the family members or medical fraternity for organ donation
- Preferably a relative of the recipient
- Should be aware of morbidity, mortality and other consequences of organ donation.

The upper age limit for living donor is usually 55-60 yrs and lower age limit is 16-20 yrs. Age limit varies from center to center as per the regulation of the country's policy. Each country and each center has its own rules and regulations by the respective authorities regarding the age criteria. Some centers had used donors of 65 yrs age without any additional donor risk.^{3,4}

Living organ donation is a complex decision for the donor and his or her family.⁵ Transplant coordinator plays a vital role in donor evaluation and maintains a close liaison with donor and transplant surgeon. Every potential donor has a freedom to withdraw himself from organ donation during the course of evaluation and reason for withdrawal should not be disclosed to the recipient or relatives. Rather a technical reason may be explained to the family members by transplant surgeon. There are lot of psychological pressures in the donation process, including maladjustment, worry, and emotional demand.^{6,7} Investigations have usually focused on issues of health status and medical treatment, ignoring the problems of attitude, personal relationship, life-saving, and pressure from the family on living donors.^{8,9} Evaluation of live donor is shown in **Table 6.1**.

Contraindications

- Active bacterial, viral or fungal infections
- HBsAg positive
- Hepatitis C Antibody positive
- CMV/EBV IgM positive
- Body mass index >30
- Moderate to severe degree of macrovesicular steatosis
- Hyperlipidemia
- Extra-cranial malignancy
- Coagulation disorder

Tuberculosis is a major concern. Active disease is a contraindication. Past h/o tuberculosis with complete

TABLE 6.1: Evaluation of a potential living donor

Step I

a. History	b. Physical examination	c. Hematology	d. Biochemical
Hypertension,	Body weight	Hemoglobin, Hematocrit	Liver
IHD, DM, COPD	Body height	TRBC, Platelets	Bilirubin (Direct and total)
Malignancy	Body mass index	MCV, MCHC, MCH	AST, ALT
Asthma, Tuberculosis	Body surface area	TWBC, DC	Alkaline phosphatase
Mental illness	Pulse rate	PT, APTT, INR	LDH, GGT
Allergy	Blood pressure	ABO Blood typing	Kidney - Urea
			Creatinine
			Metabolic
Drugs- Alcohol	Urine analysis		Blood sugar
Smoking			(fasting, PP)
IV drug abuse			Lipid profile
Chest, heart examination			Cholesterol
			LDL, VLDL, HDL
Females- Pregnancy			Uric acid
Contraceptive practice			Amylase
e. Serology	f. Others	g. USG of Abdomen	
HBsAg, HBeAg	Ceruloplasmin		
Anti HBc, Anti HBsAb	Ferritin, Transferrin		
Anti HBe, Anti HBc,			
Anti HCV Ab	Antinuclear antibody		
CMV- IgG and IgM	Tumor markers (AFP, CEA, CA-19-9)		
EBV- IgG and IgM			
VDRL/ RPR			
HIV Screening			

Step II**Psychological assessment**

Chest X-ray, Arterial blood gas analysis
 ECG, 2D-Echocardiogram (in selected cases, particularly marginal donors)
 Computerized Tomography of liver and liver volumetry
 MRI and MRCP for assessment of liver and biliary tree

Step III

Liver biopsy (in selected cases of fatty livers)

Step IV

Lymphocytotoxic antibody screening (Class 1 and 2)
 HLA Typing and crossmatching (optional , not routine)
 Informed consent from donor, recipient and relatives.

treatment can be accepted for donation. But possibility of reactivation of tuberculosis should be kept in mind. CMV/EBV IgM positive donors are not accepted. Body mass index >30 are not considered for donation as there is increased risk of macrovesicular steatosis in liver and postoperative complication rate.¹⁰ But this cut-off is mostly applied to western population. In Asian people the BMI cut-off can be taken at a lower level of 27.5¹¹

$$\text{Body Mass Index (BMI)} = \frac{\text{Donor weight in kilograms}}{\text{Donor height in square meter}}$$

CORE ANTIBODY (HBcAb) POSITIVE DONORS

HBcAb positive donors can be accepted, but these donors should be evaluated for HBV DNA (viral load) levels and the recipient should receive postoperative HBV prophylaxis and lifelong antiviral therapy (Lamivudine/ Entecavir/Adefovir). Postoperative antiviral treatment may be discontinued in recipients with adequate titers of HBsAb and HBV DNA negativity. Recipients with core antibody (HBcAb) allograft will have prolonged hyperbilirubinemia. Preoperatively recipient should be

immunized for HBV and check for Anti HBsAb titers, in case of recipients who are transplanted for non HBV cirrhosis.¹² One study says that short term Lamivudine is adequate for patients who develop de novo hepatitis B infection after HBcAb positive allograft.¹³

DONOR EVALUATION

CT SCAN

Three dimensional CT Scan and reconstruction of vascular anatomy is preferred. In an MDCT, volumetry of portal and venous regional volume can be performed. Conventional volumetry includes estimation of whole liver volume, right lobe volume with or without middle hepatic vein (MHV), left lobe volume without caudate lobe and remnant liver volume.¹⁴ Detailed evaluation of intrahepatic anatomy pertaining to hepatic veins, portal vein, hepatic artery and bile duct is important for live donor evaluation. The evaluation of vascular and biliary anatomy is discussed here. Biliary anatomy is studied by MRC.

EVALUATION OF HEPATIC VEINS

- Origin, anatomy, course, branches and size of RHV, MHV, LHV (**Figures 6.7 and 6.8**).
- Junction of LHV and MHV.
- Branches of MHV to segment V and VIII (V5 and V8) and course and size of each branch (**Figure 6.7**).
- Presence of IRHV, MRHV and their course and size.
- Segment IVb hepatic vein in case of extended RLG or RLG with MHV.

ARTERIAL SUPPLY

Earlier reports suggest that hepatic arterial anomalies occur in 21.4 to 42.2% of all donor livers.¹⁵⁻¹⁸ Arterial evaluation includes:

- Origin, anatomy, course, distribution, variation, anomalies or aberrations in RHA and LHA.
- If middle hepatic artery originates from RHA, transection of RHA should be distal to the origin of MHA
- Segment IV arterial supply (preserved as far as possible in RLG to prevent infarction of segment IV if not possible can be ligated if it is close to hilum)
- Multiple arterial supply in one graft—difficult for reconstruction intraoperatively due to their smaller size
- Variation like RHA originates from SMA or LHA originates from LGA should be noted (**Figures 6.1 to 6.6**).

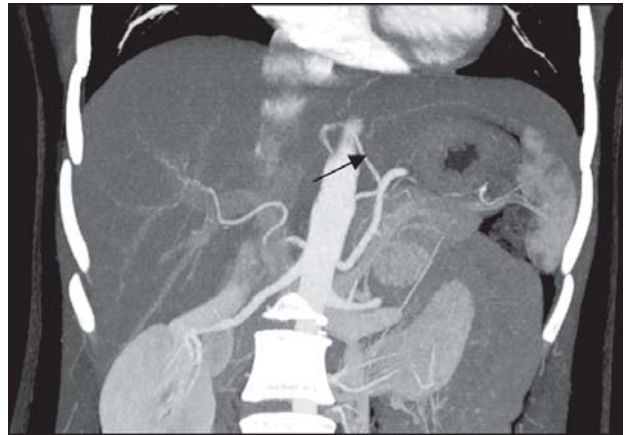


Figure 6:1: Left hepatic artery from left gastric artery

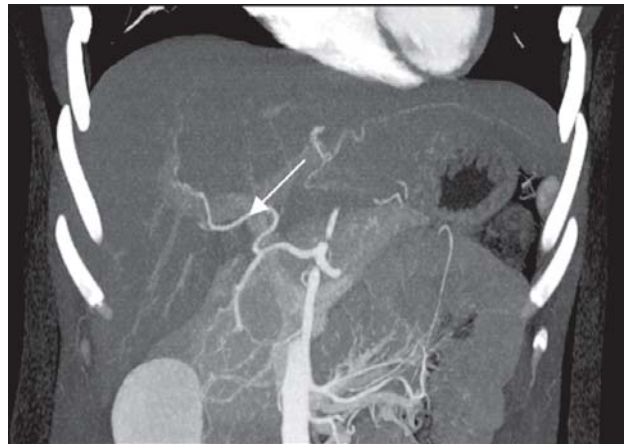


Figure 6:2: RHA as continuation of proper hepatic artery

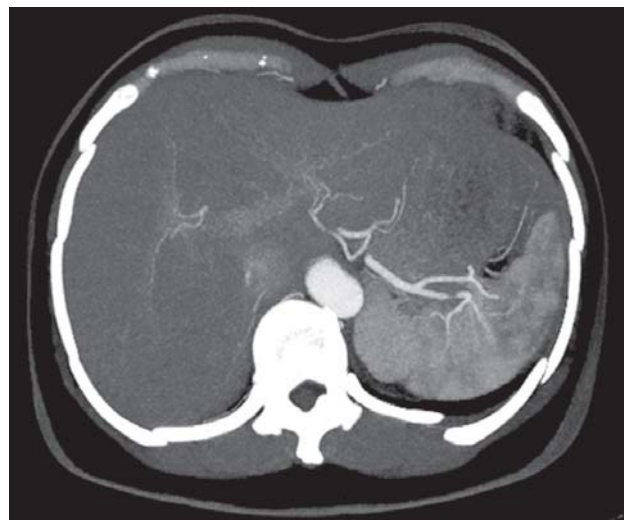


Figure 6:3: Left hepatic artery from left gastric artery

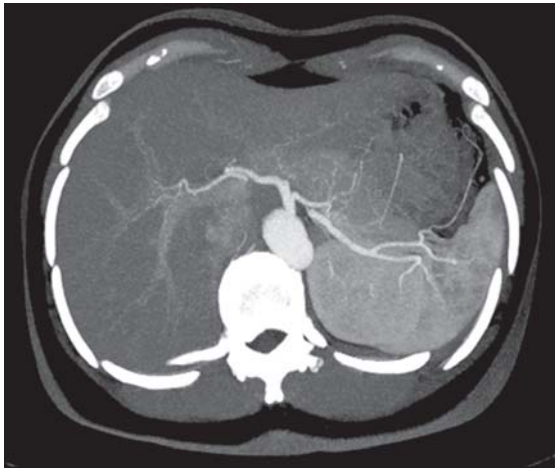


Figure 6:4: RHA as continuation of proper hepatic artery

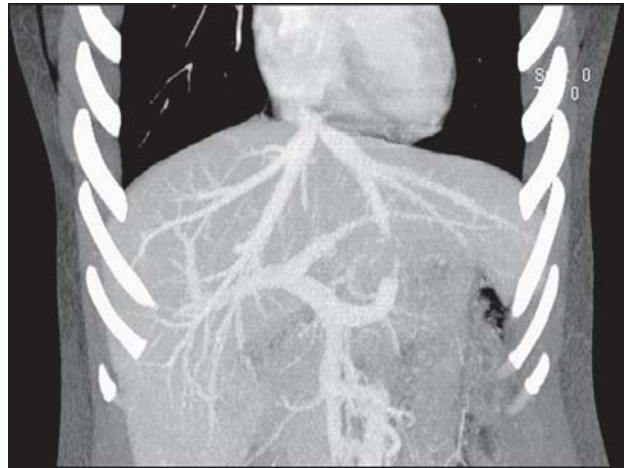


Figure 6:7: Middle hepatic vein with branches to segment V and VIII and left hepatic vein

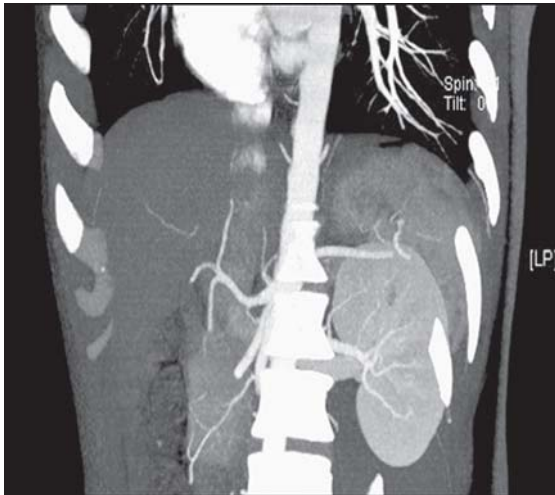


Figure 6:5: Trifurcation of hepatic artery

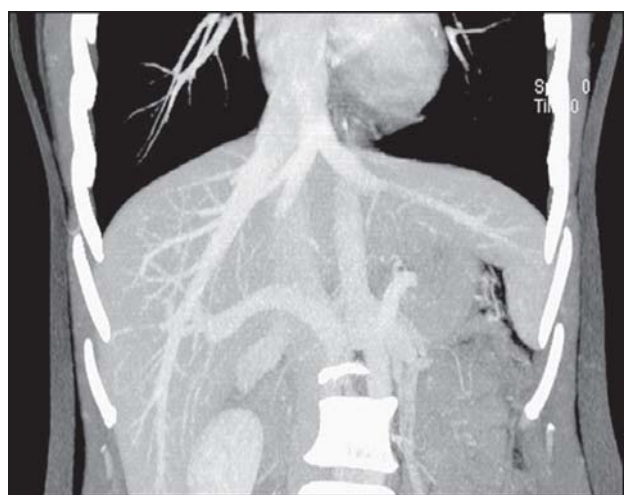


Figure 6:8: Right hepatic vein and portal vein



Figure 6:6: LHA from left gastric artery

PORTAL VEIN EVALUATION

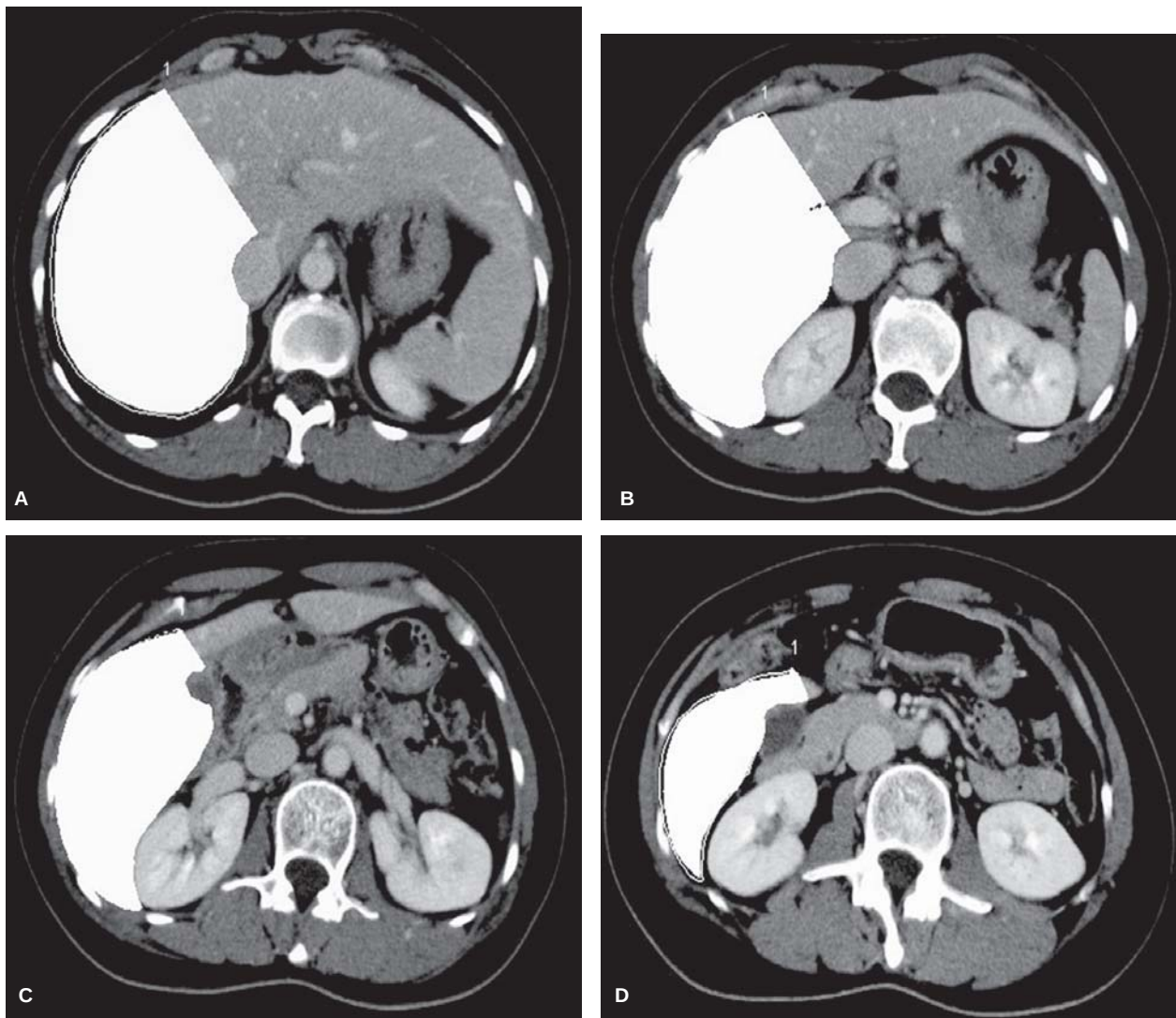
- Origin, anatomy, course, branches and size of RPV and LPV
- Any evidence of thrombosis, fibrosis, calcification or narrowing
- Trifurcation of PV if present may cause difficulty in reconstruction of portal vein in recipient
- Sometimes segment V and VIII portal vein branches may arise from LPV, if present they have usually extrahepatic course and are carefully preserved during hilar dissection. But if they are present in the umbilical fissure, they have usually intrahepatic course and are likely to be injured during parenchymal transection. So precaution should be taken accordingly during surgery to preserve those intrahepatic branches.

CT VOLUMETRY

- Total liver volume of donor liver
- Volume and weight of right lobe in RLG (40% of ESLV or 0.8 to 1% of GRWR) (**Figures 6.9A to D**)
- Volume and weight of left lobe in LLG (30% of ESLV or 0.6% of GRWR—Japanese studies, discussed elsewhere)
- Percentage of volume reduction
- Residual liver volume (RLV) in donor (usually 30–35%).

$RLV = \text{Estimated whole liver volume} - \text{Estimated graft volume}$,
 $\text{Percentage of RLV} = \frac{RLV}{\text{Estimated whole liver volume}} \times 100$

Congested area of segment V and VIII in RLG or LLG and segment IV in RLG with MHV can be estimated by three dimensional CT scan and reconstruction by specialised software as reported by Japanese studies. If the patient has ascites or fluid retention in the form of pedal edema, the size of the graft for the recipient is usually over estimated due to the weight of the ascitic fluid. The graft weight is estimated by CT volumetry is not accurate, but approximately it coincides with the original weight because the plane of parenchymal transection and the plane in which radiologist estimates the graft volume may be slightly different.



Figures 6.9A to D: CT volumetry for right lobe volume estimation (Right lobe marked as white color)

CT EVALUATION OF SEGMENTAL ANATOMY AND FATTY LIVER

Segmental anatomy of the liver is studied for the presence of any tumor, cyst or hemangioma. Assessment of hepatic steatosis in donors is measured by Hounsfield units of the region of interest (ROI) identified in the liver and spleen and calculating an index of hepatic attenuation (**Table 6.2**).^{19,20} Unenhanced CT Scan is highly accurate in enabling diagnosis of >30% macrovesicular hepatic steatosis in liver related donors. Complications of CT scan are usually 1%, mostly related to contrast injection, such as hypersensitivity reactions, anaphylaxis, nephropathy and renal failure.²¹

TABLE 6.2: Fatty change scoring in LDLT according to liver/spleen ratio calculated by CT scan

Fatty change	CT number
No fatty change	>1.1
Mild	1.0 to 1.1
Moderate	0.9 – 1.0
Severe	< 0.9

Visual assessment of degree of steatosis in liver on unenhanced CT is performed by using a five point scale. Attenuation is compared between the liver and hepatic vessels.

Grade 1: Hepatic vessels have lower attenuation than the hepatic parenchyma out to the peripheral 1/3 of liver.

Grade 2: Hepatic vessels have lower attenuation than the hepatic parenchyma out to the middle 1/3 of liver.

Grade 3: Hepatic vessels have lower attenuation than the hepatic parenchyma out to the central 1/3 of liver.

Grade 4: Hepatic vessels have same attenuation as that of hepatic parenchyma.

Grade 5: Hepatic vessels have higher attenuation as that of hepatic parenchyma.

Liver attenuation index [CT(L-S)], defined as hepatic attenuation minus splenic attenuation. Hepatic attenuation is calculated by averaging the Hounsfield units of 8 ROIs, measuring 1.5×1.5 cm each and located in 8 different sites in the right lobe (2 regions in each of Couinaud hepatic segments V, VI, VII and VIII).

MR CHOLANGIOGRAPHY FOR BILIARY TREE EVALUATION (FIGURES 6.10 AND 6.11)

- MRI delineates clear intra- and extrahepatic anatomy of the biliary tree.
- Hilum and Union of LHD and RHD, union of anterior and posterior branches of RHD in RLG.



Figure 6.10: MRC: Trifurcation of bile duct



Figure 6.11: MRC: Posterior duct opening into the left IHD. Green: Left hepatic duct; Red: Right anterior branch, White: Right posterior branch

- Segment II, III and IV ducts and their union in LLG.
- Posterior duct joining the LHD is common anomaly and other anomalies also searched.
- Lower insertion of RHD or one of the branches of RHD is also frequently encountered anomaly.
- Segment IV duct sometimes directly joins LHD very close to hilum or opens independently, if present should be mentioned so that care is taken intraoperatively.
- None of these are contraindications for donor selection, proper intraoperative planning should be done to modify the reconstruction.

INFORMED CONSENT BEFORE TRANSPLANT

- Obtaining the informed consent is the most important step in evaluation. Before transplantation, the transplant surgeon discusses the issues related to transplant with the donor, recipient and relatives in detail about the morbidity, mortality and possible outcomes after transplantation.
- Possibility of withdrawal from donation is also clearly explained to donor during this interview. Drop out rates in donors from donation ranges from 15-50% from various centers across the world.

- Complete documentation is vital before transplantation as the complications after surgery may change the attitude of relatives and to avoid future legal problems.

DONOR COMPLICATIONS

A wide range of complication rates are reported in the literature in donors after LDLT (**Table 6.3**). Overall complication rates range from 0 to 67%, with an overall crude complication rate of 31%.⁴⁶ The Clavien system⁴⁷ can be applied to complications after LDLT. According to a recent series⁴⁸ of 101 donors who underwent right liver resection, overall morbidity rate was 37%; all complications were either grade 1 or 2 of Clavien's classification, and the majority occurred during the first 30 days after surgery. Biliary complication rate is 0-7% of donors, including bile leaks and strictures. Complications related to major abdominal surgery 9-19% of donors, including wound infections, small bowel obstruction, pneumonia and incisional hernia. According to a National survey in Japan,⁴⁹ 244 postoperative complications were reported in 12% of donors (228/1853). The frequency of complications was significantly higher in donors of the right liver graft than in those of left-sided grafts. Re-operation was performed in 1% of the donors.

TABLE 6.3: Postoperative complications in Donor^{42-44, 53, 54}

	<i>Immediate</i>	<i>Early</i>	<i>Late</i>
Hematological	Primary hemorrhage	Secondary hemorrhage	-
Pulmonary	Effusion	Effusion	-
	Pneumothorax	Respiratory failure	-
	Edema	Edema	-
	-	Empyema	-
GI	Bile leak/bilioma	Ascites	Small bowel obstruction
	Duodenal ulcer related	Biliary fistula, abscess	Incisional hernia
	pancreatitis	Paralytic ileus	Post-donation dyspepsia
	CBD injury	Diaphragmatic injury	Altered gastric motility
	-	Liver failure	Cholestatic liver dysfunction
	-	Hyperbilirubinemia	Biliary stricture
	-	Duodenal ulcer related	Secondary biliary cirrhosis
Cardiac	Arrhythmia	Cardiac arrest	-
	Cardiac arrest	-	-
Infective	-	Wound complications	Pressure sores
	-	Drain related	-
	-	Sepsis	-
Neurological	-	Convulsions	Convulsions
	-	Encephalopathy	Brachial/peroneal nerve injury
Vascular	Hepatic artery injury	Deep vein thrombosis	PV narrowing / thrombosis
	Portal vein injury	-	-
Renal	Oliguria	Renal failure	
Psychological	-	-	Psychological problems
Re-exploration	Yes	Yes	-
Death	-	Yes	Yes

Clavein Grading of Complications in Live Liver Donors⁵⁶

Grade **I** (non-life threatening complications): Requires bedside intervention or postoperative bleeding with < 4 units of PRBC or ICU/hospital stay—not prolonged, not longer than twice the median population. Grade **II** (without any residual disability): **IIa**: require treatment/medication or ≥ 4 units of PRBC transfusion; **IIb**: require therapeutic intervention or readmission or ICU stay >5 days and **IIc**: Donor surgery abandoned or not resulting in transplantation. Grade **III** (with residual disability): **IIIa**: low risk of death and results in permanent, but not progressive disability; and **IIIb**: lasting disability difficult to control or significant risk of liver failure or death. Grade **IV** (liver failure or death of donor): **IV a**: results in liver transplantation in donor and **IV b** includes donor death.

Multicenter study from Europe, Asia, and USA in LDLT shows that:

- Readmission rate : 5 to 13%^{45,46,53,57}
- Reoperation rate : 1 to 4.5%^{45,46,52}

Donor risk in different countries:⁴⁶

- USA – 0.38%
- Europe – 0.31%
- South Africa – 0.17%
- Asia – 0.02%

Morbidity in live donor:^{46,52}

- Umeshita et al, Japan: 12% (228/1853 patients)
20% in 443 patients
- Ghobrial et al, USA: 21% (393)

Psychological problems in live donors⁴⁶:

- Fukunisha et al, Japan – 10%⁵⁰
- Walter et al, Germany – 20%⁵¹
- Trotter et al, USA – 4.1%⁵⁵

Total 28 deaths have been reported all over the world so far as per the data discussed in IHPBA 2008. Most of the donor deaths were reported after right lobe donation.⁴⁶ (**Tables 6.4 and 6.5**) It is reported that operative mortality for the RL donor is estimated to be as high as 0.15–1%.^{1,24,27,33,40,41}

FOLLOW-UP OF DONOR (FIGURES 6.12 AND 6.13)

Donor is followed up in OPD 2nd week, followed by 1, 3 and 12 months. During 1st and 2nd week visit, total serum bilirubin, AST, ALT, PT, INR, serum albumin levels are examined. In the following visits along with routine liver function tests, CT scan is performed at 1, 3 and 12 months to evaluate the liver regeneration and remnant liver volume assessment.

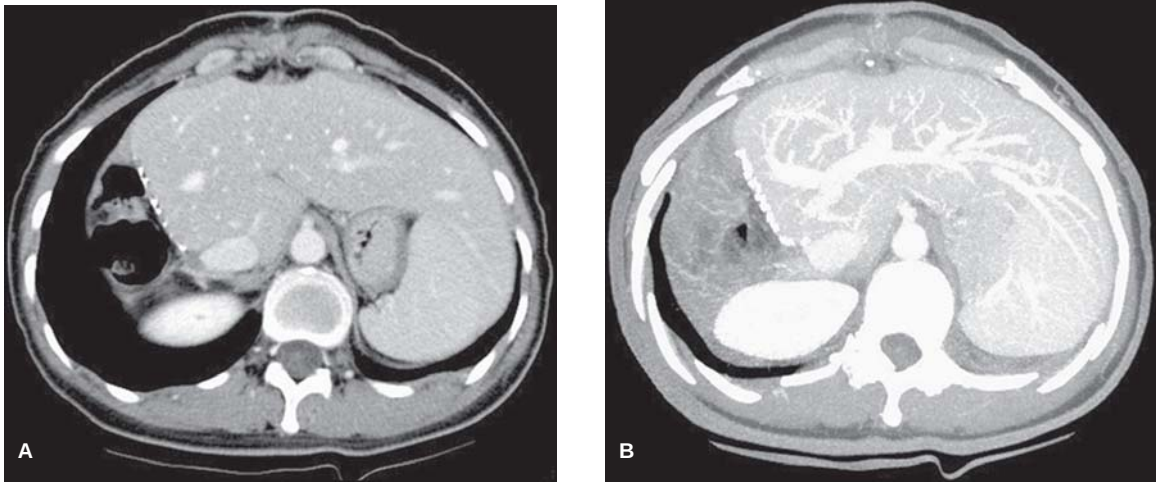
TABLE 6.4: Living donor mortality in Western countries (Till 2007)^{22-39,54}

Country location	Cause of death	Graft
North America		
USA		
New York (World's first donor death)	Aspiration, Gas Gangrene	RLG
San Antonio	Anaphylaxis	LSG
Chapel Hill	Sepsis	RLG
Los Angeles	Suicide	RLG
Philadelphia	Illicit drug overdose	LSG
California	Pulmonary embolism	LLG
—	Suicide	RLG
—	Accident	RLG
South America		
Brazil		
Curitiba	Cerebral bleeding	RLG
Recife	Bleeding	LLG
Europe		
Germany		
Hamburg	Pulmonary embolism	LSG
Essen	Liver failure, Bernardinelli-Seip syndrome	RLG
Jena	Multiorgan failure	RLG
Hamburg	Amyotrophic lateral sclerosis	LSG
France		
Lyon	Sepsis	RLG
Paris	Myeloma, Multiorgan failure	RLG
Africa		
Egypt		
Cairo	Sepsis due to bile leak	RLG
Shibin El Kom	Liver failure, Bleeding, PV thrombosis	RLG
Turkey		
Izmir	Pulmonary embolism	RLG

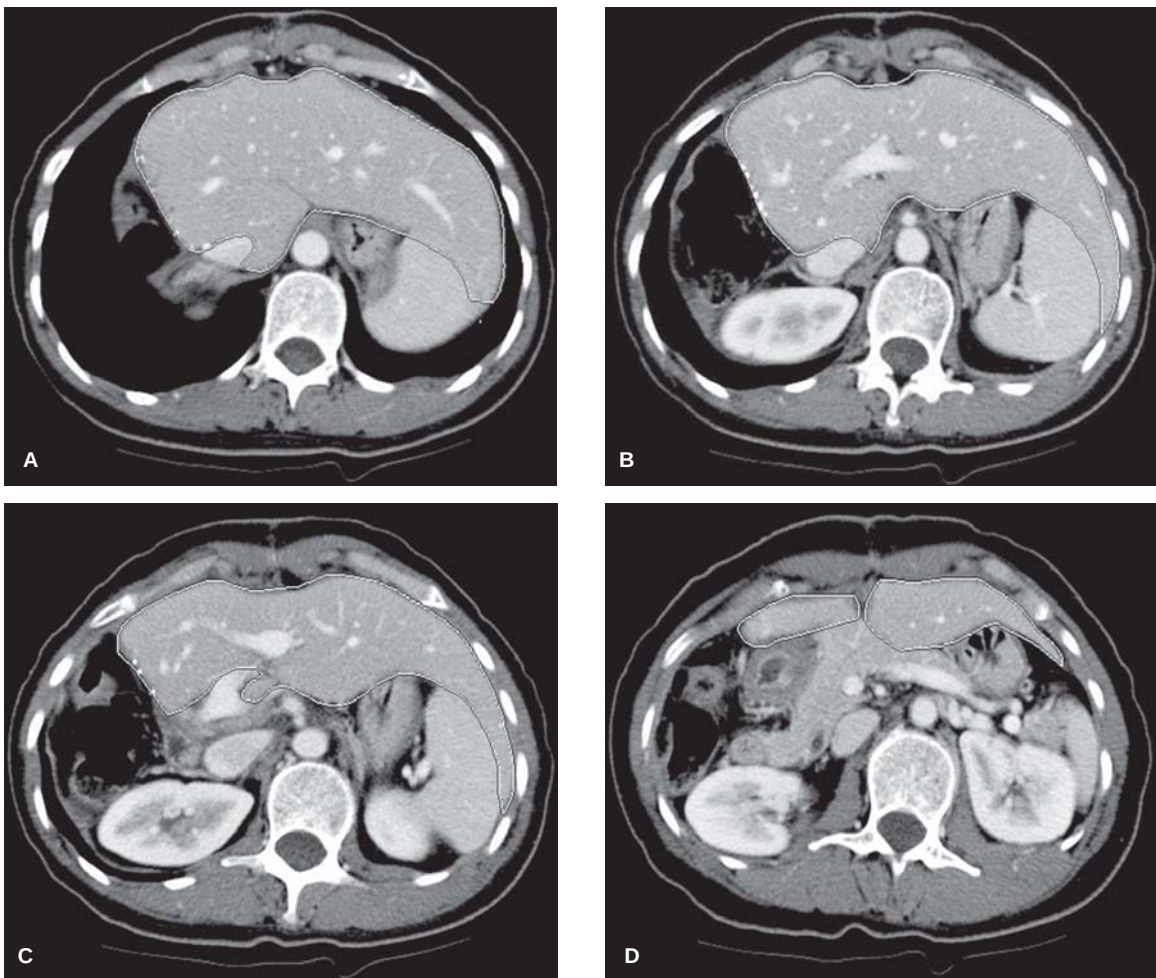
TABLE 6.5: Living Donor mortality in Asia (Till 2007)^{22-39,54}

Country location	Cause of death	Graft
India		
New Delhi	Pulmonary embolism	RLG
Hyderabad	Remained in coma state for long period and died	RLG
Coimbatore	Not reported	
Japan		
Kyoto	Remnant liver-27%, Liver failure, Nonalcoholic steatohepatitis (NASH)	RLG
Kyoto	Sudden death (unknown cause)	LSG
Singapore		
	Acute myocardial infarction	RLG
Korea		
Suwon City	Liver failure	RLG
China		
Hong Kong	Air embolism, Duodeno-caval fistula	RLG
Taiwan		
	Not reported	

(RLG - Right lobe graft; LLG - Left lobe graft; LSG - Lateral segment graft)



Figures 6.12A and B: Follow-up of donor; CT angiography image one month after transplantation



Figures 6.13A to D: Donor residual remnant liver volume estimation after one month of donation

RADIOLOGICAL EVALUATION OF POTENTIAL TRANSPLANT RECIPIENT

Radiological evaluation of the recipient includes the assessment of:

1. Detailed vascular anatomy
2. Hepatic malignancy (if any)
3. Presence of portocaval shunts and transjugular portosystemic shunt (TIPS)

DETAILED VASCULAR ANATOMY

Vascular anatomy is assessed by conventional, CT, and MR angiography.

*Hepatic Arterial Anatomy*⁵⁸⁻⁶⁰

Variations in hepatic artery are commonly seen and they alter the transplantation procedure. The various arterial variations are as follows:

- Accessory or replaced left hepatic artery from the left gastric artery or celiac trunk.
- Accessory or replaced right hepatic artery from the superior mesenteric artery.
- Replaced proper hepatic artery arising from the left gastric or superior mesenteric artery.
- Separate origin of the common hepatic artery from the aorta.
- Trifurcation of the common hepatic artery into right hepatic, left hepatic, and gastroduodenal artery.
- Early origin of right or left hepatic artery from the common hepatic artery, proximal to the origin of the gastroduodenal artery.
- Right hepatic artery originating from the gastroduodenal artery.

The incidence of splenic artery aneurysm is increased in patients with cirrhosis and portal hypertension, and they are at increased risk for rupture of aneurysm after transplantation.^{60,77} Atherosclerosis of the recipient's celiac trunk or hepatic artery needs to be assessed before transplantation, as interposition graft may be required in some cases.⁷⁷

Portal Venous Anatomy^{61,62}

Anatomical variants of the portal venous system are usually not significant but presence of portal vein thrombosis is an important aspect of the recipient with cirrhosis.⁶¹

*Tumor thrombus:*⁷⁷ Portal vein thrombus due to tumor is common in patients with hepatocellular carcinoma, due to the propensity of the tumor to grow into vessels. Transient focal hyperintensity of the liver parenchyma

distal to the thrombosed portal vein (transient hepatic intensity difference) may be present on MR images obtained during the arterial phase after gadolinium injection. The thrombosed vessel is often enlarged. On gadolinium enhanced MR images, tumor thrombus enhances heterogeneously where as bland thrombus has the appearance of a hypointense filling defect. Differentiation between bland and tumor thrombus is important, since the presence of tumor thrombus is a contraindication for hepatic transplantation. Over a period of time, a bland thrombosis might recanalize or lead to cavernous transformation of the portal vein. In case of recipient's bland portal vein thrombosis, portal vein reconstruction can be performed by interposition graft or jump graft from the recipient's superior mesenteric to the donor liver's portal vein. Diffuse thrombosis of the recipient's portal and superior mesenteric veins is a contraindication for hepatic transplantation. Portal-systemic varices adjacent to the liver and IVC can cause hemorrhage during hepatectomy. They are visualized as tortuous structures on contrast-enhanced CT or MR images.

*Inferior Vena Cava and Hepatic Veins*⁵⁹

Variations in the anatomy of the hepatic veins and the IVC are important in case of preservation of recipient IVC during hepatectomy for piggyback anastomosis technique. A common variation of hepatic veins is the presence of one or more accessory right inferior hepatic veins draining independently into the IVC. Azygos continuation of the IVC is exceedingly rare. In patients with cirrhosis, the caudate lobe enlarges and might completely surround the IVC, which complicates removal of the liver from the retrohepatic IVC during hepatectomy. Hepatocellular carcinoma may grow into the hepatic vasculature including hepatic veins or IVC and may present as tumor thrombus. Presence of this finding on CT or MR images is a contraindication for transplantation.

ASSESSMENT OF HEPATIC MALIGNANCIES

Screening for hepatic malignancies, particularly hepatocellular carcinoma is an important aspect of recipient evaluation. The size, number, extent of hepatic involvement, presence/absence of portal vein thrombosis will determine the indication for transplantation as per the Milan/UCSF criteria. Assessment can be performed with ultrasound, dynamic multiphase contrast-enhanced CT, dynamic multiphase gadolinium-enhanced MR imaging, and, more invasively, CT arterial portography (CTAP) and CT hepatic arteriography (CTHA). MR imaging is preferred over CTAP and CTHA due to its

noninvasiveness, high sensitivity and accuracy in patients with cirrhosis.⁶³⁻⁶⁷ But MR imaging is insensitive for the diagnosis of small hepatocellular carcinoma measuring < 2 cm.⁶⁶

Hepatocellular carcinoma: MR imaging appearance of hepatocellular is variable, with the most specific finding is an arterial enhancing lesion, which becomes hypointense compared with the liver parenchyma on delayed phase after gadolinium injection. Some hepatocellular carcinomas may contain lipid. An enhancing pseudocapsule is often present on delayed images. Benign abdominal lymphadenopathy is common in cirrhotic patients due to hepatitis C;⁶⁸ abdominal lymph node enlargement does not affect staging of hepatocellular carcinoma, but abdominal lymph node biopsy is necessary before transplantation. Distant metastasis to the lungs, abdominal lymph nodes, and bone is also searched during evaluation.⁶⁹ Presence of extrahepatic metastasis is an absolute contraindication for transplantation.⁶⁹

Cholangiocarcinoma: Initially cholangiocarcinoma was regarded a contraindication for liver transplantation because of its high recurrence rate.⁷² Later improved survival has been reported in selected patients with tumor <3 cm particularly perihilar cholangiocarcinoma who were treated with pre-transplant chemoradiation.^{70,71} Cholangiocarcinoma is usually associated with focal biliary ductal dilation distal to the tumor and capsular retraction is another ancillary finding.⁷² Cholangiocarcinoma often enhances late on dynamic contrast or gadolinium-enhanced CT or MR images. An optional finding is peripheral rim enhancement during the earlier phases after contrast injection.^{73,74}

Other intrahepatic tumors which require transplantation are:⁷⁵

- a. Fibrolamellar carcinoma
- b. Epithelioid hemangioendothelioma
- c. Metastatic neuroendocrine tumors.

PRESENCE OF PORTOCAVAL SHUNTS AND TRANSJUGULAR PORTOSYSTEMIC SHUNT (TIPS)

Presence of surgical shunts or TIPS need some technical modifications during transplantation in a recipient. Presence of portocaval shunts makes the recipient surgery more difficult. Distal splenorenal shunts will not have much impact on transplantation surgery. However, creation of surgical shunts in obsolete after introduction of TIPS. Assessment of location of TIPS is an important aspect, prior to transplantation. Intrahepatic location of the TIPS is confirmed if the superior tip is located within the right hepatic vein and the inferior tip in the right portal vein. An intrahepatic located TIPS is removed during

recipient hepatectomy and does not interfere with the transplantation procedure.⁷⁶ TIPS migration into the suprahepatic IVC or right atrium or distally into the main portal vein may complicate hepatectomy. The inflammatory response around the vessel wall renders the affected vein unusable for primary anastomosis.⁷⁸

REFERENCES

1. Strong RW, Lynch SV, Ong TH, et al. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990;322:1505.
2. www. eltr. Org and OPTN/SRTR annual report 2003.
3. Soejima Y, Shimada M, et al. Use of steatotic graft in living donor liver transplantation. *Transpl* 2003;76:344-48.
4. Hwang S, Lee SG, et al. Lessons learnt from 1000 living donor liver transplantations in a single center: How to make living donations safe. *Liver transpl* 2006;12:920-27.
5. Myungsun: Decision-making process for living kidney donors. *J Nurs Scholar* 2003;35:61.
6. Olbrish ME, Benedict SM, Haller DL, et al. Psychosocial assessment of Living organ donors: Clinical and ethical consideration. *Prog Transplant* 2001;11:40.
7. Dixon DJ, Abbey SE. Religious altruism and the living organ donor. *Prog Transplant* 2003;13:169.
8. Surman O: The ethics of partial-liver donation. *N Engl J Med* 2002;346:1038.
9. SC. Chen, HT Hsu, SL Hwang and PH Lee. Attitude Toward Living Donor Liver Transplantation in Taiwan. *Transplantation Proceedings* 2006;38:2108-10.
10. Kabon B, et al. Obesity decreases the preoperative tissue oxygenation. *Anaesthesiol* 2004;100:274-80.
11. Appropriate BMI for Asian population and its implication for policy and intervention strategy. *Lancet* 2004;363:157-63.
12. Fabrega E, et al. Liver transplant with allograft from HBcAb positive donors: A new approach. *Liver transpl* 2003;9:916-20.
13. Umeda M, Marusawa H, et al. Beneficial effects of short term Lamivudine treatment for denovo hepatitis B reactivation after liver transplantation. *Am J of transpl* 2006;6:2680-85.
14. Sakamoto S, Uemoto S, Uryuhara K, et al. Graft size assessment and analysis of donors for living donor liver transplantation using right lobe. *Transplantation* 2001;71:1407-13.
15. Melada E, Maggi U, Rossi G, et al. Back-table arterial reconstruction in liver transplantation: Single-center experience. *Transplant Proc* 2005;37:2587.
16. Soin AS, Friend PJ, Rasmussen A, et al. Donor arterial variations in liver transplantation: Management and outcome of 527 consecutive grafts. *Br J Surg* 1996;637:641.
17. Zhao J, Lu S, Yan L, et al. Incidence and treatment of hepatic artery complications after orthotopic liver transplantation. *World J Gastroenterol* 2003;9:2853.
18. Gruttadauria S, Fogliene C, Doria C, et al. The hepatic artery in liver transplantation and surgery: Vascular anomalies in 701 cases. *Clin Transplant* 2001;15:359.
19. Iwasaki, et al. Noninvasive evaluation of graft steatosis in LDLT. *Transpl* 2004;78:1501-05.
20. Lee SW, Park SH, et al. Unenhanced CT for assessment of macovesicular hepatic steatosis in living live donors: Comparison of visual grading with live attenuation index. *Radiology* 2007;244(2):479-85.

21. Haveman JW, Gansevoort RT, et al. Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: A retrospective analysis. *Intensive care med* 2006;32:1199-205.
22. Burckhardt Ringe, Russell W Strong. The Dilemma of Living Liver Donor Death: to Report or not to Report? *Transplantation* 2008;85: 790-93.
23. Broelsch CE, Burdelski M, Rogiers X, et al. Living donor liver transplantation. *Hepatology* 1994;20:49S.
24. Beavers KL, Sandler RS, Fair JH, et al. The living donor experience: Donor health assessment and outcomes after living donor liver transplantation. *Liver Transpl* 2001;7:943.
25. Boillot O, Dawahra M, Mechet I, et al. Liver transplantation using a right liver lobe from a living donor. *Transpl Proc* 2002;34:773.
26. Ghobrial RM, Saab S, Lassman C, et al. Donor and recipient outcomes in right lobe adult living donor liver transplantation. *Liver Transpl* 2002;8:901.
27. Malago M, Testa G, Frilling A, et al. Right living donor liver transplantation: An option for adult patients. *Ann Surg* 2003;238:853.
28. Miller C, Florman S, Kim-Schluger L, et al. Fulminant and fatal gas gangrene of the stomach in a healthy live liver donor. *Liver Transpl* 2004;10:1315.
29. Broering DC, Wilms C, Bok P, et al. Evolution of donor morbidity in living related liver transplantation. *Ann Surg* 2004;240:1013.
30. Wiederkehr JC, Pereira JC, Ekerman M, et al. Results of 132 hepatectomies for living donor liver transplantation: Report of one death. *Transpl Proc* 2005;37:1079.
31. Ringe B, Petrucci RJ, Soriano HS, et al. Death of a living liver donor from illicit drugs. *Liver Transpl* 2007;13:1193.
32. Pomfret EA, Pomposelli JJ, Jenkins RL. Live donor liver transplantation *J Hepatol* 2001;34:613.
33. Brown RS, Russo MW, Lai M, et al. A survey of liver transplantation from living donors in the United States. *N Eng J Med* 2003; 348:818.
34. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transplant* 2003;9:1231.
35. Khalaf H, El-Meteini M, El-Sefi T, et al. Evolution of living donor liver transplantation in Egypt. *Saudi Med J* 2005;26:1394.
36. Middleton PF, Duffield M, Lynch SV, et al. Living donor liver transplantation-Adult donor outcomes: A systematic review. *Liver Transpl* 2006;12:24.
37. Bramstedt KA. Living liver donor mortality: Where do we stand? *Am J Gastroenterol* 2006;101:755.
38. Barr ML, Belghiti J, Villamil FG, et al. A report of the Vancouver Forum on the care of the live organ donor: Lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation* 2006; 81:1373.
39. Trotter JF, Adam R, Lo CM, et al. Documented deaths of hepatic lobe donors for living donor liver transplantation. *Liver Transpl* 2006;12:1485.
40. Akabayashi A, Slingsby BT, Fujita M. The first donor death after livingrelated liver transplantation in Japan. *Transplantation* 2004;77:634.
41. Chan SC, Fan ST. Live liver donor mortality. *Liver Transpl* 2006; 12:1437.
42. Polido W, Hoe LK, Siang NK, et al. Acute myocardial infarction after live donor liver surgery. *Liver Transpl* 2007;13:154.
43. Lo CM. Complications and long-term outcome of living liver donors: A survey of 1,508 cases in five Asian countries. *Transplantation* 2003;75:S12.
44. Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362:687.
45. Conclusions of the IHPBA 2008 conference.
46. Beavers KL, Sandler RS, Shrestha R. Donor morbidity associated with right lobectomy for living donor liver transplantation to adult recipients: a systematic review. *Liver Transpl* 2002;8:110-17.
47. Clavien PA, Camargo CA, Croxford R, et al. Definition and classification of negative outcomes in solid organ transplantation. Application in liver transplantation. *Ann Surg* 1994;220:109-20.
48. Shah SA, Grant DR, Greig PD, et al. Analysis and outcomes of right lobe hepatectomy in 101 consecutive living donors. *Am J Transplant* 2005;5:2764-9.
49. Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362:687-90.
50. Fukunishi I, Makuuchi M, Hasegawa A, et al. Psychiatric problems in living-related transplantation (III): Pretransplant psychological assessment in living-related transplantation. *Transplant Proc.* 2002;34(7):2628-29.
51. Walter M, Bronner E, Steinmueller T, Klapp BF, Danzer G. Psychosocial data of potential living donors before living donor liver transplantation. *Clin Transplant* 2002;16:55-59.
52. Umeshita K, Fujiwara K, Makuuchi M, et al. Japanese Liver Transplantation Society. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362(9385):687-90.
53. Orii T, Ohkohchi N, Satomi S. Rehospitalization after pediatric living-donor liver transplantation. *Transplantation* 2004;77(6):880-85.
54. JF Trotter, R Adam, C M Lo, et al. Documented Deaths of Hepatic Lobe Donors for Living Donor Liver Transplantation. *Liver transplantation* 2006;12:1485-88.
55. Trotter JF, Hill-Callahan MM, Gillespie BW, et al. A2ALL Study Group. Severe psychiatric problems in right hepatic lobe donors for living donor liver transplantation. *Transplantation* 2007;83(11): 1506-08.
56. The Vancouver Forum, *Transplantation* 2006;81(10):1375-77.
57. Ghobrial RM, Freise CE, Trotter JF, et al. A2ALL Study Group. Donor morbidity after living donation for liver transplantation. *Gastroenterology* 2008;135(2):468-76.
58. Michels N. *Blood Supply and Anatomy of the Upper Abdominal Organs with a Descriptive Atlas*. Philadelphia, PA, JB Lippincott, 1955.
59. Erbay N, Raptopoulos V, Pomfret EA, et al. Living donor liver transplantation in adults: vascular variants important in surgical planning for donors and recipients. *AJR Am J Roentgenol* 2003; 181(1):109-14.
60. Kobori L, vander Kolk MJ, de Jong KP, et al. Splenic artery aneurysms in liver transplant patients. *Liver Transplant Group. J Hepatol* 1997;27(5):890-93.
61. Lerut JP, Mazza D, van Leeuw V, et al. Dult liver transplantation and abnormalities of splanchnic veins: experience in 53 patients. *Transplant Int* 1997;10(2):125-32.
62. Freedman BJ, Lowe SC, Saouaf R: MR imaging in hepatic transplantation. *Magn Reson Imaging Clin N Am* 2001; 9(4):821-39.
63. Teefey SA, Hildeboldt CC, Dehdashti F, et al. Detection of primary hepatic malignancy in liver transplant candidates:

- prospective comparison of CT, MR imaging, US, and PET. *Radiology* 2003; 226(2):533-42.
64. Yamashita Y, Mitsuzaki K, Yi T, et al. Small hepatocellular carcinoma in patients with chronic liver damage: prospective comparison of detection with dynamic MR imaging and helical CT of the whole liver. *Radiology* 1996;200(1):79-84.
65. Kwak HS, Lee JM, Kim CS. Preoperative detection of hepatocellular carcinoma: comparison of combined contrast-enhanced MR imaging and combined CT during arterial portography and CT hepatic arteriography. *Eur Radiol* 2004;14(3):447-57.
66. Krinsky GA, Lee VS, Theise ND, et al. Transplantation for hepatocellular carcinoma and cirrhosis: Sensitivity of magnetic resonance imaging. *Liver Transplant* 2002;8(12):1156-64.
67. Bennett GL, Krinsky GA, Abitbol RJ, et al. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: Correlation of pretransplantation sonography and liver explant pathology in 200 patients. *AJR Am J Roentgenol* 2002;179(1):75-80.
68. del Olmo JA, Esteban JM, Maldonado L, et al. Clinical significance of abdominal lymphadenopathy in chronic liver disease. *Ultrasound Med Biol* 2002;28(3):297-301.
69. Katyal S, Oliver JH 3rd, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000;216(3):698-703.
70. Shimoda M, Farmer DG, Colquhoun SD, et al. Liver transplantation for cholangiocellular carcinoma: Analysis of a single-center experience and review of the literature. *Liver Transplant* 2001;7(12):1023-33.
71. Heimbach JK, Haddock MG, Alberts SR, et al. Transplantation for hilar cholangiocarcinoma. *Liver Transplant* 2004;10(suppl 2):S65-S68.
72. Choi BI, Lee JM, Han JK. Imaging of intrahepatic and hilar cholangiocarcinoma. *Abdom Imaging* 2004;29(5):548-57.
73. Lee WJ, Lim HK, Jang KM, et al. Radiologic spectrum of cholangiocarcinoma: Emphasis on unusual manifestations and differential diagnoses. *Radiographics* 2001; 21:S97-S116.
74. Han JK, Choi BI, Kim AY, et al. Cholangiocarcinoma: Pictorial essay of CT and cholangiographic findings. *Radiographics* 2002; 22(1):173-87.
75. Pichlmayr R, Weimann A, Oldhafer KJ, et al. Appraisal of transplantation for malignant tumours of the liver with special reference to early stage hepatocellular carcinoma. *Eur J Surg Oncol* 1998; 24(1):60-67.
76. Zhou GW, Cai WY, Li HW, et al. Transjugular intrahepatic portosystemic shunt for liver transplantation. *Hepatobiliary Pancreat Dis Int* 2002;1(2):179-82.
77. Gisela C, Mueller MD, Joseph J, et al. Hepatic transplantation: Pretransplant evaluation of donors and recipients. *Seminars in Roentgenology* 2006:45-60.
78. Mazziotti A, Morelli MC, Grazi GL, et al. Beware of TIPS in liver transplant candidates. *Transjugular Intrahepatic Portosystemic Shunt. Hepatogastroenterology* 1996; 43(12):1606-10.

Graft Volume Estimation and Donor with Fatty Liver

INTRODUCTION

In living donor liver transplantation (LDLT), the size of the graft is a major concern for both donor and recipient safety. Small-for-size graft (<0.6-.8%) leads to graft dysfunction and other life-threatening complications.¹ Conversely, large-for-size grafts (>5%) may be associated with anatomical, immunological disadvantages and graft necrosis; however, their negative impact is less pronounced.¹⁷ In recipient, an adequate graft volume is necessary to satisfy the metabolic demands of the recipient.² The residual liver volume in the donor must be sufficient for postoperative liver regeneration and metabolic needs.³ During graft harvesting of LDLT, it should be determined on which side of the donor liver, the middle hepatic vein should be preserved to avoid congestion of parenchyma. The congestive area in the right liver graft does not function well immediately after transplantation.⁴ Therefore, an accurate preoperative estimation of the volume should be mandatory for LDLT.^{5,6} Volume estimation is usually obtained by hand-tracing the Dynamic CT Scan images of each slice and calculating the liver volume by integrating those planar dimensions⁷ and the graft weight is measured so as to meet the GRWR. This technique is gradually replaced by the region-growing method using three-dimensional (3-D) CT, mostly used in Japan.^{8,20}

3-D CT IMAGING AND VOLUMETRY^{8,20}

3-D image reconstruction and volume is measured using the region-growing method with 3-D CT software, where the liver parenchyma, PV and HV are extracted after setting a seeding point, the region was extended to neighboring voxels if the CT density of the voxel is within a specified range. Then images of parenchyma, PV and HV are reconstructed and demonstrated from any angle by the software. Volumetric measurement is performed

using an autosegmentation algorithm, which automatically delineates the liver segments according to the 3-D structure of vessels.

It can be used to calculate the territory of the individual portal vein tributaries as well as of the hepatic vein. Each volume of the left lobe, caudate lobe, right paramedian, and lateral sectors can be measured. The volumes of liver parenchyma drained by the right hepatic vein, middle hepatic vein, left hepatic vein, and inferior right hepatic vein can also be measured. To estimate the hepatic venous congestion in the right hepatic graft that emerges in the dividing tributaries of the middle hepatic vein, the volume of the territories of V5 and V8 tributaries are measured.

GRAFT VOLUME ESTIMATION

Graft Volume estimation is as follows²²: The minimum graft volume required for the recipient was 40% of the recipient's standard liver volume (SLV). The residual liver volume in the donor had to be greater than 30-35% of the total liver volume.^{11,12} Different formulas are available for estimation of SLV.

Urata et al¹³ designed formula for SLV for Japanese patients (widely accepted):

$$SLV = 706.2 \times \text{body surface area (m}^2\text{)} + 2.4$$

Makuuchi et al²¹ designed another formula for Japanese patients for calculating:

$$SLV (\text{cm}^3) = -404.8 + 961.3 \times BSA (\text{m}^2)$$

In **Western population** SLV is calculated as follows:

$$SLV = -794.41 + 1267.28 \times BSA \text{ in square meter}$$

$$SLV = 191.80 + 18.51 \times \text{weight in kg}$$

Heinemann et al³⁷ published the formula for estimation of standard liver volume (SLV) for Caucasian population:

$$SLV (\text{mL}) = 1072.8 \times BSA (\text{m}^2) - 345.7 \text{ was } 1463 \text{ mL for the recipient}$$

Body surface area can be calculated by using either Dubois formula⁹ or Mosteller's formula:¹⁰

Dubois formula = BSA (m²): BW (kg)^{0.425} × BH (cm)^{0.725} × 0.007184

Mosteller's formula = BSA: $\sqrt{(\text{Body Weight} \times \text{Body Height})/3600}$

Other formulas which are used to estimate liver volume (LV) using two- or three-dimensional computed tomography volumetry (CTV) are:

DeLand formula³⁸: LV = 1020 × BSA – 220

Noda formula³⁹: LV = 50.12 × (Body weight)^{0.78}

Vauthey formula⁴⁰: LV = 18.51 × BW + 191.8

Yoshizumi formula⁴³: LV = 772 × BSA

DeLand and North³⁸ calculate standard liver weight from body surface area (BSA) as follows:

Liver weight (kg) = 1.02 × BSA – 0.22

Recently Kayashima et al⁴² reported the **age adjusted formula** for assessing graft volume in LDLT and reported that the mean error ratio for the age-adjusted formula (9.6%) was significantly lower than that from 3D-CT (14.0%).

Age-adjusted GV = 70.767 + (0.703 × GV estimated with 3D-CT volumetry) + (1.298 × donor age).

SPLIT LIVER

In split liver transplantation and LDLT, a GV/SV ratio of $\geq 40\%$ ^{14,15} or a graft-to-recipient weight ratio (GRWR) of $\geq 0.8\%$ ¹⁶ is recommended to achieve good graft and patient survival rates. In split liver for 2 adults, problems encountered to achieve adequate GRWR of 0.8%. In such instances caudate lobe is included in the left lobe along with the IVC for a piggy back anastomosis in the recipient and right lobe is harvested in the same way as classical right lobe graft. In our center, we accept live donors with GRWR $\geq 0.8\%$ and remnant liver volume in the donor should be at least 35% with minimal or no fatty change in the donor.

FATTY CHANGE—DONOR SELECTION

Presence of fatty change in a live donor is a major concern, affecting the post-transplantation graft dysfunction. Severe steatosis of the liver graft places the recipient at risk for PNF in DDLT.¹⁸ Marcos et al proposed that every 1% of hepatic steatosis should be assumed to decrease the functional liver graft mass by 1%.¹⁹ Most authors regard macrovesicular steatosis to be more clinically relevant than microvesicular changes in liver grafts. Microvesicular steatosis of any degree will not affect graft survival following liver transplantation.^{36,37} Moderate to

severe steatosis is found in approximately 20% of potential living donors.^{29,30} In cadaveric donors the prevalence of hepatic steatosis ranges from 13 to 28%.^{23,24} Donor obesity is associated with an increased severity of liver fatty infiltration.²⁵

The degree of steatosis for selection of donors is classified as:²⁵

Live donor liver transplantation

Degree of fatty change	Percentage
Mild	0-19% steatosis
Moderate	20-35% steatosis
Severe	>35% steatosis

Pathological classification of fatty change in deceased donors:

Whole liver (Pathological classification)

Degree of fatty change	Percentage
Normal pathology	No fatty change
Mild fatty change	10-30%
Moderate	30-60%
Severe steatosis	>60%.

PREVALENCE OF HEPATIC STEATOSIS

Prevalence of hepatic steatosis with increasing age³¹

- 1% in <20 years of age
- 18% in 20 to 40 years
- 39% in >60 years.

Yoo et al demonstrated unaltered survival rates following liver transplantation of grafts with fatty change.²⁵ Even in living-donor liver transplantation, the use of organs with moderate steatosis (20-35%) is associated with similar 1 year organ survival rates as compared to nonsteatotic donors.²⁶ The prognosis of macrovesicular steatosis appears to be impaired if further risk factors such as prolonged ischemic time (>10 hours), high donor age (>65 years), HCV positive recipients, are present.²⁷ Donors with 30-60% steatosis should be considered for transplantation, only in the absence of other risk factors.²⁸ Spanish National Transplant Organization report from 2004, 38% of cadaveric donors were older than 60 years of age.³² There was a clinical consensus to exclude liver grafts with severe steatosis but to include those with mild steatosis. At present livers with moderate steatosis can be used except in the sickest recipients.³⁴ Liver donors with moderate steatosis can be used safely, without imposing increased death and disease on the recipients, except in patients with a MELD score >18.^{33,35} Grafts with moderate steatosis should not be rejected on the grounds of the degree of fatty infiltration

alone, in the absence of other contraindications they can be transplanted safely with good results for short- and long-term organ survival. However, impaired primary postoperative liver function (elevation in AST, ALT and prothrombin time) due to steatosis is to be accepted.⁴¹

PREDICTION OF EARLY GRAFT FUNCTION IN LDLT⁴⁴

A new formula for predicting early graft function and prognosis using technetium-99m galactosyl-human serum albumin (Tc-GSA) liver scintigraphy, was recently designed by Yoshizumi et al. The new formula is based on the ratio of the hepatic uptake ratio of Tc-GSA to the clearance index of Tc-GSA (LHL/HH) is as follows:

LHL/HH (predictive score) = $0.011 \times \text{graft weight (\%)} - 0.016 \times \text{donor age} - 0.008 \times \text{MELD Score} - 0.15 \times \text{shunt (if present)} + 1.757$ ($r^2 = 0.497$, $P < 0.01$).

The 6-month survival probability is improved in the group with a predictive score ≥ 1.3 . LHL/HH score is predicted by the graft size, donor age, and preoperative status of the patient. The score is found to be distinctly useful as an indicator for predicting early graft function. This is the first report of the prediction of early graft function prior to surgery for adult LDLT.

REFERENCES

1. Y Sugawara, M Makuuchi, et al. Small-for-size grafts in living-related liver transplantation, *J Am Coll Surg* 2001;192:510.
2. CM Lo, ST Fan, CL Liu, et al. Minimum graft size for successful living donor liver transplantation, *Transplantation* 1999; 68:1112.
3. ST Fan, CM Lo, CL Liu, et al. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch Surg* 2000;135:336.
4. K Sano, M Makuuchi, et al. Evaluation of hepatic venous congestion: proposed indication criteria for hepatic vein reconstruction. *Ann Surg* 2002;236:241.
5. MB Jin, Y Onodera, et al. Three-dimensional volumetric analysis for reconstruction of middle hepatic vein tributaries in living donor liver transplantation. *J Am Coll Surg* 2005;200:468.
6. S Saito, J Yamanaka, et al. A novel 3D hepatectomy simulation based on liver circulation: Application to liver resection and transplantation, *Hepatology* 2005;41:1297.
7. S Kawasaki, M Makuuchi, et al. Preoperative measurement of segmental liver volume of donors for living liver transplantation, *Hepatology* 1993;18:115.
8. S Hiroshige, M Shimada, et al. Accurate preoperative estimation of liver-graft volumetry using three-dimensional computed tomography, *Transplantation* 2003;75:1561.
9. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Nutrition* 1989; 5:303-11.
10. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.
11. CM Lo, ST Fan, CL Liu, et al. Minimum graft size for successful living donor liver transplantation, *Transplantation* 1999;68: 1112.
12. ST Fan CM Lo, CL Liu, et al. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch Surg* 2000;135:336.
13. Urata S Kawasaki, et al. Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995;21:1317-21.
14. Lo CM, Fan ST, et al. Minimum graft size for successful living donor liver transplantation. *Transplantation* 1999;68:1112-16.
15. Soejima Y, Shimada M, et al. Outcome analysis in adult-to-adult living donor liver transplantation using the left lobe. *Liver Transpl* 2003;9:581-86.
16. Kiuchi T, Kasahara M, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999;67:321-27.
17. T Kiuchi, M Kasahara, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors, *Transplantation* 1999;67.
18. Urena MA, Ruiz-Delgado FC, et al. Assessing risk of the use of livers with macro- and microsteatosis in a liver transplant program. *Transplant. Proc* 1998;30:3288-91.
19. Marcos A, Ham JM, et al. Single-center analysis of the first 40 adult-to-adult living donor liver transplants using the right lobe. *Liver Transpl* 2000;6:296-301.
20. M Zeytunlu, G Icoz, et al. Donor safety in adult-to-adult living donor liver transplantation, *Transplant Proc* 2003;35:1430.
21. Takuya H, Yasuhiko S, Makuuchi M, et al. Estimation of standard liver volume in Japanese living liver donors. *J of Gastroenterol and Hepatol* 2006;21:1710-13.
22. Satou, Y Sugawara, M Makuuchi, et al. Three-dimensional computed tomography for planning donor hepatectomy. *Transplantation Proceedings* 2007;39(1):145-49.
23. RS Markin, JL Wisecarver, et al. Radio, Frozen section evaluation of donor livers before transplantation, *Transplantation* 1993;56:1403.
24. WA Marsman, RH Wiesner, et al. Use of fatty donor liver is associated with diminished early patient and graft survival, *Transplantation* 1996;62:1246.
25. HY Yoo, E Molmenti. The effect of donor body mass index on primary graft nonfunction, retransplantation rate, and early graft and patient survival after liver transplantation. *Liver Transplant* 2003;9:72-78.
26. Y Soejima, M Shimada, et al. Use of steatotic graft in living-donor liver transplantation, *Transplantation* 2003;76:344-48.
27. M Salizzoni, A Franchello, et al. Marginal grafts: finding the correct treatment for fatty livers, *Transplant Int* 2003;16:486-93.
28. MA Urena, GE Moreno, et al. An approach to the rational use of steatotic donor livers in liver transplantation, *Hepatogastroenterology* 1999;46:1164-73.
29. HP Monsour, RP Wood, et al. Utility of preoperative liver biopsy in live-related donor patients for liver transplantation. *Transplant Proc* 1994;26:138.
30. ME Rinella, E Alonso, et al. Body mass index as a predictor of hepatic steatosis in living liver donors, *Liver Transpl* 2001;7:409.
31. M Hilden, P Christoffersen, et al. Liver histology in a "normal" population—examinations of 503 consecutive fatal traffic casualties, *Scand J Gastroenterol* 1977;12:593.

32. Available from www.ont.es. Accessed September 15, 2006.
33. J Briceño, J Padillo, et al. Assignment of steatotic livers by the Mayo model for end-stage liver disease, *Transpl Int* 2005;18:577.
34. JA Perez-Daga, J Santoyo, et al. Influence of degree of hepatic steatosis on graft function and postoperative complications of liver transplantation. *Transplant Proceed* 2006;38(8):2468-70.
35. KF Yoong, BK Gunson, et al. Impact of donor liver microvesicular steatosis on the outcome of liver retransplantation. *Transplant Proc* 1999;31:550-51.
36. F Zamboni, A Franchello, et al. Effect of macrovesicular steatosis and other donor and recipient characteristics on the outcome of liver transplantation, *Clin Transplant* 2001;15: 53-57.
37. Heinemann A, Wischhusen F, Puschel K, et al. Standard liver volume in the Caucasian population. *Liver Transpl Surg* 1999;5:366-68.
38. DeLand FH, North WA. Relationship between liver size and body size. *Radiology* 1968;91:1195.
39. Noda T, Todani T, Watanabe Y, et al. Liver volume in children measured by computed tomography. *Pediatr Radiol* 1997;27:250.
40. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. *Liver Transpl* 2002;8:233.
41. Martin K, Angele MD, et al. Effect of graft steatosis on liver function and organ survival after liver transplantation. *Am J of Surg* 2008;195(2):214-20.
42. H Kayashima, A Taketomi, Y Yonemura, et al. Accuracy of an age-adjusted formula in assessing the graft volume in living donor liver transplantation. *Liver Transplantation* 2008;14:1366-71.
43. T Yoshizumi, A Taketomi, H Kayashima, et al. Estimation of Standard Liver Volume for Japanese Adults. *Transplantation Proceedings* 2008;40:1456-60.
44. T Yoshizumi, A Taketomi, H Uchiyama, et al. Graft size, donor age, and Patient status are the indicators of early graft function after living donor liver transplantation. *Liver Transplantation* 2008;14:1007-13.

Liver Donation after Brain Death and Cardiac Death

(A) HEART-BEATING DONORS/DONATION AFTER BRAIN DEATH

Synonym: Heart-beating donors

INTRODUCTION

According to the Uniform Declaration of Death Act (UDDA) 1981, death may be declared as a result of irreversible cessation of circulatory and respiratory function (cardiopulmonary) or irreversible cessation of all functions of the entire brain, including the brainstem (brain death).

SOURCES OF DONOR ORGAN

- Heart-beating donors following diagnosis of brain death
- Non-heart-beating donors following cardio-respiratory arrest¹
- Living related organ donors

Introduction of direct brainstem testing in the 1970s' changed the emphasis to utilizing organs from so-called donation after brain death (DBD) or heart-beating donors. Initially heart-beating donors were used for organ donation. Later the concept of live related donor and non-heart-beating donor started due to:

- Shortage of donor organs from brain dead patients
- Increased demand of the long waiting list
- Improvements in diagnosis and management of severe brain injuries
- Reduction in numbers of severe head injuries.

PATHOPHYSIOLOGICAL CHANGES AFTER BRAINSTEM DEATH

Pathophysiological changes after brainstem death jeopardize the function of potentially transplantable

organs. The clinical course of a brain dead patient who was supported by ventilator is short with asystolic cardiac arrest usually occurs within 72 hours. But cardiac and other body functions can be maintained for many days in fully supported brain dead patients. Prolonged cold ischemic time in DBD donor grafts is an important cause for poor outcomes as compared to live donors. So avoiding long CIT is important in DBD donors.

HEMODYNAMIC CHANGES

Hemodynamic changes after brainstem death may cause the following:

- Endothelial shear stress
- Vasoconstriction
- Ischemia
- Endothelial activation
- Inflammatory response.

CARDIOVASCULAR CHANGES

There are two different phases, characterized by sympathetic over activity and under activity.

Hyperdynamic Phase

This phase is due to sympathetic over activity and is caused by a transient catecholamine (adrenaline and noradrenaline) surge. Catecholamine storm adversely affects the delicate balance between myocardial oxygen supply and demand and is manifested as increase in heart rate, blood pressure, cardiac output and systemic vascular resistance.

Cardiovascular Collapse Phase

Loss of sympathetic tone results in hypotension, vasodilatation and myocardial depression. Hypovolemia and hypotension also occurs due to secondary to diabetes insipidus in unsupported patients with brainstem death. Subendocardial myocardial ischemia and ventricular dysfunction are common even in previously healthy hearts.

Diabetes insipidus: It occurs in approximately 65% of organ donors due to reduced production of anti-diuretic hormone and is manifested as

- Diuresis
- Hypovolemia
- Plasma hyperosmolality
- Hypernatremia.

Hyperglycemia: Reduced insulin secretion leads to development of hyperglycemia which may be aggravated by the administration of large volumes of glucose containing fluids, if used to treat hypernatremia and increased levels of catecholamines. If hyperglycemia is not corrected, it leads to increased extracellular osmolality, metabolic acidosis, osmotic diuresis and cardiovascular instability.

T3 and T4 level: Anterior pituitary failure is less common and it causes reduction in the circulating levels of T3 and T4 leading to cardiovascular deterioration.

Pulmonary dysfunction: It is common in the organ donor and may be due to the development of pneumonia, aspiration of gastric contents, neurogenic pulmonary edema or pulmonary trauma. Rapid hemodynamic changes may disrupt capillary integrity and cause severe lung injury.

Hypothermia is due to hypothalamic failure after brainstem death leading to impaired temperature regulation. Heat production is reduced due to fall in metabolic rate and loss of muscular activity associated with an increase in heat loss due to peripheral vasodilatation.

Hepatic viability is impaired after brain death. The exact mechanism of reduced graft quality is unknown. Histological liver shows central venous congestion and leukocyte infiltration. Hepatocellular enzymes may be elevated and bile production is reduced.

Coagulopathy: PT is prolonged due to release of tissue thromboplastin by ischemic or necrotic brain. DIC is also frequently seen.

MONITORING OF BRAIN DEAD DONOR

After the brain death declaration and once willingness is obtained from the family about organ donation, there

is a change in the emphasis of care. The care is diverted to optimizing transplantable organ function instead of preserving brain function. Sufficient time must be allowed for confirmation of brainstem death but unnecessary delays should be avoided to minimise the risk of deterioration of quality of donor organs.

COMMON PROBLEMS IN ORGAN DONORS

- Myocardial dysfunction
- Reversible lung injury
- Infections
- Hypernatremia
- Deranged hepatocellular enzymes
- Elevation of creatinine

CARE OF THE DONOR**GENERAL TREATMENT**

- Aggressive chest physiotherapy
- Broad spectrum antibiotics
- Correction of electrolyte imbalance
- Arterial line, central line and pulmonary artery (swan ganz) catheters should be inserted.
- Hypovolemia should be corrected to maintenance of adequate tissue perfusion and preservation of organ viability. Avoid excessive volume replacement particularly in potential lung and heart donors.
- Echocardiography is useful to exclude major structural abnormalities of the heart and to measure left ventricular ejection fraction. Some transplant units will only request insertion of a pulmonary artery catheter is useful in patients with left ventricular ejection fraction below 45%. Transesophageal echocardiography is also useful. Assessment of right ventricular size and function is important and frequently challenging.
- Doppler US examination is performed on the liver to see the fatty change, rough estimation of vascular anatomy and flow pattern.
- CT scan: Few centers perform abdominal CT scan for detailed evaluation of liver in the donor as the donor is in critical condition to shift for a CT scan. In most of the centers CT scan is not a routine practice.

SPECIFIC TREATMENT STRATEGIES IN POTENTIAL HEART-BEATING DONOR²**Hematology**

- Hemoglobin should be maintained > 9 gm%
- Coagulation, if any is corrected by FFP and platelets.

Hemodynamic Goals for Potential Multi-visceral Adult Donor

- Heart Rate 60-100 beats/min
- Sinus rhythm is desirable
- Mean arterial pressure 60-80 mm Hg
- Central venous pressure (CVP) ~ 4-8 mm Hg
- Pulmonary artery occlusion pressure ~ 10-15 mm Hg
- Cardiac Index > 2.1 l/min/m²

Cardiovascular Care

- Maintain optimal cardiac output, normal preload and after load
- Use of high dose β adrenoreceptor agonists, other inotropes and vasopressors
- Selection of inotropic agent depends on the data of pulmonary artery catheterization:
 - Vasopressin is less likely to cause metabolic acidosis or pulmonary hypertension and is preferred over noradrenaline for the cardiovascular collapse.
 - High dose adrenaline may result in vasoconstriction in donor organs.
 - Dobutamine may lead to vasodilatation, hypotension and tachycardia.

Pulmonary Care

- Strict asepsis should be continued during physiotherapy and tracheal toilet to avoid infection
- FiO₂ is usually kept at ≤ 0.4 to minimise the risk of oxygen toxicity
- PEEP < 5 cm H₂O will prevent alveolar collapse
- Maintain normocapnia (PaCO₂ ~ 5.0-5.5 kPa)
- Ventilate with lowest FiO₂ to maintain PaO₂ of >10.0 kPa
- Avoid high inspiratory pressures.

Renal

Low dose dopamine is used to prevent hypotension associated acute tubular necrosis and renal failure.

Endocrine

Hormone replacement therapy:

- Most transplant units practice empirical use of T3 infusions in all potential organ donors
- High dose methylprednisolone, 15 mg/kg is given to decrease the inflammatory response

Infection

- Endotracheal secretions, urine and blood cultures are sent daily
- Antibiotics used to control infection.

Hypothermia

Hypothermia is avoided by using:

- Warmed intravenous fluids and warming blankets
- Heated and humidified inspired gases
- Increased ambient temperature

TREATMENT OF COMMON PROBLEMS IN POTENTIAL HEART-BEATING DONORS²*Diabetes Insipidus*

In this condition maintain

- Na⁺ = 155 mmol/L with 5% dextrose
- Urine output about 1-2 ml/kg/h by using vasopressin 1 U bolus and 0.5-4.0 U/h infusion.

Higher dose of vasopressin is usually avoided due to coronary, renal or splanchnic vasoconstriction. Intermittent desmopressin (DDAVP), which is highly selective for the V2 receptor found in the renal collecting ducts, may be used if vasopressin fails to control diuresis.

Hyperglycemia

Hyperglycemia is common in patients with brain death. Strict glycemic control (4.4-6.1 mmol/L) improves survival in critically ill patients by reducing infective complications. It is controlled by insulin infusion to maintain plasma glucose 4-9 mmol/L and maintain K⁺ > 4.0 mmol/L

Donor Hyponatremia

Donor hyponatremia >155-mmol/L is associated with hepatic dysfunction after transplantation and should be corrected.

Hypothyroidism

Tri-iodothyronine (T3) 4 μ g bolus then infusion at 3 μ g/hour.

HEPATIC GRAFT PROTECTION

Hepatic graft ischemia leads to rapid breakdown of ATP and alters mechanisms for handling the breakdown products of ATP causing free radical damage on reperfusion. Aim of cold storage is to minimise ATP depletion as metabolism decreases by 7% for every degree centigrade fall in temperature. Cooling slows down but doesn't entirely eliminate cell dysfunction. Prolonged cold ischemia is a risk factor for successful graft outcome. In hepatic grafts, sinusoidal cells may show signs of degeneration after just 4 hours of cold storage. Incidence of PNF/delayed graft function is increased after 12 hour of CIT and >1 hour of WIT.

REPERFUSION INJURY

The sinusoidal lining cells of the liver are particularly vulnerable to the effects preservation/reperfusion injury. Strategies of potential value in attempting to reduce ischemia and reperfusion injury include anti-inflammatory pre-treatment of donors, ischemic preconditioning and use of various flush solutions before reperfusion. Continuous liver perfusion has a greater potential importance in controlled non-heart-beating donations. Reperfusion and resuscitation of liver ATP stores can be undertaken before cold storage.

DONOR NUTRITION

Animal studies have shown significant improvements of hepatic lining cell viability and reduced reperfusion injuries with enteral and parenteral nutrition respectively. Most of the transplant centers continue enteral nutrition as tolerated until 4 hours prior to multi-organ donor operation.

POLICY FOR DECLARATION OF BRAIN DEATH (TAIWAN)

In Taiwan, the declaration of brain death is made of by at least 2 qualified medical professionals including the one anesthesiologist and one neurophysician or neurosurgeon. None of these professionals belong to the organ

transplantation team. The evaluation for declaration of brain death is done twice at an interval of 4 hours.

EARLY DETECTION OF BRAIN DEATH³

Bispectral index (BIS) is a tool for clinical evaluation of the moment of brain death (BD). Continuous BIS monitoring is performed using an XP BIS monitor and BIS Quatro-sensor evaluating the BIS and the suppression ratio (SR). Patients in ICU will have a sonographic monitoring with transcranial Doppler ultrasound performed every 8 to 12 hours until the diagnosis of BD. Gradual decrease in BIS and increase in SR occurs when the patients underwent clinical progression to BD. BIS monitoring is a continuous, simple method that is easy to interpret. It can help in clinical evolution and the decision of the BD moment.

REFERENCES

1. J DuBois, Non-heart-beating organ donation a defense of the required determination of death, *J Law Med Ethics* 1999;27:126-36.
2. Jonathan Mackay. Surgical and donor considerations Optimising the graft. LICAGE lecture summary 2005.
3. M Misis, J Gener Raxach, H Perez Molto, et al. Bispectral index monitoring for early detection of brain death. *Transplantation Proceedings* 2008;40:1279-81.

(B) DONATION AFTER CARDIAC DEATH (DCD)

SYNONYMS

- Donation after Cardiac Determination of Death (DCDD)
- Non-heart-beating donors (NHBD) (more widely used terminology).

The rapidly growing waiting lists with increased patient mortality while a waiting donor organ has prompted interest in the utilization of organs from non-heart-beating donors (NHBD). Prior to the introduction of brainstem death into law in the mid to late 1970s, all organ transplants from cadaveric donors came from NHBD. Before the advent of brain death guidelines, livers from donors whose hearts have stopped were the only source of allografts. The latest terminology is donation after cardiac death (DCD). Use of these livers is very selective and consideration was taken into the donor age, hemodynamic stability before withdrawal of support, total warm ischemic time and appearance of the liver intraoperatively. Warm ischemic time in NHBD is defined as the time between the cardiac arrest and cannulation and should be < 30 minutes.

Ideal non-heart-beating donor liver

- Age 15-55 years
- Time of cardiac arrest is known
- CPR is established in < 15 mins of cardiac arrest
- Cause of death known or can be diagnosed easily (exclude violence)
- Healthy individual with no risk factors for AIDS
- No penetrating/bleeding injuries in the abdomen
- Transferred to hospital with cardiac message and mechanical ventilation
- Time between the assistance and transfer is < 90 min
- Liver should be harvested by super rapid technique
- Cold ischemia time should be kept as minimum as possible
- Warm ischemic time < 120 min
- Controlled withdrawal of life support
- Cold *in situ* perfusion occurring within 30 minutes of extubation
- Possible to find next of kin in 4 hours
- Other general criteria of organ donation also applicable

After the brain death guidelines there was a sudden increase in the organs available for donation in USA and Europe. NHBD continued to be a possible source for skin,

bone, corneas, and heart valves, but less likely to be considered for major organ transplant. In the mid-1990s, new attention focused on NHBD for two main reasons.^{1,2} First, organ transplantation had become an accepted mode of therapy for end-stage organ failure, increasing the need for organs. It was estimated at that time that by using NHBD the number of cadaveric organ donors could be increased by 20 to 25%.² The demand for livers, however, far surpasses the supply. In the United States in 2005, there were approximately 7000 donors for an average of 17 000 patients needing livers, and over 1000 patients died on the liver transplant waiting list.³ The situation in Europe is similar.⁴ NHBDs are a good source of livers with reasonable early results. Livers arising from unexpected DCD have been traditionally considered marginal, and there is little worldwide experience in their use. By using strict criteria and systematically maintaining them with normothermic extracorporeal membrane oxygenation prior to recovery, they offer the possibility of obtaining good quality grafts for transplant.⁷ To meet the organ shortage, use of marginal donors is currently of great interest. Donors after cardiac death (DCD) undergo a period of cardiac arrest prior to organ recovery.

DCD have traditionally been subdivided according to the **Maastricht criteria** (1995; amended 2003).¹⁰

Maastricht classification of NHBD 2003

Category	Criteria
I	Brought in dead
II	Unsuccessful resuscitation
III	Awaiting cardiac arrest
IV	Cardiac arrest after brainstem death
V	Cardiac arrest in a hospital inpatient

Categories I, II and IV are termed uncontrolled and categories III and V are controlled. Most of the work that has been reported to date, however, involves controlled DCD^{15,16} and only few series of patients transplanted with uncontrolled DCD livers have been published.

Category I: Tissues can be taken from the donors

Category II: These donors are the patients who have had a witnessed cardiac arrest outside hospital, have cardiopulmonary resuscitation by CPR-trained providers commenced within 10 minutes but who cannot be successfully resuscitated.

Category III: These donors are patients in intensive care units with non-survivable injuries who have treatment withdrawn; where such patients wished in life to be organ donors, the transplant team can attend at the time of treatment withdrawal and retrieve organs after cardiac arrest has occurred.

Category IV: Brain death is declared prior to an unanticipated cardiac arrest.

ETHICAL ISSUES

In category II uncontrolled donors, the donor may die and the transplant team arrive before the donor's next-of-kin can be contacted. It is controversial whether cannulation and perfusion can be started in these circumstances. On one hand, it can be considered a violation of the potential donor's autonomy to cannulate before their in-life wishes are known. On the other hand, delay in cannulation may mean that a patient's strongly-held wish to be donor cannot be respected. Many ethicists also feel that a doctor's duty of care to the still living outweighs any duty of care to the dead. The compromise reached is usually to cannulate if there is any evidence of a wish to donate (such as a donor card or registration as a donor) even in the absence of next-of-kin.

For category III donors, treatment is being withdrawn from a living person, who will then die and become a donor. It is important that the decisions that injuries are non-survivable, continued treatment is futile and that withdrawal is in the patient's best interests be made completely independently of any consideration of suitability as an organ donor. Withdrawal of life-prolonging treatment in the face of a hopeless prognosis should be a standard part of patient care, irrespective of whether a patient can be a donor. Only after such decisions have been firmly made should a patient be considered as a potential organ donor. Although such treatment can be continued until the transplant team arrives, no additional treatment should be started to improve the organs—until the point of death, the patient should be treated exactly as any other dying patient.

1997 Institute of medicine recommendation policy for NHBD procurement policy

- Written, locally approved NHBD protocols
- NHBD protocols open to public
- Case-by-case decisions about the pre-mortem administration of medications
- Family consent for pre-mortem cannulation

- Conflict-of-interest safeguards
- Determination of death (in controlled NHBDs) by cessation of cardiopulmonary function for at least 5 minutes by ECG monitor and arterial pressure monitoring
- Family options (e.g. attendance at life-support withdrawal) and financial protection

PROCEDURE FOR HARVESTING DCD DONORS

The time after cessation of ventilation to cardiac arrest is restricted so as not to exceed 60 minutes. After cardiac arrest, a 5-minute period is observed to ensure absence of cardiopulmonary activity. The donor is then transferred to the operating theater where a surgical team is waiting to perform organ procurement. After draping and a midline with sternotomy incision the infra-renal aorta is rapidly cannulated and the thoracic aorta clamped. Before the aortic flush with heparanized HTK/UW solution (10 L with 50,000 U of heparin), 10 mL bolus of 1.5 mega units of streptokinase is injected. Topical cooling with crushed ice is applied. Venting is done through the right ventricle. Liver is assessed before and after the perfusion to exclude organs showing patchy and nonhomogeneous areas. Otherwise, organs are retrieved in the typical manner. Portal vein perfusion and biliary duct irrigation are performed *in situ*.

In 1997, first studies on the use of the recirculation of oxygenated blood at 37°C to improve the viability of porcine livers damaged by warm ischemia and normothermic extracorporeal membrane oxygenation (NECMO) could partially restore the cellular energy load lost during a period of cardiac arrest.¹⁷ When NECMO is compared with total body cooling after cardiac arrest, it has shown that NECMO is significantly superior in improving the histological lesion and posttransplant graft function.¹⁸ The beneficial effects of NECMO were demonstrated to lie in its ability to turn the initial period of cardiac arrest into one of ischemic preconditioning.¹⁹ In 2002, Barcelona Hospital Clinic designed a clinical protocol to transplant livers arising from uncontrolled DCD by systematically maintaining them with NECMO prior to extraction.

Cardiac arrest in a potential DCD typically occurs at an extrahospitalary site. Emergency medical physicians arrive at the scene and initiate advanced cardiopulmonary resuscitation (CPR), which is continued while the individual is brought by ambulance to the Hospital Clinic. Upon arrival, death is declared, demonstration of the unequivocal and irreversible absence of electrocardiographic activity and spontaneous breathing during a period of at least 5 min.²⁰

ORGAN PRESERVATION

Transplant coordinators are contacted when the potential DCD enters the hospital but remain uninvolved until death has been pronounced. Upon the death declaration, they initiate the steps of donor preparation. The DCD is immediately heparinized (3 mg/kg of body weight, IV); orotracheally intubated, if not already; subjected to external cardiac massage by means of a cardiocompressor. Rapid cannulation is performed for NECMO. Perfusion catheters are introduced into the femoral artery and vein in the groin area and connected to a cardiopulmonary bypass (CPB) machine. CPB is primed with 500 mL of 1/6 M bicarbonate, 500 mL of 20% mannitol, 500 mL of lactated Ringer's, and 500 mL of a plasma volume expander. Mechanical ventilation and cardiac massage are terminated just before the inflation of a Fogarty balloon catheter, which is introduced via the contralateral femoral artery and positioned in the supraceliac aorta and serves to exclude the thoracic organs from the circuit. The catheter is inflated with a radio opaque contrast agent, and radiographic imaging is used to assure that it has been properly placed above the diaphragm.

Serum transaminase levels and the gaseous, acid-base, and ionic compositions and temperature of the recirculating blood are monitored throughout NECMO (Figure 8.1). CPB pump flow is a significant determinant of DCD liver graft viability.¹⁴ To assure adequate flow in the hepatic artery as well as the entire splanchnic bed, the latter of which ultimately determines portal venous flow, CPB pump flow is maintained above 1.7 L/min. The pH is kept between 7.0 and 7.4 by continuous adjustments with 1 M bicarbonate. For anticoagulation,



Figure 8.1: A patient on NECMO circuit

heparin is administered every 90 min during the course of NECMO, which is maintained while consent to donation is obtained, directly up until the moment of organ perfusion with the cold preservation solution.

Normothermic extracorporeal membrane oxygenation (NECMO) circuit (Figure 8.1). Cannulae are placed in the femoral artery and vein in the groin region. A Fogarty balloon catheter, introduced through the contralateral femoral artery, is positioned in the abdominal or thoracic aorta, proximal to the origin of the celiac trunk. The heat exchanger maintains the blood at 37°C.

DONOR EVALUATION

The donor's family is contacted and consulted for information and their consent. Abdominal and femoral vasculature is not affected by pathology or trauma that might limit the ability to run NECMO. About 30-40% DCD livers are usually not suitable due to macroscopic hepatic steatosis. In donors whose initial hepatic transaminases are high, four-to-five times the upper limit of normal are usually unsuitable due to irreparable hepatic injury. Donors with initial transaminases that is close to normal, less than three times the upper limit, are suitable for donation.

ORGAN EVALUATION

At organ recovery, the hepatic artery is perfused via the femoral artery cannula, and it is only necessary to perform additional venous cannulation to perfuse the portal vein. The presence of the Fogarty catheter in the supraceliac aorta eliminates the need to clamp it. Intraoperative evaluation is key to determine whether a DCD liver graft can be used. Ideal liver should have adequate consistency, no congested or poor perfusion and mild-to-moderate steatosis. The common bile duct is sectioned prior to perfusion with the preservation solution to judge its grade of vascularization and clarify doubts regarding its viability. A rapid-flush technique is used to perfuse the liver and all of the abdominal organs with cold (UW)/HTK solution which will wash out the liver in a uniform manner, without any patchiness during exsanguinations.

RECIPIENT OPERATION

The technique in the recipient is similar to mentioned in the recipient operation chapter. Normothermic machine preservation (NMP) has the potential to maintain and perhaps even improve the quality of unexpected DCD livers and expand their transplant use,²⁰⁻²² especially those discarded on the basis of steatosis, which are more susceptible to the damaging effects of cold ischemia.

Disadvantages of DCD donors^{5-8,12,23,26}

- Primary nonfunction is more but acceptable (PNF)
- Hepatic artery thrombosis (HAT)
- Ischemic cholangiopathy leading to diffuse nonanastomotic biliary strictures
- Graft survival is inferior as compared to heart-beating donors

Outcome after liver transplantation from non-heart-beating donors (NHBD-OLT)²³⁻²⁹

Author	PNF rate	Graft survival	Patient survival
Otero	25%	55%	80%
Fukumori	> 55 years	0%	75%
	< 55 years	0%	70%
Foley	5.5%	56%	68%
Quintela	10%	90%	90%
Muesan	3.7%	86.5%	89.6%
Monbaliu	0%	68.75%	1.25%

Early experience with NHBDs was associated with unsatisfactory patient and graft survival; particularly for the uncontrolled NHBD group.¹¹ Graft loss was mainly attributed to primary nonfunction and vascular complications.²³ Introduction of mechanical chest and abdominal compression, cardiopulmonary bypass, and extra-corporeal membrane oxygenation may contribute to improvement of the outcome of uncontrolled NHBDs.

ISCHEMIC CHOLANGIOPATHY

Biliary ducts seem to be more sensitive to ischemia than hepatocytes. In animal models of NHBD, irreversible biliary tract damage has been observed after 40 minutes of warm ischemia, despite preservation of hepatocellular function.⁷ To avoid late biliary complications, especially ischemic cholangiopathy, caution is urged with the use of organs according to strict donor and ischemic time criteria.⁸

PNF RATE RANGES

PNF rate ranges from 0-25%.²³⁻²⁹ Earlier studies reported higher rates of PNF. But recent data shows the rate of PNF is 0 to 10%.²⁵⁻²⁹ This is an acceptable percentage when the donor pool can be increased by > 20% at the cost of low rates of PNF. With the introduction of NECMO and NMP (Normothermic machine preservation) the future result could be much better.

HA THROMBOSIS AND SURVIVAL RATES

In controlled NHBD liver transplantation D'Alessandro et al¹³ reported similar vascular and biliary complications

following transplantation of cadaveric allografts; however, the rate of primary nonfunction was significantly higher (10.5% vs. 1.3%) in NHBD livers. In addition, no difference in patient's survival was found, but higher incidence of graft loss in NHBD livers (53.8% vs. 80.9%) was observed.¹³ Foley et al²⁶ reported a 16.6% incidence of hepatic artery thrombosis and 13.8% incidence of biliary stricture.

Rela et al³¹ reported that the results of controlled NHBDs are now improving and with increased experience are approaching those of heart-beating donors. It has been demonstrated that liver allografts from NHBDs present less intra-graft inflammatory events,³⁰ probably in relation to the absence of brainstem death, which potentially renders them less immunogenic, with potentially fewer episodes of rejection and longer graft survival. Important issues like prolonged period of warm ischemia (WI) in NHBD livers, which contributes to increased cell death and reduced organ viability should be taken into consideration. Thus it is understandable that when WI exceeds 30 minutes, there may be an increased risk of graft failure. In addition, the extended WI renders livers more vulnerable to further damage from cold ischemia and it is therefore imperative that cold ischemia should be minimized. Organs from older donors are more susceptible to the warm and cold ischemia and when donor age is > 40 years also appears to increase the risk of graft failure. Proper selection of the donor is important to achieve good results.

REFERENCES

1. C Zawistowski, M DeVita. Non-heartbeating organ donation a review. *J Intensive Care Med* 2003;18(4):189-97.
2. D Lewis, W Valerius. Organs from non-heart-beating donors an answer to the organ shortage, *Crit Care Nurse* 1999;19:72-74.
3. 2005 Annual Report of the US Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data 1989-2005. <http://www.optn.org/latestData/rptData.asp>. Accessed November 12, 2006.
4. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transpl* 2003;9:1231-43.
5. S Reddy, M Zilvetti, J Brockmann, et al. Liver transplantation from non-heart-beating donors: current status and future prospects, *Liver Transplantation* 2004;10:1223.
6. A Cameron, R Busuttil. Ischemic cholangiopathy after liver transplantation, *Hepatobiliary Pancreat Dis Int* 2005;4:495.
7. JC Garcia-Valdecasas, J Tabet, R Valero, et al. Evaluation of ischemic injury during liver procurement from non-heart-beating donors, *Eur Surg Res* 1999;31:447.
8. B Kaczmarek, MD Manas, BC Jaques, et al. Ischemic Cholangiopathy After Liver Transplantation From Controlled Non-Heart-Beating Donors-A Single-Center Experience. *Transplant Proceed* 2007;39(9):2793-95.

9. C Fondevila, AJ Hessheimer, A Ruiz, D, et al. Liver transplant using donors after unexpected cardiac death: Novel preservation protocol and acceptance criteria American Journal of Transplantation 2007;7(7):1849-55.
10. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. Transplant Proc 1995;27:2893-94.
11. Casavilla A, Ramirez C, Shapiro R, et al. Experience with liver and kidney allografts from non-heart-beating donors. Transplantation 1995;59:197.
12. Abt P, Crawford M, Desai N, et al. Liver transplantation from controlled non-heart-beating donors: An increased incidence of biliary complications. Transplantation 2003;75:1659-63.
13. D'Alessandro AM, Hoffman RM, Kenecht SJ, et al. Successful extrarenal transplantation from non-heart-beating donors. Transplantation 1995;59:977.
14. Fondevila AJ, Hessheimer A Ruiz, D Calatayud JF, et al. Liver transplant using donors after unexpected cardiac death: Novel Preservation Protocol and Acceptance Criteria American Journal of Transplantation 2007;7(7):1849-55.
15. Fukumori T, Kato T, Levi D, et al. Use of older controlled non-heart-beating donors for liver transplantation. Transplantation 2003;75:1171-74.
16. Muiesan P, Girlanda R, Jassem W, et al. Single-center experience with liver transplantation from controlled non-heartbeating donors: A viable source of grafts. Ann Surg 2005;242:732-38.
17. Valero R, Garcia-Valdecasas JC, Tabet J, et al. Hepatic blood flow and oxygen extraction ratio during normothermic recirculation and total body cooling as viability predictors in non-heart-beating donor pigs. Transplantation 1998;66:170-76.
18. Garcia-Valdecasas JC, Tabet J, Valero R, et al. Liver conditioning after cardiac arrest: The use of normothermic recirculation in an experimental animal model. Transpl Int 1998;11:424-32.
19. Net M, Valero R, Almenara R, et al. The effect of normothermic recirculation is mediated by ischemic preconditioning in NHBD liver transplantation. Am J Transplant 2005;5:2385-92.
20. Royal Decree 2070/1999, December 30, 1999. Article 10, Section I: Protocol of diagnosis and certification of death for the extraction of organs from deceased donors. http://noticias.juridicas.com/base_datos/Admin/rd2070—1999.html#anexo1.
21. Lauschke H, Olschewski P, Tolba R, et al. Oxygenated machine perfusion mitigates surface antigen expression and improves preservation of predamaged donor livers. Cryobiology 2003;46:53-60.
22. Imber CJ, St Peter SD, Lopez de Cenarruzabeitia I, et al. Advantages of normothermic perfusion over cold storage in liver preservation. Transplantation 2002;73:701-09.
23. Otero A, Gomez-Gutierrez M, Suarez F, et al. Liver transplantation from maastricht category 2 non-heart-beating donors. Transplantation 2003;76:1068.
24. Fukumori T, Kato T, Levi D, et al. Use of older controlled non-heart-beating donors for liver transplantation. Transplantation 2003;75:1171.
25. Manzarbeitia CY, Ortiz JA, Jeon H, et al. Long-term outcome of controlled, non-heart-beating donor liver transplantation. Transplantation 2004;78:211.
26. Foley DP, Fernandez LA, Levenson G, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Ann Surg 2005;242:724.
27. Quintela J, Gala B, Baamonde I, et al. Long-term results for liver transplantation from non-heart-beating donors maintained with chest and abdominal compression-decompression. Transplant Proc 2005;37:3857.
28. Muiesan P, Girlanda R, Jassem W, et al. Single-center experience with liver transplantation from controlled non-heartbeating donors: a viable source of grafts. Ann Surg 2005;242:732-38.
29. D Monbaliu F Van Gelder R, Troisi B, de Hemptinne J, et al. Liver transplantation using non-heart-beating donors: Belgian experience Transplant Proceed 2007;39(5):1481-84.
30. Jassem W, Koo DD, Muiesan P, et al. Non-heart-beating versus cadaveric and living-donor livers: differences in inflammatory markers before transplantation. Transplantation 2003;75:1386.
31. M Rela, W Jassem. Transplantation from non-heart-beating donors. Transplantation Proceedings 2007;39:726-27.

Marginal Donor and Donor Risk Index

MARGINAL DONORS

The discrepancy between the donor pool and number of patients on waiting list led to use of split liver and use of marginal grafts. To expand the donor pool, the so-called “marginal graft” has been increasingly used in DDLT.¹ Presence of steatosis, elevated liver function tests, arteriosclerosis, hemodynamic status before harvesting, reduce capacity for the functional recovery of the allograft and its regeneration.

Characteristics of a marginal donors^{2-8,12}

- Donor age > 65 years
- Obesity (BMI > 27)
- Moderate-to-severe macrovesicular steatosis
- Prolonged cold ischemic time > 12 hr
- High dose of inotropic drug use
- History of alcoholism/Drug abuse
- HBsAg+ve/HBcAb+ve/HCV+ve
- Hemodynamically unstable (prolonged hypotension, SBP < 60 mm Hg > 2 hr in last 12 hr)
- Hypernatremia (Na > 160 mEq/L > 12 hours in the last 24 hours)
- PT < 40%
- Prolonged ICU stay (5-10 days)
- Cirrhotic liver
- Presence of Infection (Bacterial/Viral)
- Elevated LFT, Serum bilirubin > 2 mg/dl and high levels of ALT, AST (> 3-4 times)
- Extrahepatic neoplasia or previous h/o carcinoma
- Cardiac arrest
- Imported graft
- DCD (Donation after cardiac death)
- Split liver
- Cause of death—Trauma, Stroke

Many centers that set the upper limit of donor age at 55 or 60 years for donor safety are reluctant to use older donors.^{9,10} Gastraca et al reported good results are obtained using donors aged over 70 years if good donor selection is performed like steatosis < 10%, short cold ischemia time, normal or mild elevation of AST, LDH, less hypotensive episodes and a low transfusion rate.¹¹

DONORS > 80 YEARS

Old donor age is not an absolute contraindication to OLT. Liver grafts from donors > 80 years can be used knowing that there is a high-risk of postoperative complications. Furthermore, the increased risk of developing severe HCV recurrence, related to older donor age, suggests that such livers should be used in HCV negative recipients.²⁴

DONOR RISK INDEX

Donor risk assessment plays an important role in predicting the graft survival in DDLT. Each and every organ of each and every deceased donor is thoroughly evaluated by organ procurement organizations and transplant physicians. Analyses that define the effect of specific donor characteristics on the risk of post-transplant graft failure are important. Feng et al¹² reported in his study that donor characteristics identified as significantly associated with liver allograft failure. These included three donor demographic characteristics (age, race and height), three relating to cause and type of donor death (Cause of death: Cerebrovascular accident or others and DCD donors), split/partial graft, cold ischemic time and location (local/regional/national) share was also found to be statistically significant. Donor age > 60 years was the strongest risk factor for graft failure. Quality of the donor organ is such an important component of the

decision which decides whether to accept or to reject the organ for donation basing on the risk status. The study of Feng et al. provides an important quantitative assessment of relative risk for every potential graft, given the characteristics of the intended recipient, based upon donor and graft characteristics available at the time the organ is offered.

CALCULATION OF DONOR RISK INDEX (DRI)¹²

Exp [(0.154 if 40 < age < 50) + (0.274 if 50 < age < 60) + (0.424 if 60 < age < 70) + (0.501 if 70 < age) + (0.079 if COD = anoxia) + (0.145 if COD = CVA) + (0.184 if COD = other) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.066 ((170 – height)/10)) + (0.105 if regional share) + (0.244 if national share) + (0.010 × cold time)].

(DCD: Donation after cardiac death; CVA: Cerebrovascular accident; COD: Cause of death)

Feng et al¹² demonstrated that the use of organs with a DRI greater than 2.0, resulted in a reduction in 3-year graft survival of 20% (> 80% for DRI < 1.0 to 60% for DRI > 2.0). The DRI is a continuous measure that reflects the risk of graft failure (including death); a higher DRI is associated with a greater risk of graft failure.

SURVIVAL RATES ACCORDING TO DONOR RISK INDEX⁴

Donor risk index	Survival (%)	
	1 yr	3 yr
<1.0	87.6	81.2
1.0–1.5	79.7–85.0	71.1–78.7
1.5–2	75.8–79.9	65.6–70.6

Schaubebler et al also reported that donor age is one of the strongest risk factor for graft failure. Other strong risk factors include donation after cardiac death (DCD) and use of a partial or split liver.¹³ In USA, over the past decade, the number of LTXs performed using allografts from donors older than 65 years has doubled (5 to 9.8%) and the use of organs from donors after cardiac death (DCD) is 10-fold higher (0.3 to 4.0%).¹⁴ In Europe, deceased donors over 60 years have increased from less than 5% in the early 1990s to approximately 20% in the 2002 European Liver Transplantation Registry (ELTR).¹⁵ Marginal organs can be successfully used in the proper patient; they are at higher risk of graft dysfunction, graft failure and potentially decreased patient survival.^{16,17}

Following the implementation of the MELD system of organ allocation, the number of recipients with a MELD score > 30 has increased from 10 to 14%.¹⁸ By transplanting patients most likely to die without a transplant, the MELD

system has been very successful in achieving the goal of lowering wait-list mortality. Mateo et al recently reported that in 'low-risk patients', use of 'low-risk DCD livers' in which the cold ischemic time was less than 10 hours and warm ischemic time is less than 30 min, resulted in equivalent graft and patient survival rates to standard livers.¹⁹ In LDLT, use of older live donors may also have an impact on graft outcomes.²⁰ Liver graft function from older donors is equal to that of younger donors, although their regeneration capacity was impaired.²⁰ The susceptibility of aged liver grafts to ischemic injury during cold preservation, which has been highlighted in DDLT,¹² probably, has little impact on graft outcomes in LDLT.²¹ Aged donors have been related to a more rapid, aggressive HCV graft recurrence.²² Use of a marginal donor is a usual practice, with the intention of expanding the pool of deceased donors. However, such a liver is at substantial risk for primary dysfunction or even for primary nonfunction.

ORGAN PATIENT INDEX (OPI)²³

Avolio et al reported the OPI, which predicts the outcome better than DRI, increasing the gap in the long-term graft survival between the low- and the high-risk class. The inclusion of the MELD in the new index allowed better prediction of graft survival. DRI and MELD were included in a new index, namely the organ patient index (OPI), as follows:

OPI = Exp[(0.154 if 40 < age < 50) + (0.274 if 50 < age < 60) + (0.424 if 60 < age < 70) + (0.501 if 70 < age) + (0.079 if brain anoxia) + (0.145 if brain vascular accident) + (0.184 if other cause of brain death) + (0.176 if race = African American) + (0.126 if race = other) + (0.411 if cardiac death) + (0.422 if partial/split) + (0.066 (170 – height)/10) + (0.105 if regional share) + (0.244 if national share) + (0.010 × CIT) + (0.020 × MELD)].

REFERENCES

1. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transpl* 2003;9:651.
2. Tisone G, Manzia TM, Zazza S, et al. Marginal donors in liver transplantation. *Transplant Proc* 2004;36:525.
3. Totsuka E, Fung U, Hakamada K, et al. Analysis of clinical variables of donors and recipients with respect to short-term graft outcome in human liver transplantation. *Transplant Proc* 2004;36:2215.
4. Renz JF, Kin C, Kinkhabwala M, et al. Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation. *Ann Surg* 2005;242:556.
5. Gruttadauria S, Cintonino D, Mandala L, et al. Acceptance of marginal liver donors increases the volume of liver transplant: early results of a single-center experience. *Transplant Proc* 2005;37:2567.

6. Angelico M. Donor liver steatosis and graft selection for liver transplantation: A short review. *Eur Rev Med Pharmacol Sci* 2005;9:295.
7. Tisone G, Manzia TM, Zazza S, et al. Marginal donors in liver transplantation. *Transplant Proc* 2004;36:525.
8. V Scuderi, A Ceriello, et al. The marginal donor: A single-center experience in orthotopic liver transplantation. *Transplantation Proceedings* 2006;38:1069-73.
9. Fan ST, Lo CM, Liu CL, et al. Safety and necessity of including the middle hepatic vein in the right lobe graft in adult-to-adult live donor liver transplantation. *Ann Surg* 2003;238:137.
10. Trotter JF, Campsen J, Bak T, et al. Outcomes of donor evaluations for adult-to-adult right hepatic lobe living donor liver transplantation. *Am J Transplant* 2006;6:1882.
11. M Gastaca, A Valdivieso, et al. Donors older than 70 years in liver transplantation. *Transplant Proceed* 2005;37:3851-54.
12. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: The concept of a donor risk index. *Am J Transplant* 2006;6(4):783-90.
13. DE Schaubela, CS Simab. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J of Transplant* 2008;8:419-25.
14. www.ustransplant.org. Accessed October 8, 2006.
15. European Liver Transplantation Registry: Data Analysis Booklet 05/1968–06/2002. 2002, p 15.
16. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation after cardiac death donors: An analysis of OPTN/UNOS data. *Am J Transplant* 2006;6:791-96.
17. Doshi MD, Hunsicker LG. Short- and long-term outcomes with the use of kidneys and livers donated after cardiac death. *Am J Transplant* 2007;1:122-29.
18. Shiffman ML, Saab S, Feng S, et al. Liver and intestine transplantation in the United States, 1995–2004. *Am J Transplant* 2006;6:1170-87.
19. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation after cardiac death donors: An analysis of OPTN/UNOS data. *Am J Transplant* 2006;6:791-96.
20. N Akamatsu, Y Sugawara, S Tamura, J Kaneko, Y Matsui, J Togashi, M Makuuchi. Impact of live donor age (> 50) on liver transplantation. *Transplant Proceed* 2007;39:3189-93.
21. Santori G, Andorno E, Morelli N, et al. Impact of different cadaveric donor age cut-offs on adult recipient survival after liver transplantation: a single-center analysis. *Transplant Proc* 2005;37:2576.
22. Berenguer M, Prieto M, San Juan F, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002;36:202.
23. AW Avolio, M Siciliano, R Barbarino, et al. Donor risk index and organ patient index as predictors of graft survival after liver transplantation. *Transplantation Proceedings* 2008;40:1899-902.
24. I Petridis, S Gruttadauria, S Nadalin, et al. Liver transplantation using donors older than 80 years: A single-center experience. *Transplantation Proceedings* 2008;40:1976-78.

A detailed photograph of a liver surgery, showing the organ being manipulated with surgical instruments. The image is used as a background for the chapter header.

Donor Surgery

CHAPTER 10

(A) RIGHT LOBE GRAFT

The supply of liver allografts from deceased donors is far short of the number of potential recipients, a reality that has spurred the development of living donor liver transplantation. LDLT has become a viable alternative, particularly in countries where brain death law is missing or insufficient or less number of brain dead patients are available. The most common way of meeting the need for LDLT in adults is to use the right liver from a living donor as the graft.¹⁻³ Although this procedure has widened the availability of adult LDLT, there is no doubt that right hepatic lobectomy can be a serious burden for the donor. This point of view is supported by reports of hyperbilirubinemia in some right lobe donors^{4,5} and donor deaths.⁶

LDLT has not been performed as frequently in the west as anticipated and as compared to Asia. Donor mortality is a concern in LDLT. So far, 28 cases of documented donor death have been reported worldwide (till 2007). The expansion of LDLT was hampered by the issues of morbidity and mortality in living donors undergoing right lobectomy.⁸ Living related transplantation is mostly popular in Asian countries like Japan, Hong Kong, China, Taiwan and Korea with better graft and patient survival results than other countries. In eastern countries, religious beliefs and peoples reluctant attitude towards deceased organ donation has led to a revolution in living related liver transplantation unlike the USA and Europe where DDLT is well organized. Pioneers of LDLT like Tanaka K, Makuuchi M, and Fan ST developed more refined and safe techniques for LDLT. Right lobe graft was introduced by the Kyoto Team in 1994,⁷ and the procedure was applied to adult-to-adult LDLT by the Hong Kong Team in 1996.⁸

SURGICAL TECHNIQUES OF RIGHT LOBE DONOR HEPATECTOMY

Right lobe graft involves harvesting segments V, VI, VII and VIII. After complete donor evaluation and selection, patient is taken to operation theater. Care is taken in the operation theatre to prevent wound sepsis, pressure sores and deep vein thrombosis. Position of the donor for RLG is supine with abducted upper limbs. Maintenance of body temperature is by warming devices applied to lower limbs and intravenous fluid warmer to increase the temperature of fluids given intraoperatively. Routinely central line, arterial line catheters are inserted. Blood components such as PRBC, Fresh frozen plasma, platelets and cryoprecipitate are preserved preoperatively in sufficient quantity to meet the bleeding demands in case of bleeding. Prophylactic antibiotics, H₂ receptor antibiotics are given at the time of induction. Dose of antibiotics may be repeated if the surgery is prolonged. CVP should be kept very low to avoid bleeding. Intraoperative IV fluids should be given as minimum as possible to maintain low CVP. Abdomen is opened by bilateral subcostal incision with midline vertical extension. Other commonly used incisions are reverse L-shaped incision, J-incision and J-incision with thoracic extension. Gallbladder is dissected from liver bed and before cholecystectomy; a cannula (**Figure 10.1**) is inserted into the cystic duct and clamped with atraumatic vascular clamp, followed by intraoperative cholangiography (IOC) using undiluted radiographic contrast and an image intensifier.⁸ IOC is routinely performed before parenchymal transection, before transection of bile duct and after transection of the bile duct to determine the anatomy of the bile ducts and to determine the correct

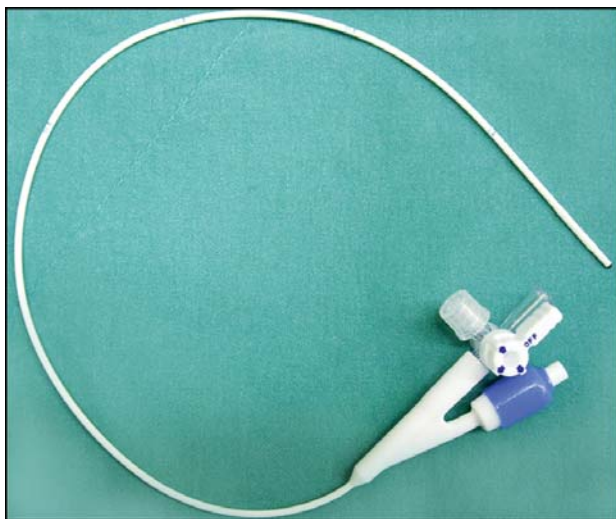


Figure 10.1: 6 Fr. intraoperative cholangiogram (IOC) catheter with an inflatable balloon at the tip for distal bile duct occlusion

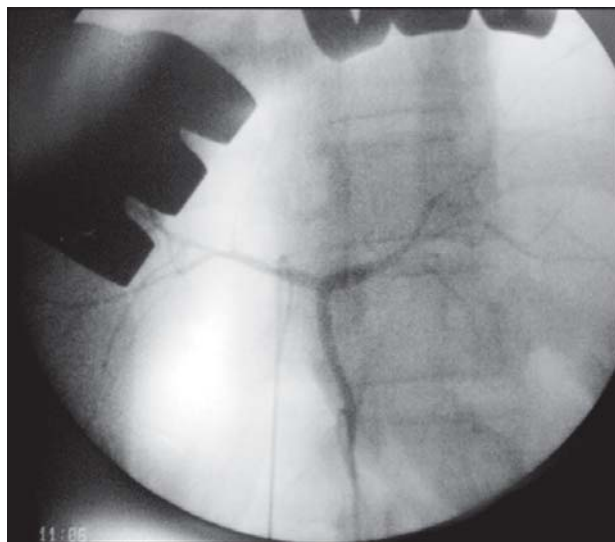


Figure 10.3: IOC with a radioopaque loop around right hepatic duct (IOC taken before transection of bile duct)

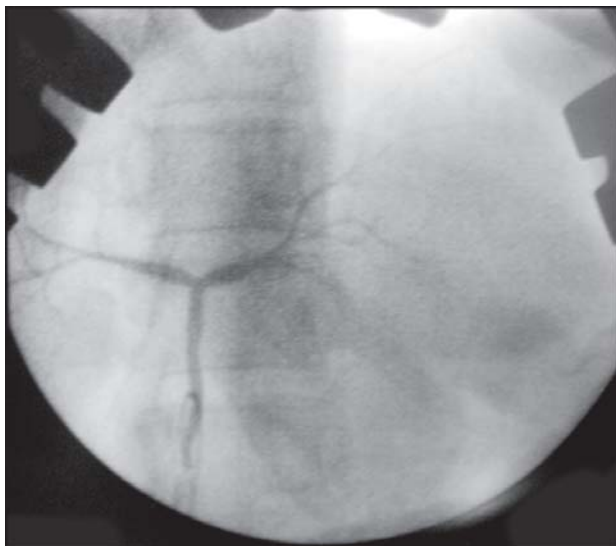


Figure 10.2: IOC before parenchymal transection

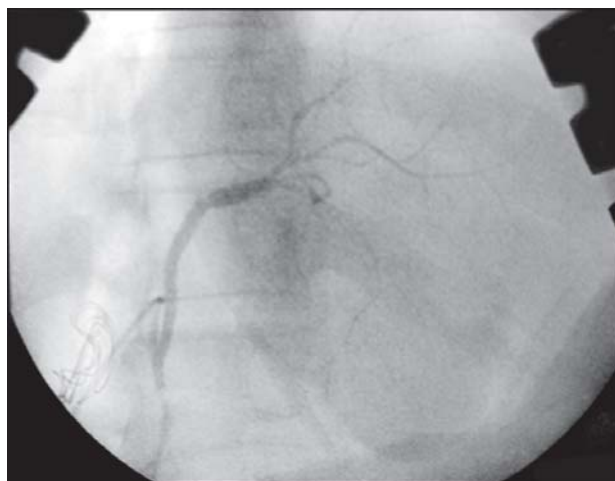


Figure 10.4: IOC after transection and closure of right hepatic duct (right lobe graft)

point for bile duct transection (**Figures 10.2 to 10.4**). Right hepatic duct dissection is not dissected until the liver is completely transected, because dissection for the right hepatic duct before parenchymal transection could be difficult and may predispose to thinning and devascularization of the wall of the duct.⁸ A marker stitch with 6-0 prolene or a ligaclip is applied at the proposed level of transection of RHD at a later stage.

Intraoperative ultrasonography was then performed to determine⁹ the course and location of MHV and its branches to segment V and VIII are marked with a

diathermy, which will guide the plane of transection at a later stage of hepatectomy. Because the MHV could be seen by the ultrasound probe placed on the liver surface at various angles, a correct plane of MHV should be where the MHV could be seen longitudinally, together with the inferior vena cava. Confirm the junction of the MHV and LHV.¹⁰ Hilar dissection is performed to isolate and encircle right hepatic artery and right portal vein (**Figure 10.5**). Presence of arterial supply to segment IV originating from RHA may be noticed in advance by preoperative imaging and care is taken to preserve it to prevent

ischemia to segment IV. Branches of the right portal vein supplying the caudate process were ligated and divided.

The right lobe of the liver was mobilized by dividing the falciform ligament, right triangular ligament, retro hepatic veins, small hepatic veins draining the right caudate lobe into the inferior vena cava.⁹ During mobilization right lobe is completely retracted towards left side by the assistant. Presence of inferior right hepatic vein (IRHV) and middle right hepatic vein (MRHV) should be confirmed while mobilizing the right lobe. The IRHV and MRHVs are preserved for outflow reconstruction in the recipient, if they are more than 5 mm in size. Care is taken to avoid bleeding from injured adrenal vein during dissection of liver around the area of adrenal gland. The inferior vena cava ligament (Makuuchi ligament/Hepatocaval ligament) or a layer of liver tissue covering the right side of the inferior vena cava close to the RHV is divided to encircle the right hepatic vein.

The rotation of the right lobe of the liver should be intermittent to prevent prolonged twisting of the inflow and outflow vascular pedicles of the liver which may cause intraoperative hypotension.⁸ Temporary clamping of RHA and RPV for a short time delineates the line of transection of right lobe by an appearance of color change, which is marked with a diathermy on the liver surface (**Figure 10.9**). Parenchymal transection is performed by using CUSA (amplitude 40-70%, irrigation about 5 ml/min and suction power 10-30%) and bipolar diathermy (**Figures 10.6, 10.9 and 10.10**), in a plane marked by intraoperative ultrasonography and temporary clamping of RHA and RPV, without any inflow or outflow vascular occlusion to avoid exposure to warm ischemia and graft injury (**Figures 10.7 and 10.8**). At the inferior surface of the liver, the transection plane approached from the gallbladder fossa towards the hilum of liver and dissection of the junction of the right and left hepatic ducts is done, but care is taken to avoid complete skeletonisation of the wall of the hepatic duct with the CUSA to avoid biliary complications due to ischemia. The liver parenchyma cranial to the right hepatic duct was cleared by the CUSA down to the caudate process.

The right hepatic duct along with the hilar plate is encircled by passing a right-angled clamp at the level of the caudate process. Hilar plate is divided by scissors without ligation of any tissue to expose the right hepatic duct opening, which may represent an anomalous right hepatic duct or right caudate lobe branches missed by the operative cholangiogram.¹¹ Minimal dissection of pericholedochal tissue is required at this point, and the hepatic ducts are separated with scissors. Care is taken to avoid skeletonization of the bile duct, which leads to increased rate of biliary complications in the recipient after transplantation due to ischemia. The anterior wall of the



Figure 10.5: Vein retractors used during hilar dissection during transplantation surgery



Figure 10.6: CUSA: Showing the adjustment of amplitude, irrigation, suction and tissue select modes



Figure 10.7: Different vascular (Bulldog) clamps used in transplantation

right hepatic duct is covered with hilar parenchymal tissue. Since this often makes it difficult to identify the proximal area of the right hepatic ducts from the surface at the front. Dissection of connective tissue between the right hepatic duct and right hepatic artery is continued. After identification of the posterior wall of the right hepatic duct and the anatomy of the bifurcation, the right hepatic duct is cut 2 or 3 mm away from the bifurcation. The defect on the common hepatic duct is closed

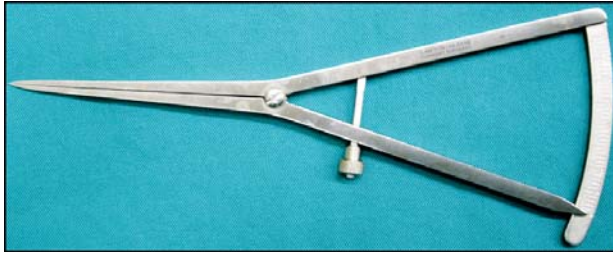


Figure 10.8: Caliper for measuring the size of the blood vessels and bile ducts during liver transplantation



Figure 10.9: Line of transection of right lobe marked with a diathermy

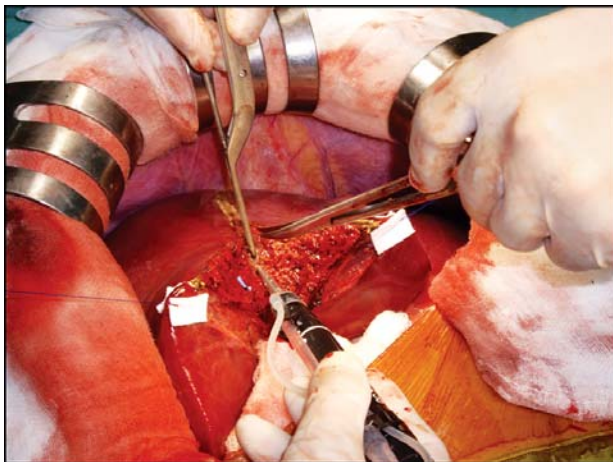


Figure 10.10: Parenchyma transection with the use of CUSA and bipolar diathermy forceps

horizontally with 5-0 or 6-0 PDS (monofilament absorbable) sutures.¹²

Liver transection was then continued down to the posterior surface of the right caudate lobe and towards

the right lateral side to the MHV. Segment V and VIII (V5 and V8) branches from MHV are dissected carefully and preserved if they are more than 5 mm in size, for further reconstruction by vascular grafts (**Figure 10.11**). MHV is preferable left with the donor left lobe in view of the donor safety. Bleeding points and bile leaks from cut surface of liver parenchymal on both donor side and allograft side are carefully ligated. If the distal end of MHV is cut during parenchymal transection, is carefully sutured with 6-0 prolene. Intraoperative blood flow in hepatic artery and portal vein is measured by a flow meter, before harvesting liver graft. The harvesting procedure is completed by clamping and dividing the right hepatic artery, right portal vein and right hepatic vein (**Figure 10.12**). Right hepatic artery is double ligated

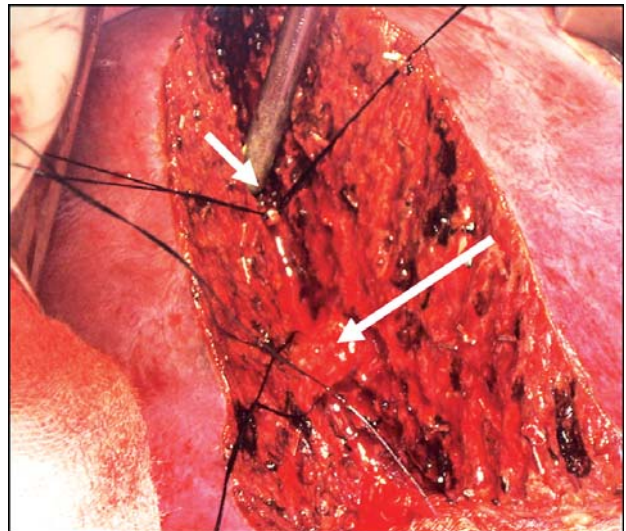


Figure 10.11: V5 (long arrow) and V8 (short arrow) during transection of liver parenchyma in right lobe graft

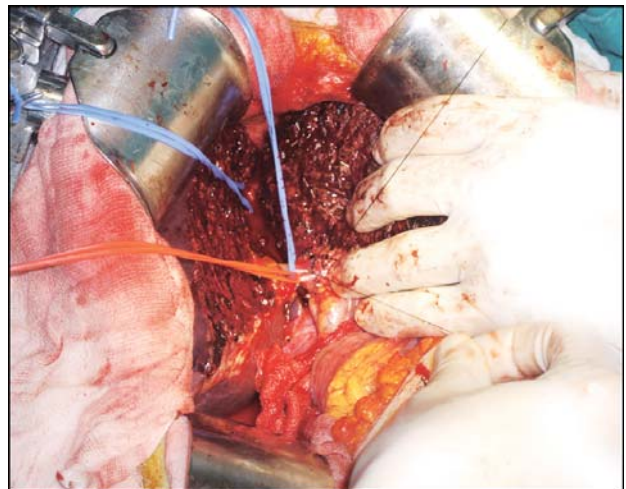


Figure 10.12: Hepatic artery (red loop), portal vein and hepatic vein (blue loops) after complete parenchymal transection

on the donor side and cut. All these major vessels are divided in such a fashion that sufficient tissue of the vessels is left on both donor and graft side for future closure and anastomosis. Technical difficulties in while harvesting the right lobe graft are encountered in case of presence of trifurcation of portal vein, multiple hepatic arterial branches and bile duct anomalies. Liver graft is harvested and 14 Fr. polyvinyl chloride cannula is inserted into RPV and ligated with a purse sting suture around the cannula (**Figure 10.14**). Graft weight is checked with a weighing machine (**Figure 10.13**).

The PV cannula (**Figures 10.23 and 10.24**) is connected to cold UW/HTK solution. At the back table, the graft is immersed in ice sludge and flushed with 1 liter of UW (University of Wisconsin) or HTK (Histidine tryptophan ketoglutarate) solution through the right portal vein cannula. If V5 and V8 branches are ligated and marked during the parenchymal dissection, these sutures are opened immediately after the graft is harvested and check for adequate drainage of UW/HTK solution. Hepatic artery and bile duct are flushed with HTK/UW solution. But in our center we don't flush the hepatic artery with UW/HTK solution to avoid intimal injury. Diluted methylene blue may be injected into the biliary tree to check any bile leak from the cut surface of liver. However, it is not a routine practice in all centers.

DONOR RESIDUAL LIVER AFTER HARVESTING RIGHT LOBE

The cut ends of right portal vein, right hepatic vein, inferior right hepatic vein (IRHV) and middle right



Figure 10.13: Weighing machine for measuring graft weight

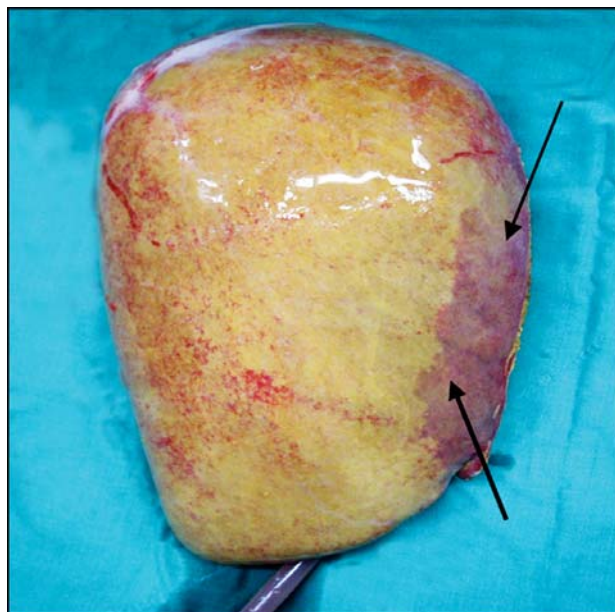


Figure 10.14: Right lobe after harvesting, with area of congestion in the anterior segments V and VIII

hepatic vein (MRHV- if present) are closed with 6-0 prolene sutures (**Figures 10.15 and 10.16**). The cut surface of donor liver is covered with fibrin glue. Few centers use greater omentum to cover the cut surface of donor liver. The falciform ligament in the donor is reconstructed to prevent the remnant donor liver (**Figures 10.17 and 10.18**) from rotating into the right subphrenic space.¹³ Drain placement in donor hepatectomy varies from center to center and many centers at present routinely do not use drain as it increases the chance of infection.¹⁴ Before wound closure, care is taken to ensure that the small bowel had not migrated into the right subphrenic space (**Figure 10.19**). After surgery, parenteral nutrition support consisting of branched-chain amino acid-enriched solution (BCAA), medium-chain triglycerides (MCT), low dose dextrose solution and vitamins administered for 2-3 days to enhance regeneration of the liver remnant.¹⁵

SELECTIVE INFLOW OCCLUSION OF DONOR HEPATECTOMY IN LDLT

How it is different from Pringles maneuver?

Tokyo group (Makuuchi et al) recommended an intermittent selective inflow occlusion technique for donor hepatectomy in LDLT without any serious consequences (**Figure 10.20**). In right hemilivers (A) or right lateral sector grafts (B), the right portal vein and arterial branches to the right paramedian sector (segment V and VIII) are occluded so that right paramedian sector become totally ischemic, while the right lateral sector (segment VI and

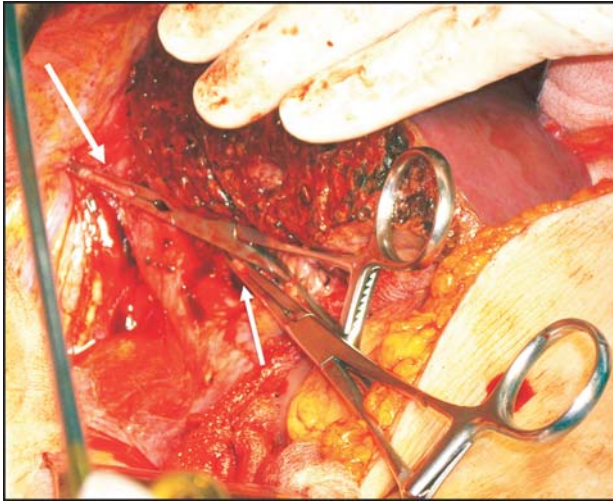


Figure 10.15: Donor RHV (long arrow) and RPV (short arrow) after harvesting right lobe graft with a remnant left lobe

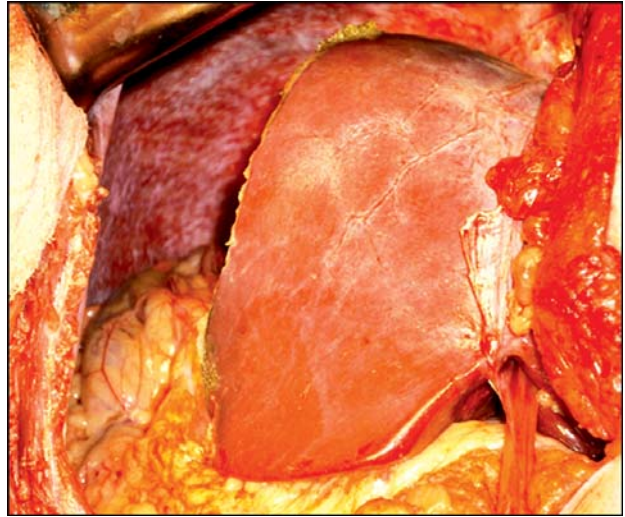


Figure 10.17: Remnant donor left lobe after right hepatectomy

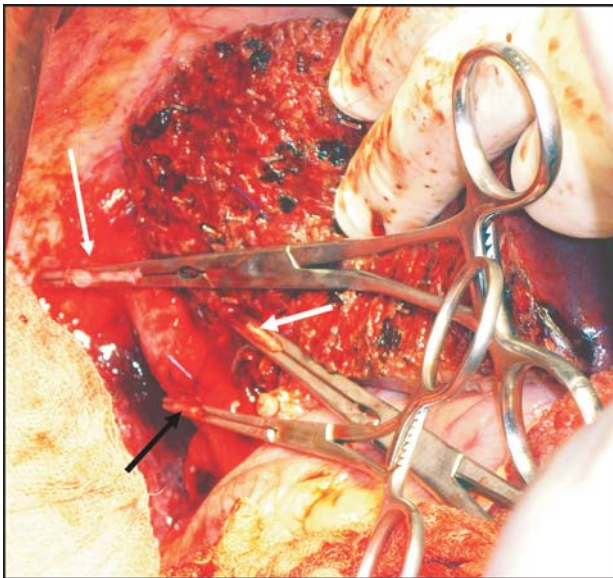


Figure 10.16: LDLT- Right lobe LDLT; RHV (white long arrow), RPV (white short arrow) and IRHV (black arrow)

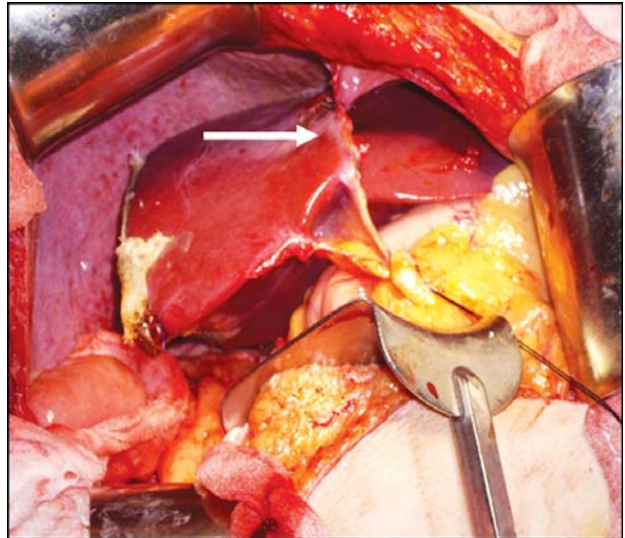


Figure 10.18: Reconstruction of falciform ligament after donor hepatectomy. Cut surface of the liver is covered with surgical

VII) is perfused by arterial flow.¹⁶ In left lateral segment (C) or extended left lateral segment (D), selective occlusion of LPV and MHA (if present). This technique causes complete ischemia of segment IV, whereas segment II and III are fed by arterial flow during transection. During harvesting whole left hemiliver grafts (E), transection is continued after selective occlusion of RHA and RPV.¹⁶

The argument in favor of selective occlusion:

- It will not lead to splanchnic congestion and ischemic injury as visceral affluent is maintained during inflow occlusion via unoccluded part of liver.¹⁶

- In cases B, C, D and E (as mentioned above in the brackets), parenchymal transection is carried out within completely ischemic part of liver but the hepatic segments in the graft are perfused by the arterial flow during occlusion. Only in a, part of the graft is exposed to temporary intermittent ischemia.¹⁶

V5 AND V8 DIVISION AND RECONSTRUCTION (FIGURE 10.21)

Dissection techniques of Tokyo group are different from other centers. They preserve V5 and V8 till complete



Figure 10.19: Incision for right lobe donor hepatectomy. Wound closed with sutures with a Jackson-Pratt drain (arrow)

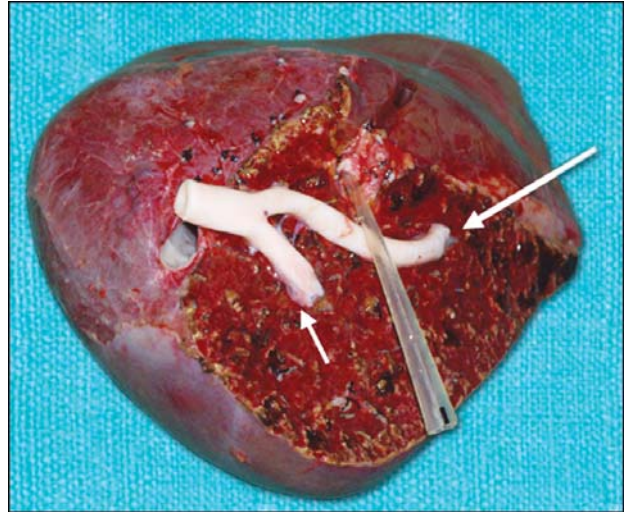


Figure 10.21: V5 (long arrow) and V8 (short arrow) reconstruction with a cryopreserved vascular graft

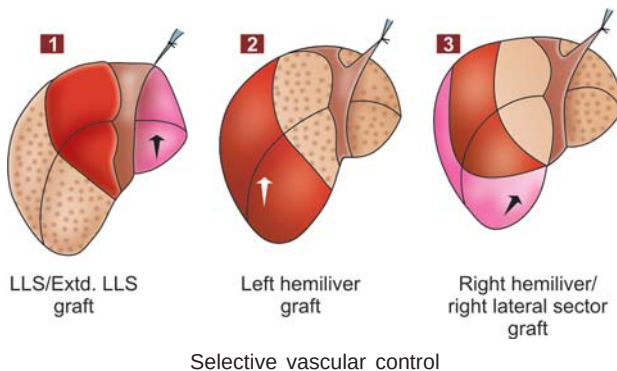


Figure 10.20: Donor hepatectomy (Makuuchi et al)—Selective vascular occlusion of donor liver. Blue arrow shows completely ischemic area of the liver, while the black arrow shows the portion with intact arterial supply. (Modified and redrawn with permission of H Imamura)¹⁶

1. Left lateral segment or extended left lateral segment graft. The middle hepatic artery and left portal vein are occluded;
2. Left hemiliver graft. The right portal vein and the right hepatic artery are occluded.
3. Right hemiliver or right lateral sector graft. The right portal vein and right paramedian arterial branch are occluded.

parenchymal transection and put bulldog clamps for temporary occlusion of V5 and V8 and mark the area of congestion on segment V and VIII on the graft side (**Figure 10.14 and 10.22**). The volumes of the V5 and V8 zones

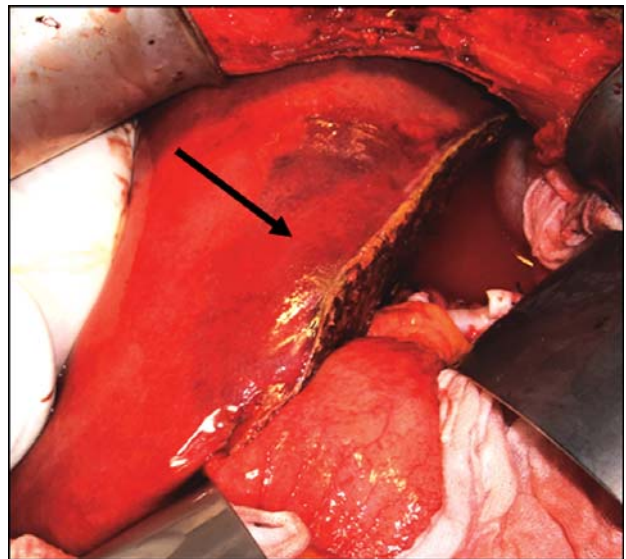


Figure 10.22: Area of congestion (arrows) in right lobe graft in absence of V5 and V8 reconstruction

are reconstructed using the 3-D CT and are compared with coincidence of congested area marked intraoperatively. According to the volumetric assessment of veno-congestive area on the graft side, venous reconstruction

is performed so that the volume of the right hepatic graft without the congestive region was in excess of 40% of the recipient's SLV.

KYOTO GROUP

Tanaka et al⁴⁷ designed algorithm for harvesting the right lobe with or without MHV depending on the based on CT angiography evaluation of dominant MHV /RHV and residual liver volume in the left lobe.

In donors with dominant right hepatic vein

(Less than 40% of the right lobe graft drains into the MHV)

1. Patients with GRWR >1%: RLG is harvested without MHV
2. Patients with GRWR <1%: Remnant left lobe > 35%, RLG is harvested with MHV.

In donors with dominant middle hepatic vein

(More than 40% of the right lobe graft drains into the MHV)

1. Patients with GRWR >1% and remnant left lobe >35%: RLG is harvested with MHV
2. Patients with GRWR <1%: Remnant left lobe > 35%, RLG is harvested with MHV.

In donors with left lobe <35%, acceptance of the donor depends on the age and degree of steatosis.

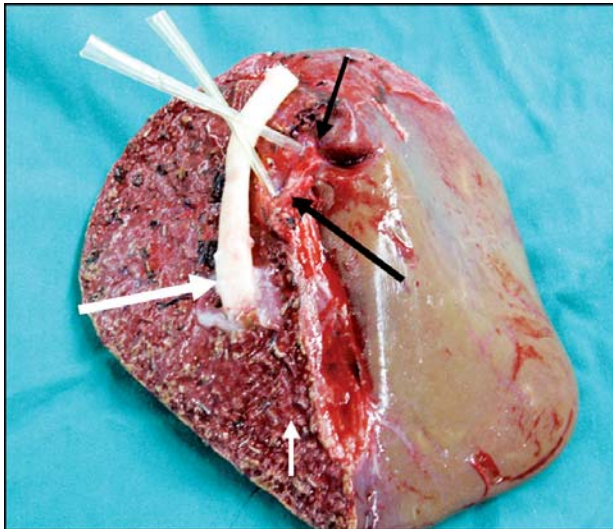


Figure 10.23: Right lobe graft in trifurcation of the portal vein. Anterior and posterior branches of RPV are separate (black arrows) and are reconstructed separately in the recipient with right and left branches of the portal vein. Cryopreserved vascular graft used for reconstruction of V5

HONG KONG GROUP

Fan et al¹⁸ preserved the MHV along with the right lobe graft without increasing the donor morbidity. In his technique he marked a plane at which MHV can be seen longitudinally in line with cranial part of retrohepatic IVC during intraoperative ultrasonography.¹⁸ Course of MHV is marked with diathermy. Liver transection is guided by MHV rather than a tape. MHV is exposed all the way up to the junction of LHV. Segment IVb hepatic vein joining the MHV is preserved to maintain the venous drainage to segment IVb. In case of large segment IVb hepatic vein joining high above MHV/LHV/IVC, it is dealt by venoplasty and modification of anastomosis or by venous grafts (LPV graft/cryopreserved grafts).

TAIWAN GROUP

Chen et al¹⁷ addressed the MHV controversy and developed an algorithm for right lobe graft (RLG)

1. If the GRWR is >1%: RLG is harvested without MHV
2. If the GRWR is <1%:
 - a. RLRSV(right lobe-to-recipient standard liver volume) <50%: RLG is harvested with MHV.
 - b. RLRSV >50%
 - i. Prominent RHV; V5 and V8 <5 mm: RLG without MHV
 - ii. Multiple and small RHV / Dominant MHV: RLG with MHV



Figure 10.24: RHV (long arrow) and IRHV (short arrow) in a RLG with V8 reconstruction, V5 branch is small and is ligated. Portal vein cannula shown by black arrow

(B) LEFT LATERAL SEGMENT (SEGMENT II AND III)

This graft is used in pediatric patients. Left lateral segment graft includes harvesting segments II and III, without caudate lobe (segment I). Donor preparation and position are same as described in donor hepatectomy for left lobe graft. Approach is by bilateral subcostal incision with midline vertical extension or midline incision extending from xiphisternum to 1 inch below the umbilicus. Cholecystectomy is not routinely performed. However some centers perform cholecystectomy for 2 reasons. One reason to perform cholecystectomy is that it facilitates to perform operative cholangiogram and the other is denervation of gallbladder during surgery, aggravates the gallstone formation. Procedure for intraoperative cholangiogram is mentioned earlier (**Figures 10.27 and 10.28**). Hilar dissection is performed to isolate LHA and LPV till the bifurcation and encircle both structures with a loop.

During dissection of LHD, a marker stitch with 6-0 prolene or a ligaclip is applied at the proposed level of transection. Occasionally right anterior or posterior sectorial ducts join the LHD. More commonly the right posterior one, if present precaution should be taken to preserve them.¹⁹ Junction of segment IV duct with biliary tract is variable and may join LHD, umbilical fissure or confluence of both ducts, and should be protected.¹⁹ Hilar dissection is continued to isolate LHA and LPV and are encircled. Caudate branches from LPV are divided and ligated to obtain sufficient length of LPV for implantation.

Check for aberrant LHA from LGA in gastrohepatic ligament (**Figures 10.26 and 10.27**), if present, maximum length of the vessel is preserved. Then the left lateral segment is lifted medially and ductus venosum is dissected and divided. Line of parenchymal transection is slightly towards the right of falciform ligament and is marked on the liver surface with a diathermy. Liver transection is performed with CUSA without inflow control to avoid warm ischemia (**Figure 10.29**). Near the umbilical fissure, the line of transection is deviated to right in order to avoid damage to segment II and III pedicles.

Segment IV pedicles are encountered during transection are individually ligated and divided. Occasionally segment IV duct joins the LHD near the confluence. These variations should be kept in mind during dissection. If the transection is made very close to the umbilical fissure, segment II and III ducts may be injured. When LHD is reached, it is partially opened with scissors (previously marked by cholangiogram) and probe is passed proximally and distally into the LHD to confirm safety of confluence of the RHD and LHD. Then LHD is divided completely with scissors (**Figure 10.32**) and opening of CHD is closed with 6-0 PDS sutures. Minor caudate lobe bile ducts if present are ligated and divided to prevent bile leak. Transection is continued towards cranial end till MHV and LHV junction. Segment IV hepatic vein draining the LHV is ligated and divided.

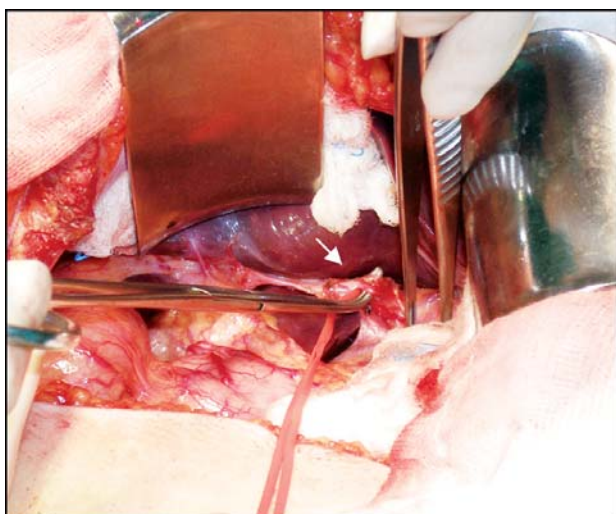


Figure 10.25: Left hepatic artery originating from left gastric artery

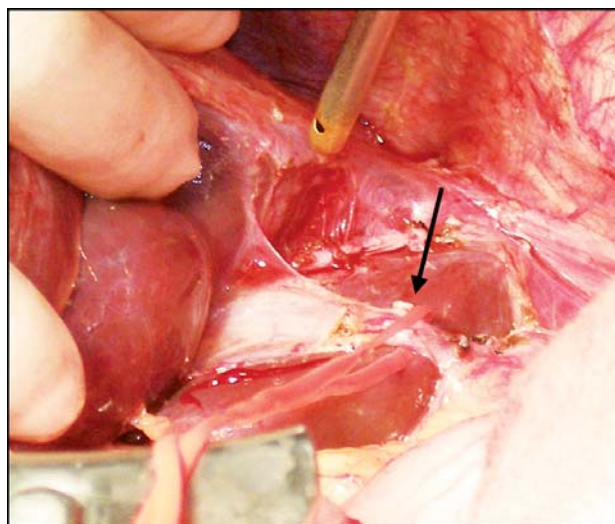


Figure 10.26: LHA after complete dissection from left gastric artery

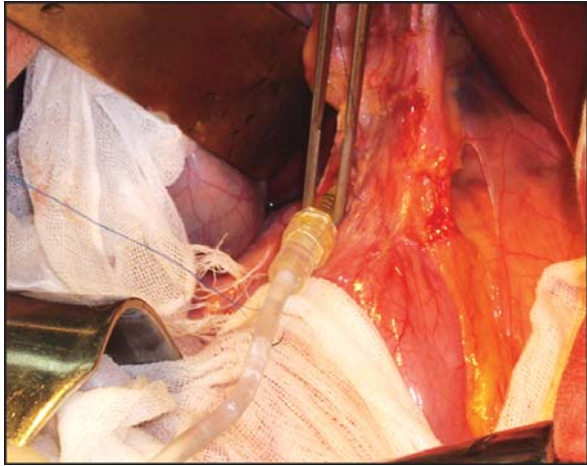


Figure 10.27: CBD cannulation for cholangiogram in a donor with a narrow cystic duct

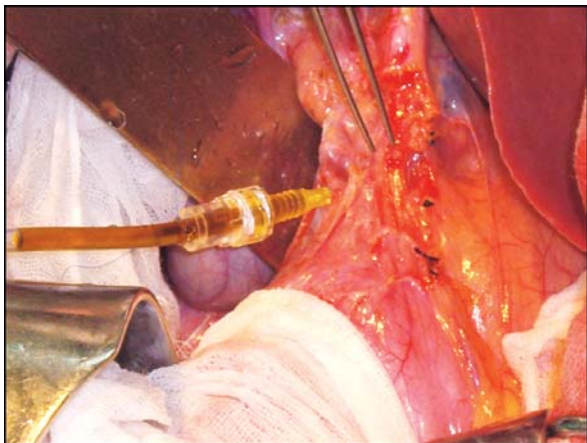


Figure 10.28: CBD cannulation for cholangiogram. Bile flow in the cholangiogram catheter

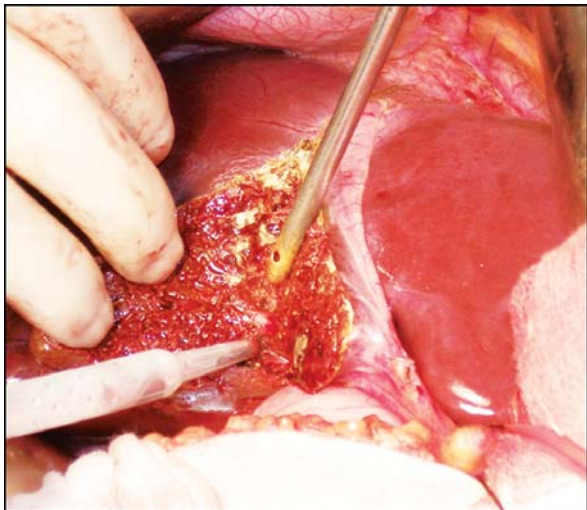


Figure 10.29: Parenchymal transection

During the deep dissection of parenchyma, MHV is visible and care is taken not to injure it and dissection is followed along the MHV to reach the confluence of LHV or IVC. Dissection plane is turned more horizontally towards the ductus venosum. Lateral segment graft (**Figure 10.33**) is harvested by double ligation of LHA on donor side and clamping of LPV and LHV (**Figures 10.30 and 10.31**). Then divide all the structures. Care is taken to preserve long LPV. All the vessels on donor side are closed with 6-0 prolene. Methylene blue test is optional to check for bile leak. Graft is flushed with UW/HTK solution 500-1000 ml through left portal vein cannulation (**Figure 10.33**). Some centers flush the bile duct and artery with HTK solution. But the probability of intimal damage of hepatic artery must be kept in mind while flushing the hepatic artery. Abdomen is closed in layers after hemostasis.

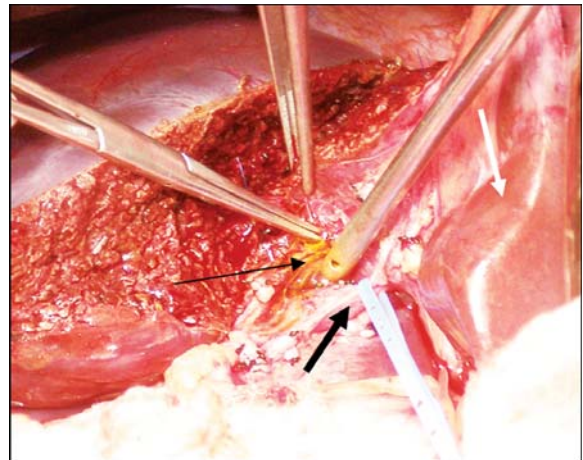


Figure 10.30: Left portal vein (black arrow), left lateral segment (white arrow) and bile duct (long black arrow)

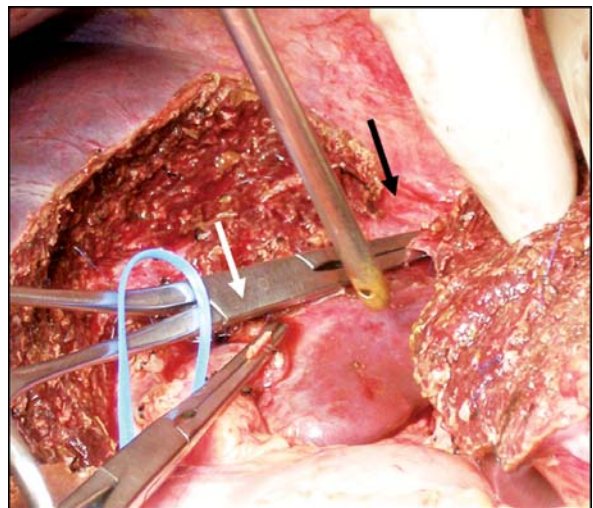


Figure 10.31: Left hepatic vein (black arrow) left portal vein (white arrow)

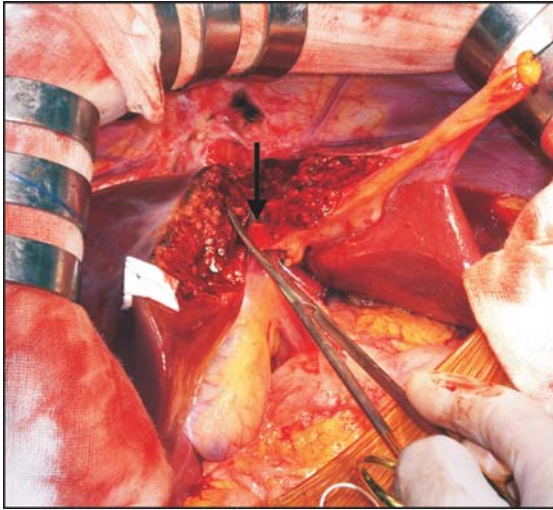


Figure 10.32: Transection of bile duct in a lateral segment graft (black arrow)

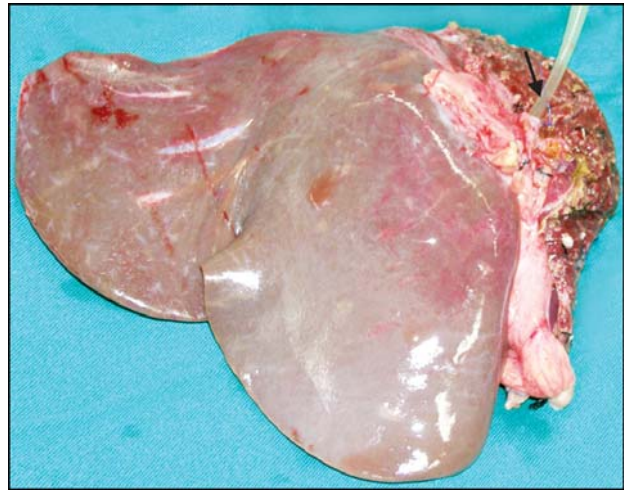


Figure 10.33: Left lateral segment graft (Segment II and III). Cannulation of left portal vein (black arrow)

(C) RIGHT POSTERIOR SEGMENT OR RIGHT LATERAL SECTOR GRAFT

Right lateral sector grafts were used in Japan. Right posterior segment graft includes segment VI and VII of liver. These grafts are harvested less frequently due to the technical difficulties. It is indicated when the left lobe graft along with caudate lobe is too small to use in the recipient and <30% of standard liver volume. It is indicated when donor right liver is >70% of total donor liver volume, thus precluding full right lobe donation and is greater than that of left lobe along with caudate lobe.^{22,23} It is also indicated when posterior segment is >40% of recipient's standard liver volume.²²

Advantages

- Risk of graft rotation is very less
- Easy positioning
- Complete venous drainage.

Disadvantages²⁰⁻²²

- Intrahepatic branching of relevant portal vein, hepatic artery and bile duct make it technically difficult to harvest
- Anatomical variation of biliary and venous systems
- More biliary complications
- Increased bleeding during parenchymal transection.

Sugawara et al reported that there is an increased biliary complication rate and increased blood loss in harvesting these grafts.^{2,4} Few results of these grafts are reported from Japan and Korea, where the deceased donors are not easily available. Surgical techniques are similar to right lobe graft regarding right lobe mobilization, intraoperative ultrasonography except that hilar dissection involves isolation of posterior branches of RHD, RPV and RHA. Temporary short time clamping of posterior branches of RHA and RPV will delineate the line of demarcation and parenchymal transection is carried as mentioned earlier without inflow control.

(D) LEFT LOBES GRAFT

In LDLT, left lobe graft is an important option provided that the benefit to the recipient is balanced against the safety of the donor.²⁴ Left lobe graft can maintain good viability and regeneration after adult to adult LDLT.²⁵ Minimizing the risk to the donor, left lobe LDLT could be an ideal option in adult to adult LDLT. In the Western world, the concept of left-lobe graft donation for adult recipients has been almost abandoned, without sufficient data having been accumulated. In 1993, first successful left lobe LDLT was performed in Japan.³⁸ The patient was 53 years old female patient with primary biliary cirrhosis was successfully treated by a left lobe of her son's liver as a graft. Volumetric analysis demonstrated rapid enlargement of the graft from 402 to 1141 ml as early as 2 weeks after the operation.³⁸

Left lobe grafts are frequently too small for adult recipients, and this may lead to small for size (SFS) syndrome presenting as prolonged ascites or cholestasis.^{26,27} Portal vein pressure (PVP) showed a significant correlation with daily production of ascites during the first 2 weeks after surgery. It is well known that leakage of ascites into the peritoneal space occurs as a result of sinusoidal hypertension.³⁷ It has been speculated that graft exposure to excessive portal vein flow (PVF) plays a major role in the development of SFS syndrome. To avoid graft congestion due to excessive portal perfusion, several techniques for modulation of graft portal inflow, such as splenic artery ligation,^{27,28} splenectomy²⁸ and portosystemic shunt,²⁹⁻³¹ has been performed in LDLT. PVF should be reduced to less than 250 mL/min/100 gm of graft weight using graft inflow modification.^{27,32} General selection criteria for grafts in adult-to-adult LDLT included an estimated graft volume-to-recipient standard liver volume (GV/SV) ratio equal to or greater than 30%.

Based on this early success, LDLT using left liver grafts for adult patients good results achieved in Japan, when the graft volume (GV) exceeds 30% of the SV. Kyoto group developed an algorithm for graft selection in which left lobe donation is considered primarily if the GRWR is estimated to be greater than 0.6% in preoperative assessment with utilization of a hepatoporticaval shunt (HPCS) based on PVP. Purpose of HPCS is to reduce the PVP. Japanese have devised left liver along with caudate lobe graft, which avoids the limitations imposed by a low GV to some extent. The procedures involved in left hepatectomy pose less risk to the safety of the living donor than right lobectomy. A lower limit of 30% of the

recipient's SV was set as the GV necessary and when the estimated GV did not exceed 30% of the recipient's SV if only the left liver was used, but did exceed 30% if the graft included the caudate lobe, then left liver plus the caudate lobe as the graft is harvested.

Hemodynamic study from earlier reports already confirms that in standard liver transplantation, increased portal flow is a common feature.^{33,34} In DDLT using a whole liver graft, the mean PVF has been reported to be around 130 mL/min/100 gm graft weight.³³ But in partial liver grafts are exposed to even higher portal inflow.³⁵ Hemodynamic changes are much more pronounced than those occurring in DDLT, and are inversely correlated with the GV/SV ratio. An increase in flow of this magnitude could be predicted if it is assumed that a left lobe graft, representing about 30–40% of the mass of the native organ, must passively receive all of the native portal inflow. Patients with a PVF exceeding 260 mL/min/100 g graft weight or PVP to 20 mmHg or more is associated with a poor outcome and graft dysfunction with hyperbilirubinemia, coagulopathy and severe ascites.³⁶⁻³⁸

An increase in portal pressure may cause elevation of hydrostatic pressure within the liver sinusoids. In Japan patient survival rates after LDLT using left liver grafts were 89%, 84% and 84% at 1, 3 and 5 years, respectively.^{39,40} Efforts to avoid portal venous congestion and to shorten the graft preservation period might have contributed to good results. Using the left lobe graft along with the caudate lobe and temporary APOLT (Auxiliary partial OLT) have allowed the indications to be widened to some extent, particularly in Japan.^{41,42}

SURGICAL TECHNIQUES

Left lobe graft involves harvesting segments II, III and IV with or without caudate lobe (segment I). Caudate lobe is included in graft when left lobe graft size is less to meet the demand of recipient.⁴³ Donor preparation and position are same as described in RLG. Abdomen is opened by bilateral subcostal incision with midline vertical extension or inverted L-shaped incision. Gallbladder is dissected from liver bed and before cholecystectomy, a 3.5 Fr. cannula is inserted into the cystic duct and clamped with atraumatic vascular clamp, followed by intraoperative cholangiography using undiluted radiographic contrast and an image intensifier (Figures 10.38 and 10.39).

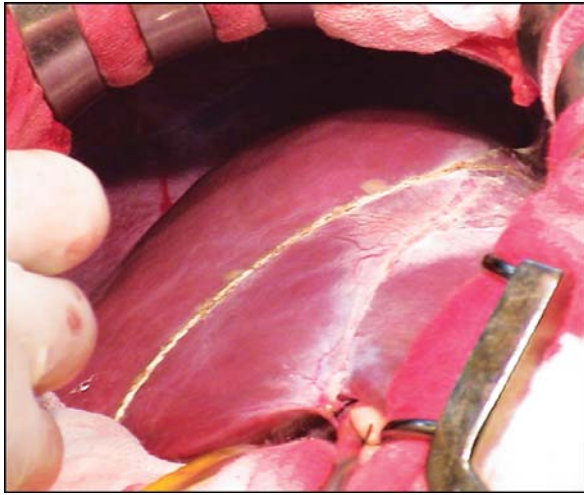


Figure 10.34: Line of transection for left lobe graft, marked with diathermy

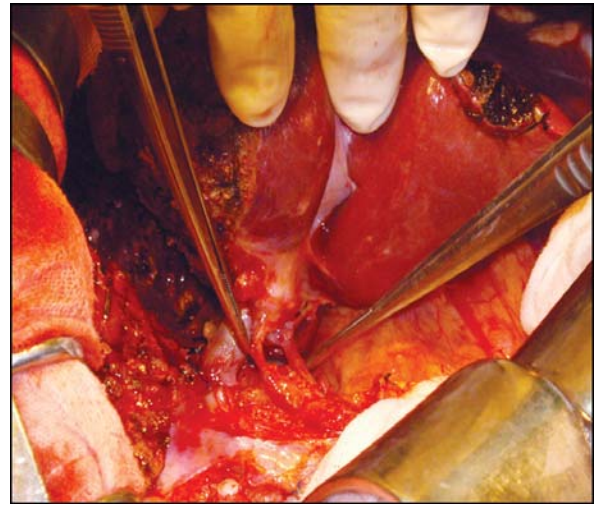


Figure 10.36: Left hepatic duct, middle (segment 4) and left hepatic arteries in a left lobe graft

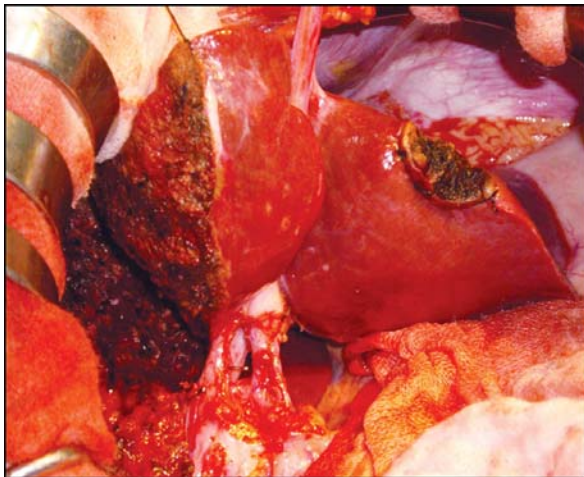


Figure 10.35: Left lobe graft with left hepatic duct and hepatic artery

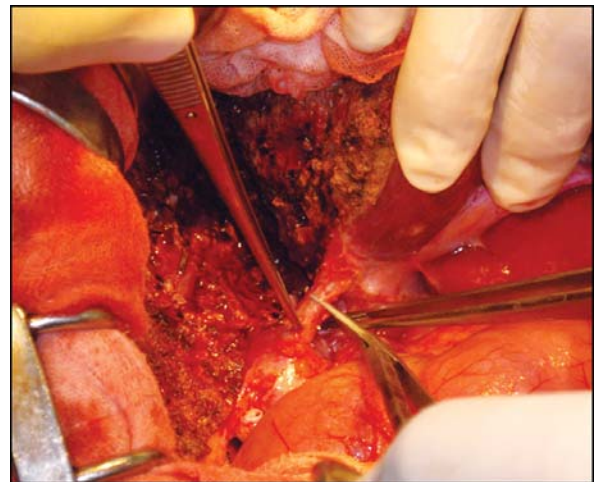


Figure 10.37: Transection of left hepatic duct in a left lobe graft

A marker stitch with 6-0 prolene or a ligaclip is applied at the proposed level of transection of LHD at a later stage. Hilar dissection is performed to isolate and LHA and LPV till the bifurcation and encircle both structures with a loop. Dissection of part of LHA near the umbilical fissure is avoided to prevent ischemia. Search for any aberrant LHA from left gastric artery is performed, if present; carefully dissect as long as possible. Caudate lobe branches near junction of RPV and LPV are divided, but the branches from LPV to caudate lobe are preserved.

Intraoperative Doppler US study will allow the surgeon to study:

- The anatomy and confluence pattern of LHV and MHV, draining the segment II, III and IV.
- A small branch of segment II hepatic vein may drain directly into IVC.
- The course and location of MHV and its branches to segment 5 and 8, which will guide the plane of transection at a later stage of hepatectomy.
- Configuration of the junction of the MHV and LHV⁴⁴

The position of MHV is marked on the liver surface with a diathermy after intraoperative USG examination. Falciform, coronary and left triangular ligaments are divided to mobilize the left lobe. Avoid injury to left phrenic vein during mobilization. Left phrenic vein entering LHV is ligated to get longer length of LHV during graft delivery.⁴⁵ Small caudate lobe veins to IVC are divided and large branch to IVC is preserved with the

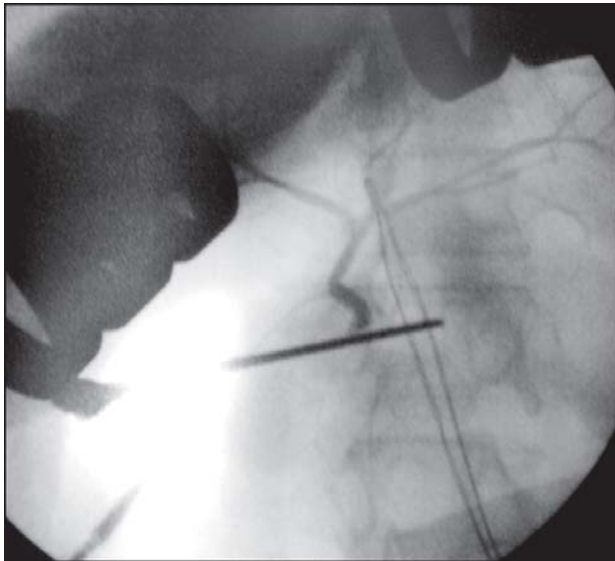


Figure 10.38: Intraoperative cholangiogram in a left lobe donor before transection of bile duct. Radioopaque loop in the left hepatic duct

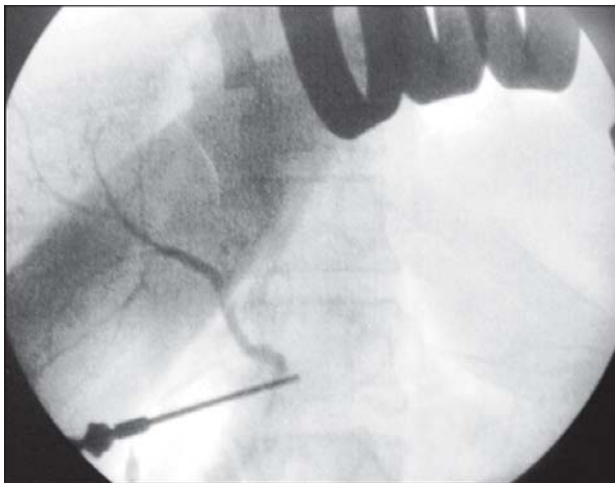


Figure 10.39: Intraoperative cholangiogram in a left lobe donor after donor hepatectomy

graft for anastomosis in the recipient. Ductus venosus is dissected, ligated and divided. Common trunk of MHV and LHV is dissected and looped close to the IVC. A demarcation line will appear after clamping of LPV and LHA for short time and liver surface is marked with diathermy (**Figure 10.34**) in the line of transection according to color change. Course of MHV is also considered during marking the line of demarcation. On the inferior surface of liver, line of transection starts from gallbladder fossa and turns medially towards the hilar plate and ends at the proposed level of transection of LHD as marked earlier by cholangiography. The course of

MHV guides the plane of transection of left lobe. Donor LPV flow and donor LHA flow (HAF) are measured before starting dissection of the liver parenchyma. Parenchymal transection is carried out with CUSA without inflow control to avoid warm ischemia to graft.

Usually segment V hepatic vein draining the MHV is ligated. When segment VIII hepatic vein draining into MHV is large, it can be preserved along with a part of MHV, but the length of MHV in the graft will become shorter in this case. MHV in graft can be reconstructed by dissecting and keeping MHV or RHV of the recipient long enough to reconstruct MHV of the graft. Care is taken not to injure the MHV when dissecting very close to it because massive bleeding from MHV is difficult to control. An injury to MHV can be repaired with 6-0 prolene with inflow control. Parenchymal transection is continued till the caudate lobe in an oblique fashion guided by MHV and a penrose drain or tape is passed behind the caudate lobe to lift the liver which guides the proper plane of transection.

After parenchymal transection, hilar plate is approached and the LHD duct partially opened with scissors (as marked during cholangiography) and probe is passed proximally and distally into the LHD to confirm safety of confluence of the RHD and LHD. Skeletonization of LHD is avoided to preserve its blood supply and to avoid biliary complications in the recipient. Then LHD is divided completely with scissors (**Figure 10.37**). If the caudate lobe hepatic duct is small, it can be ligated and if it is large then preserve it for anastomosis in the recipient. Bile duct opening on hilar side is closed with 6-0 PDS sutures. Graft harvesting is completed by double ligation of LHA on donor side, followed by clamping and division of LPV (**Figures 10.35 and 10.36**), caudate lobe vein and confluence of MHV and LHV.

During the back table procedure, the graft is immersed in ice sludge and flushed with 1 liter of UW (University of Wisconsin) or HTK (Histidine tryptophan ketoglutarate) solution through the left portal vein cannula. Openings of all the veins (**Figure 10.40**) are sutured on the donor side, LPV with 6-0/7-0 prolene and MHV, LHV with 4-0/5-0 prolene sutures. Methylene blue test is optional to check bile leak from the cut surface of liver, depending on the center protocol. Cut surface of the remnant liver is checked for hemostasis (**Figure 10.41**). Cut surface of the graft is covered with fibrin glue. Most of the centers at present don't use drain. Abdomen is closed in layers after hemostasis. If a donor left hepatectomy is performed without harvesting caudate lobe, the left portion of the caudate lobe is left without a blood supply or bile drainage system, because of the anatomy of the liver. This results in atrophy of the left

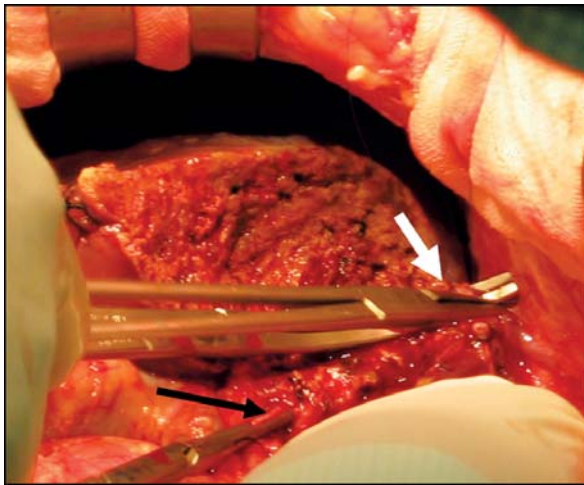


Figure 10.40: Vascular clamps applied on left hepatic vein (white arrow) and left portal vein (black arrow)

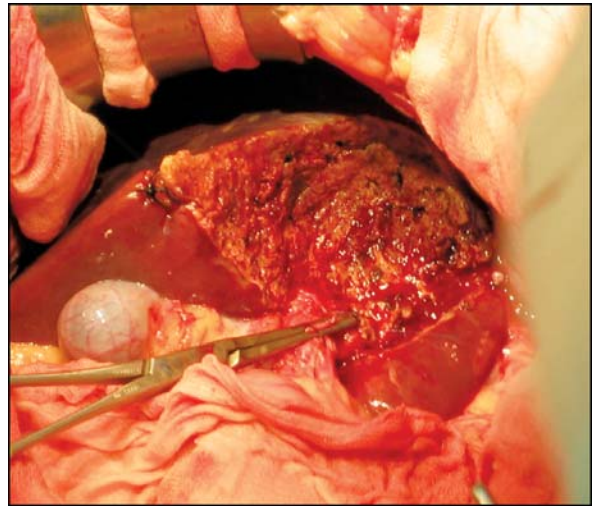


Figure 10.41: Remnant right lobe in a live donor after left lobectomy

caudate lobe in the donor. When the caudate lobe is included in the left lobe graft, caudate lobe is able to function in the recipient. Kawasaki et al. developed a technique for harvesting the donor's left liver along with the caudate lobe.⁴⁶

Postoperatively parenteral nutrition support consists of branched-chain amino acid-enriched solution (BCAA) and medium-chain triglycerides (MCT). Low dose dextrose solution, vitamins and phosphates are given for 2-3 days to enhance regeneration of the remnant liver.¹⁵

(E) DECEASED DONOR HEPATECTOMY

DECEASED DONOR HEPATECTOMY

Whole liver can be harvested from 2 sources:

- Heart-beating donors/Donation after brain death (DBD)/Neurological death (DND)
- Non-heart-beating donors/Donation after cardiac death (DCD)

IDEAL DONOR

Criteria for an ideal donor are mentioned in the table on next page. Any deviation from the ideal donor criteria, are considered as marginal donors. Practically in most of the centers in USA and Europe, many of the donors are marginal due to the organ shortage and long waiting list. Practically it is always difficult to get an ideal donor. In older donor with severe fatty change increases the

incidence of primary nonfunction or initial poor function. In the present transplant scenario, marginal donors are no longer considered as absolute contraindication.

The decision to accept a marginal donor depends on the severity of recipient's disease. Inspection of by an experienced transplant surgeon and histological examination by liver biopsy specimen will help in taking proper decision to select the deceased donor. ABO blood type matching is required. In pediatric patients, reduction in the size (reduced size transplant) of the graft is required allowing 1/10 of mismatch between donor and recipient. Smaller grafts can be accommodated to larger individuals but is not true for vice versa. While using older donors cold ischemic time should be kept as minimum as possible and in donors of age >60 years, the graft outcome is similar as compared to younger donors.

Ideal deceased donor

- Age < 50 years
- No hepatobiliary disease/abnormal liver function tests-not more than 3 times the normal limit for LFTs)
- Hemodynamic and respiratory stability (SBP>100 mm of Hg, CVP <5 cm of H₂O)
- Acceptable hemoglobin and pO₂
- No H/O severe abdominal trauma, malignancy, systemic infection, hypernatremia
- Urine output >50 ml/hr with diuresis
- Absence of acidosis
- No signs of hypothermia
- Normal creatinine level
- Lower requirement of ionotropic agents
- ICU stay not >5 days
- Absence/Mild degree of fatty change
- No H/O alcohol dependency
- Seronegativity for hepatitis B and C

Prediction of donor risk factors associated with worse clinical outcome

- All marginal donors
- Female gender
- Race other than Caucasian
- Prolonged cold ischemic time
- ABO mismatch
- Death due to stroke

Contraindications for harvesting deceased donor liver

- HIV positive patients
- Active viral disease (Hepatitis B/C)/Cirrhosis
- Extra-cerebral malignancy
- Profound irreversible hypotension
- Severe trauma to liver

SURGICAL TECHNIQUES FOR HARVESTING DECEASED LIVER

Patient is placed in supine position with arms abducted. Abdomen is opened by an incision extending vertically from suprasternal notch to pubic symphysis and transversely extending upto both flanks at the level of umbilicus for multiorgan donation (**Figure 10.42**). Sternum is split opened and self-retaining retractors are applied. Liver is inspected as a whole for color, texture, pathological lesions and any anomalies of arterial supply. Round ligament is ligated and cut. Right colon and terminal small intestine are mobilized cephalad and retracted to left. Kocher maneuver is performed to mobilize the duodenum. Peritoneal reflections between the duodenum and retroperitoneal areas are dissected and incised exposing entire retroperitoneal structures like Aorta, IVC, both renal veins, SMA, IMA, IMV and both iliac arteries and veins. Peritoneal coverings and lymphatic tissue over the aorta are dissected to expose the aorta. Inferior mesenteric artery is ligated and divided.

DONORS WITH POSITIVE SEROLOGY HBV/HCV

- Donors with positive serology for hepatitis B (HBcAb +ve) or hepatitis C can be used in the respective positive serology patients provided that a baseline liver biopsy demonstrating no active hepatitis or cirrhosis.
- In these cases post-transplant prophylaxis for the respective viruses should be continued as per the standard protocols.
- In recipients with +ve serology for HBV who are positive for Anti HBsAb can be protected from infection, but positive for only HBcAb (core antibody) can still become infected when transplanted from a HBV +ve serology donor. Post-transplant antiviral treatment is determined by recipient anti HBsAb titers.
- HCV positive donors can be used in HCV +ve recipients depending upon the severity ESLD or MELD score. However such use is limited unless there is an emergency situation. They can't be used in HCV -ve recipients.

Adequate management of the donor prior to and during the transplantation is required for early graft function. Always avoid prolonged warm (WIT) and cold ischemia (CIT). For multiorgan donation, respective thoracic, cardiac teams must be coordinated with the abdominal team.

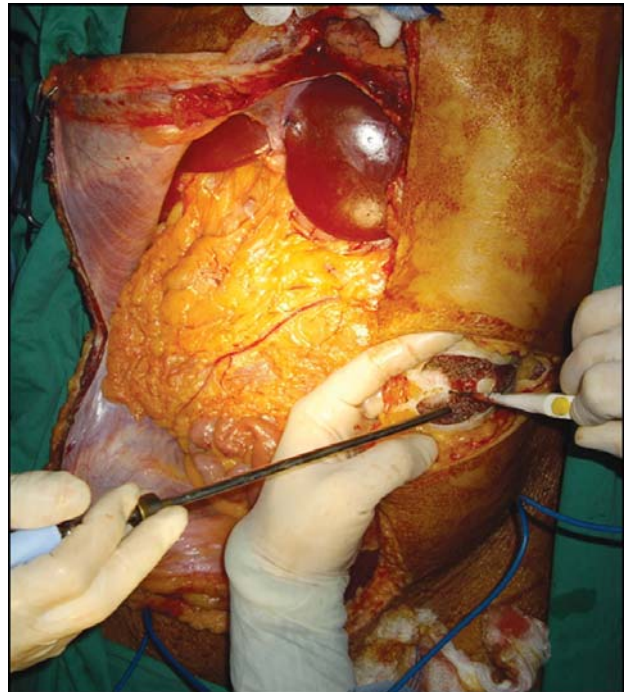


Figure 10.42: Abdominal incision in deceased donor

Aorta is looped with 2 loops/umbilical tapes for cannulating (**Figures 10.43 and 10.44**) at a later stage.

After complete dissection of IMV/Splenic vein, it is cannulated for infusion of cold plasmolyte solution for precooling (**Figures 10.49 to 10.51**). Left lobe of liver is mobilized by dividing the falciform, coronary and left triangular ligaments. Left lateral segment is retracted medially and dissection is carried around proximal stomach on lesser curvature, gastroesophageal junction and crura of diaphragm, to retract the esophagus to left for exposing the supraceliac aorta (**Figure 10.46**). Dissection around the anterior and lateral aspects of supraceliac aorta is completed to encircle it with an umbilical tape/loop (**Figures 10.47 and 10.48**) for cross clamping at a later stage.

Search for anomaly/variation/aberrant vascular supply to liver by careful inspection and finger palpation method. Dissection is continued around the duodenum and distal CBD, care is taken to avoid injury to replaced/low take off RHA. Distal CBD is ligated and cut distal to the insertion of cystic duct. Gallbladder is flushed with isotonic saline solution to flush the GB and bile duct completely.

Then mobilization of the left colon is performed and a space is prepared for ice cooling for left kidney. 30,000 units of heparin is given via central line before clamping the aorta and the abdominal aorta is cannulated by ligating with umbilical tape proximally and a cross clamp distally (**Figure 10.45**). Cannula is secured by a suture on the wall of aorta. Umbilical tape and cross clamp are released. Then a cross clamp is applied over the supraceliac aorta. Another surgeon transects the vena cava at the caval-atrial junction to allow exsanguinations of abdominal organs. 3-5 liters of UW/HTK solution (50-60 ml/kg) is run through the aortic and IMV/Splenic vein cannulae. 2-3 liters of UW/HTK soln. is flushed through aortic cannula and 1-2 liters through IMV/splenic vein. Liver, kidney and pancreas are completely covered with crushed ice for facilitating rapid cooling of abdominal viscera.

Diaphragm is divided vertically in anteroposterior direction down to the aorta in midline. Retraction of esophagus gives better field for dissection. Right diaphragm is cut along the right lobe and part of diaphragm is left on the liver surface which can be cleared during back table dissection. Duodenum is retracted and gastroduodenal artery (GDA) is dissected and traced till common hepatic artery (CHA) and minimal dissection is carried out along proximal and distal parts of CHA. GDA is ligated and cut with silk away from its junction to CHA. Splenic artery is dissected, ligated and divided. Dissection around the celiac trunk and aorta is carried out and the celiac trunk is lifted along with part of aortic

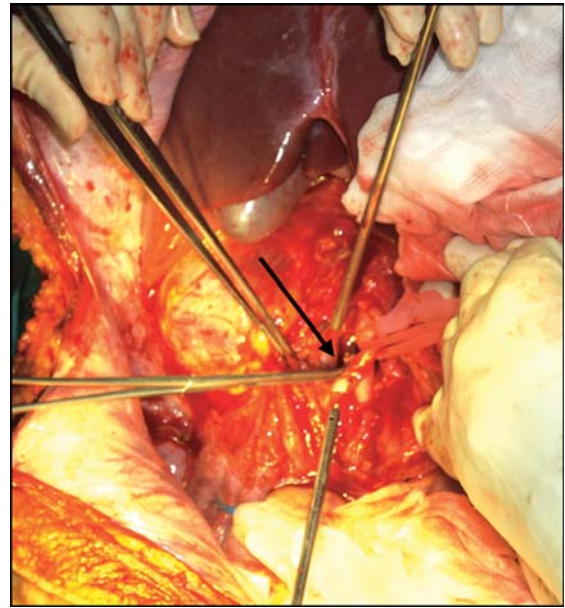


Figure 10.43: Looping of infrarenal aorta

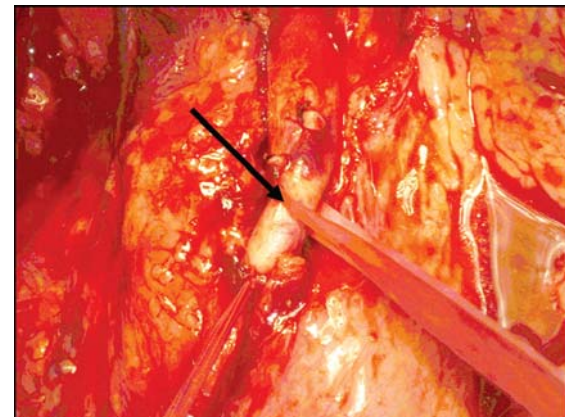


Figure 10.44: Looping of abdominal aorta (Infrarenal aorta: close view) for multiorgan donation

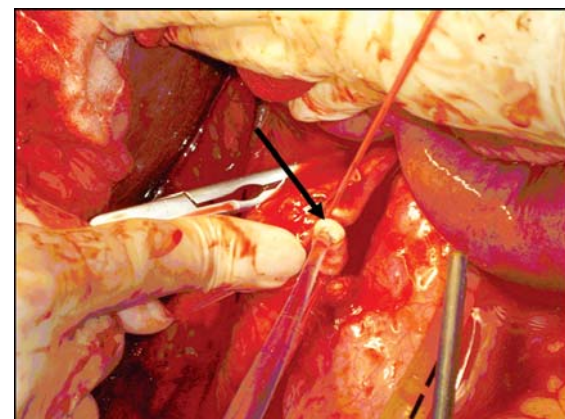


Figure 10.45: Transection and cannulation of abdominal aorta

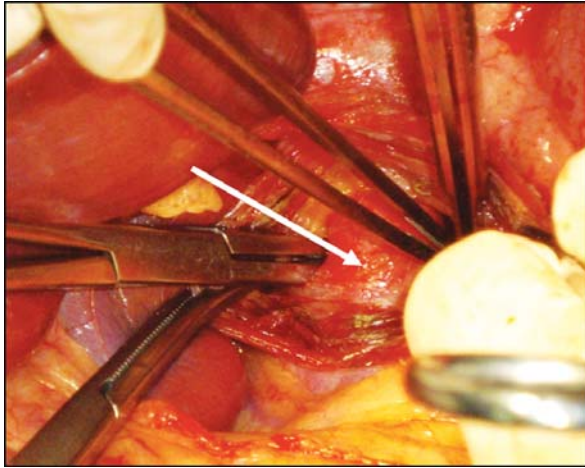


Figure 10.46: Dissection of supra-celiac aorta

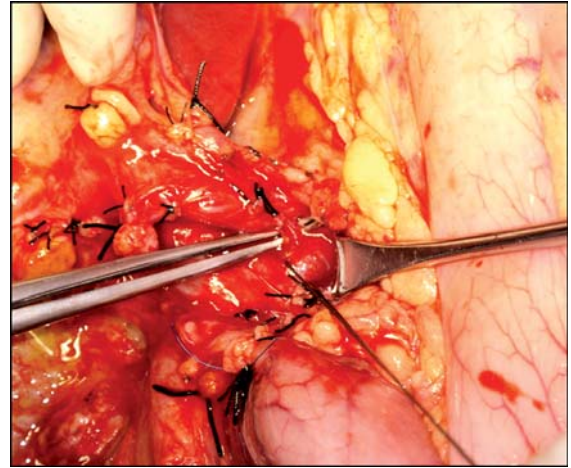


Figure 10.49: Dissection of splenic vein

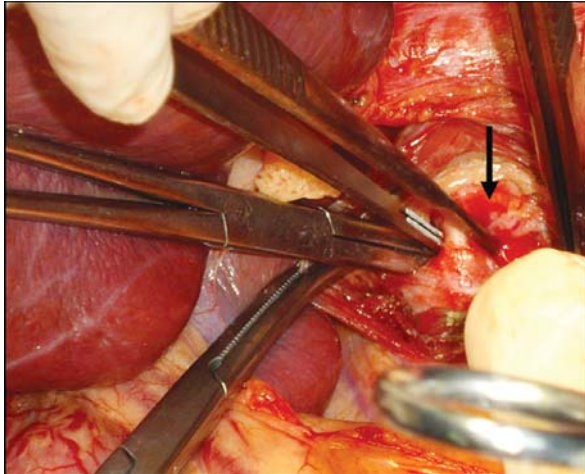


Figure 10.47: Mobilization of supra-celiac aorta. Left lateral segment is retracted medially and esophagus is retracted laterally

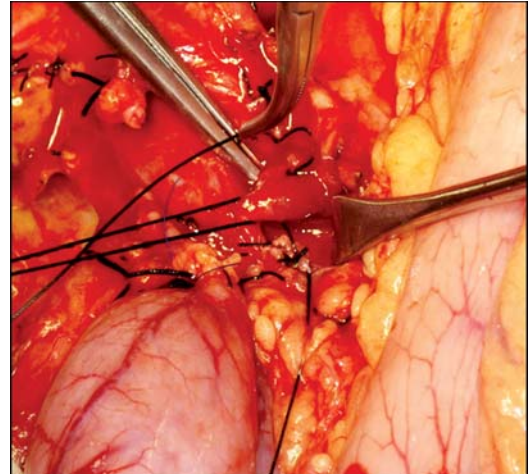


Figure 10.50: Looping of splenic vein for cannulation

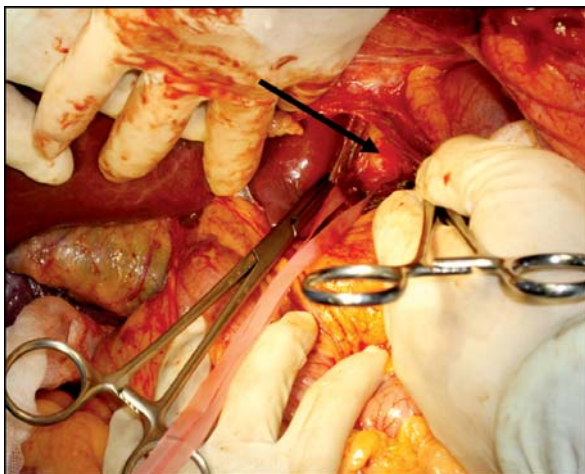


Figure 10.48: Looping of supra-celiac aorta

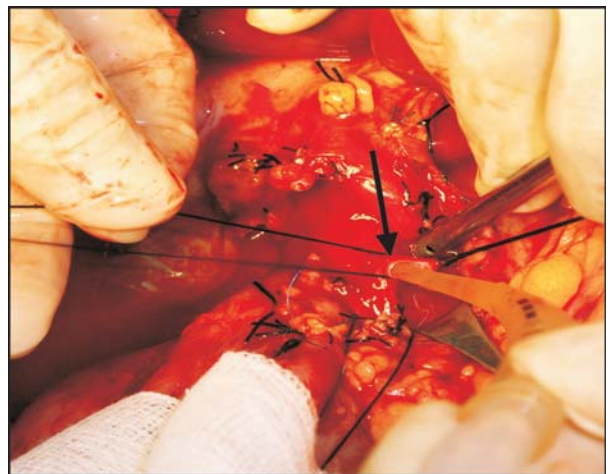


Figure 10.51: Splenic vein cannulation

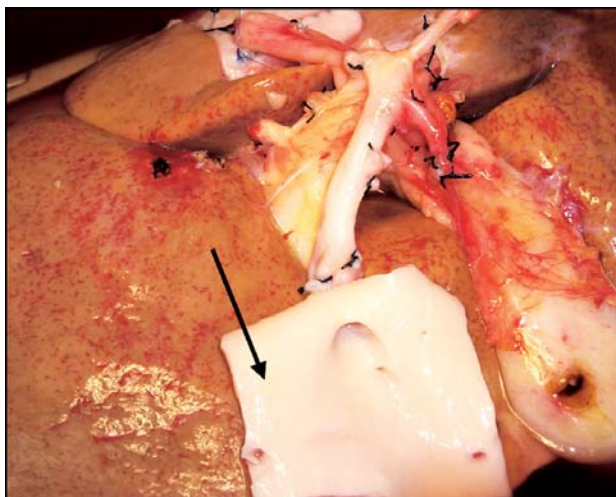


Figure 10.52: Carrel patch

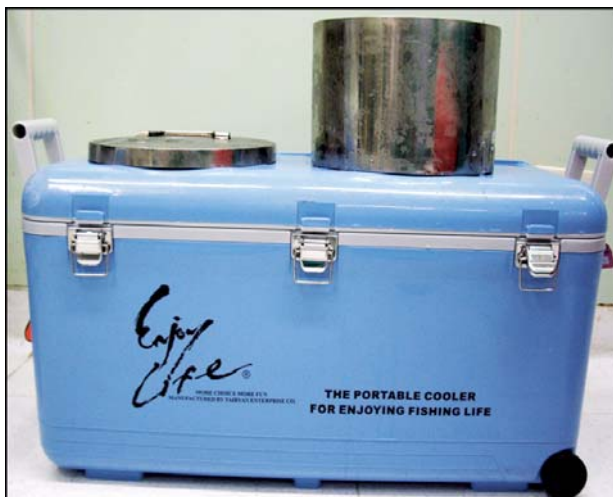


Figure 10.54: Box packed with ice for transporting liver graft after harvesting from the donor



Figure 10.53: Brain dead donor liver. (DDLT)

wall (used as carrel patch in recipient) (Figure 10.52) after transecting the supraceliac aorta below the cross clamp. Left gastric artery must be preserved along with celiac trunk, if there is a replaced LHA from LGA. While dividing the lower end of aorta along with the celiac trunk care is taken not to injure the renal vessels.

Portal vein (PV) is identified by dividing the fibrous tissue at the superior margin of pancreas. If the pancreas is not harvested, the head of pancreas is divided and superior mesenteric vein (SMV) is identified and cut and mobilized proximally along with PV. Splenic vein/IMV are divided distal to the placement of cannula. Coronary

vein is also ligated. If the pancreas is to be harvested, then PV is divided distal to the coronary vein. Fibrous tissue around the liver hilum, celiac trunk and superior mesenteric artery (SMA) are divided. If RHA originates from SMA, then the aortic patch includes both celiac trunk and SMA opening along with it. A renal artery may arise from SMA; it should be preserved in such cases. Infrahepatic IVC is transected above the renal veins and whole liver (Figure 10.53) is lifted completely by dividing any minor adhesions and placed in a sterile bag and with 500-1000 ml of UW/HTK solution, surrounded by an ice filled container. The Iliac vessels are harvested after the removal of kidneys, if there is a facility for cryopreservation (Figure 10.54). Other vessels like carotid and SMA can also be harvested.

Acknowledgements: Figures 10.1 to 10.5, 10.8 to 10.10, 10.32, 10.38 and 10.39, Contributed and reproduced with permission of Chen CL, CGMH- Kaohsiung medical center, Taiwan.

REFERENCES

1. Marcos A, Ham JM, Fisher RA, et al. Surgical management of anatomical variations of the right lobe in living donor liver transplantation. *Ann Surg* 2000;231:824-31.
2. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med*. 2002;346:1074-82.
3. Hashikura Y, Kawasaki S, Terada M, et al. Long-term results of living-related donor liver graft transplantation: a single-center analysis of 110 transplants. *Transplantation* 2001;72:95-99.
4. Strong RW. Whither living donor liver transplantation? *Liver Transpl Surg* 1999;5:536-38.
5. Surman OS. The ethics of partial-liver donation. *N Engl J Med* 2002;346:1038.

6. Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:818-25.
7. Yamaoka Y, Washida M, Honda K, et al. Liver transplantation using a right lobe graft from a living related donor. *Transplantation* 1994;57:1127-30.
8. Lo CM, Fan ST, Liu CL, et al. Adult-to-adult living donor liver transplantation using extended right lobe grafts. *Ann Surg* 1997;226:261-70.
9. Kawasaki S, Makuuchi M, Miyagawa S, et al. Extended lateral segmentectomy using intraoperative ultrasound to obtain a partial liver graft. *Am J Surg* 1996;171:286-88.
10. Fan ST, Lai ECS, Lo CM, Ng IOL, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995; 130:198-203.
11. Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M. Hilar cholangiocarcinoma-surgical anatomy and curative resection. *J Hep Bil Panc Surg* 1995;2:239-48.
12. Takatoshi I, Tanaka K, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Annals of Surg* 2002;236(2):235-40.
13. Pitre J, Panis Y, Belghiti J. Left hepatic vein kinking after right hepatectomy: A rare cause of acute Budd-Chiari syndrome. *Br J Surg* 1992;79:7948-49.
14. Liu CL, Fan ST, et al. Safety of donor hepatectomy without abdominal drainage: a prospective evaluation of 100 consecutive donors. *Liver transpl* 2005;11:314-19.
15. Fan ST, Lo CM, Lai ECS, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med* 1994;331:1547-52.
16. Hiroshi I, Makuuchi, et al. Anatomical keys and pitfalls in living donor liver transplantation. *J Hepatobil Pancr. Surg* 2000;7:380-94.
17. de Villa VH, Chen CL, et al. Right lobe donor liver transplantation-addressing MHV controversy. *Ann of Surg* 2003;238:277-82.
18. Fan ST, et al. Technical refinement in adult-to-adult living donor liver transplantation using right lobe graft annals of surgery 2000;231(1):126.
19. Ohkubo M, Nimura Y, et al. Surgical anatomy of the bile ducts at the hepatic hilum as applied to living donor liver transplantation. *Ann surg* 2004; 239:82-86.
20. Sugawara Y, Makuuchi M, et al. Right lateral sector graft in adult living donor liver transplantation. *Transplantation* 2002;73(1):111-14.
21. Belghiti J, Kianmanesh R, et al. Surgical techniques used in living donor liver transplantation. *Liver transpl* 2003;9(10):S29-S34.
22. Sugawara Y, Makuuchi M, et al. Right lateral sector grafts as feasible option for partial liver transplantation. *Liver Transpl* 2004;10(9):1156-57.
23. Hwang S, Lee SG, et al. Donor selection for procurement of right posterior segment graft in living donor liver transplantation. *Liver transplantation* 2004;10(9):1150-55.
24. Konishi N, Kawasaki S, et al. Impact of a left-lobe graft without modulation of portal flow in adult-to-adult living donor liver transplantation. *Am J of Transpl* 2008;8(1):170-74.
25. Kawasaki S, Makuuchi M, Matsunami H, et al. Living related liver transplantation in adults. *Ann Surg* 1998;227:269-74.
26. Kiuchi T, Tanaka K, Ito T, et al. Small-for-size graft in living donor liver transplantation: how far should we go? *Liver Transpl* 2003; 9:S29-S35.
27. Tucker ON, Heaton N. The "small for size" liver syndrome. *Curr Opin Crit Care* 2005;11:150-55.
28. Troisi R, Cammu G, Militerno G, et al. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? *Ann Surg* 2003;237:429-36.
29. Shimada M, Ijichi H, Yonemura Y, et al. The impact of splenectomy or splenic artery ligation on the outcome of a living donor adult liver transplantation using a left lobe graft. *Hepato-gastroenterol* 2004;51:625-29.
30. Boillot O, Delafosse B, Mechet I, Boucaud C, Pouyet M. Small-for-size partial liver graft in an adult recipient: A new transplant technique. *Lancet* 2002;359:406-07.
31. Takada Y, Ueda M, Ishikawa Y, et al. End-to-side portocaval shunting for a small-for-size graft in living donor liver transplantation. *Liver transpl* 2004;10:807-10.
32. Masetti M, Siniscalchi A, De Pietri L, et al. Living donor liver transplantation with left liver graft. *Am J Transplant* 2004;4:1713-16.
33. Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 2005; 5:1397-04.
34. Paulsen AW, Klintmalm GB. Direct measurement of hepatic blood flow in native and transplanted organs, with accompanying systemic hemodynamics. *Hepatology* 1992;16:100-11.
35. Payen DM, Fratacci MD, Dupuy P, et al. Portal and hepatic arterial blood flow measurements of human transplanted liver by implanted Doppler probes: Interest for early complications and nutrition. *Surgery* 1990;107:417-27.
36. Marcos A, Olzinski AT, Ham JM, Fisher RA, Posner MP. The interrelationship between portal and arterial blood flow after adult to adult living donor liver transplantation. *Transplantation* 2000; 70:1697-03.
37. Shimamura T, Taniguchi M, Jin MB, et al. Excessive portal venous flow as a cause of allograft dysfunction in small-for-size living donor liver transplantation. *Transplant Proc* 2001;33:1331.
38. Garcia-Tsao G. Ascites. In: Boyer TD, Wright TL, Manns MP, eds. *Zakim and Boyer's hepatology: A textbook of liver disease*, 5th Ed.
39. Yagi S, Iida T, Taniguchi K, Hori T, et al. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. *Liver Transpl* 2005;11:68-75.
40. Hashikura Y, Makuuchi M, Kawasaki S, et al. Successful living-related partial liver transplantation to an adult patient. *Lancet*. 1994;343:1233-14.
41. Y Hashikura, S Kawasaki, et al. Living donor liver transplantation: issues regarding left liver grafts *HPB* 2004;6(2):99-105.
42. Sugawara Y, Kaneko J, Akamatsu N, et al. Left liver grafts for patients with MELD score of less than 15. *Transplant Proc* 2003; 35:1433-34.
43. Soejima Y, Taketomi A, Yoshizumi T, et al. Feasibility of left lobe living donor liver transplantation between adults: An 8-year, single-center experience of 107 cases. *Am J Transplant* 2006;6:1004-11.
44. Takayama T, makuuchi M, et al. Living related transplantation of left liver plus caudate lobe. *K Am coll Surg* 2000;190:635-38.
45. Kawasaki S, Makuuchi M, Miyagawa S, et al. Extended lateral segmentectomy using intraoperative ultrasound to obtain a partial liver graft. *Am J Surg* 1996;171:286-88.
46. Hashikura Y, Kawasaki S, Miyagawa S, et al. Recent advance in living donor liver transplantation. *World J Surg* 2002;26:243-46.
47. Koichi Tanaka and Takako Yamada Living donor liver transplantation in Japan and Kyoto University: what can we learn? *Journal of Hepatology* 2005;42(1):25-28.

Graft Preservation and Bench Procedure

INTRODUCTION

The overall outcomes after liver transplantation have improved significantly, but early graft failure still remains a serious concern because it is associated with higher morbidity and mortality. Cold ischemia and subsequent reperfusion are crucial factors for graft outcome in organ transplantation. Once the graft is harvested, graft PV is flushed with preservation solution and preserved in cold preservation solution (**Figure 11.1**). Maximum tolerable cold ischemic time of liver is 12-24 hours using preservative solution at lower temperature (4°C).²³ Maximum tolerable warm ischemic time (WIT) is usually 2-4 hours, but the allograft should not be exposed more than one hour. In DCD donors the maximum limit of WIT should be 30 minutes.

Currently, in the transplant setting, the term “warm ischemia” is used to describe two physiologically distinct periods.

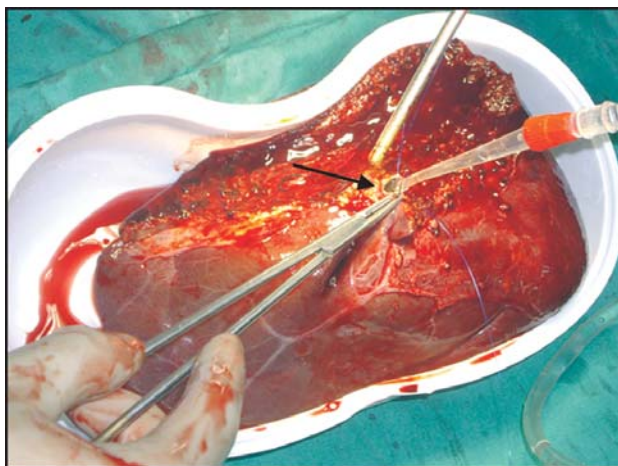


Figure 11.1: LDLT: Right lobe graft—purse-string suture around portal vein for fixation of cannula to perfuse with cold HTK solution

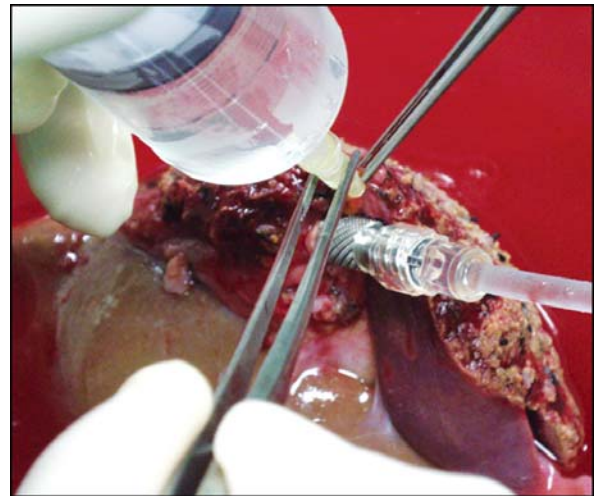


Figure 11.2: Flushing the PV and bile duct with HTK solution in a left lateral segment graft

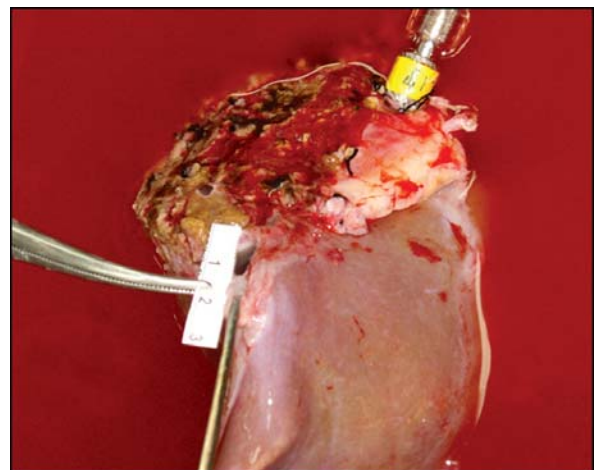


Figure 11.3: Measuring the diameter of hepatic vein with a measuring scale

1. Ischemia of rewarming during implantation, from the time the organ is removed from ice until it is reperfused with recipient blood.
2. Warm ischemia at body temperature (37°C), as may happen in the donor, from the time of cross-clamping or in the case of non-heart-beating donors from the time of asystole until cold perfusion.

Factors influencing increased graft loss after transplantation⁹⁻¹⁸

- Prolonged cold ischemia time (PCIT)
- Moderate to severe macrovascular steatosis
- Operative factors–venovenous bypass
- Venting of mesenteric blood prior to reperfusion and sequence of reperfusion such as early arterialization of the grafts
- DCD (donation after cardiac death) donors
- Older donors
- Diabetic recipient
- Obesity in recipient
- African-American race in the donors

The introduction of UW in liver transplantation improved graft and patient survival.⁵ Components like impermeants, an effective buffering system, and the provision of substrates to regenerate high-energy phosphates may have contributed to this result.⁶ HTK was originally developed for heart preservation and was subsequently introduced in the preservation of human liver grafts.⁷ Both UW and HTK solutions were routinely used in human liver transplantation, and their efficacy to prevent preservation injury was confirmed in experimental and clinical studies.^{7,8} (Table 11.1)

Different organ preserving solutions¹⁻³

- Euro–Collins solution (EC)
- University of Wisconsin solution (UW)
- Histidine–Tryptophan–Ketoglutarate solution (HTK)
- Celsior solution (CS)

Upregulation of adhesion molecules, neutrophil infiltration, microcirculatory alterations, release of chemokines from Kupffer cell activation and lipid peroxidation have all been shown to increase susceptibility to injury of steatosis compared to normal livers for a given cold ischemic time (CIT).^{4,12} The cytochrome P-450 content of the liver has been reported to decline by 16% from the age of 40 to 69 years and by 32% after the age of 70 years.¹⁴ Impairment of energy-dependent and microtubule-dependent transport processes with aging result in 35–40% and 50% decrease in hepatic arterial and bile flow, respectively. Donor age augment the prolonged CIT on graft survival.¹⁹

TABLE 11.1: Composition of different types of preservative solutions

Different components	HTK	UW
Hydroxy ethyl starch (HES), g/L		50
Histidine, mmol/L	198	
Mannitol, mmol/L	30	
Lactobionate, mmol/L		105
Raffinose, mmol/L		30
Glutamic acid, mmol/L		
Phosphate, mmol/L		25
Glutathione, mmol/L		3
Allopurinol, mmol/L		1
Adenosine, mmol/L		5
α-ketoglutarate, mmol/L	1	
Sodium, mmol/L	15	27
Potassium, mmol/L	10	125
Chloride, mmol/L	50	
Calcium, mmol/L	.015	
Magnesium, mmol/L	4	
Magnesium sulfate, mmol/L		5
Tryptophan, mmol/L	2	
Insulin, U/l		100
Dexamethasone, mg/L	8	
Bactrim (Penicillin), mg/L		.5

Different hemodynamic and immunologic alterations exist in heart-beating brain-dead donors (DBD) and donation after cardiac death (DCD) prior to organ procurement which leads to increased graft loss. The negative effects of brain death on donor organ quality have been attributed to increased intracranial pressure and brain ischemia leading to major pathophysiologic changes including cytokine up regulation and autonomic 'storm'. Liver grafts from DCD donors that were subjected to PCIT resulted in worse outcomes.^{19,20} Recipient acuity, intrinsic quality of the organ before procurement, graft ischemia times, and subsequent ischemia-reperfusion injury are important inter-related factors that affect graft function.²¹

CRYOPRESERVATION OF VASCULAR GRAFTS

Cryopreserved vascular grafts are frequently used in liver transplantation mostly in LDLT. These harvested vessels are kept at –180° temperature in liquied nitrogen cylinders in the cryobank.²² Not enough reports available in literature to support how long these grafts can be preserved. Sugawara et al²³ reported that these vessels are packed in a sterile bag and frozen slowly in a programmable freezer at a rate of 1°C/min to –40°C. They can be semipermanently stored in liquid nitrogen until use.

Cryopreservation of vascular grafts is similar to hepatocyte preservation. Vascular grafts are collected

initially in HTK/UW solution. Later they are washed and preserved for a short time of 12-24 hours in antibiotic solution mixed with RPMI 1640 solution. Then they are preserved in using a combination of RPMI medium 1640 and Dimethyl sulfoxide (99.5%) in the ratio of 9:1. Temperature of the cryo-bags/containers with grafts should be gradually lowered over few hours to -40 to -80°C and then they are preserved in cryocylinders at -180°C . Vascular grafts are preserved upto 3 to 5 years by using the above mentioned protocols. In our experience we have safely used these cryopreserved grafts as long as 2 to 3 years after harvesting. Blood type

matching is required while using these vascular grafts in liver transplantation. Each vessel is kept in a sealed container with labeling on the contained mentioning type of vascular graft, date of collection, approximate length and blood type of the deceased donor from whom the graft is harvested. A separate book is maintained mentioning their date of collection, blood group, length of the graft and type of graft (arterial/venous–iliac, ext. jugular, etc.). They are arranged according to their blood groups in the cryocylinder, so that it will be easier to collect the necessary graft whenever it is required (**Figures 11.4 to 11.15**) shows the cryobank and collection of vascular graft from cryobank.



Figure 11.4: Cryocylinder



Figure 11.6: Container with liquid nitrogen



Figure 11.5: Complete circuit



Figure 11.7: Protective gloves



Figure 11.8: Removing the grafts from cryocontainer



Figure 11.9: Grafts are kept in a stand for easy recognition

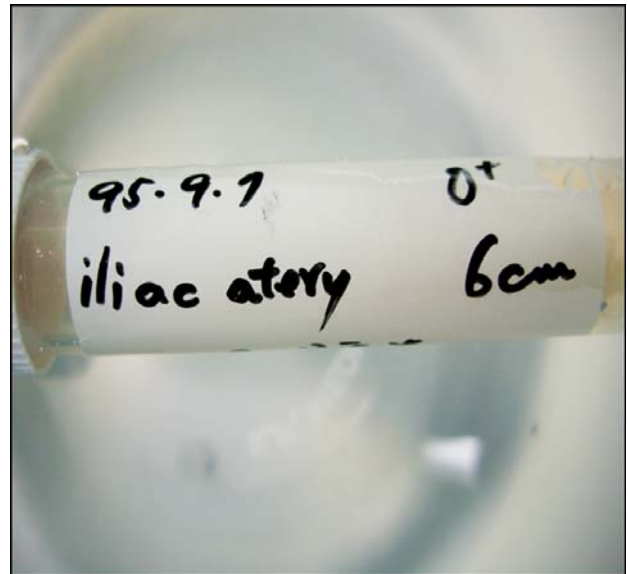


Figures 11.10 and 11.11: Vascular grafts inside a container

BACK TABLE PROCEDURE/BENCH PROCEDURE

During back table procedure, the harvested allograft is prepared for transplantation. After harvesting graft, it is flushed with cold (4°C) HTK or UW solution (1-2 liters in RLG/LLG and 2-3 liters in whole liver graft) as soon as possible through the portal vein (Through the RPV in RLG, LPV in LLG and main PV in whole liver graft). A purse sting suture is applied to secure the cannula in the PV (**Figure 11.1**). Some centers don't use this suture

to preserve max length of PV. Graft is thoroughly flushed with HTK solution until the blood in the venous system is completely washed out. HA and bile duct are also flushed with around 20 ml of HTK solution (**Figure 11.2**). In our experience, we don't flush the HA to avoid intimal damage which may lead to graft loss. During the recipient's operation, some modifications are designed to improve the reconstruction of right hepatic vein, inferior right hepatic vein, and the reconstruction of the tributaries of middle hepatic vein to segment V (V5) and VIII (V8), using interposition vein/arterial grafts.



Figures 11.12 and 11.13: Vascular graft in preservation solution containing sealed container kept in a bowl with distilled water at body temperature



Figure 11.14: Closing the cryocontainer



Figure 11.15: Cryopreserved arterial graft

LIVE DONOR

In LDLT, right lobe graft, V5 and V8 reconstruction is performed with cryopreserved iliac vessel or any vascular graft harvested like internal iliac vein/inferior mesenteric vein/great saphenous vein/external jugular vein/ePTFE graft (**Figure 11.17**). The diameter of the graft vessels is measured with a measuring scale or caliper (**Figures 11.3 and 11.16**) and suitable vascular graft is selected from the cryo-bank. If RLG is harvested with MHV, then a common channel is made with RHV by venoplasty.

Similarly in LLG, a common channel is made with LHV and MHV. If 2-3 IRHVs are present, a common channel may be made by venoplasty or they may be reconstructed separately depending on the location and diameter. In majority of grafts we prefer to preserve the vessels which are more than 5 mm in diameter. Cut surface of the graft is coated with a thin film of glue or tissue glue and then graft is covered with a sterile bag and immersed in an ice packed sterile container with HTK solution.

DECEASED DONOR

The preparation in case of whole liver grafts is very similar to live donor liver. But in whole liver grafts harvested from deceased donors, usually the liver is harvested with part of diaphragm and lot of soft tissue around the CBD, celiac trunk and PV. During the back table dissection all the diaphragmatic tissue is resected and all the vessels are dissected, but care is taken not to dissect CBD completely and not to separate it from HA proper to avoid ischemia to the bile duct and future biliary complications in the recipient. A carrel patch (**Figure 11.20**) is prepared with the celiac trunk for arterial anastomosis. Now a day's usually many centers use

piggyback anastomosis of IVC to IVC with a partial clamp on recipient IVC instead venovenous bypass and replacing the recipient IVC with deceased donor IVC. So in such condition, both ends of IVC are closed with 4-0 prolene sutures (**Figures 11.18 to 11.20**) and a wide opening is made in the center of IVC (**Figure 11.21**) for anastomosis with recipient IVC. All vascular anastomoses and reconstructions with vascular grafts are checked for any leak by flushing HTK solution and making them air and water tight. If any leaks are detected they are sutured. Cold ischemia time should be kept as minimum as possible for better graft function and to avoid complications.



Figure 11.16: Measurement of size of hepatic veins with caliper (Reproduced with permission of chen CL)

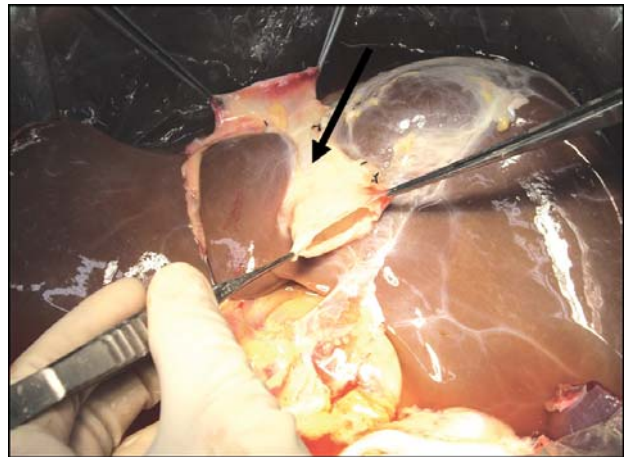


Figure 11.18: Preparation of IVC for piggyback anastomosis (DDLT-whole liver)

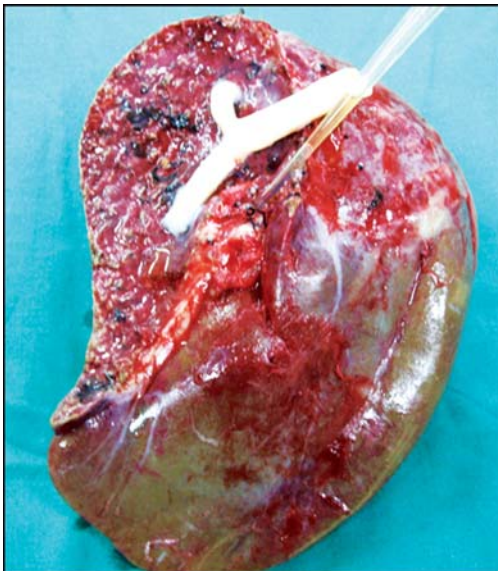


Figure 11.17: Right lobe grafts-V5 and V8 reconstruction with a cryopreserved iliac artery graft during back table procedure

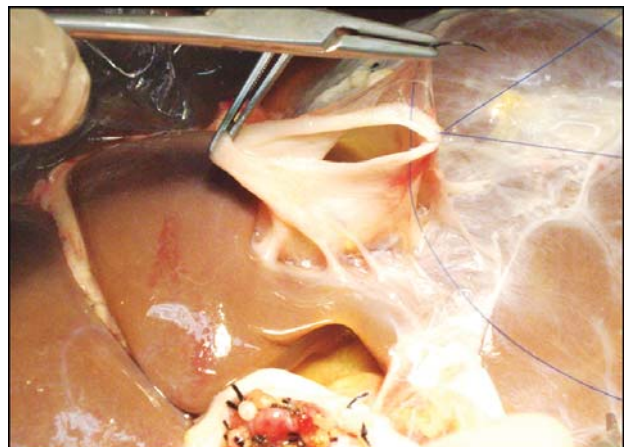


Figure 11.19: Closure of lower end of IVC

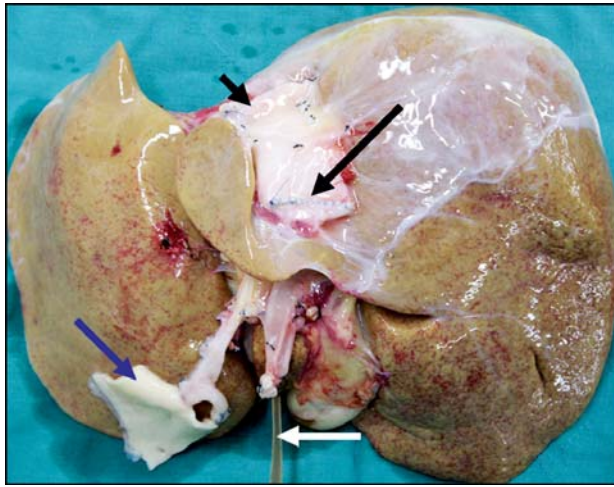


Figure 11.20: Whole liver with IVC closed at both ends (black arrows) with a Carrel patch (blue arrow) and portal vein cannula (white arrow)

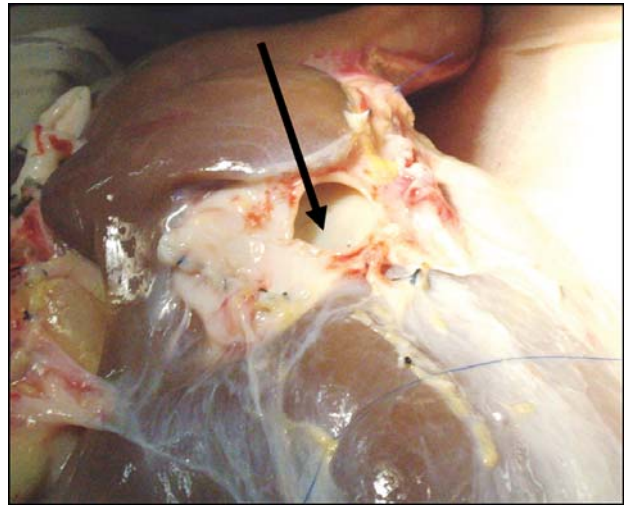


Figure 11.21: Opening in the IVC for piggyback anastomosis

REFERENCES

1. Cavallari A, et al. A multi center pilot prospective study comparing celsior and UW preserving solutions For use in liver transplantation. *Liver transpl* 2003;9(8):814-21.
2. Cofer JB, Klintmalm GB, Howard TK, Morris CV, Husberg BS, Goldstein RM, Gonwa TA. A comparison of UW with Eurocollins preservation solution in liver transplantation. *Transplantation* 1990;49:1088-93.
3. Menasché P, Termignon JL, Pradier F, Grousset C, Mouas C, Alberici G, et al. Experimental evaluation of Celsior®, a new heart preservation solution. *Eur J Cardiothorac Surg* 1994;8:207-13.
4. Hermann J, Petra HE, et al. UW is superior to Celsior and HTK in the protection of human liver endothelial cells against preservation injury. *Liver Transplant* 10(12):1514-23.
5. Porte RJ, Ploeg RJ, et al. Long-term graft survival after liver transplantation in the UW era: Late effects of cold ischemia and primary dysfunction. *European Multicenter Study Group. Transpl Int* 1998; 11: 164-167.
6. Southard JH, Belzer FO. Organ preservation. *Annu Rev Med* 1995;46:235-47.
7. Erhard J, Lange R, et al. Comparison of histidine-tryptophan-ketoglutarate (HTK) solution versus University of Wisconsin (UW) solution for organ preservation in human liver transplantation. A prospective, randomized study. *Transpl Int* 1994;7:177-81.
8. Spiegel HU, Schleimer K, et al. Organ preservation with EC, HTK, and UW, solution in orthotopic rat liver transplantation. Part II. Morphological study. *J Invest Surg* 1999;12:195-203.
9. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: A single-center experience. *Ann Surg* 2005;241:905-16.
10. Marsman WA, Wiesner RH, Rodriguez L, et al. Use of fatty donor liver is associated with diminished early patient and graft survival. *Transplantation* 1996;62:1246-51.
11. Salizzoni M, Franchello A, Zamboni F, et al. Marginal grafts: Finding the correct treatment for fatty livers. *Transpl Int* 2003;16:486-93.
12. Selzner M, Rudiger HA, Sindram D, Madden J, Clavien PA. Mechanisms of ischemic injury are different in the steatotic and normal rat liver. *Hepatology* 2000;32:1280-88.
13. van As AB, Lotz Z, Tyler M, Kahn D. Effect of early arterialization of the porcine liver allograft on reperfusion injury, hepatocellular injury, and endothelial cell dysfunction. *Liver Transpl* 2001;7:32-37.
14. Lee KW, Simpkins CE, Montgomery RA, Locke JE, Segev DL, Maley WR. Factors affecting graft survival after liver transplantation from donation after cardiac death donors. *Transplantation* 2006;82:1683-88.
15. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: An analysis of OPTN/UNOS data. *Am J Transplant* 2006;6:791-96.
16. Yersiz H, Shaked A, Olthoff K, et al. Correlation between donor age and the pattern of liver graft recovery after transplantation. *Transplantation* 1995;60:790-94.
17. Hoofnagle JH, Lombardero M, Zetterman RK, et al. Donor age and outcome of liver transplantation. *Hepatology* 1996;24:89-96.
18. Hong JC, Busuttil RW, et al. Cold Ischemia Time and Liver Graft Survival *American Journal of Transplantation* 2008;8(3):481-82.
19. Zehe J, Platt D. The aging liver: Structural and functional changes and their consequences for drug treatment in old age. *Gerontology* 2002;48:121-27.
20. Yamagami K, Hutter J, Yamamoto Y, et al. Synergistic effects of brain death and liver steatosis on the hepatic microcirculation. *Transplantation* 2005;80:500-05.
21. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: An analysis of OPTN/UNOS data. *Am J Transplant* 2006;6:791-96.
22. JC Hong, RW Busuttil. Cold ischemia time and liver graft survival *Am J of Transplant* 2008;8:481-82.
23. Y Sugawara, M Makuuchi, et al. Refinement of venous reconstruction using cryopreserved veins in right liver grafts. *Liver Transplantation* 2004;10(4):541-47.

Recipient Surgery

(A) LIVE DONOR LIVER TRANSPLANTATION: RECIPIENT HEPATECTOMY

GENERAL CARE AND PREPARATION OF RECIPIENT

Care is taken in the operation theatre to prevent wound sepsis, pressure sores and deep vein thrombosis. Patient is placed in spine with abducted upper limbs on the operating table. Transplantation surgery is technically challenging as the anesthesiologist has to maintain the homeostatic temperature, circulation, oxygen carrying capacity, gluconeogenesis, electrolytes and adequate coagulation profile. So an anesthesiologist trained in liver transplantation is an essential part of liver transplant team. Body temperature is maintained with warming devices applied to lower limbs and intravenous fluid warmer to increase the temperature of fluids given intraoperatively. Central line, arterial line and swan ganz catheters are inserted for adequate vascular access for perfusion.

Continuous monitoring of BP, O₂ saturation, CVP, pulmonary arterial pressure, cardiac output, cardiac index, systemic vascular resistance and end diastolic volume is carried out throughout the surgery. The measurement of cardiac output (CO) in these patients is useful for guiding clinical therapy, including fluid administration and use of vasopressors. Pulmonary artery catheter thermodilution (PAC-TD) has been the standard method of CO measurement in liver transplantation. Recently, attention has turned to other measurement techniques. One such method, which is noninvasive, is the ultrasound cardiac output monitor (USCOM), which was introduced into clinical practice in 2001.³⁸ The USCOM monitor has been studied in surgical intensive

care patients, Doppler derived CO being compared with that determined by PAC-TD. Good agreement was found between the 2 techniques, but there was an increased difference at higher Cos. USCOM is acceptable for the clinical determination of noninvasive cardiac output, particularly in situations in which tracking changes over time is more important than knowing the precise value.³⁸

Blood components such as PRBC, fresh frozen plasma, platelets and cryoprecipitate are preserved preoperatively in sufficient quantity to meet the bleeding demands. Thromboelastography (TEG) is used to monitor the coagulation profile and Intraoperative cell saver is used to meet the demands of intraoperative blood loss. Cell saver is avoided in patients with subacute bacterial peritonitis and HCC as it can transmit abdominal infection or malignant cells to blood stream leading to dissemination of infection and malignancy, respectively. Prophylactic antibiotics usually a 3rd or 4th generation cephalosporins along with an aminoglycoside and antifungal agents are used. Many centers start 1st dose of immunosuppression usually Tacrolimus / Cyclosporine 6 hours before surgery. Laxatives are given preoperatively for bowel preparation.

Abdomen is opened by bilateral subcoastal incision with midline vertical extension or inverted T-shaped incision. A Book Walter or Thomson or Kent retractor (**Figures 12.1 to 12.3**) is used to retract the abdominal wall. Ascitic fluid if any is taken out with a suction cannula. Hilar dissection is performed to isolate, ligate and divide CBD. Hilar dissection is continued to isolate the hepatic

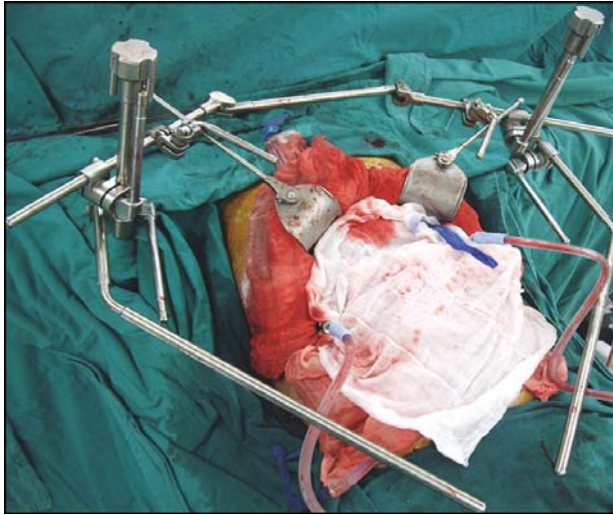


Figure 12.1: Thomson abdominal retractor

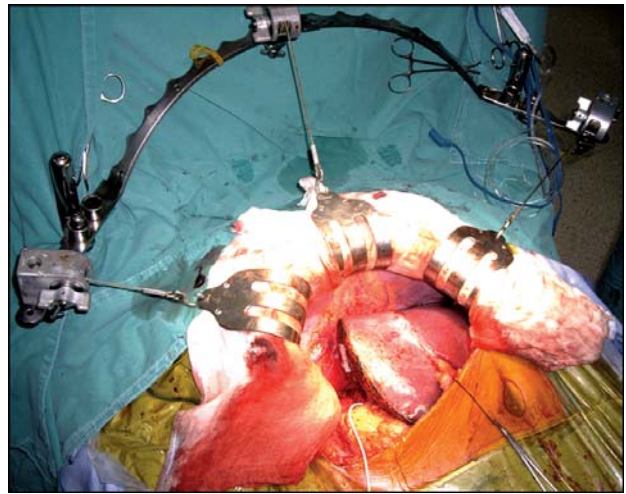


Figure 12.3: Kent abdominal retractor (*Reproduced with permission of Chen CL*)

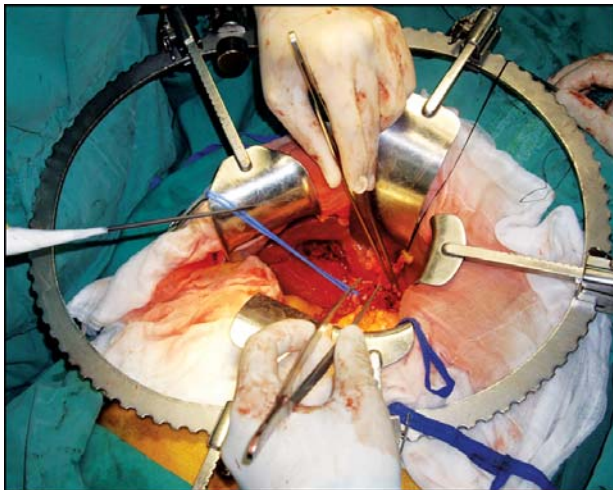


Figure 12.2: Book Walter abdominal retractor

artery proper and its branches RHA, LHA and MHA.⁷ Maximum lengths of the hepatic arterial branches are preserved distally. Portal vein is isolated and dissected to keep as long as possible (**Figure 12.23**). A microvascular clip is used to control the proximal end while the distal end of the hepatic artery is clamped, divided, and ligated. The microvascular clips are released intermittently

throughout the procedure until anastomosis to prevent clogging of the lumen of the hepatic artery. Right and left lobe is mobilized by dividing the falciform, coronary right and triangular ligaments.

During right lobe mobilization, carefully ligate all the retrohepatic veins, IRHV, MRHV (if present) and caudate lobe veins. IVC ligament (Makuuchi ligament) is divided and RHV is encircled. RHV is divided over vascular clamps and closed with continuous 4-0 prolene sutures on both ends. Always try to keep long RHV on recipient side for anastomosis with the graft RHV. Dissection is completed on the left side by medially turning the left lateral segment, followed by mobilization of the caudate lobe. In some cases a rim of liver parenchyma is encircling the IVC along with the caudate lobe. So careful dissection is needed around the caudate lobe and meticulous ligation of all branches of caudate lobe vein, which directly drain into the IVC, is essential. LHV and MHV common trunk is dissected and encircled, both these veins are dissected more distally to preserve maximum length of both these vein as far as possible. After complete mobilization, the recipient liver along with the gallbladder is removed (**Figures 10.4, 10.21 and 10.24**) by clamping and dividing the PV, followed by LHV and MHV. Any oozing from the diaphragmatic surface is carefully controlled by coagulation or ligation.

(B) RIGHT LOBE GRAFT

In LDLT using a right lobe graft, the LHV opening is closed with 4-0 prolene sutures. MHV can be used for anastomosis with vascular graft from V5 and V8. Now the RLG is placed in the right upper fossa and position is adjusted so that vascular anastomosis can be done without any tension on the anastomosis (**Figure 12.11**). Graft RHV is either directly anastomosed with recipient RHV in end-to-end fashion or can be directly anastomosed with IVC on its lateral aspect, followed by anastomosis of IRHV and MRHV. Vascular graft from V5 and V8 usually constructed as V or Y shaped anastomosis and is they are anastomosed to the MHV or directly to the IVC with 4-0 prolene sutures.¹ The reconstruction of the vascular outflow tract of partial liver grafts has received considerable attention in the past, especially in the setting of right liver grafts with undrained segments. If no primary reconstruction of the MHV or V5 and V8 is performed, most right liver grafts show morphological signs of congestion,² as well as impaired liver regeneration in the affected segments.³ Therefore V5 and V8 outflow reconstruction with a vascular graft in right lobe LDLT is mandatory if there is significant contribution of outflow from these 2 branches. The vascular graft may be anastomosed to bifurcation or LHV or MHV (**Figure 12.5**).

Before closing the openings of HV, IRHV and MRHV, graft is thoroughly flushed with lactate ringer solution or isotonic saline with albumin. This flush helps in

removing air to prevent air emboli as well as to remove the excessive high concentration of potassium, resulting from preservation solution. RPV or Main PV is anastomosed with the graft PV with 6-0 prolene sutures, care is taken not to tighten it too much to constrict the diameter of PV. Best way to do it is to tighten the knot on PV anastomosis, once the PV clamp is released. Adequate dilatation of PV is allowed before tying the knot for adequate graft flow and PV dilates due to its elastic nature when the PV clamp is released. Before reconstruction of portal vein, heparin solution is injected into the recipient portal vein to avoid thrombotic complications. Wait for the color change in the graft as whole, segment V and VIII. Usually congestion on segment V and VIII will disappear once adequate outflow is constructed with a vascular graft.³

Lee et al⁴⁵ reported the different techniques of reconstruction of portal vein in case of portal vein variations are shown in **Table 12.1**.

DIFFERENT TECHNIQUES OF V5 AND V8 RECONSTRUCTION (FIGURES 12.6 TO 12.10)

Kim et al⁴ demonstrated a different technique of reconstruction of MHV. V5 and V8 are arranged along the groove formed by MHV after tailoring donor hepatectomy with exposing the right side of the MHV. Cryopreserved vein patch is connected to MHV

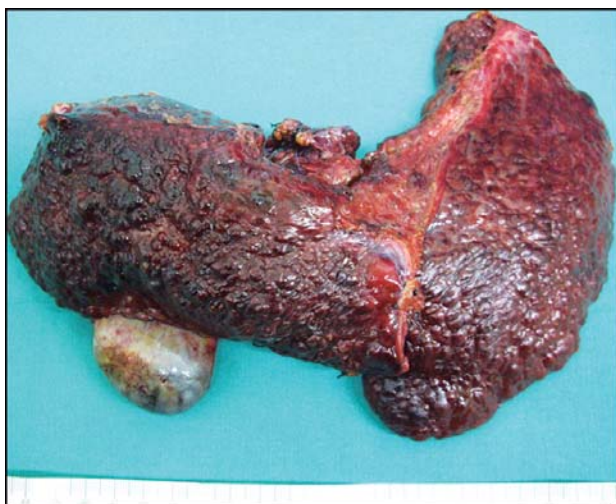


Figure 12.4: HBV related cirrhosis of liver, right lobe atrophy and left lobe hypertrophy

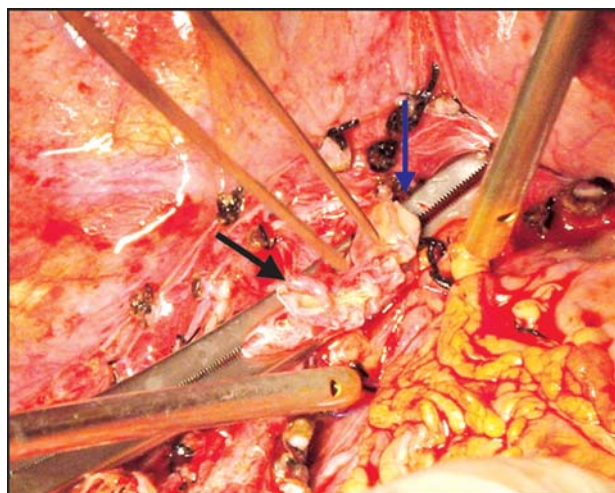


Figure 12.5: MHV (black arrow) and LHV (blue arrow) shown during anhepatic phase

TABLE 12.1: Portal vein variations in right lobe graft in LDLT and reconstruction of portal vein in the recipient⁴⁵**Type I: Donor—Normal bifurcation along with normal anatomy of anterior and posterior branches of PV**

Recipient: End to end anastomosis of graft and recipient PV

Type II: Donor—Trifurcation of PV

- A. Donor anterior and posterior right PV branches divided separately. Create a common orifice for graft PV in the back table. Donor right PV branches are closed separately.
- B. Discoid patch excision of Donor PV, so that graft side has common orifice for reconstruction. Defect in donor PV can be closed by either an autologous vein patchplasty or reconstructed by segmental resection and end to end anastomosis.
- C. Donor PV can be divided at the PV confluence. The PV defect on the donor side is repaired by primary closure in transverse direction to prevent PV stenosis. Graft PV can be anastomosed as a common single opening to the recipient PV.

Type III: Donor—Independent posterior branch from the main trunk of PV

Donor PV branches are divided separately and each stump on donor side is closed primarily.

Recipient:

- A. 2 separate graft PV branches are anastomosed each to right and left PV branches of the recipient (or)
- B. 2 separate graft PV branches are anastomosed to each of the corresponding branches of right anterior and posterior PV branches (or)
- C. Y-shaped interposition graft can be used for reconstruction of 2 branches of PV of graft to donor single PV (or)
- D. Discoid excision of donor PV: 2 separate branches excised with a discoid patch leaving a large PV defect on donor, which can be reconstructed with an autologous vein patchplasty or by segmental resection and end to end anastomosis of PV.

Type IV: Donor—Anterior sectorial branch from the umbilical portion of left PV

Donor PV branches are divided separately and each stump on donor side is closed primarily. Recipient reconstruction is similar to type III A, B and C.

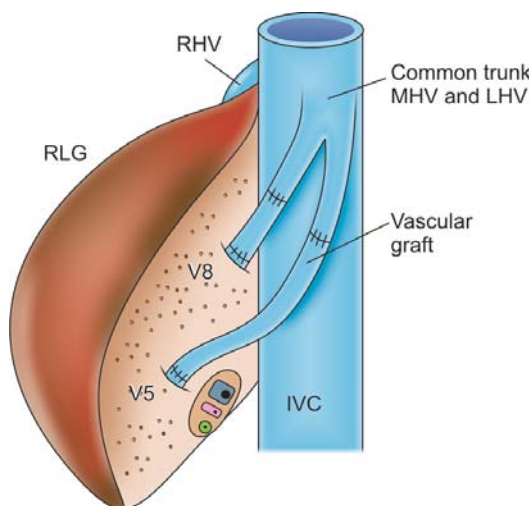


Figure 12.6: Schematic presentation of vascular graft for V5 and V8 reconstruction (Makuuchi et al)

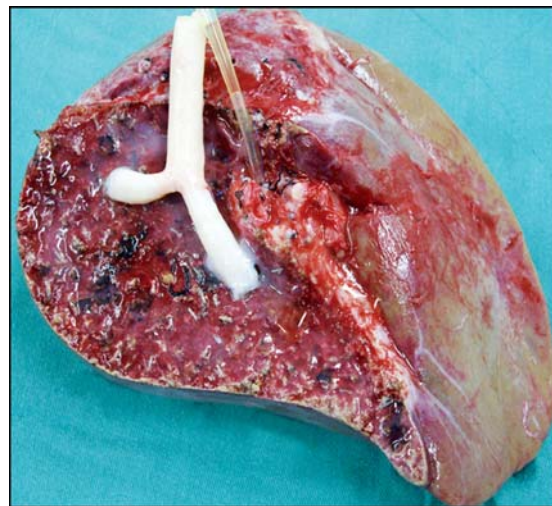


Figure 12.7: Right lobe graft after back table used reconstruction of V5 and V8 with a cryopreserved vascular graft

tributaries and anterior wall of right hepatic vein. After reclosure of interposition vessel, its shape closely resembles extended right lobe graft. Roofing of graft hepatic vein outlet is performed with a cryopreserved aorta patch. One side of the aorta patch is anastomosed to a side of the triangle formed by MHV and right hepatic vein first, and then the other side of the patch is flipped and anastomosed. However this reconstruction can be performed without using the aortic patch. Modified piggyback anastomosis of graft outflow is reconstructed.

Lee et al⁶ from Korea, reported the use of ePTFE (6 or 7 mm diameter) grafts for reconstruction of V5 and V8 (Figure 12.9) and early patency rate of ePTFE group as good as the RLG with MHV or conventional right lobe transplantation and late obstruction of the ePTFE graft had no impact on congestion in the anterior section or patient survival. Therefore, he mentioned that an ePTFE graft may be a useful interposition material for anterior section drainage in right lobe transplantation without any serious complications. The long-term patency of the

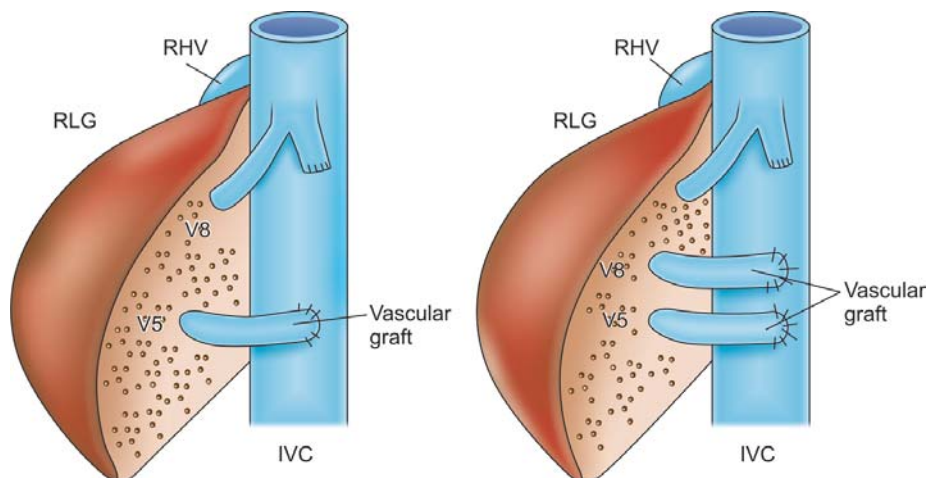


Figure 12.8: V5 and V8 br. may be directly anastomosed to the IVC instead of LHV or MHV⁵

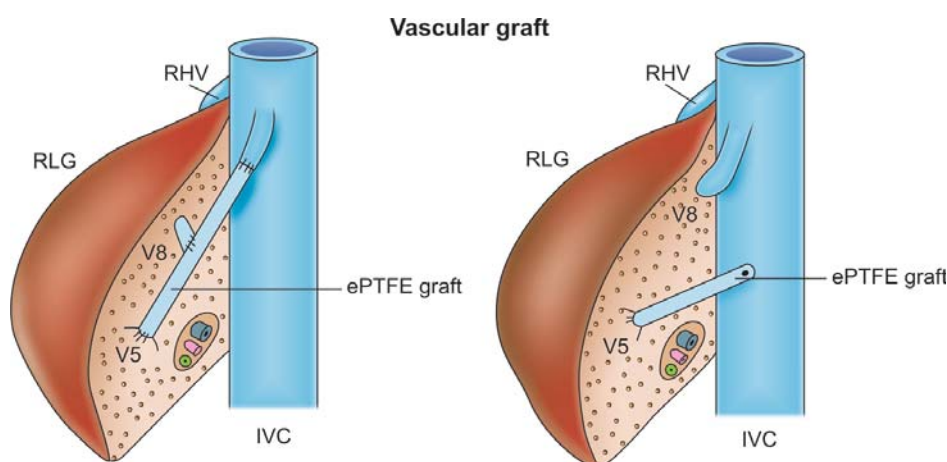


Figure 12.9: Use of ePTFE grafts for V5 and V8 reconstruction⁶

interposition vessel for anterior section drainage is not an important issue because its dysfunction causes no clinical problems during long term follow-up. As for the duration of patency, 1-2 weeks is enough to achieve adequate graft function. Difference in the regeneration rates is not significant between the liver grafts with an obstructive ePTFE graft and with an intact ePTFE graft on follow-up CT Scan examination. This is because most of the regeneration occurs during the first 2 weeks after transplantation. Sometimes graft outflow may not be adequate due to wrongly positioned graft leading to venous stasis and swelling of the graft. It should be avoided by proper positioning of the graft in the right upper fossa. In selected cases use of a tissue expander with 200- 300 ml fluid may be required to lift the graft for a proper position. If used, tissue expander usually

removed in 1-3 months following transplantation. If wide outflow of hepatic veins is reconstructed by triple venoplasty in the recipient (described later in this chapter), then such maneuver for maintaining the position of graft to increase the outflow, is not required.

HEPATIC ARTERIAL ANASTOMOSIS (FIGURES 12.12 AND 12.13)

It is completed by 9-0 prolene sutures either to the RHA or LHA whichever is comfortable. In our center, HA anastomosis is routinely done by microvascular surgeon. In some cases multiple hepatic arterial branches are found in the graft. Tanaka et al proposed reconstruction of all hepatic arterial branches, claiming that they basically end arteries and they are very important.¹⁵ But Makuuchi et al

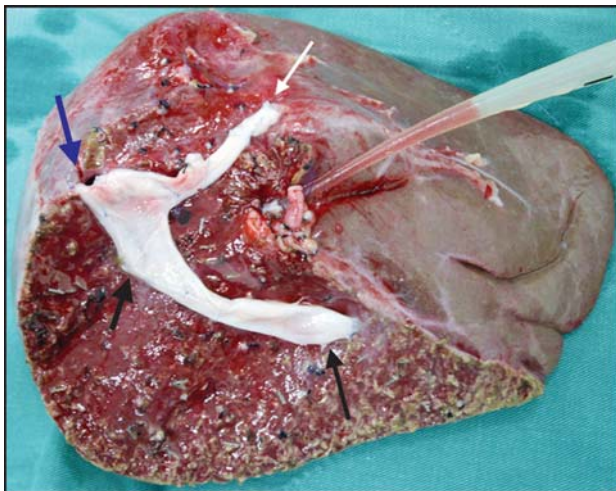


Figure 12.10: Different technique of graft outflow reconstruction. RHV (blue arrow) of the graft, V5, V8 (black arrows) and IRHV (white arrow) are reconstructed by single cryopreserved Y-shaped vascular graft with all the vessels opening into the single vascular graft and a direct single anastomosis to IVC later instead of separate outflow drainage of RHV, V5, V8 and IRHV

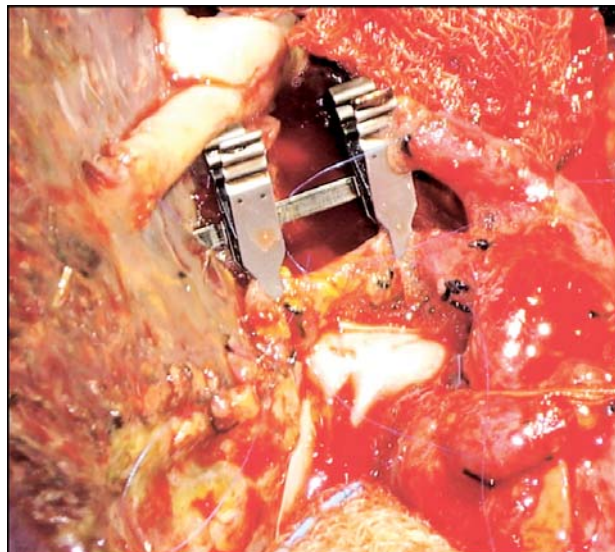


Figure 12.12: Hepatic artery anastomosis

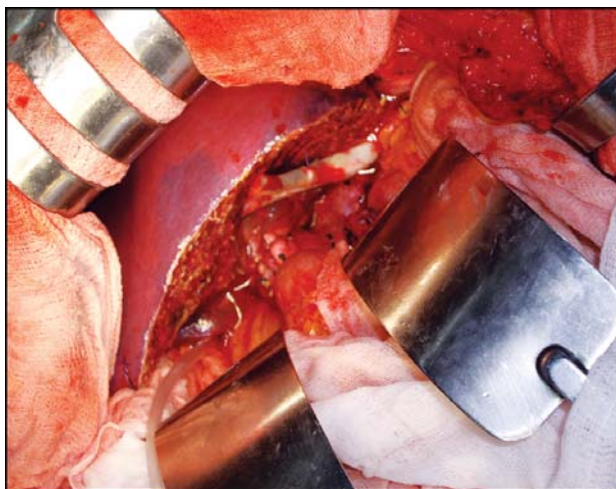


Figure 12.11: Right lobe graft in a recipient after reconstruction of portal flow

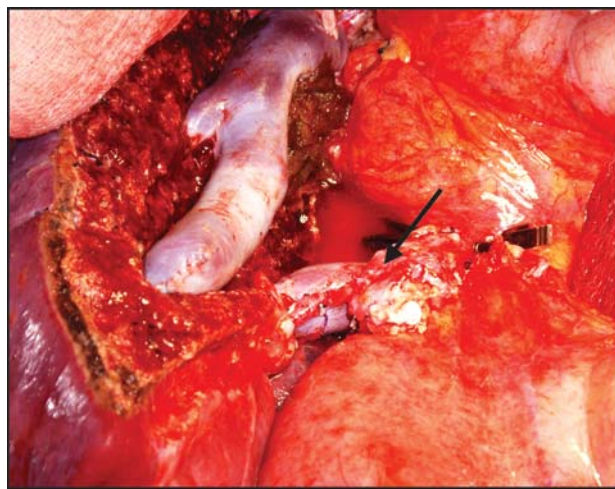


Figure 12.13: Completed hepatic artery anastomosis

reported that in majority of cases it is unnecessary to anastomose all hepatic arteries supplying the graft and no adverse effects were noticed by ligated the small branches of HA.^{31,32}

BILE DUCT ANASTOMOSIS

To ensure an adequate blood supply to the bile duct, the ends of both the recipient and donor ducts are debrided, because significant arterial bleeding from the cut ends

is a good sign; without such bleeding, the bile duct needs to be shortened.⁸ The graft hepatic duct is anastomosed in as an end-to-end fashion to the recipient bile duct or Roux-en-Y anastomosis with a jejunal limb. When bile ducts in the graft are far apart, they are anastomosed separately. Chen et al perform routine reconstruction of both arterial and biliary anastomosis by using microvascular technique (performed by microvascular surgeon) using posterior continuous and anterior continuous running and interrupted closure technique.

The technique was found to have excellent results. Different levels of transection of bile duct in donor (**Figures 12.14A to C**) and their reconstruction in the recipient (**Figures 12.14A-1 to C-1**) are shown in **Figure 12.14**.

According to Kyoto university recommendations, posterior layer continuous and anterior layer interrupted suture anastomosis of the bile duct will have better results. The anastomosis starts at the posterior wall followed by the completion of the anterior wall.⁸ Internal stent placement in biliary anastomosis was done earlier, but now many studies reported that direct duct to duct anastomosis without a stent is preferable method of

biliary reconstruction. The advantages are it is technically faster, less time consuming, less number of anastomoses, more physiologic biliary enteric continuity and sphincter of Oddi function is preserved. This provides an easy access for endoscopic treatment of post-operative biliary complications. Early oral feeding, drug administration possible and decreases the risk of ascending cholangitis. Most of the centers now a days use duct to duct anastomosis without a stent. **Figure 12.15** shows different anatomical variations in right intrahepatic bile duct and type of reconstruction during right lobe grafts without a stent.⁹

For cystic duct (external) drainage, a 4-French tube is inserted through the remnant cystic duct and placed into the common bile duct. For external stent, the tube is placed through the anastomosis as a splint and is pulled out through the CBD, above the duodenum. The tube is anchored to the anastomosis with an absorbable stitch. Stent can be fixed to the cystic duct with a rubber-band hemorrhoid ligator.

If a stent is to be placed in duct to duct biliary anastomosis, it can be placed through cystic duct or through common bile duct. If an internal stent is to be placed in Roux-en-Y anastomosis, a 2 cm of 18G silicon vascular catheter is placed as an internal stent and for external stent in Roux-en-Y, the 4-French tube was inserted through the jejunum and the tip was placed through the anastomosis.¹⁰ The stent tube is usually removed in 12-24 weeks after transplantation. Postoperative cholangiogram was performed 1 to 2 weeks after transplantation, and the tube through the cystic duct was removed when there were no further problems. The

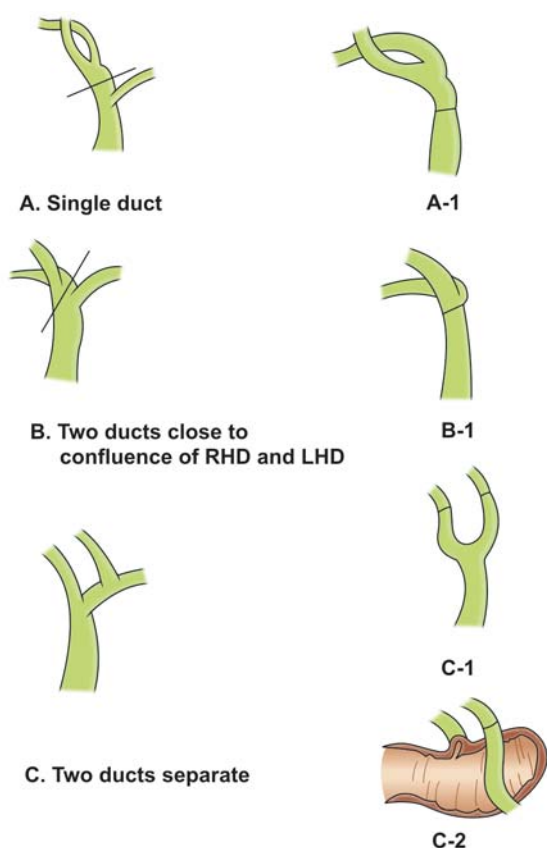


Figure 12.14: Different techniques of anastomosis of bile duct in a living donor liver transplantation⁹

- A: Level of transection of bile duct in donor,
- A1: Reconstruction of bile duct in the recipient.
- B: Level of transection in donor when anterior and posterior sectorial ducts open close to the bifurcation
- B1: Septum between the 2 ducts can be cut and make a common channel for a single bile duct reconstruction in recipient.
- C: Anterior and posterior sectorial ducts opening separately, posterior duct opening into left hepatic duct
- C1: Independent ductal reconstruction with right and left bile ducts or cystic duct and CHD in recipient
- C2: 2 ducts anastomosed separately in recipient, one with bile duct and the other with Roux-en-Y jejunal limb



Figure 12.15: Abdominal wound closure with 3 Jackson-Pratt drains (2 on the right side and one on left side)

external stent was removed 3 months after transplantation. Whenever significant symptoms were observed, an emergency cholangiogram is performed. 3 Jackson-Pratt drains are usually placed in the abdomen (Figure 12.15). One on right subphrenic space, 2nd one

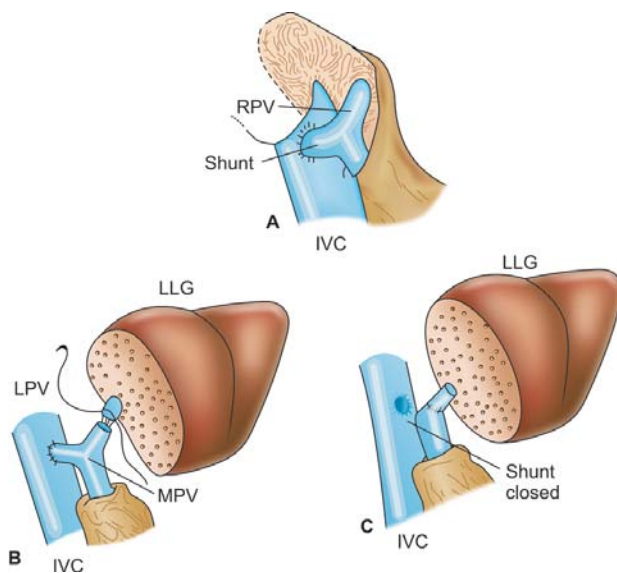
around the vascular anastomosis and subhepatic space and 3rd one on left side near the cut surface of allograft. This allows the secure identification of location of postoperative bleeding or bile leak. Abdomen is closed in layers.

(C) LEFT LOBE GRAFT (FIGURE 12.20)

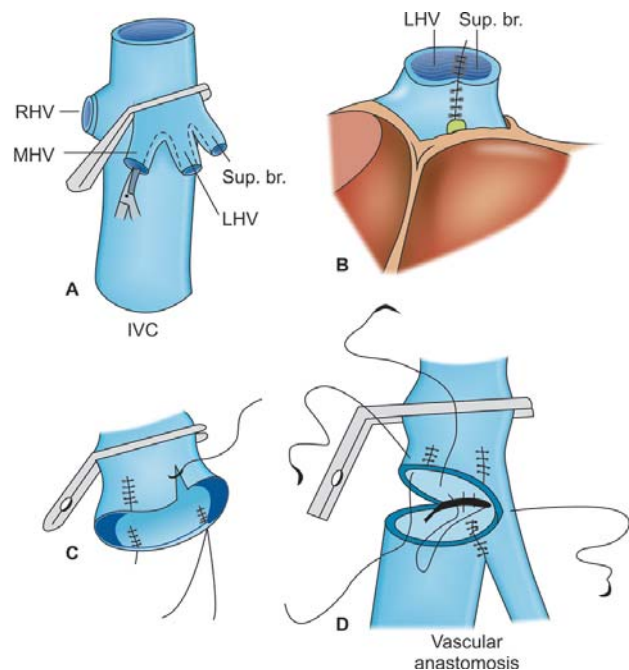
In left lobe LDLT, the LHV and MHV in the recipient are used for venoplasty. If necessary, hepatic graft venoplasty is also carried out using the LHV and MHV. The left medial vein draining segment 4 joined the MHV, and this vein and the LHV are divided separately in this donor. Venoplasty in the graft is carried out on the back table to form a common trunk for the drainage vein of the graft. After venoplasty, end-to-end anastomosis of the hepatic veins is performed, the donor left portal vein is anastomosed to the recipient left portal vein, and the graft is reperfed (Figures 12.18 and 12.19). The donor left hepatic artery is anastomosed to either the recipient right hepatic artery or the left hepatic artery with 9-0 prolene sutures, depending on the size match, under direct observation with an operating microscope. Bile duct anastomosis is completed either duct to duct or Roux-en-Y

hepaticojejunostomy technique (Figure 12.22) with or without a T-tube. Graft is usually placed orthotopically but may be placed heterotopically. If a LLG/Lateral segment graft is placed heterotopically, there may be technical difficulties in the vascular anastomosis due to reversed position of hilar structures.

Portal congestion is a problem in left lobe graft. Kawasaki et al described that prevention of portal congestion is only necessary during the anhepatic phase by a temporary shunt procedure between the right portal vein and the inferior vena cava, thus completely avoiding portal congestion during surgery (Figures 12.16A to C).¹¹



Figures 12.16A to C: (A) Temporary portocaval shunt before resection of the recipient's liver. (B) Anastomosis of recipient's left portal vein to graft portal vein. (C) Closure of shunt after anastomosis of graft portal vein (Modified and redrawn with permission from Kawasaki S)¹¹



Figures 12.17A to D: Left lobe living donor liver transplantation. (A and C) Venoplasty of MHV, LHV and superficial branch of LHV in the recipient to form a common trunk (B) Venoplasty of MHV and LHV in the graft (D) Final outflow reconstruction (Modified and redrawn with permission of H Imamura and Kawasaki S)^{11,13}

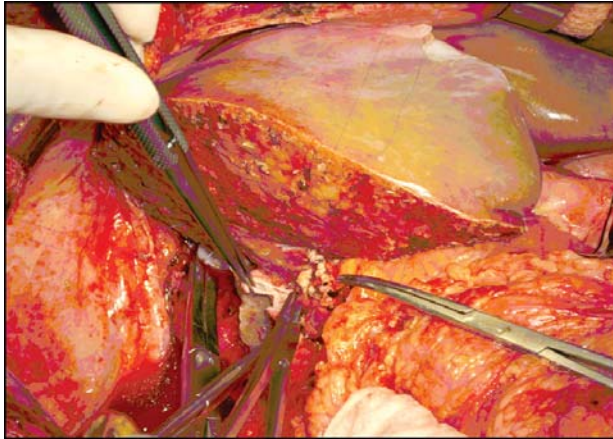


Figure 12.18: Left lobe graft: PV anastomosis



Figure 12.21: Recipient liver in a 12 years old patient of biliary atresia with previous Kasai procedure



Figure 12.19: Completed left portal vein anastomosis

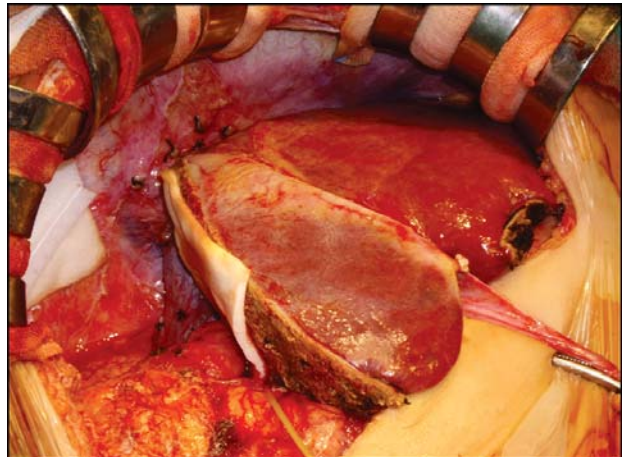


Figure 12.22: Left lobe graft without MHV in a 12 years old recipient of extrahepatic biliary atresia with a previous Kasai procedure. Biliary reconstruction performed with external drainage tube



Figure 12.20: Left lobe without MHV with area of congestion in segment 4

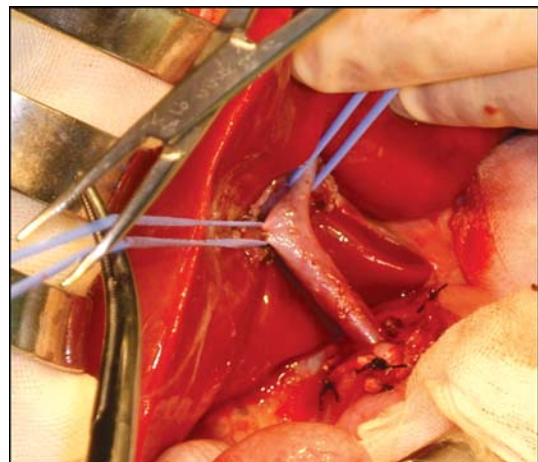


Figure 12.23: Portal vein in a 2 years old child with metabolic liver disease



Figure 12.24: Liver of a 2 years old child with metabolic liver disease (Methylmelonic acidemia)

The right portal vein is anastomosed end-to-side to the IVC, without interrupting blood flow through the left portal vein. Blood flow through this shunt is maintained until reperfusion of the graft is achieved after end-to-end

anastomosis between the recipient's left portal vein and the left portal vein of the graft. As the volume of the left lobar graft is usually much smaller than the hepatic mass required by the recipient's metabolic demand in adult LDLT, avoidance of portal congestion is considered beneficial in minimizing the functional burden on the graft. Kawasaki et al. recommended the use of postoperative anticoagulant treatment in LDLT as the diameter of HA and PV of these vessels is smaller than in whole liver transplantation.¹²

Makuuchi et al¹³ demonstrated the techniques used for Y-reconstruction of the hepatic venous outflow by end-to-end anastomosis after venoplasty in left lobe grafts (**Figures 12.17A to D**). When the superficial branch of the LHV did not form a common orifice with the main left hepatic vein in the donor, venoplasty to construct such an orifice was undertaken to avoid partial congestion in grafts with a small volume.

Takayama et al¹⁴ mentioned that when the caudate lobe is harvested along with left lobe, routine reconstruction of the veins of the caudate lobe when the diameter of the vein is >3 mm. Tanaka K et al devised the techniques of modulation of graft portal inflow using techniques such as splenectomy, splenic arterial ligation (SAL) and porto-systemic shunt.

(D) LEFT LATERAL SEGMENT GRAFT

Recipient hepatectomy is same as mentioned earlier except that pediatric patients are mostly transplanted for biliary atresia and most of these patients had already a previous Kasai procedure (Hepatopuertoenterostomy) or had recurrent attacks of cholangitis. Hence more adhesions around the hilar area need more careful and meticulous dissection to avoid injury to hilar structures and jejunum. Once the hepatectomy is completed, the lateral segment graft is placed orthotopically on left side.

HEPATIC VEIN RECONSTRUCTION¹⁵

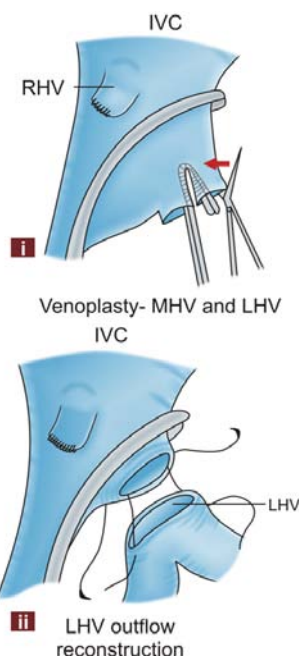
Tanaka et al. reported that recipient MHV and LHV are joined by venoplasty to increase the diameter of outflow vein (**Figures 12.25A to 12.29**). Graft hepatic vein is anastomosed to the recipient common channel of MHV and LHV with 6-0 prolene sutures. During this procedure (venoplasty), a clamp is applied on the common channel of LHV and MHV. If the common channel of MHV and LHV is very short, a partial clamp can be applied on the IVC for outflow reconstruction. When the V2 and V3 open

independently, the outflow of V2 and V3 can be reconstructed independently with LHV and MHV [**Figure 12.25B**].

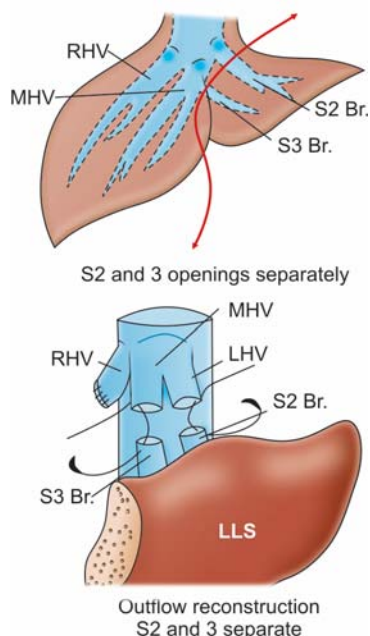
Chen et al³⁷ reported a different technique of outflow reconstruction. The RHV, MHV and LHV are opened completely opened (triple venoplasty) to reconstruct single wide opening (total IVC clamp is applied during venoplasty). This modification creates a wide opening for outflow reconstruction (**Figures 12.30 to 12.34**).

PV ANASTOMOSIS

It is the most difficult part in pediatric patients. Many biliary atresia patients have atretic portal vein (**Figure 12.36**). So various form of modification is required for portal vein anastomosis (**Figures 12.39 and 12.40**). The most important part of portal vein anastomosis is to obtain enough diameter and length to allow for adequate portal flow and to obtain size matching between the graft portal vein and the recipient portal vein.⁴⁷ Congenital absence of the portal vein, thrombosed portal vein, atresia of portal



A. (i) Venoplasty of MHV and LHV to make a common trunk; (ii) Outflow reconstruction by anastomosis of common trunk of MHV and LHV of the graft with recipient's common trunk of MHV and LHV after venoplasty



B. Outflow veins of V2 and V3 widely separated. Curved arrow shows the line of transection of hepatic veins; Independent outflow reconstruction of V2 and V3 with LHV and MHV respectively (Modified and redrawn)¹⁵

Figures 12.25A and B: Different techniques of outflow reconstruction in left lateral segment graft (LDLT)

vein, web in the portal vein, and preduodenal portal vein can be encountered in EHBA and often require placement of vein graft between the recipient portal vein confluence and the donor portal vein. When EHBA is associated with polysplenia, there may be abdominal situs that requires expert positioning of the allograft during liver transplantation.¹⁹

At dissection of the recipient portal vein during hepatectomy recipient portal vein flow is assessed for the portal flow by unclamping the portal vein. When there is no stenosis leading to reduced portal flow, the native trunk for anastomosis is used. When there was diameter mismatch, branch patch anastomosis is preferred. When the trunk is significantly stenotic (< 4 mm in diameter), the native trunk is removed to obtain adequate portal flow. The portal vein is usually large enough at the level of the confluence. But the distance between the confluence of a recipient and the graft portal vein is also important. When the graft portal vein could reach the confluence, an anastomosis is performed between the graft portal vein and the confluence (**Figures 12.7 and 12.38**). When the graft portal vein could not reach easily the confluence, vein graft is used. The interposition graft technique is used when the diameter and the length of the vein graft are optimal. The patch technique is preferable when the diameter of the vein graft is too small for the interposition technique. Major risk of PV anastomosis is portal vein thrombosis due to poor flow. If the poor flow is detected intraoperatively by Doppler USG with normal HV flow, consideration may be given to ligation of coronary vein to increase the portal flow.

Portal vein reconstruction in biliary atresia¹⁶⁻¹⁸ (Figure 12.39)

Type I: Normal diameter of PV: Standard direct end-to-end anastomosis.

Type II: PV diameter is narrow:

- A.** Cuff of RPV and LPV is opened for venoplasty to widen the diameter and is used for anastomosis with graft PV.
- B.** Graft PV is anastomosed with the bifurcation/confluence of the recipient right and left portal vein (branch patch).

Type III: Atresia of Main PV

- A.** Long donor PV and atretic recipient MPV:
 - (i) Graft PV anastomosed with the splenic vein
 - (ii) Graft PV is sutured to the confluence of the recipient SMV and splenic vein.
- B.** A venous graft conduit may be used
- C.** A venous patch can be used to enlarge the diameter of atretic MPV
- D.** A venoplasty technique can also be used

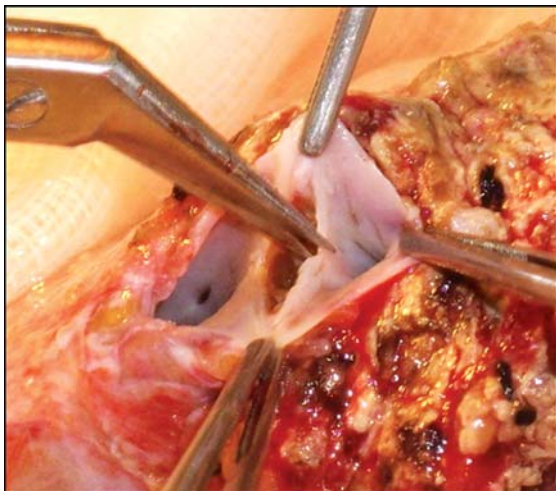


Figure 12.26

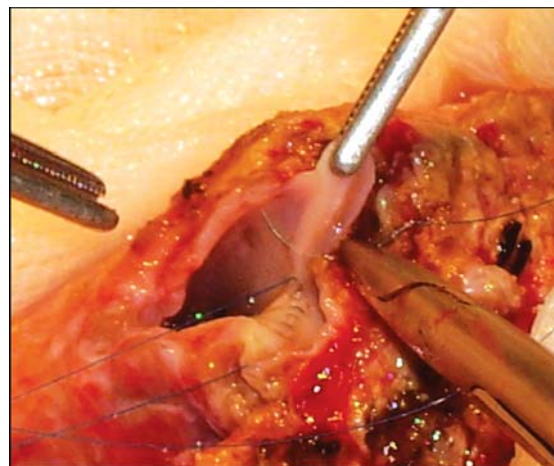


Figure 12.28

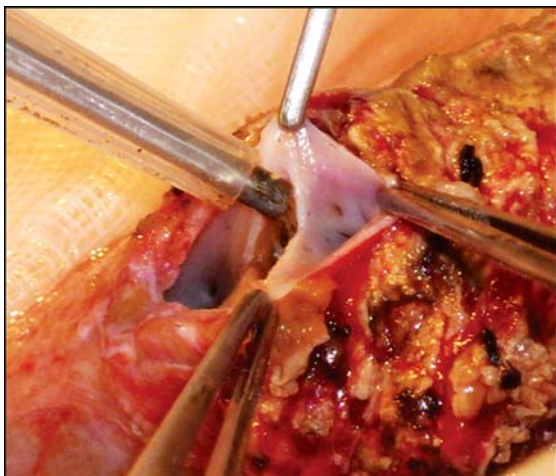


Figure 12.27

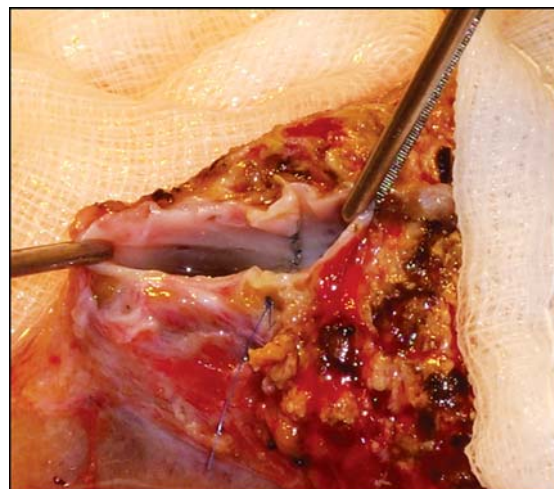


Figure 12.29

Figures 12.26 to 12.29: Venoplasty of V2 and V3 in a left lateral segment graft

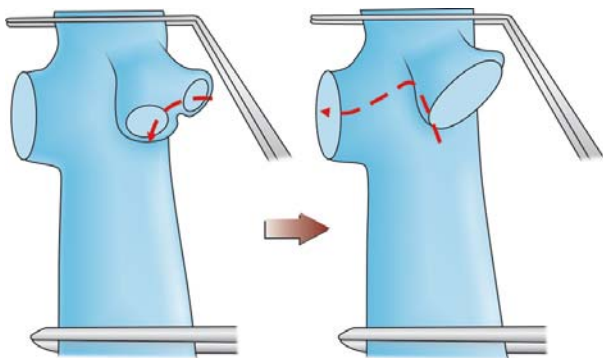


Figure 12.30: Arrow shows the line for incising the RHV, LHV, and MHV

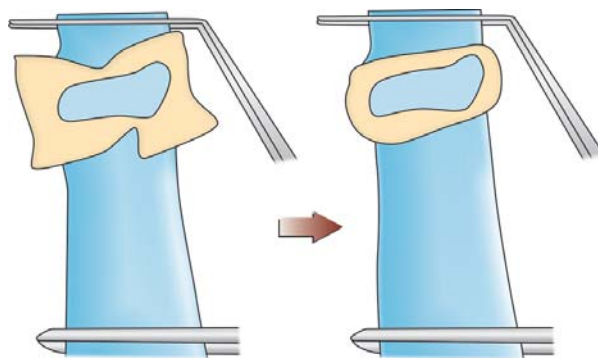


Figure 12.31: Wide opening is made opening the 3 hepatic veins (triple venoplasty)

Figures 12.30 and 12.31: Shows the venoplasty of RHV, MHV and LHV in a recipient IVC to make a wide opening for outflow reconstruction (Triple venoplasty) (Reproduced with permission of Chen CL).

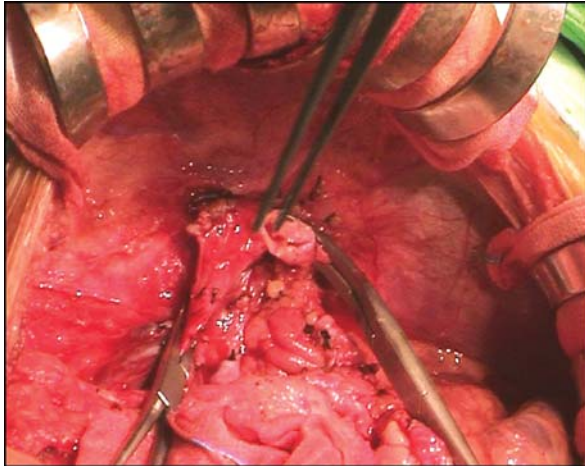


Figure 12.32: Total IVC cross clamping



Figure 12.35: Different types of vascular clamps used for cross clamping of inferior vena cava in a recipient (*Reproduced with permission of Chen CL*)

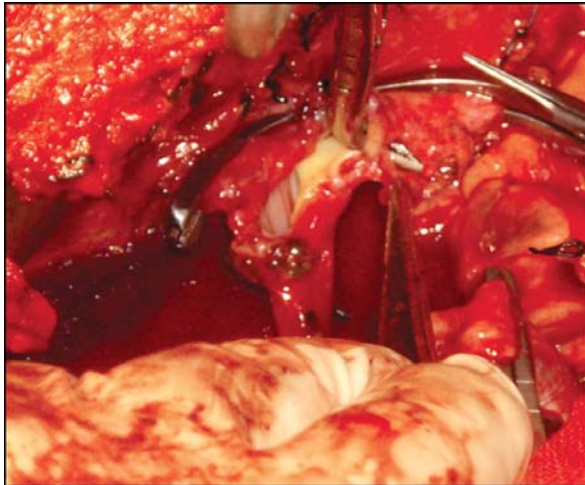


Figure 12.33: Line of transection through RHV, MHV and LHV to widen the opening for wide outflow reconstruction

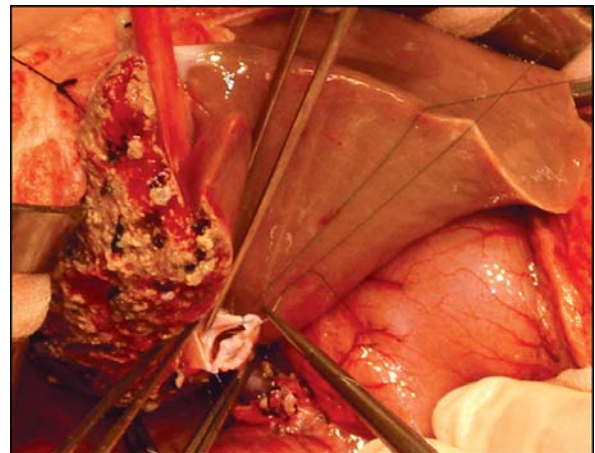


Figure 12.36: Atretic main portal vein in a 13-year-old recipient with biliary atresia

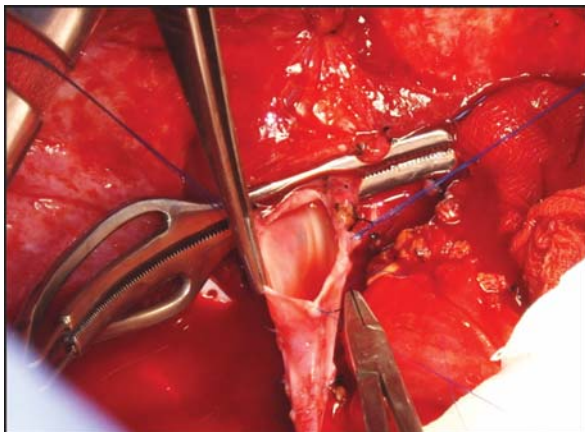


Figure 12.34: Total IVC cross clamp with triple venoplasty of RHV, MHV and LHV for construction of a wide outflow for the graft (*Reproduced with permission of Chen CL*)

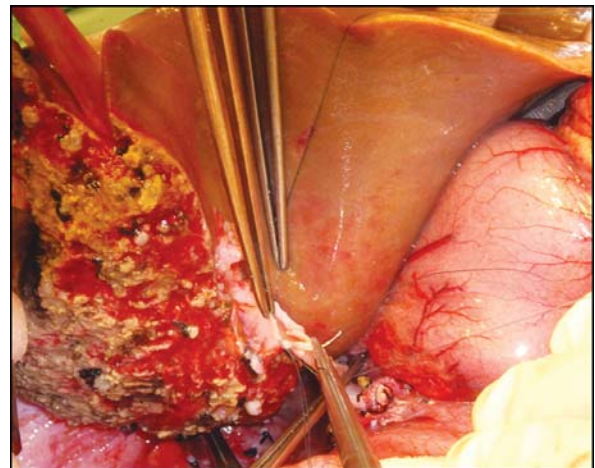


Figure 12.37: Portal vein anastomosis in a lateral segment graft

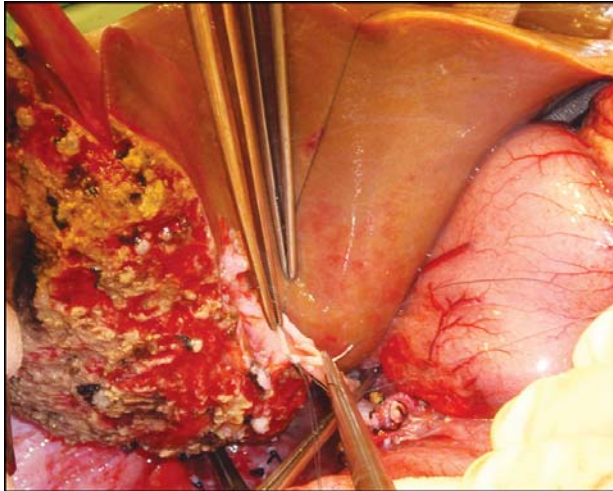


Figure 12.38: Portal vein reconstruction in a lateral segment graft

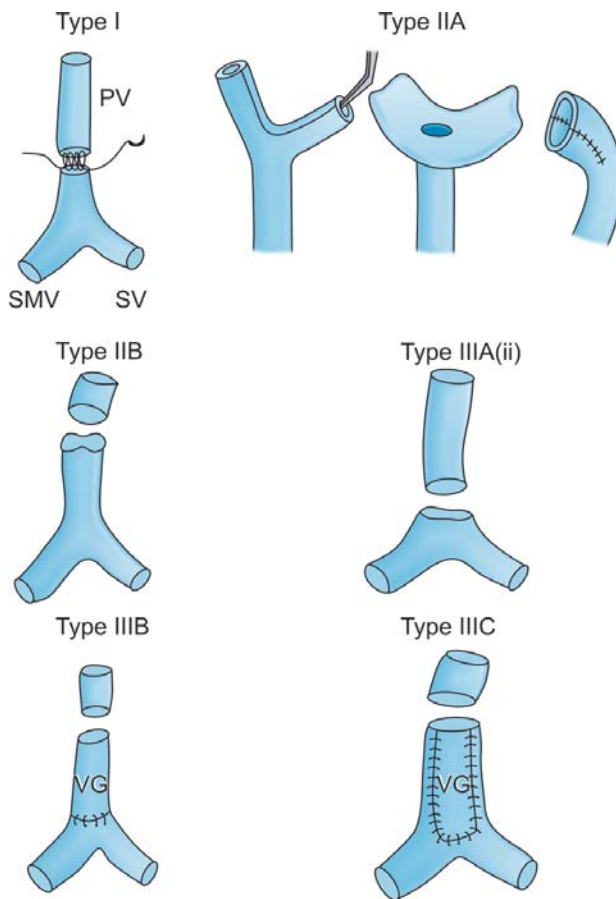


Figure 12.39: Different types of portal vein reconstruction in case of narrowing or atresia of recipient portal vein. (Modified and redrawn with permission of H Egawa)^{18,46}

Different vascular grafts can be harvested from the donor depending requirement and availability. Different sources of vascular grafts are:

- Left ovarian vein
- Inferior mesenteric vein
- External iliac vein
- Left ovarian vein
- Left gastric vein
- Recipient PV or IMV

Indication for different PV reconstruction techniques depends on several factors as shown below.

Type of PV reconstruction is chosen according to the:

- Diameter of PV
- Wall status of PV
- Length of the recipient's PV
- Diameter and length of the graft PV.

HEPATIC ARTERY ANASTOMOSIS (FIGURES 12.40 AND 12.41)

It is done by microvascular technique with 9-0 prolene sutures. Graft HA may be anastomosed to LHA or the HA proper of the recipient. The arterial anastomosis in small children is challenging. After the introduction of the operating microscope, the incidence of hepatic artery thrombosis has decreased dramatically. In situations where the recipient hepatic artery is too small in diameter, either the infrarenal or supraceliac aortic graft can be used to establish arterial inflow to the allograft liver.

BILIARY RECONSTRUCTION

Biliary reconstruction (**Figures 12.42 to 12.47**) is usually performed using interrupted 6-0 PDS sutures. Roux-en-Y Hepaticojejunostomy is usually performed in children who had earlier Kasai procedure. End-to-end choledochocholedochostomy (CC) is possible in older children. In small children due to small size of the bile duct, postoperative stricture is more common. Placement of stent is a matter of debate. Many centers in present transplant scenario do not prefer to use stents in biliary anastomosis. Doppler USG is performed before closing the abdomen to confirm adequate inflow and outflow. Abdomen is closed in layers with 2 Jackson-Pratt drains (**Figure 12.48**).

Graft Regeneration in LDLT

The liver regenerates rapidly in donors and recipients within 6 to 8 weeks, although the majority regenerate in the first 2 weeks after transplant. Partial liver grafts and

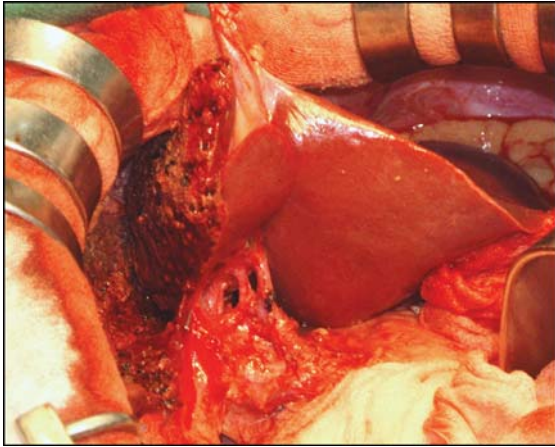


Figure 12.40: Double arterial reconstruction in lateral segment graft

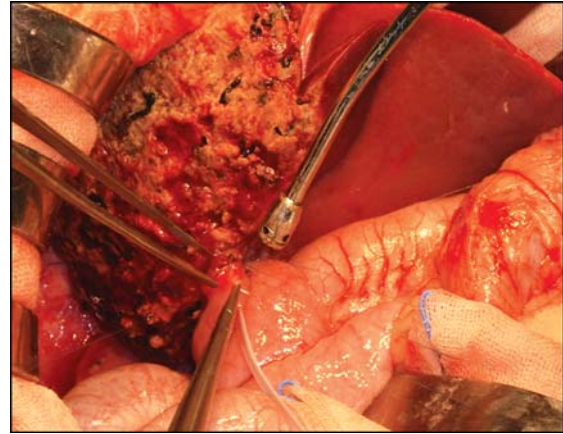


Figure 12.43

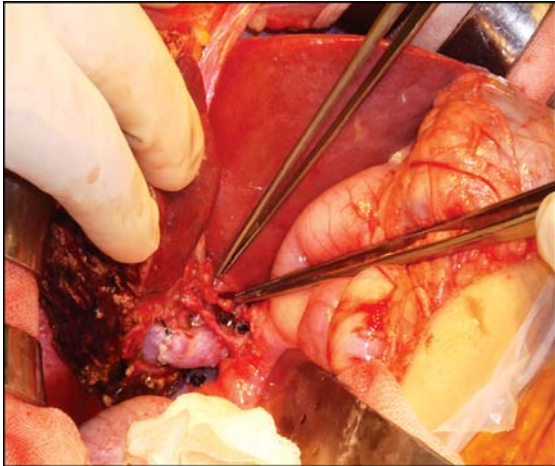


Figure 12.41: Graft after reperfusion with (2 hepatic arteries reconstructed by microvascular surgery)

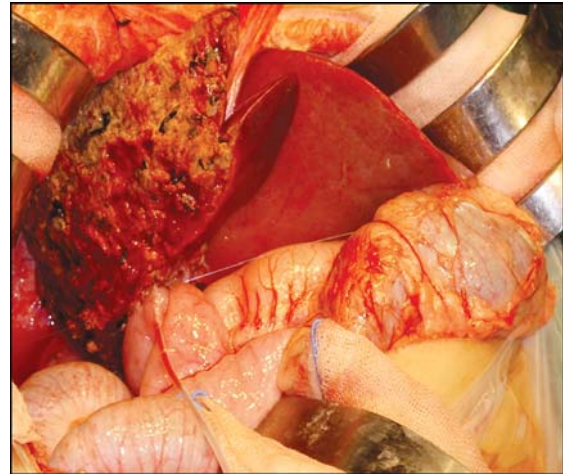


Figure 12.44

Figures 12.43 and 12.44: Roux-en-Y hepaticojunostomy with a T-tube

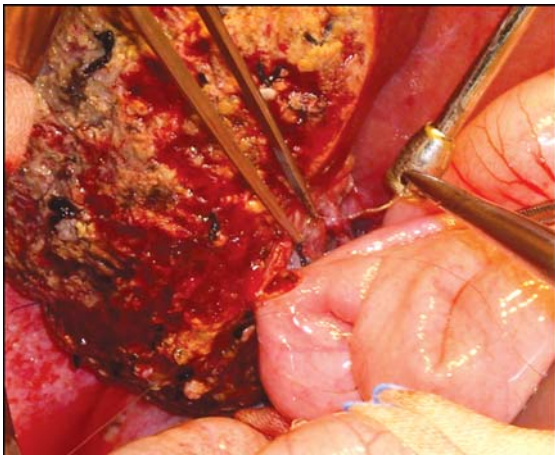


Figure 12.42: Roux-en-Y hepaticojunostomy

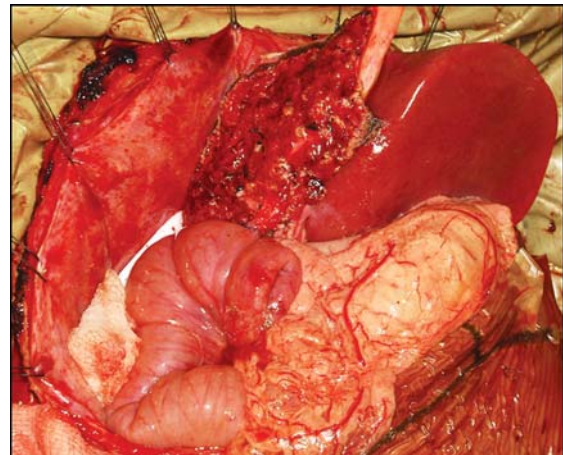


Figure 12.45: Biliary reconstruction by Roux-en-Y hepaticojunostomy technique without a T-tube/biliary stent in a lateral segment graft in a biliary atresia patient

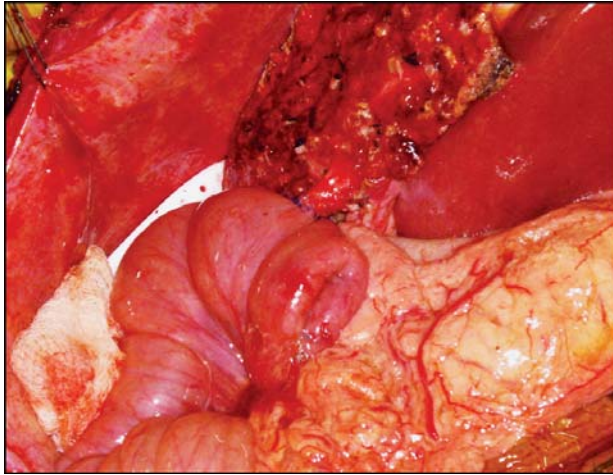


Figure 12.46: Roux-en-Y hepaticojejunostomy without a stent/T-tube (magnified view) (Reproduced with permission of Chen CL)



Figure 12.47: Different types of biliary probes used during intraoperative cholangiogram and bile duct reconstruction (Reproduced with permission of Chen CL)

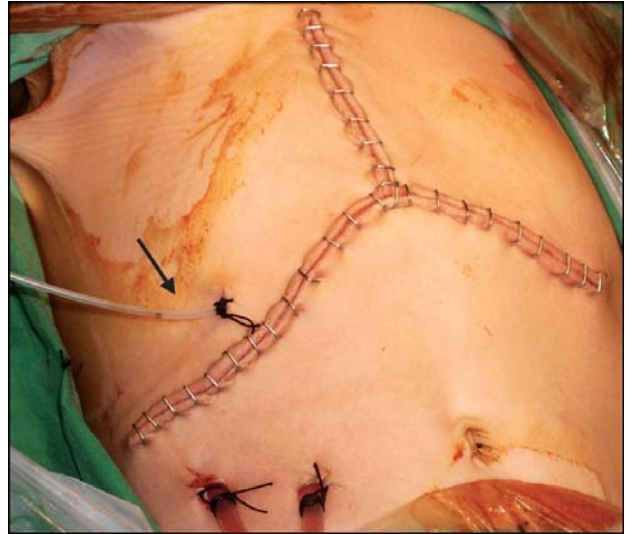


Figure 12.48: Abdomen closure with a T-tube (arrow) and 2 Jackson-Pratt drains in child with lateral segment graft

remnant donor livers undergo a rapid regenerative response.²⁰ Three months after the procedure, the liver volume slightly exceeds 100% of the SLV in recipients but reaches only about 80% of the SLV in donors.²¹ Cirrhotic patients receiving a partial graft show faster regeneration than noncirrhotics, which could be due to a higher portal flow,²² higher portal pressure²³ or a more pro-proliferogenic environment in patients with chronic hepatic insufficiency. Warm ischemia²⁴ and cold ischemia²⁵ have been shown to impair regeneration after partial liver transplantation by interfering with the production of interleukin-6 and tumor necrosis factor α .

Results of LDLT in Japan, USA and Europe^{11,33-36}

Years	Japan			USA	Europe		
	Adult	Children	Overall		Adult	Children	Overall
1 year	75.6%	85.6%	81.8%	89%			
3 years	71.7%	84.1%	79.5%	80%			
5 years	69.1%	82.6%	77.5%	80%	66%	80%	75%

(E) RECIPIENT SURGERY FOR DECEASED DONOR LIVER TRANSPLANTATION

Recipient hepatectomy techniques are different depending on the type of IVC anastomosis either piggyback IVC-IVC anastomosis or older technique of harvesting whole liver along with the donor IVC, after resection of part of recipient's IVC and later end-to-end IVC anastomosis. Most of the centers now perform piggyback technique. For piggyback technique the recipient hepatectomy is same as in LDLT recipient hepatectomy. But when recipient liver is removed with part of IVC, then before transecting the IVC, venovenous bypass (VVB) is set up by cannulating the PV (by means of the left portal vein orifice: 24-28 French cannula), left saphenous vein (22 French cannula), and left subclavian/axillary vein (22 French cannula). Forced cannulation is not advised. If there is difficulty in cannulating then it should be down sized. Axillary cannulation is sometimes difficult due to inadvertent kinking and presence of valves. If there is a difficulty in cannulating the portal vein due to dense hilar adhesions or large collaterals, then IMV/splenic vein may be used for cannulation.

The IVC is mobilized from the retroperitoneum. After the liver is freed from the IVC, a tape is used to control the infrahepatic IVC, and vascular clamps are placed horizontally in suprahepatic and infrahepatic IVC with the liver in normal position and to avoid rotation of these vessels. Supra hepatic clamp is placed on the very edge of the diaphragmatic reflections to avoid injury to phrenic nerve. Divide the IVC, taking care to retain as much as of RHV and LHV as possible by pulling up these veins by almost cutting into the liver substance. The infrahepatic IVC is divided as far as possible and liver is removed along with part of IVC. Suprahepatic IVC is now prepared by opening the RHV, MHV and LHV into a common opening into IVC. Phrenic vein openings are closed with 4-0 pzoletene sutures.

IMPLANTATION TECHNIQUE

- Standard technique
- Piggyback IVC-IVC anastomosis

STANDARD TECHNIQUE

The donor liver is now brought into the wound and corner stitches are placed in the 2 opposite ends of the IVC with a 3-0 prolene and anastomosis is completed on suprahepatic IVC. Care is taken to ensure perfect intimal

opposition. Infrahepatic IVC end-end anastomosis is completed in a similar manner. Portal flush is run with normal saline or lactate ringer solution and 25 gm of albumin per liter through the PV during the completion of infrahepatic IVC anastomosis. This flush helps in removing air to prevent air emboli as well as to remove the excessive high concentration of potassium, resulting from preservation solution. The portal bypass cannula is now clamped, continuing only systemic VVB. Cannula from PV is removed and a vascular clamp is placed. The donor PV is shortened as per the need. Recipient PV should be kept as long as possible or at least 1 cm, which may be useful in case of future need for retransplantation. PV end-to-end anastomosis is completed with 6-0 prolene sutures to preserve the widest possible diameter as there is stretching of PV due to elasticity when the inflow clamp is released. Care is taken to avoid kinking, folding or flow obstruction. Is there is a mismatch in donor and recipient PV diameter a fish mouth reconstruction may be used?

Different methods of reperfusion of liver after PV anastomosis:

- Reperfusion through PV with/without IVC venting
- Opening IVC followed by portal reperfusion
- Reperfusion of PV and HA simultaneously.

When the PV clamp is released slowly in 3-4 partial decompressions keeping an eye on the ECG and blood pressure. During reperfusion (the release of inflow clamp) care is taken by anesthesiologist to avoid hypotension and cardiac arrest by giving high doses of inotropes and calcium chloride. Prevent prolonged warm ischemia and maintain the PV inflow and IVC outflow as early as possible. If there is no bleeding from IVC and PV anastomosis, then systemic bypass is discontinued. Saphenous vein is ligated and axillary vein is reconstructed or ligated.

Hepatic artery anastomosis is completed by using the Carrel patch (with an aortic cuff) on the recipient hepatic artery at the gastroduodenal junction or a branching point on the donor common hepatic artery, with a running suture using 7/0 polypropylene. When there are additional arteries like LHA originating from LGA, then care is taken to preserve the vessel by proper anastomosis with LGA/ Splenic artery or directly to supraceliac aorta. Other technique of arterial anastomosis is performed between the proper hepatic artery at the level of the stump of the gastroduodenal or splenic artery of the graft (without an aortic cuff). Jain et al,²⁶ reporting arterial

complications in 1000 liver transplant recipients, suggested that when there is a redundancy of the hepatic artery, instead of the entire length of donor hepatic artery with an aortic cuff, a shorter length may be a better option with a patch at the level of splenic artery branch. Lorenzin et al,²⁷ reported that application of a technique of arterial anastomosis that avoids kinking, redundancy, or malposition of the artery is achieved by patching at the level of the gastroduodenal artery or the splenic artery stump of the graft, representing a better option than an aortic cuff (Carrel patch) seeking to reduce the risk of arterial complications after liver transplantation. Technique of arterial anastomosis is aimed at avoiding kinking, redundancy, or malposition of the artery, may be a viable option to reduce the risk of HAT after OLT.

After the gallbladder is removed from the donor liver, CBD is shortened proximal to the cystic duct. Choledochocholedochostomy is carried in an end-end (**Figures 12.49 and 12.50**) or side-to-side fashion with 6-0 PDS sutures with or without a T-tube. Duct to duct anastomosis without T-tube drainage is the preferred method. Redundancy in bile duct anastomosis is prevented to avoid postoperative bile duct obstruction. Donor cystic duct is usually ligated and resected to avoid postoperative complications like ductocele and bile duct obstruction in an inadequately drained cystic duct.

Roux-en-Y choledochojejunostomy is preferred in the following conditions

- Insufficient length of bile duct
- Severe mismatch in donor and recipient bile duct
- Pediatric recipients
- Excessive pericholedochal collaterals in recipient
- Retransplantation
- Extrahepatic biliary atresia in recipient/stenosis like PSC, bile duct atresia, etc.

PIGGYBACK TECHNIQUE

Synonym: Caval preservation technique (**Figure 12.51**).

Calne et al first described this technique for transplanting small-for-size grafts.²⁸ Piggyback technique is increasingly used in both DDLT and LDLT. It has gained wide acceptance when it was described again and popularized by Tzakis.²⁹

This hepatectomy technique avoids clamping of the IVC while maintaining flow from the lower half of the body to the heart throughout the transplant unlike the conventional method which requires clamping of both portal flow from the viscera and caval flow from the lower



Figure 12.49: Duct to duct biliary anastomosis without a T-tube



Figure 12.50: Completed duct-to-duct anastomosis without a T-tube in DDLT



Figure 12.51: Side-to-side anastomosis of RHV and IVC in right lobe graft LDLT

part of body. Preservation of cardiac preload serves to maintain hemodynamic stability and avoid large infusions of fluid volume or vasopressors that may be necessary to maintain blood pressure during the anhepatic phase.

In this technique, donor hepatectomy is similar to the technique mentioned in LDLT. IVC of the deceased donor liver is prepared on the back table by closing the both ends of IVC, care is taken to avoid any leak from IVC and making a wide opening in the middle part of IVC for anastomosis with the recipient IVC in a side to side fashion with 4-0 prolene sutures by putting a partial vascular clamp on recipient IVC. Care is taken to make a wider anastomosis.

Piggyback Technique³⁰

Advantages

- Eliminates the need for venovenous bypass (VVB)
- Quick, easy to perform and Short warm ischemia time as the time spent in IVC anastomosis is saved.
- Maintain hemodynamic and physiological stability.
- Less perioperative and postoperative morbidity due to lesser blood loss and less renal complications.
- Improved outcomes.

Disadvantages

- Technically more demanding
- Time consuming during dissecting phase of donor hepatectomy while ligating the short hepatic veins than the conventional approach.
- A large caudate lobe or an intrahepatic IVC increases the complexity and risk of this technique.

ROLE OF TEMPORARY PORTOCAVAL SHUNTS (TPCS) IN LIVER TRANSPLANTATION

Clamping of the portal vein and the subsequent rise in portal venous pressure, congestion of the splanchnic bed, and intestinal edema led to the description by Tzakis et al³⁹ of the use of a TPCS, in which an end-to-side anastomosis is formed between the recipient's portal vein and infra hepatic IVC. The use of a TPCS has now become common practice. Anecdotally, it has been shown to improve retrohepatic dissection and decreases the splanchnic congestion, but the evidence is scarce. The aim of this study was to systematically review the literature on the use of TPCS in LT and determine whether there is evidence to support its routine use.

Portal vein clamping induces a reflexive increase in systemic vascular resistance that helps to maintain mean arterial pressure despite a fall in the cardiac index as a result of the interruption of portal flow (**Figures 12.52A to D**). However, with re-establishment of portal flow,

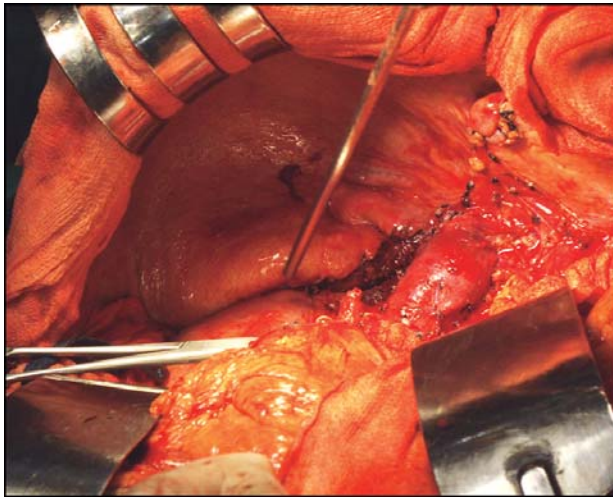
there is a reflex fall in blood pressure as well as the elaboration of vasoactive metabolites from the splanchnic circulation.⁴⁰ This is usually short-lived and well tolerated, but with prolonged clamping and in the presence of hemodynamic instability, the re-establishment of portal flow causes results in increased permeability of the splanchnic vessels, interstitial edema of the gut, and the accumulation of acute inflammatory cells with evidence of mucosal cell damage.⁴³⁻⁴⁵ With the release of portal clamping, inflammatory cytokines are released into the liver and subsequently the systemic circulation, leading to vasodilatation and end organ damage, including subpericardial hemorrhage, myocardial necrosis, and pulmonary infiltration and edema.⁴³⁻⁴⁵ It has been postulated that a temporary portocaval shunting prevents splanchnic congestion and helps to maintain portal venous return, thereby abrogating the regional and systemic consequences associated with prolonged portal vein clamping. It was initially recommended in fulminant hepatic failure with portal hypertension in the absence of portosystemic venous collaterals.⁴⁰

Figuera et al⁴² reported that only 55% of patients with a TPCS required a blood transfusion versus 78% of patients without a TPCS. The clinical benefits of a TPCS appear to be greatest in patients with severe portal hypertension and high portal flow. In patients with a portal flow of greater than 1000 mL/minute and a portocaval gradient of greater than 16 mm of Hg, only 33% of patients with a TPCS required a blood transfusion versus 85% of patients without a TPCS.⁴²

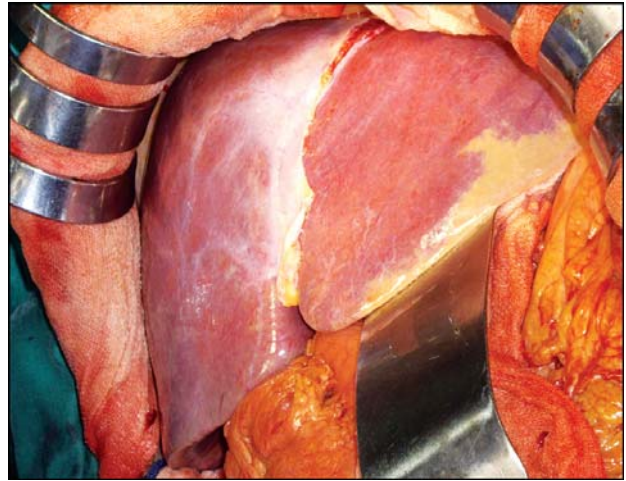
A number of studies have demonstrated an improvement in renal function with the use of a TPCS.^{41,42} In a prospective randomized trial comparing patients with a TPCS and patients without one, Figueras et al⁴² demonstrated that the urine output during transplantation was greater in all patients with a TPCS but reached statistical significance only in those patients with both high portal flow (>1000 ml/min) and high portocaval gradient (>16 mm Hg). In addition, postoperative serum creatinine levels were stable in patients with a TPCS, whereas the serum creatinine increased over the first 48 hours post-transplant in those without one.⁴²

TEMPORARY PORTOCAVAL SHUNT HAS THE FOLLOWING ADVANTAGES⁴⁷

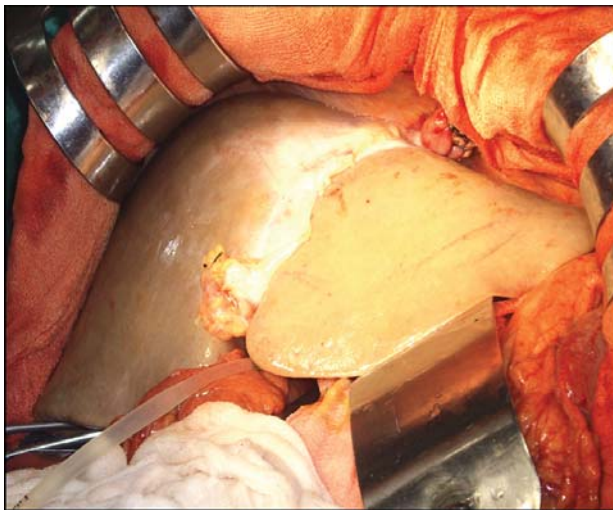
- Intraoperative cardiovascular stability and decreases blood transfusion requirement
- Improvement in renal function
- Reduces the urgency to implant the liver graft



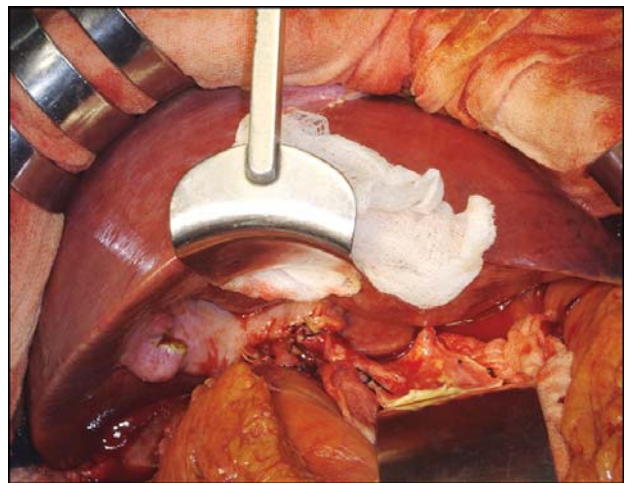
A. Anhepatic phase



C. Whole liver just after portal perfusion



B. Whole liver before portal perfusion



D. Whole liver after PV and HA reconstruction

Figures 12.52A to D: Marked color change from a pale looking liver to well vascularized organ after reconstruction of portal vein and hepatic arterial flow

REFERENCES

1. Makuuchi M, Kawasaki S, Noguchi T, et al. Donor hepatectomy for living related partial liver transplantation. *Surgery* 1993; 113:395-402.
2. Yamamoto H, Maetani Y, Kiuchi T, et al. Background and clinical impact of tissue congestion in right-lobe living-donor liver grafts: a magnetic resonance imaging study. *Transplantation* 2003;76:164-69.
3. Maetani Y, Itoh K, Egawa H, et al. Factors influencing liver regeneration following living-donor liver transplantation of the right hepatic lobe. *Transplantation* 2003;75:97-102.
4. BW Kim, YK Park, OJ Paik, et al. Effective Anatomic Reconstruction of the Middle Hepatic Vein in Modified Right Lobe Graft Living Donor Liver Transplantation. *Transplant Proceed* 2007;39:3228-33.
5. Lu Nan Y, Bo Li, et al. Modified techniques of adult to adult living donor liver transplantation. *Hepatobiliary panc. Diges int* 2006; 5(2):173-79.
6. NJ Yi, KS Suh, H W Lee, et al. An artificial vascular graft is a useful interpositional material for drainage of the right anterior section in living donor liver transplantation. *Liver transpl* 2007; 13:1159-67.
7. Stapleton GN, Hickman R, Terblanche J. Blood supply of the right and left hepatic ducts. *Br J Surg* 1998;85:202-07.
8. Rouch DA, Emond JC, Thistlethwaite JR Jr, et al. Choledochochole-dochostomy without a T tube or internal stent in transplantation of the liver. *Surg Gynecol Obstet* 1990;170:239-44.
9. Takatoshi I, Tanaka K, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Annals of Surg* 2002;236(2):235-40.

10. Egawa H, Inomata Y, Uemoto S, et al. Biliary anastomotic complications in 400 living related liver transplantation. *World J Surg.* 2001;25:1300-07.
11. Kawasaki S, Hashikura Y, Matsunami H, et al. Temporary shunt between right portal vein and vena cava in living related liver transplantation. *J Am Coll Surg* 1996;183:74-76.
12. Hashikura Y, Kawasaki S, Okumura N, et al. Prevention of hepatic artery thrombosis in pediatric liver transplantation. *Transplantation* 1995;60:1109-12.
13. Matsunami H, Makuuchi M, Kawasaki S, et al. Venous reconstruction using three recipient hepatic veins in living related liver transplantation. *Transplantation* 1995;59:917-19.
14. Takayama T, Makuuchi M, Kubota K, et al. Living-related transplantation of left liver plus caudate lobe. *J Am Coll Surg* 2000; 190:635-38.
15. Tanaka K, Uemoto S, et al. surgical techniques and innovations in living donor liver transplantation. *Ann Surg* 1993;217:82-91.
16. Makuuchi, et al. Portal venoplasty for recipients in living related liver transplantation. *Transplant* 1999;68:1199-200.
17. Mitchell A, et al. Improved technique of PV reconstruction in pediatric liver transplant recipients with portal vein hypoplasia. *Transplantation* 2002;73:1244-47.
18. Marwan IK, Fawzy AT, Egawa H, et al. Innovative techniques for and results of portal vein reconstruction in living related liver transplantation. *Surg* 1999;125:265-70.
19. Farmer DG, Shaked A, Olthoff KM, et al. Evaluation, operative management, and outcome after liver transplantation in children with biliary atresia and situs inversus. *Ann Surg* 1995;222(1):47-50.
20. Marcos A, Fisher RA, Ham JM, et al. Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. *Transplantation* 2000;69:1375-79.
21. Humar A, Kosari K, Sielaff TD, et al. Liver regeneration after adult living donor and deceased donor split-liver transplants. *Liver Transpl* 2004;10:374-78.
22. Eguchi S, Yanaga K, Sugiyama N, Okudaira S, Furui J, Kanematsu T. Relationship between portal venous flow and liver regeneration in patients after living donor right-lobe liver transplantation. *Liver Transpl* 2003;9:547-51.
23. Yagi S, Iida T, Taniguchi K, et al. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. *Liver Transpl* 2005;11:68-75.
24. Selzner N, Selzner M, Tian Y, et al. Cold ischemia decreases liver regeneration after partial liver transplantation in the rat: a TNF-alpha/IL-6-dependent mechanism. *Hepatology* 2002;36:812-18.
25. Selzner M, Camargo CA, Clavien PA. Ischemia impairs liver regeneration after major tissue loss in rodents: protective effects of interleukin-6. *Hepatology* 1999;30:469-75.
26. Jain A, Costa G, Marsh W, et al. Thrombotic and nonthrombotic hepatic artery complications in adults and children following primary liver transplantation with long-term follow-up in 1000 consecutive patients. *Transpl Int* 2006;19:27.
27. Lorenzin D, Adani GL, Comuzzi C, et al. Comparison of two techniques of arterial anastomosis during adult cadaveric liver transplantation. *Transplantation Proceedings* 2007;39:1879-80.
28. Calne RY, Williams R: Liver transplantation in man. I. Observations on technique and organization in five cases. *Br Med J* 1968;4630:535.
29. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. *Ann Surg* 1989;2105:649.
30. RS Mangus, SB Kinsella, et al. Predictors of blood product use in orthotopic liver transplantation using the piggyback hepatectomy technique. *Transplantation Proceedings* 2007;39:3207-13.
31. Satou S, Makuuchi M, et al. Preoperative estimation of right lateral sector graft by three-dimensional computed tomography. *Transplantation Proceedings* 2006;38(5):1400-03.
32. Ikegami T, Makuuchi, et al. Should all hepatic arterial branches be reconstructed in live related liver transplantation? *Surgery* 1996;119:431-36.
33. Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:816-23.
34. Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003;9:1231-43.
35. Shimada M.,Fuji M, Morine Y, et al. Living donor liver transplantation, present status and future prospective. *Journal of medical investigations* 2005;52:22-32.
36. Y Sugawara, M Makuuchi. Living donor liver transplantation: present status and recent advances. *British Medical Bulletin* 2005;75 and 76:15-28.
37. de Villa VH, Chen CL, Chen YS, et al. Outflow tract reconstruction in living donor liver transplantation. *Transplantation* 2000; 70(11):1604-08.
38. Lai-Size G Wong, BH Yong, KK Young, et al. Comparison of the USCOM ultrasound cardiac output monitor with pulmonary artery catheter thermodilution in patients undergoing liver transplantation. *Liver transplantation* 2008;14:1038-43.
39. Tzakis A, Reyes J, Starzl T. Temporary end to side portacaval shunt in orthotopic hepatic transplantation in humans. *Surg Gynecol Obstet* 1993;176:180-82.
40. Turnage R, Guice K, Oldham T. Endotoxemia and remote organ injury following intestinal perfusion. *J Surg Res* 1994;56:571-78.
41. Margarit C, de Cenarruzabeitia I, Lazaro J, et al. Portacaval shunt and inferior vena cava preservation in orthotopic liver transplantation. *Transplant Proc* 2005;37:3896-98.
42. Figueras J, Llado L, Ramos E, et al. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. *Liver Transpl* 2001;7:904-11.
43. Liu D, Jeppsson B, Hakansson C, et al. Multiplesystem organ damage resulting from prolonged hepatic inflow interruption: electron microscopic findings. *Arch Surg* 1996;131:442-47.
44. Marzi I, Knee J, Menger M, et al. Hepatic microcirculatory disturbances due to portal vein clamping in the orthotopic rat liver transplantation model. *Transplantation* 1991;52:432-36.
45. Lee SG, Hwang S, Kim KH, et al. Approach to anatomic variations of the graft portal vein in right lobe living-donor liver transplantation. *Transplantation* 2003;75(3):S28-32.
46. Harihara Y, Makuuchi M, Kawasaki H, et al. Portal venoplasty for recipients in living related liver transplantation. *Transplantation* 1999;68:1199-1200.
47. Diego Davila, Adam Bartlett, Nigel Heaton. Temporary portocaval shunt in orthotopic liver transplantation: Need for a Standardized Approach? *Liver transplantation* 2008;14: 1414-19.

Reperfusion Syndrome and Preservation Injury

INTRODUCTION

Graft reperfusion during orthotopic liver transplantation (OLT) is generally associated with a variety of transient haemodynamic disturbances.^{1,2} Post-reperfusion syndrome (PRS) is defined as a decrease in mean arterial pressure (MAP) to >30% below the baseline value for at least 1 minute, occurring during the first 5 minutes after reperfusion.³ PRS presents as systemic hypotension and pulmonary hypertension. PRS occurs in 15 to 30% of cases, resulting in intense hemodynamic instability.^{4,5}

ETIOLOGY OF PRS

Many potential mechanisms for the hemodynamic changes in PRS have been proposed including

- Sudden influx of cold, acidic, and hyperkalemic blood^{6,7}
- Minute air and Thrombotic embolization
- Release of vasoactive substances (Arginine and Thromboxane A₂) from the graft.^{8,9}
- Prolonged cold ischemic time (CIT).¹⁵

Acute hyperkalemia (>6 mEq/L) caused by influx of potassium from the liver at the beginning of reperfusion may induce various arrhythmias and myocardial depression, or "cardioplegia."¹⁰ Hyperkalemia reduced conduction velocity and myocardial contractility by decreasing the resting membrane potential and the number of open calcium channels during depolarization.⁶ Treat the possible increase in serum potassium during the anhepatic phase 8 and before reperfusion.¹²

Allografts withstand poorly to prolonged CIT. The ischemia and reperfusion that accompany organ transplantation are known to be associated with release of proinflammatory mediators, generation of free radicals, neutrophil sequestration, and activation. More vasoactive substances such as arginase, thromboxane A₂ are released from these prolonged or poorly preserved grafts into the

recipient systemic circulation on graft revascularization. Chui et al. reported that it is important to keep the CIT short and to perform the wash out when dealing with suboptimal grafts to reduce the risk of significant PRS.¹⁵

Hemodynamic changes during the anhepatic period, especially systemic vascular resistance (SVR) increase has been suggested to correlate with the occurrence of PRS but mean arterial pressure and cardiac output have no effect on occurrence of PRS.¹¹ Ayanoglu et al reported that unclamping of the porta vein (but not inferior vena cava) might be the main cause of PRS because this blood represents a source of vasoactive or inflammatory mediators released after reperfusion of the new liver.¹⁴

PREVENTION AND TREATMENT OF REPERFUSION SYNDROME

To reduce the risk of PRS occurrence, it is advisable to keep the CIT short, and to routinely wash out the liver graft immediately prior to revascularization with cold and warm albumin based solutions during OLT to minimize the effects of hyperkalemia and hypothermia. Venovenous bypass has been reported to be ineffective in preventing PRS.¹³

Before reperfusion, prophylactic treatment consists of

- Atropine (0.2 mg/kg)
- Sodium bicarbonate (1 mEq/kg)
- Calcium chloride (0.5 g) or of Calcium gluconate (1-2 g)
- 20% Mannitol
- Hyperventilation.

During the first 5 minutes after reperfusion, a decrease in MAP >30% below the baseline and a tendency to continue decreasing were diagnostic of PRS and immediate treatment to correct hypotension includes:

- Ephedrine (5 to 10 mg) or
- Adrenaline (10- to 50-ug IV bolus doses)

PRESERVATION INJURY

Preservation injury (PI) is the hepatocyte injury due to cold preservation or reperfusion of the allograft. Preservation injury is common following cadaveric liver transplantation. Severe PI may result in initial poor function or primary nonfunction. The laboratory abnormalities include a marked increase in AST and ALT levels during the first 24–48 hours after transplantation, with subsequent slowly declining levels. Later, serum alkaline phosphatase and bilirubin levels are elevated. These changes occur in the absence of other recognized causes of graft failure. The diagnosis is made by liver biopsy, but hepatic arterial thrombosis can cause a similar histologic appearance and must be excluded by DUS studies.

REFERENCES

1. Zadrobilek E, Mauritz EW, Feil W, et al. *Anaesthetist* 1998;37:672.
2. Paulsen AW, Valek TR, Blessing WS, et al. Hemodynamics during liver transplantation with veno-venous bypass. *Transplant Proc* 1987;19(1 Pt 3):2417-19.
3. Aggarwal S, Kang Y, Freeman J, et al. Is there a post-reperfusion syndrome? *Transplant Proc* 1989;21(3):3497-99.
4. Blumhardt G, Ringe B, Pichlmayr R, et al. Vascular problems in liver transplantation. *Transplant Proc* 1987;19(1 Pt 3):2412.
5. Gabriel A, Müller C, Tüchy G, et al. Reperfusion during orthotopic liver transplantation: Analysis of right ventricular dynamics. *Transplant Proc* 1993;25(2):1811-12.
6. Aggarwal S, Kang Y, Freeman JA, et al. Postreperfusion syndrome: Hypotension after reperfusion of the transplanted liver. *J Crit Care*. 1993;8(3):154-60.
7. Bellamy MC, et al. *Br J Anaesth* 1997;79:338.
8. Längle F, Roth E, Steininger R, et al. Arginase release following liver reperfusion. Evidence of hemodynamic action of arginase infusions. *Transplantation* 1995;59(11):1542-49.
9. Ishikawa T, Yagi T, Ishine N, et al. Energy metabolism of the grafted liver and influence of preretrieval feeding process on swine orthotopic liver transplantation. *Transplant Proc* 1997;29(1-2):397-99.
10. De Wolf AM. Does ventricular dysfunction occur during liver transplantation? *Transplant Proc* 1991;23(3):1922-23.
11. Martinez IG, et al. *Anesthesiol Analg* 1997;84:254.
12. Acosta F, Diaz J, Sansano T, et al. Prophylactic treatment of metabolic alterations during revascularization in liver transplantation. *Transplant Proc* 1994;26:3667.
13. Jugan E, et al. *Transplant Proc* 1999;31:2382.
14. HO Ayanoglu, S Ulukaya, and Y Tokat. Causes of post reperfusion syndrome in living or cadaveric donor liver transplantations. *Transplantation Proceedings* 2003;35:1442-44.
15. AKK Chui, L Shi, K Tanaka, et al. Post reperfusion syndrome in orthotopic liver transplantation. *Transplantation Proceedings* 2000;32:2116-17.

Technical Modifications in Recipient Surgery

PRE-TRANSPLANT PV THROMBOSIS IN RECIPIENT

Portal vein thrombosis (PVT) is no longer considered an absolute contraindication for liver transplantation (LTX). A variety of surgical techniques have been used to provide satisfactory portal vein inflow to the liver graft in the presence of portal venous thrombosis in the recipient.^{1,2} Incidence of pretransplant PVT in recipients is 2 to 26% in liver transplant patients.^{3,4} Recurrence rate of thrombosis after initial eversion thrombectomy during transplantation is 2.4 to 28.5%.⁵ Studies have indicated improved outcomes among recipients with PVT with 1-year survival of 85% and similar 3 years and 6 years mortality rates between recipients with or without PVT.⁶ PV flow (PVF) < 5 mL/min/kg is a risk factor to develop graft PVT, a search and occlusion of a spontaneous shunt is recommended to avoid the steal.⁷ Another option is to perform a Reno-portal anastomosis (RPA).⁸ In the scenario of poor PVF diagnosed prior to transplantation, an arterial reconstruction should be performed first to prevent graft failure.⁹

Earlier studies reported that PVT associated with liver transplantation increased surgical complexity, transfusion needs, and prolonged interventions. In addition, all of these studies showed increased postoperative complications: acute pancreatitis, recurrent PVT, kidney failure, and severe graft dysfunction.¹⁰⁻¹²

Risk factors for PVT in cirrhosis¹³⁻¹⁵

- Male sex
- Previous treatment of portal hypertension
- Advanced cirrhosis
- Hypercoagulable state

PATHOGENESIS OF PVT⁵⁹

The pathogenesis of PVT among patients with liver cirrhosis is still unclear, but can be explained as mentioned below:

- Decreased portal blood flow and the presence of periportal lymphangitis and fibrosis may be associated with the development of portal vein thrombus.
- Coagulation factors and anticoagulation factors are altered, because of reduced liver synthetic activity which is a possible precipitating factor for PVT.
- Other risk factors are splenomegaly, the width of main portal vein, and the terminal stage of liver function.
- Liver cirrhosis concomitant with hepatocellular carcinoma enhances the tendency for PVT development.
- Cancer is associated with PVT through a combination of neoplasm related prothrombotic changes and either compression or the surgical injury to the portal vein.

Compensatory mechanism in case of PVT in cirrhotic patients

- Increased liver blood flow through the hepatic artery
- Rapid development of tortuous collateral veins around a thrombosed portal vein.
- Portal hypertension due to PVT is prehepatic, characterized by a high pressure in the obstructed splanchnic bed, which results in extensive portal-systemic collateral circulation and hyperdynamic flow due to the reduced systemic vascular resistance associated with high cardiac output.

DIAGNOSIS

Doppler ultrasound is the first line investigation and have a diagnostic sensitivity and specificity of 73 and 99%,

respectively.¹⁶ 2-phase CT Scan and MR angiography can provide excellent visualization of portal vein thrombosis and can facilitate the differentiation of thrombosis from slow flow.^{17,18} Angiography is no longer used for routine pretransplant assessment of recipient. Angiography can accurately delineate the extent and precise localization of PVT and provide information about the patency of regional collaterals, which could potentially be used for a portal vein anastomosis during LTX. An angiogram is particularly required to grade PVT in all unclear situations, as various forms and extents of PVT require different surgical strategies.¹⁶

GRADING OF PVT

Yerdel et al¹⁹ classified PVT into four grades basing on the intraoperative assessment

GRADING OF PORTAL VEIN THROMBOSIS³⁰

Grade 1: PVT in <50% of vessel lumen + Minimal extension to SMV; **Grade 2:** PVT in >50% of vessel lumen occlusion or total occlusion + Minimal extension to SMV; **Grade 3:** Complete thrombosis of both PV and proximal SMV. Distal SMV is open along with presence of dilated collaterals; **Grade 4:** Complete thrombosis of both PV and proximal as well as distal SMV along with presence of fine collaterals (**Figure 14.1**).

The majority of patients with PVT can be managed by PV thrombectomy. Venous conduits were required for 20% of OLT recipients in this series.⁴³⁻⁴⁵ Most authors have suggested eversion thromboendovenectomy (ETEV) as

the surgical technique of choice for PVT grades I, II, and III.²⁰⁻²² In cases where the thrombus extends beyond the junction of superior mesenteric and splenic veins (grade IV), ETEV is often unsuccessful and vein grafts have to be taken into account.^{16,20,21} One possible graft type in this situation is a jump graft to a patent segment of the proximal SMV using an iliac vein segment of the donor. The vein graft should be tunneled through the transverse mesocolon and positioned anterior to the pancreas and posterior to the pylorus. This approach to gain splanchnic inflow from the proximal SMV avoids extensive peripancreatic dissection and associated morbidity.²¹ In all cases if the SMV is also thrombosed, the coronary vein or large, unnamed collateral veins can also be potentially used to provide portal venous inflow.^{16,19,21} Postoperatively, all these patients are treated with anticoagulant therapy.

SURGICAL TREATMENT PLAN OF PVT (GRADE I TO IV)

Various surgical treatment options for PVT

- End-to-end portal anastomosis +/- Thrombectomy
- Thrombectomy +/- SMA anastomosis
- Thromboendovenectomy
- Reconstruction with an interposition graft or vascular jump grafts between donor and recipient PV/ SMV
- Anastomosis with a collateral vein
- Cavoportal hemitransposition
- Portal vein arterialization
- Renoportal anastomosis (RPA)
- Combined liver-intestine transplant

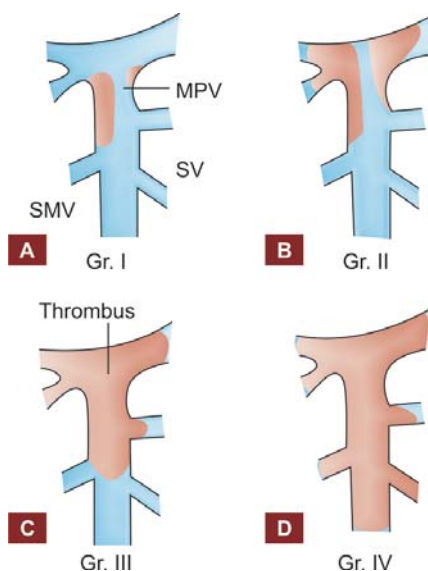


Figure 14.1: Shows grade I to IV portal vein thrombosis (Modified and redrawn with permission from Laura Llado)³⁰

Grade I

End-to-end portal anastomosis +/- Thrombectomy. When thrombectomy is performed, eversion of the vein and sharp dissection of the thrombus and sometimes resection of part of PV is necessary until complete patency is achieved. Portal inflow is measured to confirm adequate flow. If flow is inadequate other procedures should be tried.

Grades II and III

Grades II and III can be resolved by thrombectomy. Anastomosis at the confluence of SMV may be required. If the PV lumen is narrow due to a fibrosis of the wall, an anastomosis can be performed to either the coronary vein or a large collateral vein or by use of an interposition graft or vascular jump graft from donor iliac vein to anastomose to SMV/SV junction (**Figures 14.2 to 14.5**). If PVF is low (<800 mL/min), search for residual thrombus or spontaneous splenorenal shunts and/or ligate the coronary vein to improve portal flow.²⁸ For

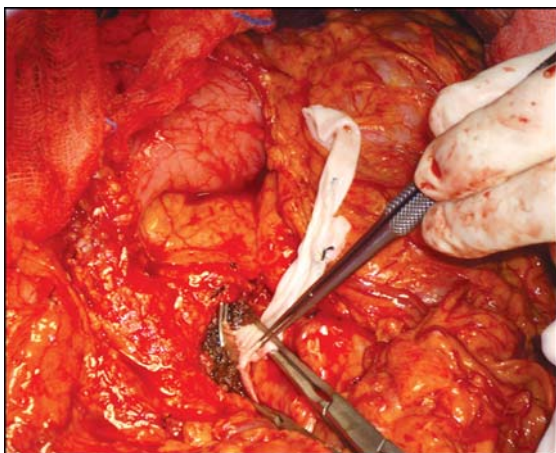


Figure 14.2: Vascular graft anastomosed to the junction of SMV and splenic vein

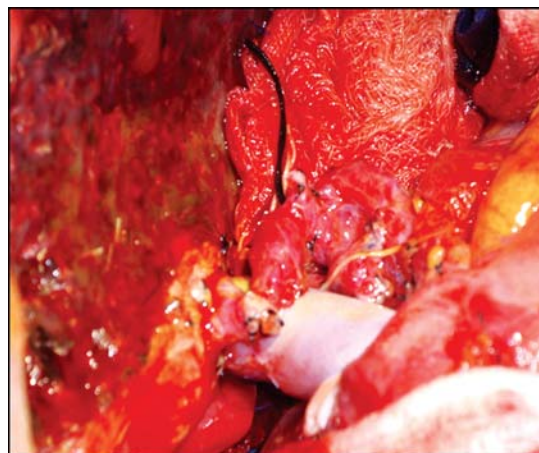


Figure 14.5: Completed portal vein anastomosis, dilated portal vein (vascular graft) after release of vascular clamps

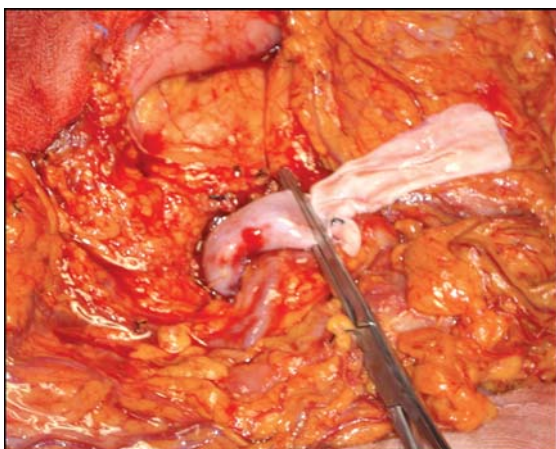


Figure 14.3: Completed anastomosis and displacement of vascular clamp to check any leak in the anastomosis

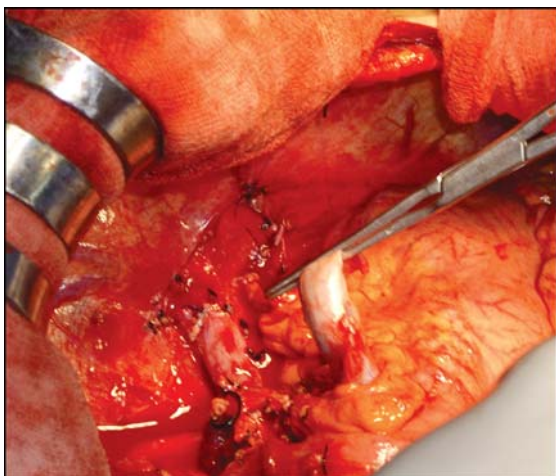


Figure 14.4: Vascular graft tunneled through retroduodenal area, anterior to pancreas and brought anteriorly close to the graft (to be placed) for anastomosis

portal vein reconstruction, cryopreserved vascular grafts should not be used as the long term results of patency is not good. Fibrosis and contraction of the graft, leading to stenosis of portal vein requiring further intervention.

Grade IV

Anastomosis to either coronary vein or another large collateral vein. If no collateral veins available, in such cases there is a controversy regarding the treatment option. Various techniques are described, such as²⁴⁻²⁹

- Cavoportal hemitransposition (CPHT)
- Portal vein arterialization
- Renoportal anastomosis (RPA)
- Combined liver-intestine transplant

All of these procedures are technically complicated and are associated with high mortality, may not resolve portal hypertension.²⁹ If no suitable collateral vein is found in grade IV type, LTX may be contraindicated due to its poor outcome.²⁵

CAVOPORTAL HEMITRANSPOSITION (CPHT)

Portocaval transposition was first described by Child et al³² in 1953. It was performed to study hepatic and gastrointestinal physiology. The suprarenal IVC and proximal PV are transposed, supplying the hepatic venous inflow with systemic venous return while shunting the mesenteric circulation systemically. In 1967 Marchioro et al.³³ described partial portocaval transposition in an experimental animal model where the right or the left PV branch was detached from the main PV and revascularized by end-to-end anastomosis to the suprarenal IVC, resulting in one lobe with systemic IVC inflow and the other retaining the portal inflow.

Tzakis et al²⁶ who introduced the term cavoportal hemitransposition to describe the procedure in which the supra-renal IVC constitutes the sole portal inflow to the liver allograft in nine patients undergoing liver transplantation. The low portal venous blood flow following end-to-end portal vein anastomosis could only be augmented by the addition of systemic venous return.

Cavoportal transposition is a nonphysiological procedure that was performed in the pretransplantation era in experimental animal models to study the effects of systemic venous flow on the liver. It was found that liver function tests and histology were normal, but because of the high portal flow, liver congestion and retroperitoneal collaterals developed.³¹ Conventional portocaval transposition is not feasible in patients with PVT. Thus a modification has been described where the supra-renal IVC is transposed into the portal circulation (cavoportal hemitransposition) constituting half of the reconstruction originally described. This procedure relies on spontaneous shunting to decompress the mesenteric venous system to avoid the complications associated with portal hypertension.

COMPLICATIONS OF CPHT³⁴⁻³⁷

- Petal hypertension (when GRWR ratio is <0.8 and Portal flow > 2 L/min)
- Severe ascites
- Renal insufficiency
- Variceal bleeding

Surgical techniques for portal vein reconstruction in grade IV PVT³⁰

- End-to-end cavoportal anastomosis between the native IVC and graft PV
- Side-to-end cavoportal anastomosis between native IVC and graft PV with retro-hepatic caval vein constriction.
- Side-to-end anastomosis between native IVC and graft PV preserving the retro-hepatic caval flow by calibration of retrohepatic caval vein.
- End-to-side cavoportal anastomosis using donor iliac vein interposition graft distal to the conventional PV anastomosis.
- Renoportal anastomosis (RPA): End-to-end anastomosis between native left renal vein and graft portal vein.

Bakthavatsalam et al³⁸ reported the use of cavoportal shunt in PV thrombosis. They reserve this procedure for unique cases where the more traditional methods for obtaining portal inflow to the transplanted liver are not feasible or prove unsuccessful. A cavoportal shunt does offer the advantage of mesenteric decompression

compared with portocaval hemitransposition. A possible modification of this procedure, to limit the hepatic congestion, would be the use of the left renal vein, which would offer enhancement of venous return without the volume or pressure transmitted from the IVC. The use of this procedure in patients with existing distal splenorenal shunts has been reported.²⁷ So in every case of PVT, initially look for the SMV or splenic vein or accessible collateral vein or IMV for alternative procedures.

PORTAL VEIN ARTERIALIZATION (PVA)

DIFFERENT TECHNIQUES

- PVA is created by laterally anastomosing hepatic artery to the portal vein. Arterial reconstruction is performed by anastomosing the gastroduodenal stump to the donor celiac trunk. In LDLT, hepatic artery of the allograft can be anastomosed to the supra-celiac aorta after PVA.
- PVA is performed using a donor iliac graft between the aorta and graft portal vein. Recipient portal vein is ligated.
- Donor portal vein may be anastomosed to the branch of the iliac artery.

TECHNICAL COMPLICATIONS OF PVA

Portal Hypertension and Increase the Risk of Variceal Bleeding

PV remains completely disconnected from the splanchnic area because high pressure from the arterial system and the lack of drainage of mesenteric blood is the main cause of for the bleeding risk.

Liver Allograft Injury and Right-sided Heart Failure

This problem can be addressed by artificial stenosis of the artery proximal to the anastomosis to decrease blood flow, aiming at a portal blood flow of approximately 0.6 to 0.8 L/min¹; while arterial blood via the portal vein can promote and enhance liver regeneration.³⁹

Neelamekan et al⁴⁰ reported complications due to portal hypertension that required surgical disconnection of the arteriportal fistula, or performing a portosystemic shunt.⁴¹ Auxiliary heterotopic liver transplant with PVA has been used in cases of fulminant hepatic failure with the aim of leaving the hilum of the native liver untouched and preserving all portal inflow. Therefore, the native liver has the optimum chances of rapid regeneration. PVA is an acceptable salvage alternative when insufficient portal venous flow to the graft is present and normal liver function can be achieved.⁴²

Post-transplant Follow-up and Arterialized Hepatic Allograft Study

Postoperative recurrence rate of PVT ranges from 0% to 30%. Recurrence depends on the size of the portal vein, extension and severity of preoperative thrombosis and also on the time the transplantation performed.⁴⁴ Portal decanalization and reconstruction with endovascular stents are emerging effective radiological procedures to treat PVT. Portal blood flow and signs of portal hypertension (ascities, esophageal varices) are evaluated by abdominal DUS, upper GI endoscopy, and helical CT scan.⁴³ Liver biochemistry also gives a clue to the diagnosis. If hepatic infarctions in the liver develop despite performed thrombectomy, they need to be monitored to recognize focal abscess formation or to evaluate resolution of infarction foci. According to many authors the best diagnostic tool for such follow-up is CT examination, and infarction areas are seen at CT as wedge-shaped, low attenuation, peripheral lesions.⁴³

Renoportal Anastomosis

RPA was firstly described by Sheil and later modified with a venous interposition graft by Kato and Azoulay.⁴⁵⁻⁴⁷ For RPA the left renal vein is always used. A renoportal end-to-end anastomosis is performed between the native left renal vein and the portal vein of the graft. This vascular reconstruction is used for patients with a pre-existent patent spontaneous or surgically constructed distal spleno-renal or lienorenal shunt (without dismantling the shunt).

Combined Liver-intestine Transplant

When extensive splanchnic venous thrombosis is present and sufficient portal blood flow to the liver graft cannot be restored, combined liver and intestinal transplantation is an option.^{21,23}

ARTERIAL COMPLICATIONS

Pretransplant Hepatic Artery Thrombosis

In pretransplant conditions this complication is less common than PV thrombosis. But adequate arterial blood flow to the graft is important to avoid biliary ischemia. If the recipient hepatic artery is thrombosed, the options for the hepatic arterial reconstruction are by anastomosis to:

- Infrarenal aorta using an arterial conduit
- Supra celiac aorta
 - Direct anastomosis
 - Indirect anastomosis using an arterial conduit
- Anastomosis to the splenic artery

The arterial conduit used from the donor iliac artery or cryopreserved arterial graft. Apart from iliac vessels from cadaveric donors,⁵² the other preferred vascular conduits are saphenous vein,⁴⁸ splenic artery,⁴⁹ and sigmoid artery,⁵⁰ etc.

Long term patency rate of the arterial conduits is less than the direct anastomosis. Itabashi et al. reported the use of right gastroepiploic artery⁵¹ for hepatic artery reconstruction. Patency rate is higher in direct supraceliac anastomosis and use of a short arterial conduit. End to end splenic arterial anastomosis is less preferred as it decreases the portal flow by 20 to 40%. For splenic arterial anastomosis, distal part of splenic artery is ligated and end to end anastomosis is done.

PREVIOUS SHUNT PROCEDURES

Brems et al. reported that previous abdominal surgery, and portocaval shunts in particular, should be avoided in potential candidates for OLT.⁵³ Whereas others^{48,56,57} have found no significant differences in the outcomes of patients with and without previous PSS. Menegaux et al.⁵⁵ reported that the patients in whom TIPS had been installed presented less intraoperative consumption of blood products secondary to less blood loss owing to control of portal hypertension. Surgical shunt procedures in ESLD are obsolete in present days after the introduction of TIPS. The recipient with previous TIPS (**Figures 14.6 and 14.7**) should be properly evaluated by CT scan for the position of the TIPS stent. If the stent migrates into the IVC or into the portal vein, there will be difficulty in mobilizing the liver and subsequent inflow and outflow reconstruction. Misplacement of the TIPS, most frequent in cirrhotic, atrophic, or small livers, is the main cause of technical complications that require the interposition of vascular grafts.^{54, 55} Guerrini et al reported that 28%

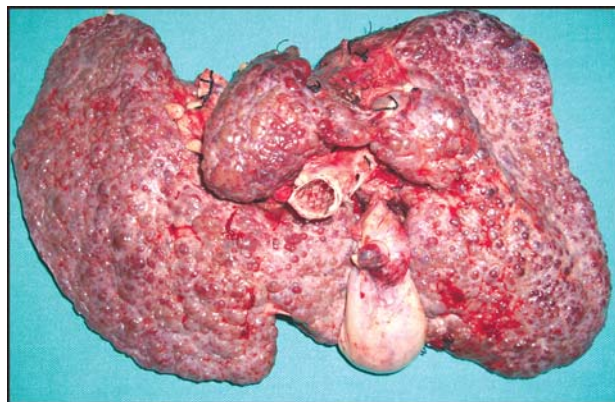


Figure 14.6: Recipient liver with previous TIPS for control of variceal bleeding due to HBV related cirrhosis and portal hypertension

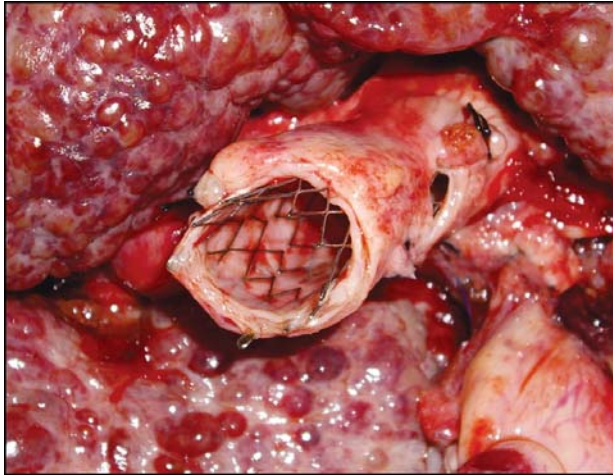


Figure 14.7: Portal vein with transjugular intrahepatic portosystemic shunt stent (TIPS)

(17 out of 61 patients) of his series, TIPS had migrated, increasing the time spent on bypass and complexity of the recipient operation.⁶⁰ Regarding the surgical shunts DSRS (distal splenorenal shunt) is the best that can be done in ESLD patient on waiting list. Other surgical shunts are best avoided in these patients.

REFERENCES

- Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. *Ann Surg* 1991;213:199-206.
- Moreno Gonzalez E, Garcia Garcia I, Gomez Sanz R, Gonzalez-Pinto I, Loinaz Seguro C, Jimenez Romero C. Liver transplantation in patients with thrombosis of the portal, splenic or superior mesenteric vein. *Br J Surg* 1993;80:81-85.
- Nonami T, Yokoyama I, Starzl TE, et al. The incidence of portal vein thrombosis at liver transplantation. *Hepatology* 1992;16:1195.
- Davidson B, Gibson M, Dick R, et al. Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. *Transplantation* 1994;57:1174.
- Dumortier J, Czyglik O, Poncet G, et al. Eversion Thrombectomy for portal vein thrombosis during liver transplantation. *Am J Transplant* 2002;2:934.
- Seu PH, Shackleton CHR, Shacked A, et al. Improved results of liver transplantation in patients with portal vein thrombosis. *Arch Surg* 1996;131:840.
- Margarit C, Lazaro JL, Charco R, et al. Liver transplantation in patients with splenorenal shunts: Intraoperative flow measurements to indicate shunt occlusion. *Liver Transpl Surg* 1999;5:35.
- Kato T, Levi DM, DeFaria W, et al. Liver transplantation with renoportal anastomosis after distal splenorenal shunt. *Arch Surg* 2000;135:1401.
- J. Bueno, A. Escartýn, J. Balsells, et al. Intraoperative flow measurement of native liver and allograft during orthotopic liver transplantation in children. *Transplantation Proceedings* 2007;39:2278-79.
- Langnas AN, Marujo WC, Stratta RJ, et al. A selective approach to preexisting portal vein thrombosis in patients undergoing liver transplantation. *Am J Surg* 1992;163:132.
- Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. *Ann Surg* 1991;213:199.
- Shaked A, Busuttil RW. Liver transplantation in patients with portal vein thrombosis and central portocaval shunts. *Ann Surg* 1991;214:696.
- Loinaz C, Gornes R, Jemenez C, et al. *Transplant Proc* 2002;34:248.
- Genunda GE, Merenda R, Neri D, et al. *Liver Transpl* 2002;8:72.
- S. Lyass, A. Eid, O Jurim. Coronary Vein "Steal" and Portal Vein Thrombosis After Orthotopic Liver Transplantation. *Transplantation Proceedings* 2000;32:702-03.
- Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: Risk factors, screening, management, and outcome. *Transplantation* 2000;69:1873.
- Stafford-Johnson DB, Hamilton BH, Dong Q, et al. Vascular complications of liver transplantation: Evaluation with gadolinium-enhanced MR angiography. *Radiology* 1998;207:153-60.
- Unsinn KM, Freund MC, Ellemunter H, et al. Spectrum of imaging findings after pediatric liver transplantation. II. Posttransplantation complications. *AJR Am J Roentgenol* 2003;181:1139-44.
- Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. *Ann Surg* 1990;213:199.
- Robles R, Fernandez JA, Hernandez Q, et al. Eversion thrombovenectomy for organized portal vein thrombosis encountered during liver transplantation. *Transpl Proc* 2003;35:1915.
- Seu P, Shackleton CR, Shaked A, et al. Improved results of liver transplantation in patients with portal vein thrombosis. *Arch Surg* 1996;131:840.
- Robles R, Fernandez JA, Hernandez Q, et al. Eversion thromboendovenectomy in organized portal vein thrombosis during liver transplantation. *Clin Transplant* 2004;18:79.
- R Charco, J Fuster, C Fondevila, et al. Portal vein thrombosis in liver transplantation. *Transplantation Proceedings* 2005;37:3904-05.
- Erhard J, Lange R, Giebler R, et al. Arterialization of the portal vein in orthotopic and auxiliary liver transplantation. *Transplantation* 1995;27:877-79.
- Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: Risks factors, screening, management, and outcome. *Transplantation* 2000;69:1873.
- Tzakis A, Kirkegaard P, Pinna AD, et al. Liver transplantation with cavoportal hemitransposition in the presence of diffuse portal vein thrombosis. *Transplantation* 1998;65:619.
- Kato T, Levi DM, Tzakis AG, et al. Liver transplantation with renoportal anastomosis after distal splenorenal shunt. *Arch Surg* 2000;135:1401.
- Florman SS, Fishbein TM, Schiano T, et al. Multivisceral transplantation for portal hypertension and diffuse mesenteric thrombosis caused by protein C deficiency. *Transplantation* 2002; 15:406
- Azoulay D, Adam R, Castaing D, et al. Liver transplantation with cavoportal or renoportal anastomosis. A solution in cases of diffuse portal thrombosis. *Gastroenterol Clin Biol* 2001;25:325.

30. Llado L, Fabregat J, Castellote J, et al. Management of portal vein thrombosis in liver transplantation: influence on morbidity and mortality. *Clin Transplant* 2007;21:716-21.
31. M Paskonis, J Jurgaitis, A Mehrabi, et al. Surgical strategies for liver transplantation in the case of portal vein thrombosis-current role of cavoportal hemitransposition and renoportal anastomosis. *Clin Transplant* 2006;20: 551-62.
32. Child CG, Barr D, Holswade GR, et al. Liver regeneration following portocaval transposition in dogs. *Ann Surg* 1953;138:600.
33. Marchioro TL, Porter KA, Starzl TE, et al. The effect of partial portacaval transposition on the canine liver. *Surgery* 1967;61:723.
34. Azoulay D, Adam R, Castaing D, et al. *Gastroenterol Clin Biol* 2001; 25:325.
35. Genunda GE, Merenda R, Neri D, et al. *Liver Transpl* 2002;8:72.
36. Urbani L, Cioni R, Catalono G, et al. *Transplant Proc* 2002;34:3331.
37. Kumar N, Atkison P, Fortier MV, et al. *Liver Transpl* 2003;9:874.
38. Bakthavatsalam R, Christopher LM, Kuhr CS, et al. Rescue of acute portal vein thrombosis after liver transplantation using a cavoportal shunt at retransplantation. *American Journal of Transplantation* 2001; 1:284-287.
39. Stange B, Glanemann M, Nossler NC, et al: *Transplant Proc* 2001; 33:1414.
40. Neelamekan TK, Geoghegan JG, Curry M, et al. Delayed correction of portal hypertension after portal vein conduit arterialization in liver transplantation. *Transplantation* 1997;63:1029-30.
41. Erhard J, Lange R, Giebler R, et al. Arterialization of the portal vein in American Journal of Transplantation 2001;1:146-51.
42. Ramo  n C, Carlos M, et al, Antonio S, et al. Outcome and Hepatic Hemodynamics in Liver Transplant Patients with Portal Vein Arterialization. *American J of Transplantation* 2001;1:146-51.
43. Quiroga S, Sebastia MC, Margarit C, et al. Complications of orthotopic liver transplantation: spectrum of findings with helical CT. *Radiographics* 2001;21:1085.
44. Buell JF, Funaki B, Cronin DC, et al. Long-term venous complications after full-size and segmental pediatric liver transplantation. *Ann Surg* 2002;236:658.
45. Azoulay D, Hargreaves GM, Bismuth H, et al. Caval inflow to the graft: a successful way to overcome diffuse portal vein system thrombosis in liver transplantation. *J Am Coll Surg* 2000;190:493.
46. Kato T, Levi D, Tzakis AG, et al. Liver transplantation with renoportal anastomosis after distal splenorenal shunt. *Arch Surg* 2000;135:1401.
47. Sheil AGR, Stephen MS, Chui AKK, et al. A liver transplantation technique in patient with a thrombosed portal vein and a functioning renal-lien shunt. *Clin Transplant* 1997;11:71.
48. EE Rubio Gonzalez, JM Moreno Planas, MC Jimenez Garrido, et al. Results of liver transplantation in patients with previous portosystemic shunts. *Transplant Proceed* 2005;37:1491-92.
49. Garcia-Valdecasas JC, Grande L, Rimola A, et al. *Transplant Proc* 1990; 22:2376.
50. Katz E, Fukuzawa K, Schwartz M, et al. *Transplantation* 1992; 53:1373.
51. Inomoto T, Nishizawa F, Terajima H, et al. *Transplantation* 1995; 60:881.
52. Itabashi Y, Hakamda K, Narumi S, et al. A case of living related liver transplantation using right gastroepiploic artery for hepatic artery reconstruction. *Hepatogastroenterology* 2000;47(32):512-13
53. Muralidharan V, Imber C, Leelaudomlipi S et al. Arterial conduits for hepatic artery vascularisation in adult liver transplantation. *Transpl internation* 2004;17(4):163-68
54. Brems J, Hiatt J, Klein A, et al: Effect of a prior portosystemic shunt on subsequent liver transplantation. *Ann Surg* 1989;209:51.
55. Menegaux F, Baker E, Keefe EB, et al: *World J Surg* 1994;18:866.
56. Clavien P, Selzner M, Tuttle-Newhall JE, et al. *Ann Surg* 1998;227:440.
57. Abou Jaoude MM, Almawi WY. Liver transplantation in patients with previous portosystemic shunt. *Transplant Proc* 2001;33:2723.
58. Jenkins RL, Gedaly R, Pomposelli JJ, et al. Distal splenorenal shunt. *Arch Surg* 1999;134:416.
59. Arcadipane A, Nadalin S, Gruttadauria S, et al. The Recipient With Portal Thrombosis and/or Previous Surgery. *Transplantation Proceedings* 2008;40:1183-86.
60. GP Guerrini, M. Pleguezuelo, S. Maimone, et al. Impact of Tips Preliver Transplantation for the Outcome Posttransplantation. *American Journal of Transplantation* 2009;9:192-200.

Small for Size Syndrome

INTRODUCTION

Adult living donor liver transplantation has been widely expanded in the world after the introduction of right lobe grafting.¹⁻³ This expansion was hampered by the issues of morbidity and mortality in living donors undergoing right lobectomy.⁴ Some institutions, especially in Japan, were extending Adult LDLT using a left lobe graft (LLG) for selected patients.^{5,6}

Small for size syndrome is defined as graft that is smaller than the required liver volume or weight.

Manifestations of small for size syndrome (SFSS)⁷⁻⁹

- Persistent hyperbilirubinemia and elevations of AST and ALT.
- Coagulopathy
- Ascites
- Portal hypertensive bleeding
- Renal dysfunction after transplantation
- Pulmonary complications
- Encephalopathy
- Irreversible graft failure leading to death in absence of retransplantation.

A partial liver graft unable to meet the functional demands of the recipient results in liver failure including coagulopathy, ascites, prolonged cholestasis and encephalopathy, often associated with pulmonary and renal failure, and frequently leads to death of the recipient in the absence of retransplantation.¹ This ill-defined clinical picture is considered to be primarily linked to an insufficient graft size, and hence termed 'small-for-size-syndrome' (SFSS). In Japan, multi-center studies have shown that the incidence of postoperative complications was higher for right lobe donation than for left lobe donation, and that the incidence of biliary tract complications was also higher for right lobe donation.¹⁰

Based on this morbidity, LLG for adult recipient is being reexamined. The minimum amount of liver graft necessary for successful transplantation for adult recipients is proposed to be greater than 0.8% of GRWR.¹¹ Small for size graft (SFSG) is defined as less than 0.8% of GRWR,¹¹ SFSS can occur in a range of GRWR 0.8–1% and in rare instances in grafts with greater than 1% of GRWR despite sporadic successes using small grafts less than 0.8% of GRWR.

Pierre-Alain Clavien et al.¹² divided SFSS into 2 types

- Small for size dysfunction
- Small for size nonfunction.

PROPOSED DEFINITION OF SMALL FOR SIZE SYNDROME (SFSS)

SMALL FOR SIZE DYSFUNCTION (SFSD)

SFSD is the dysfunction of a SFSG less than 0.8% of GRWR during the first postoperative week after the exclusion of other causes.¹² Graft dysfunction is defined as presence of 2 of the following criteria on 3 consecutive days:

- Bilirubin >100 µmol/l,
- INR > 2,
- Encephalopathy grade 3 or 4.

SMALL FOR SIZE NON-FUNCTION (SFSNF)

Failure of a SFSG less than 0.8% of GRWR during the first postoperative week after the exclusion of other causes.¹²

Graft failure is defined as a condition which retransplantation or ends in death of the recipient.

Exclusion criteria (Other causes of graft dysfunction or nonfunction)¹²

- Technical (e.g. arterial or portal occlusion, outflow congestion, bile leak),

- Immunological (e.g. rejection),
- Infectious (e.g. cholangitis, sepsis).

Factors contributing to pathogenesis of SFSS

- **Graft related**
 - Graft size (GRWR < 0.8%)
 - Pre-existing liver disease (e.g. steatosis)
 - Donor age
 - Regeneration
 - Vascular inflow (portal hyperperfusion, arterial hypoperfusion)
- **Recipient related**
 - Preoperative recipient condition
 - Degree of portal hypertension

Parenchymal injury due to reperfusion results in prolonged hyperbilirubinemia and impaired regenerative capacity ultimately resulting in infection.¹¹ Survival after transplantation of a small partial graft has been shown to be lower for Child B and C recipients compared to Child A, while the difference was less pronounced with larger grafts.¹³ In another study, SFSS developed much more frequently in cirrhotic recipients of small grafts (mean GRWR 0.79%) than in noncirrhotics.¹⁴ Importantly, the safe threshold for liver volume was higher in cirrhotics.

MEDICAL MANAGEMENT OF SFSS

- FK 409, FTY 720, Heme oxygenase -1 and IL-10 are useful in SFS syndrome¹⁵
- **FK 409** may reduce the portal pressure by¹⁶
 - Decreased production of inflammatory cytokines and chemokines such as nitric oxide synthetase, TNF- α and macrophage inflammatory protein 2.
 - Increase the production of IL-10 and Heme oxygenase -1.
- **FTY 720**, an immune modulator acts is useful in SFSS and acts by¹⁷
 - Sequestration of peripheral blood lymphocytes to secondary lymphoid organs,
 - Activation of cell survival Akt signaling and down regulation of MAPK pathway
 - Vasoregulatory protection of integrity of hepatic sinusoids

Graft over perfusion, severity of portal hypertension, increase in portal vein flow (PVF) and portal vein pressure (PVP) are important predictors of graft failure in SFSS.¹⁹ Graft survival deteriorated significantly when PVP was more than 20 mm Hg in the early postoperative period. In addition, PVP was significantly elevated when GRWR was less than 0.8%. Histological examination showed the parenchymal injury caused by high PVP.¹⁸

Inflow modulation is effective in preventing SFSS in LDLT using SFSSG greater than 0.6% of GRWR.^{21,22} The impact of high PVF and PVP on the graft function has led to the development of techniques of inflow modulation as shown in the table below.

Different techniques of inflow modulation¹⁹⁻²⁴

- Splenic artery ligation (SAL)
- Splenorenal shunt
- Splenectomy
- Mesocaval shunt with downstream ligation of the superior mesenteric vein (SMV)
- Hemi-portocaval shunt (HPCS)
- Preservation of spontaneous portosystemic shunts

SAL has not been uniformly successful in modulating PVP (portal venous pressure) because of early rebound of PVP.¹⁹ Splenectomy is able to lower PVP, but it cannot be recommended as a routine procedure. In addition, portal vein thrombosis is one of the lethal complications of splenectomy. Another method of inflow modulation is the creation of an artificial portosystemic shunt by diverted the superior mesenteric venous flow by mesocaval shunt with downstream ligation of the SMV,²² however, long term follow up of this procedure has not been reported.

Kyoto group developed an algorithm for graft selection in which left lobe donation is considered primarily if the GRWR is estimated to be greater than 0.6% in preoperative assessment with utilization of a HPCS based on PVP. Purpose of HPCS is to reduce the PVP.

GRAFT SELECTION AND CRITERIA FOR HPCS

Graft selection and criteria for HPCS (Hepatoportocaval shunt)²⁵: Yamada et al. reported an algorithm for selection of HPCS. Kyoto group³⁰ used LLG as first choice when GRWR of LLG was more than 0.6% in preoperative volumetry and RLG transplantation when estimated GRWR of LLG was less than 0.6% and estimated GRWR of RLG was greater than 0.6% after confirming that the remnant liver volume was larger than 30% of the whole liver. When actual graft volume (GV) was less than 1.0% of GRWR and PVP was more than 20 mm Hg at the time of laparotomy, they considered the construction of HPCS with the branch of recipient portal vein.

In left lobe graft:

1. When the GRWR is <0.6%, right lobe graft is harvested.
2. When the GRWR is 0.6% to 1%
 - a. Portal vein pressure >20 mm of Hg: HPCS is considered
 - b. Portal vein pressure <20 mm of Hg: No portal flow modulation
3. When the GRWR is >1%: No portal flow modulation.

MEASUREMENT OF PORTAL VEIN PRESSURE²⁵

A 16-gauge antithrombotic catheter is inserted through the IMV after recipient laparotomy. The tip of the catheter was positioned approximately 7–8 cm from site of insertion and then exited from the abdominal wall. PVP is monitored continuously using a transducer during the recipient operation. PVP and CVP measurements (usually <10 mm of Hg) are done at the time of laparotomy, just before temporary portocaval shunt in anhepatic phase, just after PV reperfusion, just after arterial reperfusion and before abdominal closure.

Shunt function is confirmed by noting an increase in PVP after shunt clamping. PV flow direction and velocity are assessed with Doppler US after arterial reperfusion. Continuous monitoring PVP and CVP for additional 5 days if the PVP is more than 20 mm Hg at the end of operation in spite of a functioning shunt. The catheter, which is reinforced using rubber bands intra-operatively, is pulled out in the ICU.

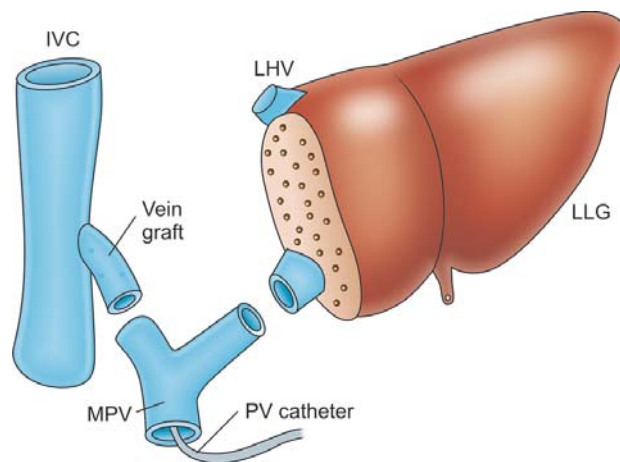


Figure 15.1: Left lobe graft implantation with portocaval shunt. Right PV branch is anastomosed to IVC with a vein graft. Left PV branch is anastomosed to graft portal vein. (Modified and redrawn) (Yamada T et al)³⁰

SURGICAL TECHNIQUES²⁵

Graft is weighed ex-situ after portal flushing with HTK solution and decision is taken to construct HPSCS. A crucial point of hilar dissection in HPSCS cases is to leave the pedicle of PV with the greatest possible length. The RPV and LPV are dissected distal to the bifurcation with dividing a few small branches at the level of the hilar plate. The right PV branch is usually short, but with large diameter, in contrast, the left PV branch is prepared with a longer pedicle, which attenuated gradually near the hilar plate. To elongate the PV pedicle, the trunk is dissected proximally from the surrounding tissue. To avoid splanchnic congestion during the anhepatic phase, a temporary end to side portocaval shunt between IVC and PV branch is constructed in all cases. In HPSCS, the distal end of the PV branch is anastomosed with IVC using a vein graft since a short shunt may seriously hamper adequate mobilization and difficulty in anastomosis of with RPV. When more time is needed to obtain a vein graft, a temporary portocaval shunt first. The interpositional vein grafts is obtained from the auto PV branch, recipient paraumbilical vein or left renal vein. In RLG, recipient RPV and graft PV is anastomosed and in LLG, the anastomosis is conducted between recipient left portal branch and graft portal vein (**Figure 15.1**).

During anastomosis of PV, the recipient PV is cut near the bifurcation leaving a diameter as large as possible. Reperfusion of the graft is performed after opening the shunt in order to avoid hyperperfusion. In cases without HPSCS, the temporary shunt is divided and closed, and then PV reconstruction is done in an ordinary fashion.

EVALUATION OF SHUNT PATENCY

- PVF and velocity in the graft are evaluated by Doppler US. Doppler US is performed every day for 2 weeks after operation and once a week after patient discharge.
- The regeneration rate is determined on the basis of the increase of GV by CT volumetry at 1, 3 and 6 months postoperatively.
- Shunt patency is confirmed by both MDCT and US at the same intervals postoperatively.

Graft size is a key factor for overcoming SFSS. SFSS leads to inhibition of graft regeneration resulting in graft failure within 2 or 3 months in approximately 50% of recipients.²⁶ So RLG LDLT is more popular in most centers. Basani et al.²⁷ described that Octreotide (0.5 ug/kg/h) and (50 ug/kg/min) infusion allowed a manipulation of portal vein pressure, which ought to always be measured in left lobe transplantation with a small-for-size graft. Troisi et al.²² reported that the reduction of PVF by means of HPSCS improves overall patient survival and risk of complication by avoiding the occurrence of SFSS in grafts less than 0.8% of GRWR in adults. By doing HPSCS the graft PVF is adjusted to around two times of the PVF, which was recorded in the donor side with banding of HPSCS to decrease excessive shunting and prevent a steal phenomenon. HPSCS can avoid the initial graft injury due to high PVP, and provide adequate PVF to the graft.

A study from Kyoto University Hospital and Kobe City General Hospital, Japan shows that if left lobe grafting is selected, GRWR would have been =1% in 10% of the patients, 0.8–1.0% in 10% of the patients, 0.6–0.8% in 55% and <0.6% in 25%. Earlier reports of left lobe Adult LDLT

series (1994–2001), the patient survival was 82.1% in recipients with $\geq 0.8\%$ of GRWR ($n = 28$), whereas 54.5% in recipients with $< 0.8\%$ of GRWR ($n = 11$).²⁸ Japanese argue that despite greater safety for the donor, there is anatomical superiority in LLG compared to RLG.²⁹ The LLG contains sufficient outflow tributaries, a single branch of the PV, and especially, a single bile duct in most cases.

Small graft of greater than 0.6% of GRWR could be used in adult recipients and potentially LLG could be used in 75% of adult recipients in LDLT.³⁰ Rapid volumetric regeneration of GV is observed and reached a mean of 84.3% of SLV for RLGs and 95.4% of SLV for LLGs at 3 months after LT.³⁰ Tanaka et al reported that selective HPCS based on PVP is an effective procedure and results in excellent patient and graft survival with avoidance of SFSS in grafts greater than 0.6% of GRWR. Selective HPCS could achieve a better outcome of adult LDLT for sicker patients and split liver transplants.³⁰

REFERENCES

- Lo CM, Fan ST, Liu CL, et al. Adult-to-adult living donor liver transplantation using extended right lobe grafts. *Ann Surg* 1997; 226:261-69.
- Marcos A, Fisher RA, Ham JM, et al. Right lobe living donor liver transplantation. *Transplantation* 1999;68:798-803.
- Inomata Y, Uemoto S, Asonuma K, et al. Right lobe graft in living donor liver transplantation. *Transplantation* 2000;69:258-64.
- Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:818-25.
- Sugawara Y, Kaneko J, Akamatsu N, et al. Left liver grafts for patients with MELD score of less than 15. *Transplant Proc* 2003; 35:1433-34.
- Soejima Y, Taketomi A, Yoshizumi T, et al. Feasibility of left lobe living donor liver transplantation between adults: An 8-year, single-center experience of 107 cases. *Am J Transplant* 2006;6:1004-11.
- Kiuchi T, Tanaka K, et al. Small-for-size graft in living donor liver transplantation: how far should we go? *Liver Transpl* 2003; 9:S29-S35.
- Emond JC, Renz JF, Ferrell LD, et al. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. *Ann Surg* 1996;224:544-52.
- Tucker ON, Heaton N. The 'small for size' liver syndrome. *Curr Opin Crit Care* 2005;11:150-55.
- Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362:687-90.
- Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999;67:321-27.
- Felix D, Panco G, Pierre-Alain Clavien. Small-for-Size Syndrome After Partial Liver Transplantation: Definition, Mechanisms of Disease and Clinical Implications *Am J of Transplant* 2005; 5(11):2605-10.
- Ben-Haim M, Emre S, Fishbein TM, et al. Critical graft size in adult-to-adult living donor liver transplantation: impact of the recipient's disease. *Liver Transpl* 2001;7:948-53.
- Soejima Y, Shimada M, Suehiro T, et al. Outcome analysis in adult-to-adult living donor liver transplantation using the left lobe. *Liver Transpl* 2003;9:581-86.
- Yang ZF, Fan ST, et al. Heme oxygenase-1 potentiates the survival of small for size liver graft. *Liver transpl* 2004;10:784-93.
- Man K, Fan ST, et al. FK 409 ameliorates small for size liver graft injury by attenuation of portal hypertension and downregulation of Egr-1 pathway. *Ann Surg* 2004;240:159-68.
- Zhao Y, Fan ST, et al. Attenuation of small for size liver graft injury by FTY 720: significance of cell survival Akt signaling pathway. *Am J of Transpl* 2004;4:1399-407.
- Ito T, Kiuchi T, Yamamoto H, et al. Changes in portal venous pressure in the early phase after living donor liver transplantation: Pathogenesis and clinical implications. *Transplantation* 2003; 75:1313-17.
- Troisi R, Cammu G, Militerno G, et al. Modulation of portal graft inflow: A necessity in adult living-donor liver transplantation? *Ann Surg* 2003;237:429-36.
- Sato Y, Yamamoto S, Oya H, et al. Splenectomy for reduction of excessive portal hypertension after adult living-related donor liver transplantation. *Hepatogastroenterology* 2002;49:1652-55.
- Boillot O, Delafosse B, Mechet I, et al. Small-for-size partial liver graft in an adult recipient; A new transplant technique. *Lancet* 2002;359:406-07.
- Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 2005; 5:1397-404.
- Yagi S, Iida T, Hori T, et al. Optimal portal venous circulation for liver graft function after living-donor liver transplantation. *Transplantation* 2006;81:373-78.
- Sato Y, Yamamoto S, Takeishi T, et al. Management of major portosystemic shunting in small-for-size adult living-related donor liver transplantation with a left-sided graft liver. *Surg Today* 2006; 36:354-60.
- T Yamada K, Tanaka K, et al. Selective Hemi-Portocaval Shunt Based on Portal Vein Pressure for Small-for-Size Graft in Adult Living Donor Liver Transplantation. *Am J of Transplant* 2008;8 (4):847-53.
- Heaton N. Small-for-size liver syndrome after auxiliary and split liver transplantation: Donor selection. *Liver Transpl* 2003;9:S26-S28.
- S Busani, G Marconi, L Schiavon, et al. Living Donor Liver Transplantation and Management of Portal Venous Pressure. *Transplantation Proceed* 2006;38:1074-75.
- Tanaka K, Ogura Y. "Small-for-size graft" and "small-for-size syndrome" in living donor liver transplantation. *Yonsei Med J* 2004; 45:1089-94.
- Nakamura T, Tanaka K, Kiuchi T, et al. Anatomical variations and surgical strategies in right lobe living donor liver transplantation: Lessons from 120 cases. *Transplantation* 2002;73:1896-903.
- Yamada T, Tanaka K, et al. Selective Hemi-Portocaval Shunt Based on Portal Vein Pressure for Small-for-Size Graft in Adult Living Donor Liver Transplantation. *American Journal of Transplantation* 2008;8(4):847-53.

Split Liver Transplantation

INTRODUCTION

Persistent shortage of donors and increase in the number of patients on waiting had forced the transplantation units to go for other options like LDLT and split liver transplantation. Split liver transplantation (SLT) started initially for one adult and one child. But in recent days transplant units have extended its use to 2 adults. However there are controversies in the practice of split for 2 adults related to the increased morbidity, poor results and small for size syndrome in recipients of left lobe grafts. Split liver transplantation (SLT) is a surgical technique that creates 2 allografts from 1 cadaver/donor organ. SLT is simultaneously reported by Pichlmayr¹ and Bismuth² in 1989.

PROCEDURES

This procedure is implemented to meet the organ shortage and to increase the donor pool. Liver is divided into 2 functioning allografts right and left lobe/extended right lobe and lateral segment, so that 2 recipients can be transplanted from a single donor. It is a time consuming process and prolonged cold ischemia and chances of rewarming are possible leading to more complications like PNF, vascular and biliary complications than whole liver transplant. Selection of high quality donor organs and good recipients is required for split liver transplant. Only young, haemodynamically stable and multiorgan donors are considered for split liver transplant. Only 15% of deceased donors are ideal for split livers.^{3,4} The ideal donor age threshold for splitting is not well defined, but many authors suggest that donors older than 45 to 50 years or younger than 10 years should not be considered.^{5,6}

Ideal donor for SLT^{7,8}

- Heart beating donors
- Hemodynamically stable individuals
- Age 10 to 50 years
- ICU stay <5 years
- On minimal vasopressor requirements (Dopamine <15 µg/kg/min)
- Liver function tests within 3 times upper normal limits,
- Normal renal function,
- Serum sodium level <160 mmol/L
- Negative viral serology (except cytomegalovirus)
- Minimal or absent period of cardiac arrest
- Vigorous assessment by the procurement team for vascular and biliary anatomy as well as parenchyma quality and quantity

Hypotension, shock, sepsis, and previous cardiac arrest initiate a cascade of events leading to direct organ injury. This is compounded by significant hemodynamic and neuroendocrine changes resulting from brain death. The result is a potentially injured organ that then undergoes a surgical procedure inciting further injury through parenchyma destruction. The community performing SLT has overcome this fragility of donor parenchyma through optimal donor selection to achieve acceptable outcomes. The liver is assessed for normal color and texture, equal perfusion, and sharp edges. The left lateral segment is assessed to assure fit into the recipient abdominal cavity, and the volume is estimated to provide a graft fraction (GRWR) of at least 0.8-1% [graft volume (L)/total body weight (kg) × 100].

Causes of infrequent split liver transplantation^{6,52}

- Technically difficult
- Complex personnel and logistic demands
- A potentially restrictive organ allocation policy
- Perception of inferior results have contributed to the under utilization of SLT
- There is no agreement on indications, surgical technique, and results and it is difficult to draw precise conclusions on the basis of previous reports.

Tosco et al⁴ reported that the minimum weight for a split is 70 kg, the liver weight from whom is about 1500 g with 850 g in the right and 650 g in the left liver.^{4,9} This weight allows a left lobe liver transplantation for a recipient of 65 kg or less without the risk of a small for size syndrome.^{8,10} But some groups perform liver splitting with slim donors. In such situations the proper selection of less body weight recipient is important, particularly to avoid small for size syndrome. There is no upper cut off, but probably patients over 100 kg or body mass index >28 should be excluded due the well-known relationship between overweight and steatosis.⁴ Macroscopic steatosis is an exclusion criterion for a split.

Indications of SLT

- Initial grafts
- Rescue grafts for primary nonfunction (PNF)
- Retransplantation grafts
- As components of multi visceral grafts

Surgical challenges in SLT include

- Preoperative appreciation of anatomic variations
- May require complex biliary or vascular reconstruction.
- Adequate volume of the graft (GRWR) to meet the metabolic needs of the recipient
- Proper positioning of the graft to optimize vascular inflow, venous outflow, and biliary drainage
- Higher incidence of biliary and vascular complications
- Higher incidence of reoperation among partial-graft recipients

In the first North American series of 12 adult to adult SLT procedures,¹¹ patient and graft survival at 9 months was 89% for right-lobe grafts versus 78% for left-lobe grafts. Biliary complications were a frequent cause of morbidity (27%), followed by an 11% incidence of vascular complications that resulted in 2 deaths. Complications were observed in 26% of left-graft SLT recipients and 22% of right-graft SLT recipients. Renz et al¹² observed a similar pattern in their series: more frequent vascular complications in right-lobe grafts, more

frequent biliary complications in left-lobe grafts, higher graft survival in right-lobe recipients, and rates of primary nonfunction and recipient death similar to those reported by others.

Intra- and postoperative complications¹³

- Control of bleeding of the cut-liver surface
- Acute and chronic hepatic venous outflow obstruction
- Hepatic arterial complications
- High incidence of "small-for-size syndrome." and PNF
- Management of biliary complications

The first series of 9 SLT procedures performed upon 18 recipients at the University of Chicago lead the authors to conclude SLT was "feasible and could have a substantial impact in transplant practice."¹⁴ In the climate of increasing donor scarcity, SLT remains an infrequently performed procedure.¹⁵ The University of California Los Angeles has pursued SLT as an avenue to expand the cadaver/donor pool, increase availability of allografts to children and small adults, and decrease dependence upon living donations. The Split registry began in USA in 1995 as a database to prospectively follow children under 18 years of age who receive liver transplants in the United States and Canada.¹⁶

The Split registry currently consists of 43 transplant centers with the participating centers performing roughly 79% of all transplants in the United States. The Split database demonstrated that the majority of late graft loss were caused by acute and chronic rejection (48.5%) and by the chronic effects of hepatic arterial thrombosis (11.4%) and biliary strictures (8.6%).¹⁷ Approximately 30% of the Split patients who died after their first post-transplant year succumbed due to infection, sepsis or multiorgan failure.¹⁹ Late graft loss in this large multicenter series is related to immunologic factors, rejection and delayed sequel of technical complications.¹⁷ Azoulay et al. reported that the reason for the rarity of split liver transplants is due to very poor results achieved for adult recipients of left split-liver grafts.¹⁰ Higher threshold of liver volume has been considered in SLT as compared to LDLT because split deceased donor grafts are subjected to a longer period of cold ischemia and to a more relevant ischemia-perfusion injury due to the split procedure itself. Increase in SLT for two adult patients, will decrease the number of patients on the waiting list. Warm ischemia¹⁹ as well as cold ischemia¹⁸ has been shown to impair regeneration after partial liver transplantation by interfering with the production of interleukin-6 and tumor necrosis factor α and/or defective progression from the IL-6 signaling pathway to cellular proliferation.²⁰ This could be important for split grafts from cadaveric donors where longer cold ischemia occurs.

TYPES OF SPLITTING THE DONOR LIVER

- In-situ splitting
- Ex-situ splitting

In-situ splitting of liver and transection of bile duct of the left lobe or lateral segment close to the parenchyma without damaging the vasculature of right lobe helps in preventing biliary complications and avoids prolonged cold ischemia. Previously the 2 allografts were used for one adult and one pediatric transplant. Extended right lobe is used in adult and lateral segment I used in the child. Recently many studies have reported split liver for 2 adult recipients. In case of 2 adults, a small size recipient is selected for left lobe graft, so that GRWR of 1% or >40% of standard liver volume, otherwise chances of small for size syndrome or PNF are more than the usual transplant subjecting an elective patient to high risk of emergency surgery. On the basis of the experience in LDLT, a GRWR above 0.8% is considered adequate and safe.^{21,22} However, the quality of the right or left lobe in LDLT is definitively higher than the quality of the same lobe harvested from a deceased donor. Therefore, a greater liver mass should be ensured, and further prospective studies are required to investigate this point.⁵²

DIFFERENCE IN IN-SITU AND EX-SITU SPLIT

In-situ technique is clinically efficacious, can be used alternatively with the ex-vivo technique, and is comparable to whole-liver allograft transplantation.²³ Decreased results observed in ex-situ versus in-situ SLT.

In-situ/In-vivo Split liver transplantation

Advantages

- Parenchyma perfusion is maintained during the in-situ SLT
- Biliary and vascular structures are readily identifiable.
- Hemostasis is achieved prior to graft revascularization, which lowers
- Transfusion requirements
- Potential disseminated intravascular coagulopathy
- Graft stress after reperfusion.
- Minimal cold ischemia time
- Reduced potential for biliary complications facilitated by easier identification of biliary structures reduces the chance of later sepsis and graft dysfunction

Disadvantages:

- Quality of thoracic organs may be affected due to increased blood loss and volume replacement incurred during in-situ SLT
- Increased time duration of donor surgery (approximately 90-120 mins. of additional time)

Ex-vivo / Ex-situ split²⁴⁻²⁶

Advantages

- Less blood loss

Disadvantages

- Unintentional graft rewarming
- Longer cold ischemia and extended parenchyma injury incurred during ex vivo SLT contribute to the inferior outcomes of ex vivo SLT grafts applied to urgent status recipients
- Troublesome bleeding from the surface after reperfusion of the graft

Rate of complications of ex-situ and in-situ SLT in different reports^{7,23,27-31}

Author	Type	Biliary compli- cations (%)	HAT (%)	PVT(%)	year
Roegier	In-situ	0	0	0	1996
Rela	Ex-situ	14.6	2.5	0	1998
Mirza	Ex-situ	8	8	0	1998
Busuttil	In-situ	2.8	2.8	1.4	1999
Spada	In-situ	26	7	10	2000
Reyes	In-situ	3	7	0	2000
Huda	Ex-situ	20	3	0	2003

SURGICAL TECHNIQUES: SPLIT LIVER FOR ADULT AND CHILD (EXTENDED RIGHT LOBE AND LATERAL SEGMENT)

SURGICAL TECHNIQUE (IN-SITU TECHNIQUE) (FIGURE 16.1)

The anatomic classification of the liver by Couinaud³³ and refined by Bismuth³⁴ is the universal reference system for describing allografts created by SLT. The parenchymal transection is performed at the falciform ligament to create a Couinaud segment II/III graft, termed a left lateral segment graft for pediatric recipients and a Couinaud segment I, IV-VIII right trisegment graft or extended right lobe for transplantation of older children or adults. Lateral segmentectomy is similar to described earlier in the LDLT chapter.

Donor Procedure

The cardiothoracic surgeon is asked to come 1 hour later than usual in case of multi organ donation. The operation is started with a sternolaparotomy and inspection of the abdominal organs. The infrarenal aorta (**Figure 16.2**) and vena cava are freed and controlled so that rapid perfusion is possible in case of donor instability.³⁵ The vascular anatomy and the parenchyma of the liver were evaluated. The left lateral lobe (segments II and III) is mobilized and

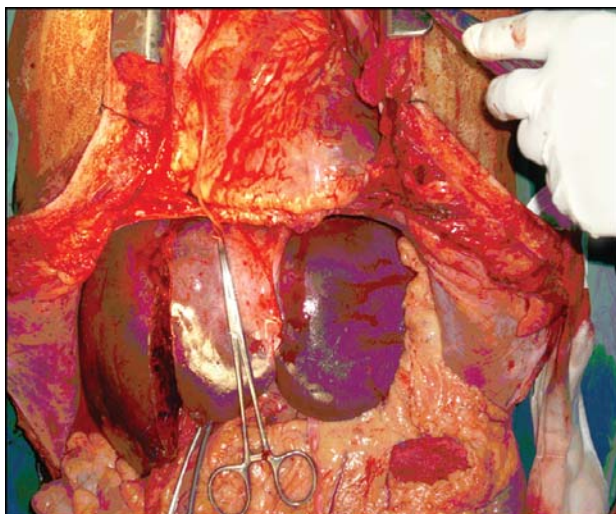


Figure 16.1: In-situ split liver for 2 adults

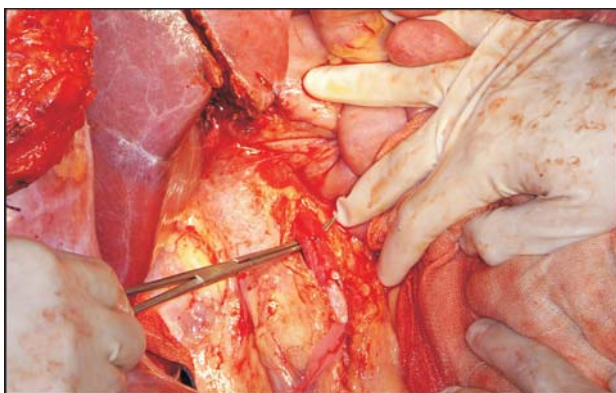


Figure 16.2: Mobilization of infrarenal aorta for cannulation in a split liver donor

prepared identical to a living donor.^{36,37} The left hepatic artery and left portal vein are isolated. The right portion of the hepatoduodenal ligament is left untouched. Attention is paid to save the arterial branch to segment IV whenever possible. The portal branches to segment IV (median left segment) are suture-ligated and transected to allow Rex's recessus to progressively roll over toward the left lateral lobe until the hilar plate is exposed. Frequently, the artery for segment IV runs up at the right edge of the umbilical fissure. The left portal vein branches to the caudate lobe are also suture-ligated and severed. Next, the left hepatic vein is controlled by placing a vessel loop around it. Then the parenchymal phase is started using CUSA or clamp crushing technique to divide the parenchymal bridge between the left lateral lobe and the left median segment in continuity with the remaining right liver. The dissection is performed without vascular exclusion.

During this phase, the hilar plate is controlled with a dissecting clamp and sharply cut with a knife or vascular scissors. It is important to avoid coagulation near the fragile hilar structures. When the dissection is completed, two livers are separated, each with its own vascular pedicles and venous drainage. The quality of graft perfusion of both sides is observed carefully. Shortly before excision the left hepatic artery, left portal vein and left hepatic vein are clamped and severed, followed by rapid removal of both lobe. The vascular and biliary branches of the remaining liver are suture-ligated and hemostasis of the cut section was completed. On the back table, the graft is perfused immediately with UW/HTK solution, first via the portal vein and then by arterial perfusion. Cooled and appropriately wrapped. **Figures 16.3 and 16.4** show the two different techniques of harvesting the hilar structures in case of split liver for one adult (extended right lobe) and one child (lateral segment).

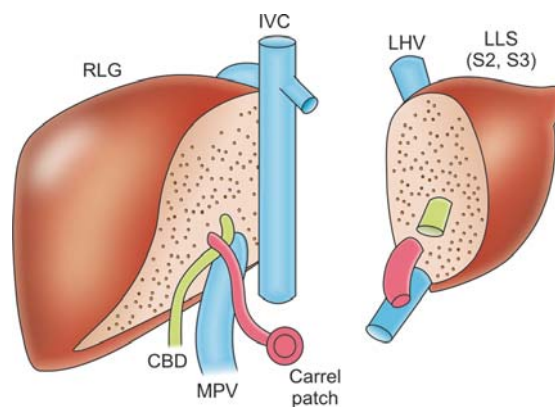


Figure 16.3

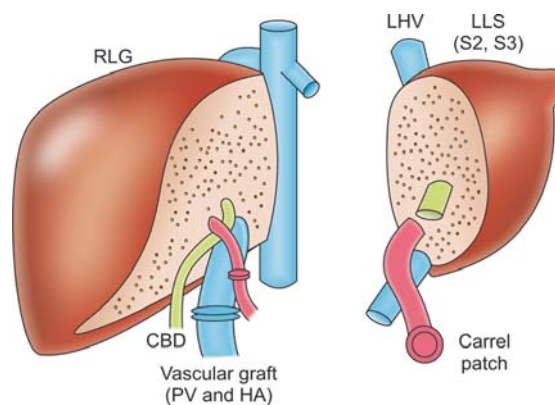


Figure 16.4

Figures 16.3 and 16.4: Schematic representation split liver for extended right lobe and lateral segment

Figure 16.3 shows the celiac trunk, main portal vein, and common bile duct with an extended right lobe graft. The left lateral segment graft has the sectioned left hepatic artery, left portal vein, and left bile duct. **Figure 16.4** shows right lobe graft with sectioned right hepatic artery, right portal vein, and common bile duct. The left lateral segment graft has celiac trunk along with a carrel patch, left portal vein and left hepatic duct. (Modified and redrawn from Busuttill et al).⁷

Recipient Surgery for Split Liver for Adult and Child

Right graft: After procurement, the right graft was benching like a normal full-size liver containing the full length of the hepatic artery, the portal vein, and vena cava. The transplantation was identical to the whole-liver procedure.³⁸ After portal and arterial revascularization, the perfusion of segment IV was observed carefully. Usually a slight congested appearance around the anterior part of the segment IV and no further surgery is needed. Vascular outflow is constructed by using donor IVC-recipient IVC by piggyback technique.

Left lateral segment graft: The left lateral lobes are transplanted using standard techniques, like LDLT.^{36,37} The use of vascular interpositions usually was not necessary. Direct portal vein anastomosis or a venous graft harvested from the donor can be used. The arterial reconstruction is performed via a direct anastomosis or an interposition of an arterial graft. Majority of vascular anastomosis can be done directly instead of using vascular grafts. A Roux-en-Y Hepaticojejunostomy or direct duct to duct anastomosis can be used for biliary reconstruction depending on the availability of bile duct.³²

SLT for 2 adults (full right and left lobe): Full right and full left SLT was first described in 1999, but despite the initial enthusiasm, this procedure did not maintain its attractive promise.³⁹

Recipient selection: SLT for two adults is feasible and can provide outcomes equivalent to those of whole-liver transplantation. Recipient selection mandates unique considerations in the performance of SLT. A greater amount of hepatic mass for an individual SLT recipient than would be required in living-donation with a graft fraction of at least 1% recipient body mass. A 6.5-fold increase in the risk of graft failure is noticed when the ratio was less than 1%.¹⁰ Preferable the left graft recipients should be younger, smaller size with better native liver function for 2 adults SLT. The principal factors influencing patient survival are graft steatosis, GRWR>1% and hospital status of the recipient. Male donor to female recipient liver transplantation has a higher association with chronic rejection, particularly in recipients with

primary biliary cirrhosis,³⁹ and appears to have a higher incidence of post-transplant malignancies.⁴¹

Technical Difficulties and Modifications in SLT for 2 Adults

The technical difficulties in split liver transplantation for two adults are focused mainly on two questions: how to share the blood vessels, especially the hepatic veins and vena cava, and how to achieve safe biliary drainage of all segments transplanted. Intraoperative cholangiography (**Figure 16.6**) helps to identify anatomical bile duct variations, which may either indicate a switch to a left lateral splitting procedure or may totally prohibit liver splitting. The decision whether to leave the common bile duct to the left or right hemi-liver depends on the individual anatomy. In most instances the common bile duct should stay with the right graft, as the right main bile duct is shorter than the left and anatomical variations of the bile ducts are more frequent within the right lobe. The bile ducts should be shortened as much as possible to ensure sufficient perfusion.

Some authors recommend an arteriography,¹⁰ but in most cases arterial anatomy can be safely identified by hilar dissection. Sharing of the arterial trunk depends on the individual anatomy of the donor, especially the origin of the segment IV artery. In most cases the main arterial trunks stay with the left graft. In conventional techniques, usually the middle hepatic vein is retained with the left graft and the vena cava with the right graft. The indispensable division of the caudate lobe veins led to uncertain viability of liver segment I, and resection might be necessary.

Surgical Procedure

Which partial graft, right or left, should retain the celiac trunk remains controversial. Most groups demonstrated that by maintaining the entire length of the celiac axis in continuity with the right grafts organ sharing among centers is improved without worsening patient and graft outcomes.⁴³⁻⁴⁵ Other authors^{35,47} showed that maintenance of the celiac trunk with the left-sided allograft (**Figure 16.5**) does not increase the overall incidence of HAT and avoids the need for a left hepatic artery microvascular anastomosis. The recent literature reports an incidence of vascular complications of around 10%.⁴³⁻⁴⁵

Careful evaluation of the macroscopic appearance of the liver should be carried out to confirm the feasibility of SLT before any splitting technique. Visual assessment by the surgeon for colour, consistency and signs of any fatty change on gross examination is important. A standard in-situ split (**Figure 16.1**) technique is followed. Preoperatively USG examination of the liver is carried



Figure 16.5: Left lobe with caudate lobe (black arrow) LHA harvested very long with a carrel patch. LPV- Cannula in-situ

out to study the fatty change and vascular anatomy of liver. Intraoperative ultrasound is carried out before split to verify the quality of the liver and to map the middle hepatic vein (MHV) on the liver surface. Preoperative CT volumetry is carried out only in few centers. Volume of right and left lobe is approximately estimated by USG examination. Usually right, left and lateral segments are taken as 60%, 40% and 25% of standard liver volume, respectively. Portal vein diameter will guide in assessing the volume of both lobes.

Transection plane is defined both by the intraoperative ultrasound and by the parenchymal demarcation obtained by the temporary clamping of the RHA and RPV at the hepatic hilum and thus marking the line of parenchymal transection just a few millimeters from the right side of the MHV. Parenchymal transection is carried out by Kelly crush method or using CUSA without using Pringles maneuver. If there is severe bleeding, Pringles maneuver may be considered. The biliary anatomy is mapped by intraoperative cholangiogram (**Figure 16.6**). Division of bile duct, hepatic artery and portal vein (**Figure 16.7**) is completed in-situ and the two liver grafts (**Figure 16.8**) are removed after flushing of the abdominal organs with a cold HTK solution via the aorta and splenic vein. MHV is retained with the right lobe graft and the IVC along with caudate lobe are retained with the left lobe. In our center we always keep the IVC with the right lobe for a piggyback anastomosis with recipient IVC (**Figure 16.9**).

In right lobe transplantation, the RHV is anastomosed end to side to the recipient IVC through a caval slitting or cavoplasty to optimize the venous outflow with a 4/0 running prolene suture. V5 and V8 reconstruction is performed similar to the right lobe transplantation

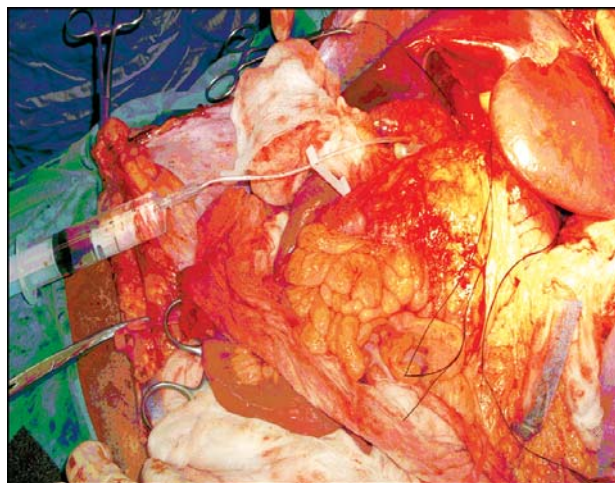


Figure 16.6: Intraoperative cholangiogram in a deceased donor for split liver for 2 adults

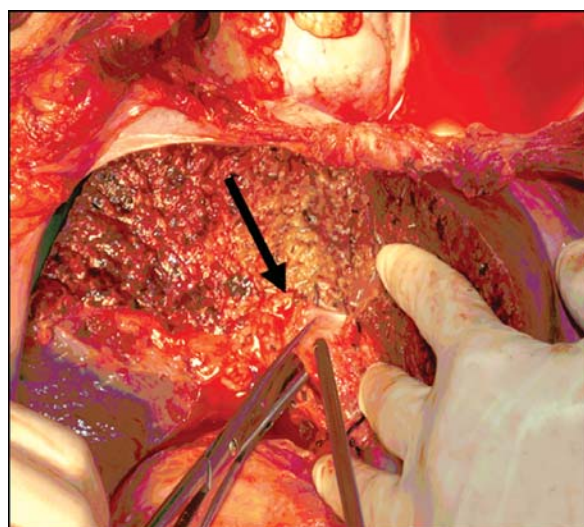


Figure 16.7: In-situ splitting of deceased donor liver: Dividing the right portal vein (black arrow)

depending on the area of congestion after splitting. **Figure 16.10** shows end-to-end side hepatic vein anastomosis with IVC in a left lobe split liver graft; IVC is left with the right lobe.

In left lobe transplantation, a side-to-side caval-caval anastomosis is performed with a 4/0 running prolene suture. End-to-end PV anastomosis is done with a 6/0 running prolene suture. Arterial anastomoses (**Figures 16.11 to 16.13**) are performed with a 9/0 running prolene by direct suture/carrel patch/use of vascular graft (**Figures 16.12 and 16.13**). Bile duct anastomosis is done end to end anastomosis with 6/0 PDS sutures without a biliary stent, in both the recipients.



Figure 16.8: In-situ split liver for 2 adults, right and left lobe

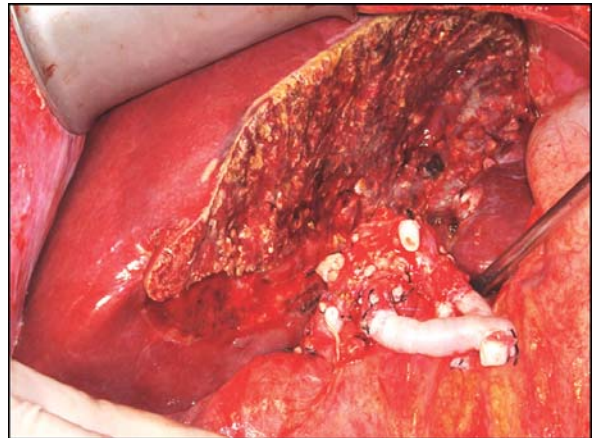


Figure 16.11: Split right lobe with caudate lobe, hepatic artery and bile duct after anastomosis

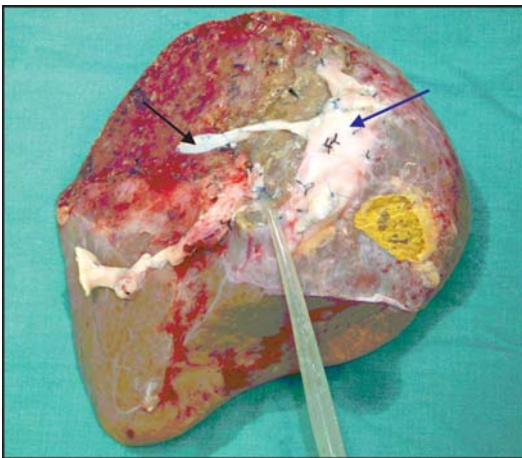


Figure 16.9: Rt lobe graft with V5 (black arrow) reconstructed to drain into IVC (blue arrow). RHA harvested till the aorta to form a carrel patch

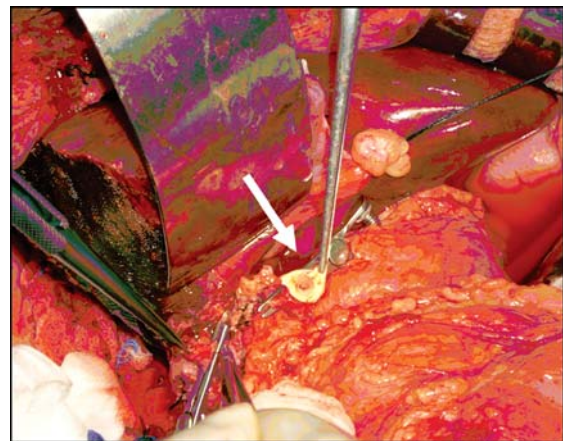


Figure 16.12: Arterial pedicle with a carrel patch in a left lobe split liver graft (white arrow)

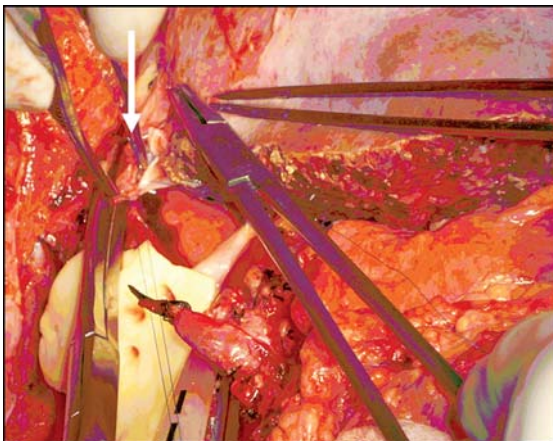


Figure 16.10: End-to-side hepatic vein (black arrow) anastomosis with IVC in a left lobe split liver graft, IVC is left with right lobe



Figure 16.13: Completed arterial reconstruction in a left lobe split liver graft

Patient and graft survival in split liver for left lateral segment and extended right split liver series^{23,30,46-48}

Author	Year	Graft survival (%)	Patient survival (%)
Spada	2000	79/—	84/85
Reyes	2000	61/81	74/96
Hamberg	2002	78.4	85.6
Wilms	2006	77.3/77.3	86.3/82.6

Audet et al reported 1, 5, and 15 years of patient versus graft survivals of 88.9.1%, 84.5%, 62.1% versus 78.6%, 74.2%, 57.4%, respectively.⁵²

Patient and graft survival in split liver transplantation for 2 Adults^{10,46,49-51}

Author	Year	No. of cases	Graft survival (%)	Patient survival (%)
Colledan	2000	6	66.6	83.3
Humar	2001	12	83.3	83.3
Azoulay	2001	34	74/75	74/88
Hamburg	2002	16	80	86
Giacomoni	2008	16	69	69

OUR CENTER TECHNIQUES IN SPLIT LIVER FOR 2 ADULTS

- Routine in-situ splitting till all the major vascular structures are divided, followed by ex-situ splitting of small amount of remnant parenchyma.
- IVC always kept with right lobe for piggyback IVC-IVC anastomosis with recipient. V5 and V8 are anastomosed with IVC separately depending on the diameter of V5 and V8
- Caudate lobe is kept with left lobe. Caudate lobe outflow veins are reconstructed with donor portal vein graft if it is > 3 mm in diameter. Venoplasty is constructed between donor portal vein graft and common trunk of MHV and LHV to form a common channel for a single anastomosis with recipient IVC.
- RHA, RPV and right bile duct are divided distal to the bifurcation at the hilum on right side similar to right lobe LDLT.
- CHA is harvested with carrel patch and is kept intact with left lobe, so that left lobe has a long arterial pedicle available for arterial anastomosis.
- Portal vein on left side is kept short and MPV is used as vein graft for caudate lobe outflow reconstruction.
- CHD and proximal CBD are kept with left lobe.

REFERENCES

1. Pichlmayr R, Ringe B, Gubernatis G, et al. Transplantation of a donor liver to 2 recipients (splitting transplantation)—a new method in the further development of segmental liver transplantation. *Langenbecks Arch Chir* 1988;373:127-30.
2. Bismuth H, Morino M, Castaing D, et al. Emergency orthotopic liver transplantation in two patients using one donor liver. *Br J Surg* 1989;76:722-24.
3. Poncet G, Dumortier J, Choucair A, et al. Split-liver transplantation in two adult recipients: evaluation of feasibility in 100 consecutive cadaver liver grafts. *Gastroenterol Clin Biol* 2002;26:578-83.
4. Toso C, Ris F, Mentha G, et al. Potential impact of the number of available grafts. *Transplantation* 2002;74:222-26.
5. Emond JC, Freeman RB, Renz JF, et al. Optimizing the use of donated cadaver livers: analysis and policy development to increase the application of split-liver transplantation. *Liver Transpl* 2002; 8:863-72.
6. Emond JC, Ascher NL, Busuttil RW. Split liver transplantation in the United States: Creation of a national registry and preliminary outcomes. *Am J Transplant* 2000;1:260.
7. Busuttil RW, JA Gross. Split liver transplantation. *Ann Surg* 1999; 229(3):313-21.
8. Yersiz H, Renz, JF, Farmer DG, et al. One hundred in-situ split-liver transplantations: A Single-Center Experience. *Ann surg* 2003; 238(4):496-505
9. JM Ramia, A Mansilla, J Villar, et al. Split for two adults: What is the real feasibility? *Transplantation Proceedings* 2005;37:3855-56.
10. Azoulay D, Castaing D, Adam R, et al. Split liver transplantation for two adults recipients: feasibility and long term outcomes. *Ann Surg* 2001;233:565.
11. Humar A, Ramcharan T, Sielaff TD, et al. Split liver transplantation for 2 adult recipients: an initial experience. *Am J Transplant* 2001; 1:366-72.
12. Renz JF, Emond JC, Busuttil RW, et al. Split-liver transplantation in the United States: outcomes of a national survey. *Ann Surg* 2004; 239:172-81.
13. Sugawara Y, Makuuchi M. Small-for-size graft problems in adult-to-adult living-donor liver transplantation. *Transplantation* 2003; 75:S20-S22.
14. Emond JC, Whittington PF, Thistlethwaite JR, et al. Transplantation of two patients with one liver. Analysis of a preliminary experience with 'split-liver' grafting. *Ann Surg* 1990;212:14-22.
15. Emond JC, Freeman RB, Renz JF, et al. Optimizing the use of donated cadaver livers: analysis and policy development. *Liver Transplant* 2002;8:863-72.
16. The SPLIT research group. Studies of Pediatric Liver Transplantation (SPLIT): Year 2000 outcomes. *Transplantation* 2001; 73:463-76.
17. KA Soltys, GV Mazariegos, RH Squires, et al. The Split Research Group^d Late Graft Loss or Death in Pediatric Liver Transplantation: An Analysis of the SPLIT Database *American Journal of Transplantation* 2007; 7(9):2165-71.
18. Selzner N, Selzner M, Clavien PA, et al. Cold ischemia decreases liver regeneration after partial liver transplantation in the rat: a TNF-alpha/IL-6-dependent mechanism. *Hepatology* 2002;36:812-18.
19. Selzner M, Camargo CA, Clavien PA. Ischemia impairs liver regeneration after major tissue loss in rodents: protective effects of interleukin-6. *Hepatology* 1999;30:469-75.
20. Debonera F, Wang G, Xie J, et al. Severe preservation injury induces IL-6/STAT3 activation with lack of cell cycle progression after partial liver graft transplantation. *Am J Transplant* 2004;4:1964-71.
21. Marcos A. Right lobe living donor liver transplantation: a review. *Liver Transpl* 2000;6:3-20.

22. Marcos A. Split-liver transplantation for adult recipients. *Liver Transpl* 2000; 6:707-709.
23. J Reyes, D Gerber, George V, et al. Split-liver transplantation: A comparison of ex vivo and in-situ techniques¹ *Journal of Pediatric Surgery* 2000; 35(2):283-290
24. Noujaim HM, Mayer DA, Buckels JAC, et al. Division of vascular medical and vascular complications after ex vivo split liver transplantation. Report of the European Liver Transplant Registry. Joint Meeting of the International Liver Transplantation Society, European Liver Transplantation Association, and the Liver Intensive Care Group of Europe, Berlin, Germany, July 11-13, 2001.
25. Noujaim HM, Gunson B, Mirza DF, et al. Ex-situ preparation of left split-liver grafts with left vascular pedicle only: is it safe? A comparative single-center study. *Transplantation*. 2002;74:1386-90.
26. Kilic M, Seu P, Goss JA. Maintenance of the celiac trunk with the left-sided liver allograft for in-situ split-liver transplantation. *Transplantation* 2002;73:1252-57.
27. Rogiers X, Malago M, Gawad K, et al. In-situ splitting of cadaveric livers. The ultimate expansion of a limited donor pool. *Ann Surg* 1996; 224:331-39.
28. Rela M, Heaton N. Split liver transplantation. *Br J Surg* 1998; 85:881-83.
29. Mirza D, Achilleos OA, Pirenne J, et al. Encouraging results of split-liver transplantation. *Br J Surg* 1998; 85:494-97.
30. Spada M, Gridelli B, Colledan M, et al. Extensive use of split liver for paediatric liver transplantation: A single centre experience *Liver Transpl* 2000;6:415-28.
31. Huda M N, Bridget G, David AM, et al. Worth Continuing Doing Ex-situ Liver Graft Splitting? A Single-Center Analysis. *Am J of Transplant* 2003;3(3):318-23.
32. PR Reichert, JF Renz, LAC D'Albuquerque, et al. Surgical anatomy of the left lateral segment as applied to living-donor and split-liver transplantation A Clinicopathologic Study. *Ann of Surg* 2000;232(5):658-64.
33. Couinaud C. Portal segmentation. In: Couinaud C, ed. *Controlled Hepatectomies and Exposure of the Intrahepatic Bile Ducts*. Paris, France: C Couinaud 1981;9-27.
34. Azoulay D, Astarcioglu I, Bismuth H, et al. Split-liver transplantation. The Paul Brousse policy. *Ann Surg*. 1996;224(6):737-46.
35. Squifflet JP, de Hemptinne B, Gianello P, et al. A new technique for en bloc liver and pancreas harvesting. *Transpl Proc* 1988; 20:994-996.
36. Broelsch CE, Whittington PF, Emond JC, et al. Liver transplantation in children from living related donors: surgical techniques and results. *Ann Surg* 1991;214:428-39.
37. Tanaka K, Uemoto S, Tkunaga Y, et al. Surgical techniques and innovations in living related liver transplantation. *Ann Surg* 1993;217:82-91.
38. Sauer IM, Pascher A, Steinmuller T, et al. Split liver and living donation: the Berlin experience. *Transplant Proc* 2001;33:1459-60.
39. Colledan M, Andorno E, Gridelli B, et al. A new splitting technique for liver grafts. *Lancet* 1999;353:1763.
40. Candinas D, Gunson BK, Nightingale P, et al. Sex mismatch as a risk factor for chronic rejection of liver allografts. *Lancet* 1995; 346:1117-21.
41. Jonas S, Neumann U, Guckelberger O, et al. Donor-recipient sex matching and posttransplant malignancies after induction therapy in hepatic transplantation. *Transplant Proc* 1998;30:1490-91.
42. Pascher A, Neuhaus P. Bile duct complications after liver transplantation. *Transpl Int* 2005;18:627-42.
43. Renz JF, Yersiz H, Reichert PR, et al. Split-liver transplantation: a review. *Am J Transplant* 2003;3:1323-35.
44. Rela M, Vougas V, Muiesan P, et al. Split liver transplantation: King's College Hospital experience. *Ann Surg*. 1998; 227:282-88.
45. Yersiz H, Renz JF, Farmer DG, et al. One hundred in-situ split-liver transplantation: a single-center experience. *Ann Surg*. 2003; 238:496-507.
46. DC Broering, J Schulte am Esch, L Fischer, X Rogiers. Split liver transplantation HPB (Oxford) 2004;6(2):76-82.
47. C Wilms, J Walter, MD, M Kaptein, et al. Long-term Outcome of Split Liver Transplantation Using Right Extended Grafts in Adulthood. *Ann Surg* 2006;244(6):865-73.
48. Massimo Cardillo, Nicola De Fazio, Paola Pedotti, et al. Split and Whole Liver Transplantation Outcomes: A Comparative Cohort Study. *Liver transplantation* 2006;12:402-10.
49. Colledan M, Segalin A, Spada M, et al. Liberal policy of split liver for pediatric liver transplantation. A single centre experience. *Transpl Int* 2000;13(Suppl 1):S131-3.
50. Humar A, Ramcharan T, Sielaff TD, et al. Split liver transplantation for two adult recipients: an initial experience. *Am J Transplant* 2001; 1(4):366-72.
51. A Giacomoni, A Lauterio, M Donadon, et al. Should we still offer split-liver transplantation for two adult recipients? A Retrospective Study of Our Experience. *Liver transplantation* 2008; 14:999-1006.
52. M Audet, M Cag, T Piardi E, et al. Twenty Seven Years of Experience in Pediatric Liver Transplantation in Strasbourg: Focus on the Ex-situ Split Techniques. *Transplant Proceed* 2008; 40:1932-36.

Dual Grafts

INTRODUCTION

Early experiences with LDLT in adult patients were achieved by using the left lobe to keep a high level of safety for the donors.¹ Approximately 20% of the evaluated donors are suitable to donate the right liver for LDLT, depending mainly on the critical remnant liver volume. On special occasions, the volume of liver graft is insufficient for adult recipients even with the use of the right lobe. As an alternative solution, right and left lateral lobe grafts from two donors have been employed.² But the right lobectomy in the donor is not always safe, mainly depending on the volume of the remaining left lobe.³ The remnant liver volume should not be less than 30% of the total liver volume of the donor to maintain donor security.⁴ Even though a donor's right lobe is suitable in size as a graft for an adult recipient, the remaining left lobe may be too small with regard to the donor's own safety. To solve this problem, a second donor has to be found with which to perform dual graft liver transplantation, in which one graft from each of two donors is implanted into one recipient.

Lee SG from Korea was the first to perform successful dual graft transplantation. The first experiences used two left lobe grafts, but every probable combination of graft types can be used.⁵ So far Lee and his team have performed more than 150 dual grafts in Korea. The pioneering work, while technically complex, can offer sufficient liver volume to the recipient by utilizing two grafts (mainly left-side grafts) while preserving an acceptable risk to each donor. However, this procedure has not been widely accepted, probably due to its ethical problem of putting two living donors at risk simultaneously.

There have been only a few reports^{6,7} regarding dual graft LDLT. Nonetheless, this could be an ideal and promising procedure especially for a large-size patient who otherwise can not be transplanted with a single graft.

The experiences in LDLT showed that a graft volume of less than 40% of the SLV means a high risk for the negative outcome of the recipient.⁸ The minimum required graft volume to avoid postoperative liver failure is considered to be at least 40-50% of the SLV.⁹ Regarding the donor, right lobectomy is associated with a higher risk for the donor, mainly depending on the volume of the remaining left liver lobe.

Since, the number of adult-to-adult LDLT using right liver grafts increased over the last decade, the latest results pointed out a higher mortality and morbidity for the right lobe donors.^{10,11} Donor mortality after left lateral segmentectomy is estimated to be approximately 0.1%,¹² the risk of death for donors of a right lobe ranges from 0.4 to 0.5%.¹³ Experiences from the transplant community are consistent with a higher morbidity after donation of the right liver lobe compared with the left lobe.^{14,15} The overall morbidity in right lobe donation is also higher than after donation of the left liver lobe due to the observation that the rate of complications corresponds to the extent of liver resection.¹⁶ Aside from the most frequent minor complications like wound infection, pleural effusions, etc. biliary complications are reported after right hepatectomy with rates of 4 to 8%.¹⁷⁻²⁰

Dual graft LDLT solves the problem of graft-size insufficiency and can be safely performed and opens up the possibility of LDLT to even more families in the Western world. In dual graft transplantation, placing two donors at risk has to be justified. But if the combined risk of the two donors undergoing a minor extensive resection is lower than the risk of a single donor exposed to a major right lobectomy in the same situation, the use of dual grafts should be seriously discussed to minimize the family's risk.²¹ Although, LDLT using dual lobe grafts takes more effort and is a technical, complicated procedure, it is safely feasible and can increase the donor pool and sustains the option of adult-to-adult LDLT to

even more families in the Western world, where the largest graft available is too small for the recipient or remnant liver volume in the donor is less than 30%.²¹ LDLT using dual grafts can be justified in large size recipients in selected cases to avoid small-for-size graft problems without increasing independent donor risks.²² LDLT has two inevitable potential risks:

- Small-for-size syndrome (SFSS)
- Increased donor risk

It is often difficult to obtain an appropriate sized graft from living donors, especially for a large-size patient. It has been shown that 50% of the SLV of the recipient is the minimum liver GV required to provide functional hepatocytes.²³ Generally speaking, a left lobe graft can provide only 30–50% of the required liver volume for an adult recipient and has been thought to be too small for adult recipients to sustain their metabolic demand.²⁴ The safe remnant liver volume after RL donation has been reported to be ≥ 30 –35% of the whole liver volume of the donor^{25,26} whereas the safe limit of the GV is ≥ 50 % of the recipient's standard liver volume (SLV).²⁷ Thus, in such instances where donors have a large RL and a small LL, neither lobe can be donated. Leelaudomlipi et al.²⁸ reported that in 25% of donors evaluated, the volume ratio of the RL was over 70%, or in other words, the remnant liver volume after RL donation was less than 30%.

Regarding the GV, two LL grafts are probably sufficient and that there may be no need to include the RL grafts in dual LDLT in most situations. It is conceivable that each donor's risk does not increase in dual graft LDLT, while the total risk of the two donations would be doubled as compared to regular LDLT from a single donor. However, we believe that the potential risk of the recipient due to a SFSG would be alleviated by summing up the volume of the two grafts. In this case, LDLT using dual grafts preserving the donors' safety should be justified. The ethical issue of putting two donors at risk simultaneously for one recipient is debatable.

DIFFERENT DUAL GRAFTS THAT CAN BE USED IN LDLT

- 2 Left lobes
- Right lobe(V-VIII) + lateral segment
- Left lobe (with or without caudate lobe) + Lateral segment (Seg. II, III)
- Right lobe + Left lobe
- 2 Lateral segments

Harvesting of the right lobe, left lobe and lateral segments are discussed in the respective chapters.

RECIPIENT OPERATION

TWO LEFT LOBE GRAFTS (FIGURE 17.1)

First liver graft is orthotopically implanted on left side. Second graft is heterotopically positioned on right upper fossa with rotated 180°.

Technical Difficulties

- Difficulty in direct anastomosis of the LHV of right side graft with IVC.
- Rotation of the heterotopic second liver graft through 180° of sagittal orientation brings the hilar structures into a reversed location.
- Operation time is long.

TECHNICAL MODIFICATION^{5,22,29}

Dissection Phase

In the recipient, both the right and left branch of the portal vein and the hepatic artery are dissected free from the surrounding tissue as long as possible to obtain maximal length for future bilateral vascular anastomoses. The bile duct is similarly dissected to the level of the hilum, dividing the right and left hepatic duct separately. To preserve the arterial blood supply of the proximal hepatic duct, care must be taken to ensure that the right hepatic artery crossing behind the common bile duct is not dissected.

Back Table Procedure

Cryopreserved cadaveric iliac interposition vein graft is sutured to the right graft's hepatic vein with 5-0 continuous Prolene sutures.

First Left Lobe Graft

First left lobe graft is orthotopically implanted (**Figure 17.1**) in the usual manner. HV of graft is anastomosed to common trunk of LHV and MHV followed by PV with recipient's LPV in end to end fashion or a vascular graft (gonadal vein) can be used. First graft (left) is perfused by releasing the clamp on LPV.

Second Left Lobe Graft

Second left lobe graft is placed heterotopically (**Figure 17.1**) with 180° rotation and hepatic vein anastomosis is completed by piggyback technique with a partial clamp on IVC followed by PV anastomosis with recipient right PV. Right graft is perfused by releasing the vascular clamp on the RPV.

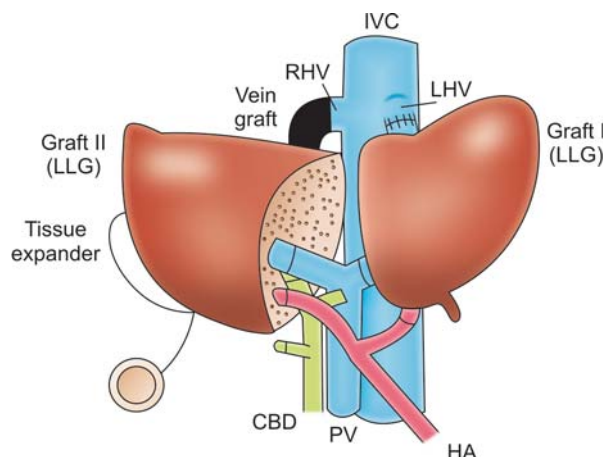


Figure 17.1: Schematic presentation of LDLT using dual grafts. (2 left lobe grafts) (LLG:left lobe graft, CBD: common bile duct, PV: portal vein, HA: hepatic artery, IVC: inferior vena cava, HV: hepatic veins right and left) (Modified and redrawn with permission of Lee SG)^{5,6,9}

Hepatic Venous Anastomosis

Hepatic venous anastomosis of the graft can be done with the use of cadaveric interposition vein graft, as direct anastomosis with the IVC is technically difficult due to smaller size of graft as compared to recipient's right lobe. If there is inadequate outflow due to malposition of the graft, it can be adjusted with the help of a tissue expander placed below the right sided graft to maintain proper position.

Bile Duct

Bile duct lies behind the PV and HA. So hepaticojejunostomy of the second liver graft is difficult in a limited area after portal vein anastomosis is established. Bile duct is reconstructed by duct-to-duct anastomosis followed by the ventrally lying portal vein anastomosis. So the graft is exposed to prolonged warm ischemic time as compared to routine procedure. But other studies report the reconstruction of bile duct after portal vein to avoid this problem. It is technically difficult, but feasible. Lee et al. described that bile duct anastomosis should be done prior to PV reconstruction due to technical difficult position of heterotopic graft. Broering et al. reported an alternative method, in which the bile duct is reconstructed after PV and HA reconstruction.³¹

Hepatic Artery Anastomosis

Arterial reconstruction is performed using 8-0 Prolene interrupted sutures under the microscope between the recipient right hepatic artery (RHA) and the graft RHA, and between the recipient left hepatic artery (LHA) and

the graft LHA. A tissue expander filled with saline solution (250-300 ml) is inserted underneath the second liver graft to relieve undue tension on hilar anastomosis (Figure 17.1).

The surgical techniques of dual grafts using left lobe and lateral segment are very similar to 2 left lobe grafts.

USE OF RIGHT LOBE AND LEFT LATERAL SEGMENT/LEFT LOBE GRAFT (FIGURE 17.2)^{5,21,30}

RECIPIENT OPERATION

Surgical techniques are very similar to LDLT using right lobe and lateral segments independently. Explantation of the recipient's cirrhotic liver is followed by implantation of the right lobe of first donor. The graft is orthotopically placed in the right upper fossa and the right hepatic vein of the graft was anastomosed to the longitudinal cavotomy in an end-to-side fashion or to the RHV. End-to-end anastomosis of the grafts and recipients right portal vein was followed by reperfusion. A cryopreserved iliac artery/vein grafts from a deceased donor is used for reconstruction of V5 and V8 and is anastomosed to the recipient's vena cava. Subsequently the graft's right hepatic artery is anastomosed end-to-end to the right hepatic artery of the recipient. After arterial reperfusion intraoperative ultrasound showed regular portal, venous, and arterial flow.

Second graft from left lateral segment left lobe graft is orthotopically placed on the left side and the graft LHV is anastomosed end-to-end fashion with the recipient common trunk of MHV and LHV. Anastomosis of the left portal vein and the left hepatic artery are also performed in an end-to-end fashion. After reperfusion, intraoperative ultrasound to confirm regular portal, venous and arterial flow in the left lateral graft as well.

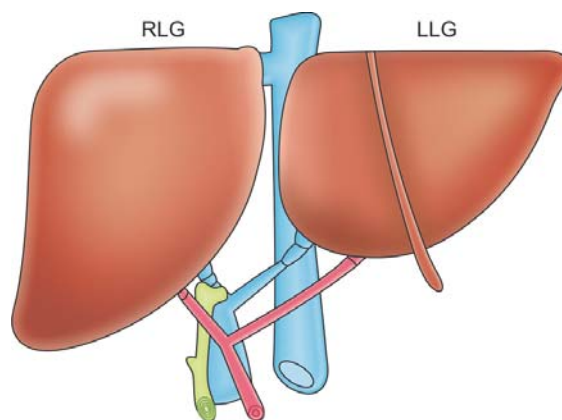


Figure 17.2: Schematic presentation of LDLT using dual grafts. (RLG and LLG) (RLG: right lobe graft, LLG:left lobe graft, LLSG: left lateral segment graft) (Modified and redrawn with permission of Lee SG).

Biliary reconstruction is performed, starting with the connection of the recipient RHD to right graft and LHD to left graft, if possible. But there is technically difficult, So LHD can be reconstructed by Roux-en-Y hepaticojejunostomy.

VANISHING GRAFT SYNDROME (VGS) IN DUAL GRAFTS

Lee et al²⁹ reported this syndrome in dual grafts in a mean period of 7.8 months. VGS is divided into 2 types. Primary VGS seen commonly in left sided graft. Portal vein flow and regenerative rate were significantly lower in the first month after transplantation. Secondary VGS was noticed due to biliary stricture, PV stenosis, HV outflow obstruction and acute cellular rejection. Similar VGS was earlier reported by Durand et al. in auxiliary liver transplantation after withdrawal of immunosuppression.³⁰

REFERENCES

- Hashikura Y, Makuuchi M, Kawasaki S, et al. Successful living-related partial liver transplantation to an adult patient. *Lancet* 1994; 343:1233-34.
- Kaihara S, Ogura Y, Kasahara M, et al. A case of adult-to-adult living donor liver transplantation using right and left lateral lobe grafts from 2 donors. *Surgery* 2002;131:682-84.
- Sugawara Y, Makuuchi M. Technical advances in living-related liver transplantation. *J Hepatobiliary Pancreat Surg* 1999;6:245-53.
- Fan ST, Lo CM, Liu CL, et al. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch Surg* 2000;135:336-40.
- Lee S, Hwang S, Park K, et al. An adult-to-adult living donor liver transplant using dual left lobe grafts. *Surgery* 2001;129:647-50.
- Lee SG, Hwang S, Park KM, et al. Seventeen adult-to-adult living donor liver transplantations using dual grafts. *Transplant Proc* 2001; 33:3461-63.
- Hwang S, Lee SG, Lee YJ, et al. Lessons learned from 1,000 living donor liver transplantations in a single center: How to make living donations safe. *Liver Transpl* 2006;12:920-27.
- Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors.[see comment]. *Transplantation* 1999;67:321-27.
- Lee SG, Park KM, Hwang S, et al. Adult-to-adult living donor liver transplantation at the Asan Medical Center, Korea. *Asian J Surg* 2002;25:277-84.
- Trotter JF, Wachs M, Everson GT, et al. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002;346:1074-82.
- Chen YS, Cheng YF, De Villa VH, et al. Evaluation of living liver donors. *Transplant* 2003;75:S16-19.
- Otte JB. Donor complications and outcomes in live-liver transplantation.[comment]. *Transplantation* 2003;75:1625-26.
- Renz JF, Kin CJ, Saggi BH, Emond JC. Outcomes of living donor liver transplantation. In: Busuttil RW, Klintmalm GB, eds. *Transplantation of the liver*. Philadelphia: Elsevier, 2005; 713-24.
- Nanashima A, Yamaguchi H, Shibasaki S, et al. Comparative analysis of postoperative morbidity according to type and extent of hepatectomy. *Hepatogastroenterology* 2005;52:844-48.
- Choi SJ, Gwak MS, Kim MH, et al. Differences of perioperative liver function, transfusion, and complications according to the type of hepatectomy in living donors. *Transpl Int* 2005;18:548-55.
- Salvalaggio PR, Baker TB, Koffron AJ, et al. Comparative analysis of live liver donation risk using a comprehensive grading system for severity. *Transplantation* 2004;77:1765-67.
- Brown RS, Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:818-25.
- Adam R, McMaster P, O'Grady JG, et al. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003;9:1231-43.
- Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan.[see comment]. *Lancet* 2003;362:687-90.
- Kim DG, Na SE, Chung ES, et al. Donor safety in living donor liver transplantation using the right lobe. *Transp Proc* 2003;35:53-54.
- DC Broering, J Walter, X Rogiers. The first two cases of living donor liver transplantation using dual grafts in Europe. *Liver Transplantation* 2006;13(1):149-53.
- Y Soejima, A Taketomi, T Ikegami, T, et al. Living Donor Liver Transplantation Using Dual Grafts from Two Donors: A Feasible Option to Overcome Small-for-Size Graft Problems? *Am J of Transplant* 2008;8(4):887-92.
- Emond JC, Renz JF, Ferrel LD, et al. Functional analysis of grafts from living donors. *Ann Surg* 1996;224:544-54.
- Soejima Y, Shimada M, Suehiro T, et al. Outcome analysis in adult-to-adult living donor liver transplantation using the left lobe. *Liver Transpl* 2003;9:581-86.
- Ibrahim S, Chen CL, Wang CC, et al. Small remnant liver volume after right lobe living donor hepatectomy. *Surgery* 2006;140:749-55.
- Cho JY, Suh KS, Kwon CH, et al. Outcome of donors with a remnant liver volume of less than 35% after right hepatectomy. *Liver Transpl* 2006;12:201-06.
- Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999;67:321-27.
- Leelaudomlipi S, Sugawara Y, Kaneko J, et al. Volumetric analysis of liver segments in 155 living donors. *Liver Transpl* 2002;8:612-14.
- Moon DB, Lee SG. Adult-to-adult living donor liver transplantation at the Asan Medical Center *Yonsei Med J* 2004;45(6):1162-68.
- F Durand, J Belghiti, D Valla, et al. Vanishing graft syndrome after auxiliary liver transplantation. *Journal of Hepatology* 2000;33(3):513.
- Broering DC, Walter J, Rogiers X. The first two cases of living donor liver transplantation using dual grafts in Europe. *Liver Transpl* 2007;13:149-53.

Auxiliary Partial Orthotopic Liver Transplantation (APOLT)

INTRODUCTION

Auxiliary transplantation had been proposed for the treatment of acute liver failure in 1956 by Goodrich et al. in an initial description of heterotopic auxiliary liver transplantation (HALT) in dogs.¹ Partial native liver resection to make room in the right hypochondrium to transplant an auxiliary partial liver in the orthotopic position (*i.e.* APOLT) in a patient with cirrhosis was first reported by Bismuth et al. in 1985.² First successful APOLT for fulminant hepatic failure was reported by Gubernatis et al. in 1991 for hemolysis, elevated liver enzymes, and low platelet count syndrome in a 33-year-old patient.³ The most common indication for APOLT in Western countries is fulminant hepatic failure. The main goal of APOLT in the setting of fulminant hepatic failure is to save the patient with no neurologic sequelae, which can be achieved only if a sufficient mass of functioning hepatic tissue is provided rapidly. The graft should serve only as temporary support and could be removed later; no essential structures of the native liver should be jeopardized.

Before the era of transplantation, most patients died, a small number (15-20%), however, recovered and in these patients, the restoration of the hepatic function usually was complete.^{4,5} The rationale of APOLT for a small-for-size graft is that the remnant native liver is expected to support the function of the implanted graft during the early post-operative period. A patient with fulminant hepatic failure needs a reliable temporary support to “tide him over” the period of illness, before regeneration of the native liver has taken place. The auxiliary graft should support the remnant native liver during regeneration.⁶ The concept of auxiliary partial orthotopic liver transplantation (APOLT), placing the graft next to the diseased organ, is therefore, appealing, when and if the native liver recovers, the graft either can be abandoned

or removed, and the patient can be freed from immunosuppression. The graft liver expands its function in proportion to volume growth. After the graft liver has grown sufficiently, it can be expected to meet the hepatic functional demands of the recipient. APOLT was initially indicated for potentially **reversible fulminant hepatic failure (FHF)** and non-cirrhotic metabolic liver disease.^{7,8} The procedure, technically more complex than standard OLT, has been rendered possible by outstanding recent advances in liver surgery and transplantation such as the reduced liver and the split-liver transplantation techniques.⁹⁻¹¹ Bismuth et al. in his series showed that the time for liver regeneration after APOLT ranges from 10 days to 10 months.¹²

Later use of APOLT was extended to **metabolic liver diseases**. In metabolic disease with ESLD, the other option is that RPV of the recipient may be narrowed to induce compensatory hypertrophy of the graft. After confirming atrophy of the native liver and hypertrophy of the graft by computed tomography, the remnant native liver is removed around 2-3 months after APOLT. The new graft corrects the enzyme deficiency. In Japan, to treat patients with a graft-to-recipient weight ratio (GRWR) of less than 0.8%, auxiliary partial orthotopic liver transplantation (APOLT) was indicated from 1996.¹³ This technique guarantees an adequate safety margin for both the donor and the recipient in LDLT for metabolic liver diseases where the donor's left lobe does not exceed 30% of ESLV. The advantage claimed for APOLT in non-cirrhotic metabolic liver disease is that it can compensate for enzyme deficiencies without complete removal of the native liver, which may have to aid the recipient in case of potential graft failure. The remaining native liver could benefit in the future from potential success in gene treatment.^{14,15}

The other potential indication for APOLT is **ABO-incompatible transplantation**. ABO-incompatible transplantation is often unavoidable due to the limited number of potential donor candidates in the LDLT program. A high incidence of early graft failure with a high rate of biliary and vascular complications in ABO-incompatible liver transplantation was reported.¹⁶ The remnant native liver could sustain a patient's life if the anticipated graft failure occurred in an ABO-incompatible case.

INDICATIONS OF APOLT¹⁷

- Fulminant hepatic failure
- Non-cirrhotic metabolic liver disease like citrullinemia
- Small for size graft
- ABO-incompatible liver transplantation.

CITRULLINEMIA

It is a rare hereditary metabolic liver disease characterized by elevated plasma levels of citrulline and ammonia, and is due to deficiency of Arginine succinate synthetase in the liver.¹⁸ Causative gene of this disorder is citrin.¹⁹ Citrullinemia can be classified into three types: Neonatal/infantile (types I and III) and adult (type II). Most of the patients with type II citrullinemia are reported in Japan. If untreated usually occurs due to cerebral edema within few years of onset of disease. In Japan, small number of patients has undergone liver transplantation showing dramatic therapeutic effects.^{20,21}

SURGICAL TECHNIQUE²²⁻²⁵

Native hepatectomy is performed prior to graft implantation, that varies in type of graft segment and volume that is to be implanted.

DIFFERENT GRAFT TYPES THAT CAN BE USED FOR APOLT

- Left lateral segment
- Left lobe
- Right lobe

LEFT APOLT IN THE RECIPIENT

Patient position and exposure are described in earlier chapters. Structures around the portal hepatis are dissected first to isolate and skeletonize the left portal vein. Left lateral segment was then resected to the left of the falciform ligament as described in the earlier chapter. Part of the caudate lobe is also excised for adequate exposure of the retrohepatic IVC to facilitate

the anastomosis of the donor left hepatic vein as close to the diaphragm as possible. Left lateral segment of the donor liver is implanted by anastomosing the left hepatic vein end-to-side to the recipient IVC just below the diaphragm with continuous 4-0 prolene sutures. Graft PV is anastomosed end-to-side to the recipient's LPV with continuous 6-0 prolene sutures. Portal inflow to the graft is encouraged by narrowing the portal vein to the native liver. Surgical narrowing of the portal vein to the native liver is achieved by placing a nonabsorbable ligature distal to the anastomosis, with the aim of reducing the diameter of the portal vein to one half to one third of its size. Surgical narrowing of PV to native liver is not routine and it depends on flow cytometry findings and is more commonly used in cases of APOLT for metabolic liver diseases. But if the graft flow is sufficient then there is no need to go for portal flow modulation. The graft is rearterialized by an anastomosis with an infrarenal iliac arterial conduit or direct anastomosis with left hepatic artery. Bile duct reconstruction is performed by Roux-en-Y Hepaticojejunostomy.

TECHNICAL DIFFICULTIES

Three technical difficulties are encountered during APOLT such as:

- Abdominal space
- Portal in flow reconstruction
- Venous drainage reconstruction

PORTAL INFLOW MODULATION IN APOLT

Portal vein modulation is useful in APOLT for metabolic liver diseases. Earlier studies reported that occluded portal flow induces hepatocyte apoptosis rather than necrosis in the native liver without changing the functional efficiency of the hepatocyte.^{28,29} Ligation of the native portal vein had no detrimental effects on the native liver supplied by arterial flow only.³⁰ APOLT with portal vein diversion is an effective technique to induce graft regeneration and to avoid functional portal flow competition in non-cirrhotic metabolic liver disease.

Competition for portal blood flow has been suggested as a possible mechanism for failure, either of the graft or of the native liver. Portal vein thrombosis has been postulated to occur as a result of a steal syndrome, and a technique of banding or surgical narrowing of the portal vein branch feeding the native liver has been devised, with improved results in an experimental model.²³ Mureo et al.²⁴ described that the stump of the native left hepatic vein and left hepatic artery can be used for anastomosis and 80% of his patients had diversion of the native portal vein to prevent functional portal vein competition between the

native and graft liver, meaning that interruption of portal flow to the native liver with all portal flow going through the graft. Hepatic artery reconstruction performed using the microvascular technique in all his cases without using vascular grafts. Biliary reconstruction was achieved using Roux-en-Y hepaticojejunostomy.²⁵ Broering et al. suggested manipulation of the venous outflow of the native liver by occluding the middle hepatic vein in APOLT is an effective technical solution for preventing portal flow competition between both livers. Additionally, it facilitates venous anastomosis of the graft, thereby optimizing the graft's venous outflow. It respects the function of both livers as well as the safety of the recipient.²⁶

ADVANTAGES OF APOLT

In most of the cases of acute liver failure, the native liver recovers its function. The native liver may be removed if regeneration has not occurred.

Once the native liver function recovers:

- Graft is removed by surgery
- Atrophy of the graft occurs after withdrawal of immunosuppression
- Patients remain free from immunosuppression

ISSUES RELATED TO DETRANSPLANTATION

When the native liver has regenerated, the question arises on the best way to deal with the graft. One option is to taper down the immunosuppression to provoke a controlled rejection of the donor liver, which is left to atrophy. Duarnd et al.³² reported vanishing graft syndrome after auxiliary liver transplantation. The theoretical disadvantage of this attitude is the risk to cause a severe rejection of the graft, requiring its prompt surgical removal, which may be a difficult procedure on an inflamed organ. The other option is to take out the graft electively without discontinuing the immunosuppression. The procedure of surgical removal of the graft, however, may be difficult and is not without risks. Deaths have been reported after graft removal.²⁷

EVALUATION OF FUNCTION OF THE GRAFT AND NATIVE LIVER

Clinical assessment along with improvement in liver function tests, suggest the improvement in patient condition and recovery of graft function.

LIVER BIOPSY

Histologic examination of regenerating livers showed the disappearance of hepatocyte necrosis and the replacement by normal hepatocytes. Some degree of portal and

interportal fibrosis was observed in all these cases, its significance is difficult to appreciate.

CT SCAN¹²

An increase in the volume of the native liver associated to a decrease of the volume of the graft on CT scan may be a sign of regeneration. However, size is only a rough indicator and may not reflect the respective function of each liver, especially for the graft. The venous phase of the angiogram showing the respective distribution of the portal flow between the graft and the native liver also may be a reflection of the function of each liver, although this procedure is invasive and can not be used for sequential evaluation.

RADIONUCLIDE HIDA SCANS¹²

It is the most useful investigation. By showing the rapidity and the magnitude of the uptake and of the biliary excretion of the tracer, these scans permit a quantitative analysis of the function of the graft relative to that of the native liver, which can be easily repeated for comparison. Progression of recovery most often appears on HIDA scans as a gradual increase of the uptake and of the biliary excretion by the native organ and as a decrease of the function of the graft.

SURVIVAL RATES AFTER APOLT

Kasahara et al. (Kyoto university)¹⁷ reported the cumulative 1 yr and 5 years survival in APOLT in different groups as per the etiology mentioned below:

- *APOLT for fulminant hepatic failure:* The cumulative 5 yrs graft and patient survival rates were 58.4 and 60.2% in the standard LDLT group, respectively. The graft survival was significantly lower after APOLT ($p < 0.01$).
- *APOLT for non-cirrhotic metabolic liver disease:* There was no significant difference in graft and patient survival between APOLT and standard LDLT for non-cirrhotic metabolic liver disease.
- *APOLT for small-for-size graft:* The overall cumulative 1yr and 5 years graft and patient survivals in the standard LDLT group were 65.0 and 65.0%, respectively. No significant difference was observed between the groups.
- *APOLT for cases of ABO-incompatibility:* There was no significant difference in graft and patient survival between APOLT and standard LDLT for ABO-incompatibility.
- *Profiles of APOLT and standard LDLT:* The 1 year and 5 years cumulative grafts were lower after APOLT

versus standard **LDLT** (57.9 and 50.6% vs. 78.8 and 73.8%, respectively), but the difference did not reach statistical significance ($p = 0.45$ and 0.18 , respectively).

Azoulay et al³¹ compared the results of APOLT with those of total orthotopic liver transplantation in the treatment of ALF and showed similar survival rates after both procedures, but the post-operative complication rates (particularly biliary complications and neurological sequelae as well as the retransplantation rate) were significantly more frequent after APOLT.

In the 'Paul-Brousse experience', both full native liver regeneration and discontinuation of immunosuppression was observed only in 25% of the cases. An APOLT survey from several centers in Europe, and we recorded that the native liver regeneration, reversal of encephalopathy and interruption of immunosuppressive therapy could be achieved after APOLT in most of the cases. The rate of regeneration ranged from 20 to 87%. Portal diversion was never used.³³

ROLE OF APOLT IN PRESENT TRANSPLANTATION SCENARIO

Unlike standard **LDLT**, the incidence of biliary complications and the need for retransplantation were shown to be higher in APOLT cases.³¹ APOLT has restricted indications in present days after the technical refinements in whole right lobe grafts and successful achievement of better long-term survival results. Fulminant hepatic failure and non-cirrhotic metabolic liver disease may be a suitable indication for APOLT. Conceptual changes were made in the treatment of small-for-size grafts, through the introduction of **LDLT** using right lobe with or without middle hepatic vein graft, and in the treatment of ABO-incompatible cases, through the use of a novel intrahepatic arterial immunosuppression, plasma exchange and Anti CD 20 protocol. With all these advances in LTX, the necessity for performing APOLT is decreasing.

REFERENCES

- Goodrich EO, Welch HF, Nelson JA, et al. Homotransplantation of the canine liver. *Surgery* 1956;39:244-51.
- Bismuth H, Houssin D. Partial resection of liver grafts for orthotopic or heterotopic liver transplantation. *Transplant Proc* 1985;17:279-83.
- Gubernatis G, Pichlmayr R, Kemnitz J, et al. Auxiliary partial orthotopic liver transplantation (APOLT) for fulminant hepatic failure: first successful case report. *World J Surg* 1991;15:660-66.
- Gazzard B, Portmann B, Murray-Lyony I, et al. Causes of death in fulminant hepatic failure and relationship to quantitative histological assessment of parenchymal damage. *QJM* 1975;44:615-26.
- Horney JT, Galambos JT. The liver during and after fulminant hepatitis. *Gastroenterology* 1977;73:639-45.
- Azoulay D, Samuel D, Ichai P, et al. Auxiliary partial orthotopic versus standard orthotopic whole liver transplantation for acute liver failure. *Ann Surg* 2002;234:723-31.
- Terpstra OT. Auxiliary liver grafting: A new concept in liver transplantation. *Lancet* 1993;342:758.
- Whittington PF, Edmond JC, Heffron T, et al. Orthotopic auxiliary liver transplantation for Crigler-Najjar syndrome type 1. *Lancet* 1993;342:779-80.
- Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. *Surgery* 1984;95:367-70.
- Bismuth H, Morino M, Castaing D, et al. Emergency liver transplantation in 2 patients with one donor liver. *Br J Surg* 1989; 76:722-24.
- Bismuth H, Azoulay D, Dennison A. Recent developments in liver transplantation. *Transplant Proc* 1993;25:2191-94.
- Bismuth H, Azoulay D, et al. Auxiliary partial orthotopic liver transplantation for fulminant hepatitis: *Ann surg* 1996; 224(6):712-26.
- Inomata Y, Kiuchi T, Kim ID, et al. Auxiliary partial orthotopic living donor liver transplantation as an aid for small-for-size grafts in larger recipients. *Transplantation* 1999;67:1314-19.
- Kasahara M, Kiuchi T, Uryuhara K, et al. Treatment of ornithine transcarbamylase deficiency in girls by auxiliary liver transplantation: conceptual changes in a living-donor program. *J Pediatr Surg* 1998;33:1-5.
- Ikegami T, Shiotani S, Ninomiya M, et al. Auxiliary partial orthotopic liver transplantation from living donors. *Surgery* 2002; 131:S205-S210.
- Demetris AJ, Jaffe R, Tzakis A, et al. Antibody-mediated rejection of human orthotopic liver allografts. A study of liver transplantation across ABO blood group barriers. *Am J Pathol* 1988; 132:489-502.
- Kasahara M, Yasutsugu T, Tanaka K, et al. Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience *Am J of Transpl* 2005;5(3):558-65.
- Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic and molecular bases of inherited disease*. 7th ed. New York: McGraw-Hill Information Service Co., 1995:1187-232.
- Kobayashi K, Sinasac DS, Iijima M, et al. The gene mutated in adult-onset type II Citrullinemia encodes a putative mitochondrial carrier protein. *Nat Genet* 1999;22:159-63.
- Ikeda S, Takei Y, Hashikura Y. Liver transplantation as treatment for neurological disorders. *Expert Rev Neurotherapeutics* 2003;3:547-55.
- Ikeda S, Yazaki M, Takei Y, et al. Type II (adult onset) citrullinemia: Clinical pictures and the therapeutic effect of liver transplantation. *J Neurol Neurosurg Psychiatry* 2001;71:663-70.
- Rela, M, Muiesan P, et al. Auxiliary partial orthotopic liver transplantation for crigler-najjar syndrome type I. *Ann Surg* 1999; 229(4):565-69.
- Nagashima I, Bergmann L, Schweizer R. How can we share the portal blood inflow in auxiliary partial heterotopic liver transplantation without portal hypertension? *Surgery* 1994;116:101-06.
- Mureo K, Yasutsugu T, Tanaka K, et al. Auxiliary partial orthotopic living donor liver transplantation: Kyoto University Experience *Am J of Transpl* 2005;5(3):558-65.

25. Kasahara M, Uryuhara K, Ogura Y, et al. Functional portal flow competition after auxiliary partial orthotopic living donor liver transplantation in a non-cirrhotic metabolic liver disease. *J Pediatr Surg* 2004;39:1138-41.
26. Broering DC, Walter J, et al. Overcoming the portal steal phenomenon in auxiliary partial orthotopic liver transplantation by modulation of the venous outflow of the native liver. *Liver Transplantation* 2005;11(9):1140-43.
27. Shaw BW. Auxiliary liver transplantation for acute liver failure. *Liver Transplant Surg* 1995;1:194-200.
28. Harada H, Imamura H, Minagawa S, et al. Fate of human liver after hemihepatic portal vein embolization: cell kinetic and morphometric study. *Hepatology* 1997;26:1162-70.
29. Shimada R, Imamura H, Nakamura A, et al. Changes in blood flow and function of the liver after right portal vein embolization. *Arch Surg* 2002;137:1384-88.
30. Yabe S, Nishizawa H, Egawa H, et al. Portal flow and liver regeneration in auxiliary partial orthotopic liver transplantation in a canine model. *Eur Surg Res* 1999;31:83-92.
31. Azoulay D, Samuel D, Ichaï P, et al. Auxiliary partial orthotopic versus standard orthotopic whole liver transplantation for acute liver failure: a reappraisal from a single center by a case-control study. *Ann Surg* 2001;234:723-31.
32. Durand F, Belghiti J, Vilgrain V, et al. Vanishing graft syndrome after auxiliary liver transplantation. *J Hepatol* 2000;33(3):513.
33. Jaeck D, Audet M, O Elie, et al. Is There Still a Place for Auxiliary Partial Orthotopic Liver Transplantation (APOLT)? *Am J of Transplant* 2005;5(10):2596-96.

Domino Liver Transplantation

INTRODUCTION

Shortage of cadaveric organs has led to a search for alternative methods to expand the donor pool, such as living donor, split liver, and sequential (Domino) transplantation.¹ Domino liver transplantation (Domino LTX) was introduced in 1997.² In Domino LTX, a patient with metabolic liver disease is transplanted from a deceased or living donor liver, but the explanted liver with metabolic liver disease of the 1st recipient is used for transplanting in another patient (2nd recipient, called domino recipient) with ESLD so that the liver with metabolic liver disease can support the domino recipient. 1st recipient will get rid of the metabolic liver disease. The domino recipient acquires a liver with metabolic disease but with better functions and is a potential candidate to develop metabolic liver disease in future. Domino LTX can expand the donor pool, especially in areas where DDLT is limited.

Domino procedures may be performed with livers from patients having transplantation for hepatic metabolic disorders that cause systemic disease without affecting other liver functions, such as familial amyloid polyneuropathy type I (FAP). In most parts of the world, Domino LTX is mainly performed in the event of a deceased donor (DDLT) for FAP.³ The central point of Domino LTX is that the procedure should not pose a negative influence on the safety of the original LT, especially in LDLT. Domino LTX using the livers from FAP patients may be justified for patients whose condition precludes a longer time on waiting list, including those with HCC and those for whom palliation rather than long-term cure is the aim and usually patients are older than 60 years.^{2,4}

Preconditions necessary for Domino LTX:⁴

- Domino liver must be fully functional

- Genetic defect in the host should recur within a sufficient latency period (like 30 years in FAP)
- Domino liver recipients must know the origin of the organ
- Domino recipients must be followed up with an extensive neurological and cardiologic protocol.

Domino LT is indicated in metabolic liver diseases like:

- Familial amyloid polyneuropathy type I (FAP)
- Familial hypercholesterolemia
- Maple syrup urine disease (MSUD).¹⁷

FAMILIAL AMYLOID POLYNEUROPATHY (FAP)

Familial amyloid polyneuropathy (FAP) is a severe form of hereditary amyloidosis. In a global perspective, the amyloidogenic TTR (ATTR) mutation, Val 122 Ile (Valine for Isoleucine at position,²² is the most common, giving rise to a senile cardiac amyloidosis. However, patients considered candidates for liver transplantation will most often have a neuropathic amyloidosis, of which familial amyloid polyneuropathy (FAP) caused by the ATTR Val 30 Met (Valine for methionine at position 30) mutation is the most common.⁶ Liver transplantation is the only successful treatment to date.⁵ It is an autosomal dominant disorder in which the liver produces a variant prealbumin called transthyretin met-30 (TTR met-30) that is deposited along nerves leading to a progressive and fatal polyneuropathy that begins in the third decade of life. Apart from the production of the variant protein, there are no other abnormalities in these FAP livers.

PREVALENCE

This disease is prevalent in Portugal, Japan, and Sweden, and it has also been described in the Spain, UK and USA.¹³

PRESENTATION OF FAP (FAP ATTR VAL 30 MET)⁷⁻¹¹

The amyloid fibrils aggregate into insoluble fibers, and clinical manifestations are associated with deposition of amyloid protein in various organs. They usually manifest in the third or fourth decade of life

- **Nervous system:** Progressive peripheral polyneuropathy, painful sensory motor polyneuropathy. Autonomic neuropathy orthostatic hypotension and impotence urinary and fecal incontinence.
- **Cardiac manifestations:** Cardiac arrhythmias with atrioventricular (AV) conduction disturbances and ventricular arrhythmias
- **Renal:** Kidney and Bladder Impairment renal insufficiency Bladder dysfunction Kidney failure
- **Ophthalmic:** Amyloid deposits in the corpus vitreum may lead to blindness if left untreated.
- GI impairment and malnutrition due destruction of celiac ganglion and vagal nerve by amyloid deposits.

Clinical presentation is variable even among patients who carry the same genotype; the disease course in symptomatic patients is invariably progressive and fatal.¹² Mean survival for patients with FAP is reported to be 9 to 13 years after the onset of symptoms.

LIVER TRANSPLANTATION FOR FAP ATTR VAL 30 MET

The mutant TTR protein is predominantly produced in the liver. Hence, liver transplantation eliminates the source of abnormal TTR production and is currently the most effective treatment to halt disease progression. Survival after LT is closely related to the patient's nutritional status before the procedure. Patients who undergo transplantation after more than 7 years of the disease have a decreased chance for survival. In counseling the patient with FAP ATTR Val 30 Met, one should never forecast an improvement after transplantation, but emphasize that the goal is to prevent further decline and the onset of new complications. This policy enables an early intervention and minimizes the risk for delaying the patient's decision for transplantation. Improvement is not the goal.

FAP World Transplant Register (FAPWTR)

The purpose of this to monitor the international results of orthotopic liver transplantation (OLT) as a treatment for FAP, as well as trends in the practice of Domino LTX. Its 10 years report in 2000 shows a total of 539 patients underwent liver transplantation.¹³ Follow-up information was available for 149 patients. 41.6% reported improvement of sensory neuropathy, 52.4% improved GI symptoms, and 37.4% improved motor and muscular function. Nutritional status improved in 39.8% of the 138

patients who had malnutrition at the time of transplant. Cardiovascular symptoms improved in only 20.8% of the patients, however; the remaining patients reported either no change or a progression of cardiovascular involvement. Overall patient survival was excellent, 77% after 5 years, which is comparable to survival after liver transplantation for other chronic liver diseases. Cause of death in this registry was most often related to cardiovascular complications (39%), infection and multiorgan failure. The rate of cardiovascular complications seems to be higher after liver transplant for FAP compared with other indications. Cardiovascular involvement seems to be a poor prognostic sign. Evaluation to determine the extent of cardiac involvement before transplant is of utmost importance.

Domino LTX in FAP

An intriguing aspect of liver transplantation for FAP is the possibility of transplanting the FAP livers into other patients (Domino LTX). The rationale is that patients who have FAP usually become symptomatic after at least 20 years of age and the liver is morphologically normal; it is therefore assumed that it would take at least 20 years for a genetically normal liver transplant recipient to develop symptoms associated with FAP. Domino LTX thus could be an option, especially in patients who have shortened life expectancy because of malignancy. The post-transplant survival rate for donors of domino FAP livers does not seem to differ from patients who had FAP whose livers were not transplanted.^{13,14}

MSUD¹⁷

Maple syrup urine disease is an autosomal recessive disorder characterized by impaired activity of the branched-chain alpha-keto acid dehydrogenase complex. The resulting accumulated branched-chain L-amino acids (BCAAs) and alpha-keto acids exert neurotoxic effects. The clinical course is typically manifests with episodes of ketoacidosis, each potentially life-threatening. Very few cases respond to supplements of thiamine but, for most, treatment is limited to dietary management with strictly reduced quantities of protein and BCAAs as well as aggressive intervention during acute episodes. The outcome is potentially favorable when the patients are kept on carefully supervised long-term therapy, but even with successful treatment late complications including brain damage or death are possible,¹⁵ and there is increasing awareness of chronic psychological burden in older patients with MSUD.¹⁶ Khanna et al reported a case of successful Domino LTX has been performed for MSUD.¹⁷

DOMINO DDLT

When the source of the liver graft for the FAP patient is a deceased donor, the whole FAP liver is harvested along with IVC and other accompanying vessels to be used in the domino recipient. Venovenous bypass is used in the 1st recipient. Some technical modifications have been made on the domino recipient of FAP liver allograft to overcome the cuff limitation such as the use of side to side cava-caval anastomosis with closure of the suprahepatic and infrahepatic IVC.¹⁸

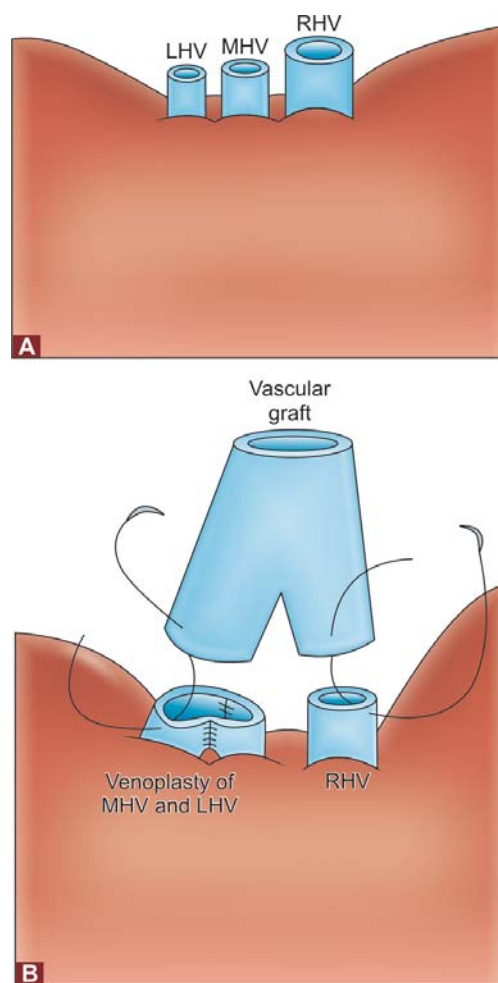
These technical innovations in the recipient AHA however have no benefit for the FA patient undergoing the hepatectomy and may in fact adversely affect the safety of the harvesting procedure by requiring high dissection of the IVC into the diaphragm.¹⁹ In addition, the IVC is removed with the liver, therefore, requiring complete supra-renal vena caval clamping and the use of venovenous bypass.^{20,21} Some authors reported that IVC preservation in FAP patient and harvesting domino liver without IVC and reconstructing the venous outflow with an additional piece of IVC with a 2 cm segment of the common iliac veins, procured from the deceased donor in anticipation of the back table reconstruction. The suprahepatic venous cuff is reconstructed using this deceased donor IVC. The common iliac veins were anastomosed to the right and the trunk of the MHV+LHV using 5/0 prolene as shown in the figure below. The implantation of domino liver is done in the standard piggyback fashion by suturing the reconstructed suprahepatic venous cuff to the junction of all three hepatic veins of the recipient, without clamping the IVC or venovenous bypass. This procedure obviates the necessity for caval clamping or venovenous bypass in the FAP patient, adding to intraoperative hemodynamic stability and maximizing patient safety.^{22,23,28}

Cescon et al. used a vascular graft harvested from deceased donor. The graft is opened longitudinally and placed upon the venous stumps (RHV, Superficial RHV, MHV, LHV) with its inferior wall, which is opened circularly in correspondence with each venous orifice and anastomosed with an everting 6/0 polypropylene suture. The external edge of the vascular graft was trimmed in order to obtain a circular stump, which is anastomosed end-to-end with the recipient cuff formed by the right, middle, and left hepatic veins using an everting 5/0 polypropylene suture.

DOMINO LDLT

When the liver graft for the FAP patient comes from a living donor, the retrohepatic IVC, the portal trunk, and the peripheral hepatic arteries have to remain in the FAP patient because they are essential for the vessel

reconstruction for the FAP patient. In these cases, the explanted FAP liver has multiple, relatively short vascular pedicles and biliary orifices that must be reconstructed in the domino recipient (**Figures 19.1A and B**). Multiple orifice reconstruction conveys a higher chance of complications, therefore using only part of the FAP liver as reduced size graft, with more accessible vascular orifices, has been the main strategy for Domino LDLT for FAP.^{24,25} Inomata et al. reported, in Domino LDLT, use of whole FAP liver without splitting or reducing in spite of technical difficulties in reconstruction of the vessels in adult recipients, as large liver grafts denote a better outcome for the recipient.^{26,27}



Figures 19.1A and B: Schematic representation of outflow reconstruction using a vascular graft from deceased donor IVC with both iliac veins in Domino LTX.²⁸ Vascular graft, is usually an IVC graft along with bifurcation of iliac veins is harvested. The end of iliac veins is anastomosed to the RHV and venoplasty site of MHV and LHV (RHV - Right hepatic vein, LHV - Left hepatic vein, MHV - Middle hepatic vein)

SURGICAL TECHNIQUES FOR USING THE WHOLE LIVER IN DOMINO RECIPIENT²⁷

Previously reported Domino LDLT for FAP have exclusively used partial livers, because either right or left lobes, can be handled just like partial liver grafts in regular LDLT. Evidently, splitting of whole FAP livers taken during LDLT theoretically permits the expansion of the donor pool. Inmate et al. reported two domino recipients who received the smaller left lobe graft after splitting, died post-transplantation. Hence, whole domino liver is a better option for the domino recipient. FAP patients generally have a smaller body size due to some degree of nutritional or digestive impairment and this may lead to smaller than average-sized livers. Smaller size of whole FAP livers might be one of the reasons for this mortality.

In most Domino LDLT, using only the right lobe after reduction is still the conventional method; however, if there is any concern about the graft volume for the second recipient, the whole liver can be safely used. Domino recipients are generally selected among candidates with more critical preoperative conditions, so splitting or reduction of an otherwise small liver may result in an inadequate sized graft for a domino recipient in a very poor condition.¹⁹

DONOR OPERATION IN THE FAP PATIENT (RECOVERY OF THE LIVER IN THE FAP PATIENT)

The advantage of using whole liver in domino recipient is due to the advantage of larger size of graft in a critically ill patient and better postoperative functional recovery. The IVC of the FAP patient is preserved as in a typical LDLT procedure; nonetheless, while respecting the priority of safety for the FAP patient, the transection site of the vessels of the FAP liver was modestly modified for use in the Domino LT.

In case of right lobe LDLT in FAP patient, the stump of the RHV of the FAP patient is left longer, but the MHV and LHV are transected as distal as possible so that a longer vascular cuff remained on the FAP liver. In case of left lobe is used, the length of the hepatic venous stump is treated in opposite fashion. The short and right-inferior hepatic veins (RIHV) is ligated and transected, but if its diameter larger than 7 mm, then it is preserved for a possible reconstruction in the recipient operation. If the PV of the partial graft for the FAP patient had multiple orifices, then the PV of the FAP liver is transected distal to the bifurcation of the left and right branch. However, if the PV of the partial liver graft had a single orifice, then the PV of the FAP liver is transected just proximal to the bifurcation. The HA of the FAP liver is transected distal to the branching of the proper HA in all the cases;

however, as in the case of the hepatic vein, the transection site is modified modestly according to the partial liver graft intended for the FAP patient with the aim of assisting the Domino LTX while ensuring the safety of the original LDLT.

When multiple biliary orifices were expected in the partial liver graft for the FAP patient, FAP patient's bile duct had to be transected relatively distal in order to secure multiple orifices for duct-to-duct reconstruction. However, in cases with a single bile duct in the partial liver graft, the common hepatic duct of the FAP liver was transected to leave a single orifice. Duct-to-duct reconstruction was preferred for FAP recipients as well as for all other LDLT recipients in our center because it is a safe option with a lower probability of bile leak or life-threatening peritonitis in the immediate post-operative period, than hepatico-jejunostomy. Neither a veno-venous bypass nor a temporary portocaval shunt was used because the complete PV clamping time was within 30 min, and it did not represent a risk nor cause circulatory instability in the FAP patient.²⁷ The explanted FAP liver was perfused with UW/HTK solution via the PV and was preserved in the same solution. If the orifices of the middle and the left hepatic veins were separated, they were unified by venoplasty in the back-table before implantation into the domino recipient.

DOMINO TRANSPLANTATION PROCEDURE IN THE SECOND RECIPIENT

After total hepatectomy of the domino recipient is performed, the FAP liver is put into the abdominal cavity and vascular reconstruction initiated; reconstruction of the hepatic veins is performed first and then followed by the PV anastomosis before reperfusion. Along with an effort to obtain long RHV stumps in the domino recipient, the lateral wall of the IVC around the RHV is dissected for better mobility of the RHV stump. The most difficult part of Domino LTX using the whole FAP liver without the retrohepatic vena cava is the reconstruction of the hepatic veins, especially the RHV. The difficulty consists in obtaining a suitable operative field for the reconstruction, because the relatively short hepatic veins are hidden under the liver parenchyma. Extensive mobilization of the IVC wall around the RHV of the domino recipient is essential to facilitate reconstruction.²⁷

Reconstruction of the hepatic veins began with the anastomosis RHV of FAP liver and recipient's RHV in an end-to-end fashion followed by the common trunk MHV + LHV stump of the FAP liver the recipient the unified trunk of MHV + LHV of the recipient in an end-to-end fashion. Then PV is anastomosed without difficulty in an end-to-end fashion, after which the graft liver is

reperfused before microsurgical reconstruction of the HA. If there is PV thrombus, it can be reconstructed by a cryopreserved jumping graft. Most of the FAP livers have two or more HA stumps. The MHA is always ligated. RHA and LHA are reconstructed separately or a simple back-table procedure justifying single HA reconstruction. For biliary reconstruction, duct-to-duct anastomosis is primarily considered, but if it is not possible, reconstruction by Roux-en-Y Hepaticojejunostomy with or without stent.²⁷

Various possible options for Domino LTX in living donors²⁴

A. Donor	→ B. Liver from FAP patient	C. Domino recipient
Donor	→ LLG	Whole liver
Donor	→ LLG	Split liver
Donor	→ LLG	RLG
Donor	LLG as APOLT	LLG
Donor	LLG as APOLT	RLG 2nd Transplantation

Temporary auxiliary partial orthotopic liver transplantation (APOLT) is possible for patients with metabolic liver disease but right lobe transplantation for metabolic liver disease is not preferred, keeping in view of donor safety.

In Domino recipients, the surgical procedure is technically demanding due to the advanced stages of the recipient's original disease and the relative difficulty of the vessel reconstruction. Prolonged cold ischemia time (CIT) than usual LDLT as the domino recipient operation routinely started after the FAP liver is taken from the FAP patient. The warm ischemia time is also longer than usual LDLT because of the complicated vascular reconstruction. Hashikura et al. described the possible options Domino LTX in living donors focusing more on the left lobe to be used in the 1st recipient as shown in the flow chart. Because temporary auxiliary partial orthotopic liver transplantation is feasible for patients with FAP patients, transplantation using the right liver for FAP is invalid from the viewpoint of donor. With careful decision-making during the procedure, such as where to divide the vessels in the FAP patients, Domino LTX may help address the shortage of liver grafts.²⁷

Inomata et al. reported 2 cases of domino split liver transplantation. They used left lobe graft for the FAP recipient. Domino split-LTX after a LRLT of a patient with FAP proved to be successful without apparent short-term risks and appears to be a promising option for expansion of the donor pool for critically ill recipients on the waiting list for DDLT.

REFERENCES

1. Azoulay D, Samuel D, Bismuth H, et al. Domino liver transplants for metabolic disorders: Experience with familial amyloidotic polyneuropathy. *J Am Coll Surg* 1999;189:584-93.
2. Furtado A, Tome L, Oliveira FJ, et al. Sequential liver transplantation. *Transplant Proc* 1997;29:467-68.
3. Monterio E, Perdigoto R, et al. Liver transplantation for familial amyloid polyneuropathy. *Hepatogastroenterol* 1998;45:1375-80.
4. V Muny'tiz, P Ramy'rez, R Robles, sequential (Domino) liver transplantation in familial amyloidotic polyneuropathy type II. *Transplant Proceed* 2002;34:309.
5. Parrilla P, Andreu F, Ramirez P, et al. Transplantation 1994;57:473.
6. Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med* 1997;336:466-73.
7. Olofsson B-O. Cardiac involvement in familial amyloidosis with polyneuropathy. *Int J Cardiol* 1983;4:71-73.
8. de Freitas A. The heart in Portuguese amyloidosis. *Postgrad Med J* 1986;62:601-05.
9. Steen L, Ek B. Familial amyloidosis with polyneuropathy. A long term follow up of 21 patients with special reference to gastrointestinal symptoms. *Acta Med Scand* 1984;214:387-97.
10. Fonseca C, Ceia F, Carvalho A, et al. Assessment of autonomic dysfunction in familial amyloidotic polyneuropathy: A challenge *Neuromuscul Disord* 1996;6(suppl):S48A.
11. Ando E, Ando Y, Okamura R, et al. Ocular manifestations of familial amyloidotic polyneuropathy type I: Long term follow up. *Br J Ophthalmol* 1997;81:295-98.
12. Holmgren G, Haettner E, Nordenson I, et al. Homozygosity for the transthyretin-met 30-gene in two Swedish sibs with familial amyloidotic polyneuropathy. *Clin Genet* 1988;34:333-38.
13. Herlenius G, Wilczek HE, Larson M, et al. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: Results from the familial amyloidotic polyneuropathy world transplant registry. *Transplantation* 2004; 77(1):64-71.
14. Furtado A, Tome L, Oliveira FJ, et al. Sequential liver transplantation. *Transplant Proc* 1997;29:467-68.
15. Chuang DT, Shih VE, Scriver CR. Maple syrup urine disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, vol 2. New York: McGraw-Hill, 2002:1971-2005.
16. Strauss KA, Morton DH. Branched-chain ketoacyl dehydrogenase deficiency: maple syrup disease. *Curr Treat Options Neurol* 2003; 5:329-41.
17. A Khanna, M Hart, WL Nyhan, et al. Domino liver transplantation in maple syrup urine disease. *Liver transplantation* 2006; 12:876-82.
18. Nishida S, Pinna A, Verzaro R, et al. Domino liver transplantation with end-to-side infrahepatic vena cavocavostomy. *J Am Coll Surgeons* 2001;192:237-40.
19. Inomata Y, Nakamura T, et al. Domino split-liver transplantation from a living donor: Case reports of in situ and ex situ splitting. *Liver Transplant* 2001;7:150-53.

20. H Shokouh-Amiri M, Osama GA, Bagous WA, et al. Choice of surgical technique influences perioperative outcomes in liver transplantation. *Ann Surg* 2000;231:814-23.
21. Cabezuelo JB, Ramirez P, Acosta F, et al. Does the standard vs piggyback surgical technique affect the development of early acute renal failure after orthotopic liver transplantation? *Transplant Proc* 2003;35:1913-14.
22. Nicolas J, Singh G, Yuri G, et al. Caval preservation with reconstruction of the hepatic veins using caval-common iliac bifurcation graft for domino liver transplantation. *Liver transpl* 2006;12:324-25.
23. LF Pacheco-Moreira, M Enne de Oliveira, et al. A new technical option for domino liver transplantation. *Liver Transplantation* 2003;9(6):632-33.
24. Y Hashikura, T Ikegami, Y Nakazawa, K, et al. Domino liver transplantation in living donors. *Transplant Proceed* 2005; 37:1076-78.
25. Nishizaki T, Kishikawa Y, Yoshizumi T, et al. Domino liver transplantation from a living related donor. *Transplantation* 2000; 70:1236-39.
26. Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation* 1999;67:321-27.
27. Y Inomataa, ME Zeledo' na, et al. Whole-liver graft without the retrohepatic inferior vena cava for sequential (Domino) living donor liver transplantation. *Am J of Transplant* 2007;7:1629-32.
28. CM Lacerda, LEC Miranda, AG Amorim, et al. Reconstruction of venous outflow of domino liver graft using deceased donor iliac/cava veins. *Transplant Proceed* 2008;40:811-13.

Postoperative Care and Immunosuppression

INTRODUCTION

Every post-transplant patient is a critical patient and patient is kept in ICU for 3-5 days. It is always better to have a separate ICU for liver transplantation patients to reduce the possibility of cross infections from other patients. Each patient should have a closed room in the ICU with a specialized nurse trained in transplantation, catered for each patient. But this is possible only in high volume centers. Postoperative protocols, monitoring and care of the patient vary from center to center.

GENERAL CARE DURING POST-TRANSPLANTATION PERIOD

Respiratory Care

Patient will be on ventilator for 8-12 hours following transplantation and gradual weaning is started after 6-8 hours keeping a close watch on arterial blood gas analysis. Avoid sedation till extubation. Breathing exercises, incentive spirometry are carried out after extubation. Fluid overload and pulmonary edema should be avoided. Right sided pleural effusion is a common problem, treated with diuretics and albumin, if no response, pig tail drainage is alternative option. Improvement is monitored by daily chest X-ray.

Monitoring of Vital Signs

One hourly (1st 48 hours) monitoring of:
Pulse, BP, respiration, temperature, O₂ saturation, CVP, Pulmonary artery pressure (PAP) and continuous cardiac output (CCO), SVO₂ and intake/output chart.

Care of liver transplant patient in ICU Postoperative investigation protocols in liver transplant ICU

8 to 12 hourly:

Complete hemogram	Coagulation profile:
Hb%, Hct, Diff Count	PT, APTT, INR, Fibrinogen level
(% of Bands)	
TWBC, TRBC, Platelet count,	
MCV, MCH, MCHC	Blood sugar (F and PP)
LFT: S. bilirubin, AST, ALT	Urine analysis and Sp. gravity
RFT: BUN, S.Creatinine	
Serum electrolytes: Na ⁺ , K ⁺ , Cl ⁻	

Once a day

Total protein, albumin, globulin, Alk. ph, GGT, Ammonia
Ca²⁺, Mg²⁺, Phosphorus, Serum amylase, Lipase,
Arterial blood gas analysis, CRP
Coagulation parameters: Antithrombin III, FDP and D-Dimer
Chest X-ray
Cultures: Sputum, blood, drain fluid, urine, pleural fluid (if any),
CVP tip, Swan ganz tip and fungal culture(fungal infection?)
Immunosuppression levels: CsA/Tacrolimus trough level
Immunological studies #:
T-CD₃, B-CD₁₉,
CD₄ T-cell and CD₈ T-cell
C3 and C4 levels
IgG and IgM titer*

Once a week:

HBV infection: HBsAg and Anti HBsAb (if HBV +ve)
CMV infection: CMV IgG and IgM or CMV antigen
EBV infection: EBV IgG and IgM
AFP (only in HCC patients)

(*ABO incompatible liver transplantation-once daily for 7 days)

# Parameter	Normal value (%)
T-CD ₃	49.9-84.7
B-CD ₁₉	7.8-22.8
CD ₄ T-cells	23-53
CD ₈ T-cells	19-49
CD ₄ /CD ₈	0.59-49
C3	90-180 mg/dl
C4	10-40 mg/dl

Post-transplant immunosuppression

Corticosteroids: Methylprednisolone, IV form for the first 7 days and later changed to oral Prednisolone. **Steroids are continued for 3-6 months** in different transplant programs. Presently, early withdrawal of steroids after 3 months is followed by some centers, particularly in HCC and HCV patients. In other patients continued for 6 months.

Day of Transplantation: 20 mg/kg IV, intraoperatively (in HCV patients intraoperative steroids are avoided)

Post-transplant		
1st Day - 3 mg/kg	2nd Day - 2.5 mg/kg	3rd Day - 2 mg/kg
4th Day - 1.5 mg/kg	5th Day - 1.5 mg/day	6th Day - 1 mg/kg
7th Day - 0.5 mg/kg	10th Day - 0.35 mg/kg	14th Day - 0.3 mg/kg
From 3rd week to end of 1st month: 0.25 mg/day		
2nd Month: 0.25 mg/day	3rd Month: 0.13 mg/day	
4th and 5th Months: 0.13 mg/day	6th Month: 0.06 mg/day	

Induction therapy with anti-Interleukin-2 receptor antibodies: Not routinely used in all transplant programs (expensive). Usually used in pediatric transplants and in adult recipients with preoperative poor renal function (allows delayed use of CINs). When induction therapy with IL-2 receptors are used, then other immunosuppression like steroids may be given at a lower dosage in early post-transplant period and initiation of CINs can be delayed.

Basiliximab (Simulect—Chimeric anti-IL-2 receptor monoclonal Ab): Dose—20 mg within 6 hrs of reperfusion and on day 4 of post-transplantation. (or)

Daclizumab (Zenapax—Humanized anti-IL-2 receptor monoclonal Ab): Dose—1 mg/kg once in every 14 days for 5 doses.

Calcineurin inhibitors (CINs): Tacrolimus/Cyclosporine

Tacrolimus / FK-506: Most commonly used drug, started within 24 hours of transplantation, at a dose of 2 µg/kg/hour IV and dose adjusted according to trough levels, later shifted to oral form. **Cyclosporine A:** Mostly replaced by tacrolimus and used as 2nd option in liver transplantation.

Trough levels of calcineurin inhibitors⁶

Time	Tacrolimus (ng/ml) (Prograf-BID/Advagraf-QID)	Cyclosporine (ng/ml) (BID)
1st week:	10-15	300-350
2nd week to 1st month:	10-12	200-300
1st to 3rd month:	8-10	150-250
>3 months:	6-8	100-200
>6 months:	~ 5	100-150

Monitor trough level and for nephrotoxicity and neurotoxicity

Antimetabolites: MMF and Azathioprine

Mycophenolate Mofetil (MMF): Usually started in the first week (usually on the 1st or 2nd postoperative day) of transplantation in combination with CINs. Dose: 250 to 750 mg BID depending upon the side effects. Some centers do not use it routinely and reserve it for specific indications.

Azathioprine: Dose 1-2 mg/kg/day. It is an alternative to MMF. Less frequently used. Used for short period. It is also used in recurrent autoimmune hepatitis.

Sirolimus: Starting dose of 5-10 mg/day followed by 1-5 mg/day to maintain trough levels of 5-10 ng/ml. Used when patient is intolerant to CINs and/or antimetabolites. It is usually avoided in the first 3 months of transplantation to avoid hepatic arterial complications. Used when the patient had high creatinine (renal sparing effect) due to CINs and in recipients of HCC (antitumor effect). It can be used in combination with MMF, replacing CINs. Trough level is monitored for sirolimus.
(Immunosuppressive protocols vary from center to center)

Postural Changes

Usually started after 24 hours in DDLT. In LDLT/split liver with small graft size, early postural changes may alter the outflow of allograft.

Patient Controlled Analgesia (PCA)

This method uses a computerized pump, which is controlled by the patient through a hand-held button that is connected to the machine. The pump usually delivers medications in small regular doses, and it can be programmed to issue a large initial dose and then a steady, even flow. When the patient feels the need for medication, the patient presses a button similar to a nurse call button. When this button is pressed, usually a beep is heard, indicating that the pump is working properly and that the button was pressed correctly. The pump delivers the medication through an intravenous line. The medications most commonly used in PCA pumps are synthetic, opium-like pain-relievers (opioids), usually Morphine and Meperidine (Demerol). Important aspect of PCA is patient education. If the patient is unable to push the PCA button (due to illness or altered sensorium), either the basal rate must be emphasized or nursing staff is instructed to assess and administer the PCA dose as needed. Naloxone is generally reserved for patients who are beginning to show signs of respiratory depression or hemodynamic compromise, usually associated with bradycardia.

Continuous Infusion Analgesia

Other methods of analgesia are by using Fentanyl 1 0.05 mg/ml/hour continuous infusion in early postoperative period.

Nasogastric Tube

Nasogastric tube is removed in 24 hours.

Foley's Catheter

Foley's catheter is removed in 24-72 hours depending upon the patient improvement.

Arterial Line, Central Line and Swan Ganz Catheters

Arterial line, central line and Swan Ganz catheters are removed in 24-72 hours. One IV line is kept patent for at least 3-5 days. Swan Ganz catheter is not routinely used in all centers.

Volume Replacement

Volume replacement is monitored by input/output chart, CVP and PAP. If hypotension persists, optimization of

blood pressure can be achieved with a number of inotropes and vasopressors, both catecholamine and non-catecholamine. The following table lists commonly used vasopressors, along with dose (adjusted according to the need).

Drug	Dose
• Dopamine	3-25 mcg/kg/min
• Epinephrine	1-10 mcg/min
• Norepinephrine	1-30 mcg/min
• Phenylephrine	40-200 mcg/min
• Vasopressin	0.01-0.04 units/min

Surgical Drain Care

Output from the drains is monitored 1 hourly. Nature of the fluid like bloody or bilious has significant importance. Excessive blood in the immediate postoperative period indicates ongoing bleeding. Bile leak also carefully recognised.

Three suction (JP drains) drains usually left in the recipient:

- Left subcoastal area around the cut surface of the allograft (1st drain to be removed)
- Right subcoastal area
- Right subhepatic area

Drains b and c are removed later depending on the drain output and condition of the patients. Fluid accumulation is common on the cut surface of the liver in the form of clear fluid or minor bile leak after the removal of left subcoastal drain. In such cases, pigtail drainage is advised. In case of major bile leak ERCP and stent placement is considered (discussed in detail later).

T-Tube

Use of T-tube is gradually decreasing in the liver transplant programmes. T-tube is kept for 3-6 months in post-transplant period.

Ascites

It is a common problem in post-transplant patients particularly HCV +ve recipients. Sometimes it is difficult to control post-transplant ascites in HCV patients. Use of diuretics, adequate replacement of albumin, fluid and electrolytes is important in cases of excessive output. USG tapping also helpful if the drains are already removed. In case of chylous ascites, fat free diet for 6-8 weeks will control ascites due to spontaneous closure of lymphatics around perihilar and retroperitoneal area. Somatostatins and total parenteral nutrition are used in intractable chylous ascites.

Dressing of the Wound

Dressing of the wound is done once daily basis, but many patients have ascities and leak from the drain site make the necessity to change the dressing more than once in early transplant period.

Antibiotics

Prophylactic antibiotics are given for 5-7 days. Aminoglycosides are preferably avoided in early post-transplant period. Anaerobic cover with metronidazole is required if there is evidence of anaerobic infection.

1st line antibiotics:

- Penicillin and cephalosporin group are the 1st line antibiotics.
- **Penicillin group:** Ampicillin 1 gm IV 6 hourly
- **Cephalosporin group:** Cefotaxime or cefipime or ceftazidime 1 gm IV 8 hourly
- Ampicillin-salbutam combinations can be used.

2nd line antibiotics:

- Imipenem (250 mg)+ Cislatin (250 mg): 500 mg BID
- Vancomycin (in case of MRSA): 7.5 mg/kg IV or Oral - 500 mg tablets 6 or 8 hourly

Initially a broad spectrum group of antibiotics are selected postoperatively; later antibiotics are changed according to the sensitivity reports, in case of evidence of infection from culture.

Analgesics

In our center routine Fentanyl 0.05 mg/ml/hour is used in early postoperative period. Later shifted to oral dosage once the patient tolerate orally.

Proton Pump Inhibitors

Pantoprazole 40 mg IV infusion BID. Others like Omeprazole, Lansoprazole, Esomeprazole and Rabeprazole may also be used. They are continued for 6-8 weeks.

Albumin

Hypoalbuminemia is common in liver transplantation, corrected by 20% albumin IV infusion 1-2 bottles 6-8 hourly so as to maintain the minimum albumin level of 3.5 mg/dl.

Blood Sugar Control

Blood sugar is maintained around 6-8 mmol/L to reduce postoperative infection. Patients with previous h/o DM require aggressive blood. In early postoperative period, insulin is required. Once the patient starts oral diet, shifted

to OHAs are started. If the blood sugar control is not adequate with OHAs, then insulin may be added. Rosiglitazone with/without sulfonylureas is the standard treatment. Pioglitazone is an alternative choice to rosiglitazone.

ANTIFUNGAL TREATMENT

PROPHYLAXIS

Fungal infection should be kept always in mind in patients who are on renal replacement therapy. Routine prophylaxis is indicated in all the patients for 3-4 weeks. Fluconazole is commonly used. Various antifungal agents and their doses are mentioned below:

Mycostatin (Nystatin): 5 ml/6 hourly for prophylaxis (Each ml = 100,000 IU)

Fluconazole: 200 mg/day IV

Mycofungin: 50 mg/day IV

Amphotericin B 5-10 mg/day IV, increased gradually to maximum of 50 mg/day. Its use is avoided in case of nephrotoxicity.

In case of evidence of fungal infection like invasive pulmonary aspergillosis, any one of the following drugs can be used:

Liposomal Amphotericin B: 3-5 mg/kg/day IV

Voriconazole: 6 mg/kg IV 12 hourly followed by 4 mg/kg IV thereafter.

Fluconazole: 400 mg/day IV

Caspofungin sodium: 70 mg IV on day 1, followed by 50 mg/day IV thereafter

Mycofungin: 100-150 mg/day IV, dose not yet established

Posaconazole: 200 mg QID initially followed by 400 mg BID

Itraconazole: 200 mg IV BID followed by 200 mg IV once daily

CYTOMEGALOVIRUS PROPHYLAXIS

Routine CMV Prophylaxis

Routine CMV prophylaxis to all CMV D+/R- liver transplant recipients. Ganciclovir: 5 mg/kg IV daily (dose adjusted according to renal function). When the patient is able to tolerate oral medications, antiviral prophylaxis with oral ganciclovir, 1 gm 3 times/day or oral Valganciclovir, 900 mg QD, continued for 90-100 days after transplantation.

Pre-emptive Care

Universal antiviral therapy is not administered to all patients following LTX. Instead, weekly surveillance for

first 4-6 weeks is performed for CMV, using markers such as pp65 antigenemia and Ig G and Ig M titers by quantitative polymerase chain reaction (PCR) assays. Antiviral therapy is initiated only when CMV is detected and subsequently discontinued when the assay is negative. It usually takes 2-4 weeks for the disappearance of antigenemia.

Gancyclovir: 5 mg /kg twice daily IV for 2-4 weeks

Valgancyclovir: Oral dose: 900 mg twice daily

Pneumocystis Carinii Prophylaxis

Pneumocystis carinii prophylaxis is started on/after postoperative day 7. Cotrimoxazole (Trimethoprim + sulfamethoxazole) 80/400 mg 3 times a week (children: 0.05 g/kg/day) or Pentamidine inhalation once in every 2 to 4 weeks are used. Atovaquone is an alternative for PCP prophylaxis at a dose of 750 to 1,500 mg/day. Prophylaxis continued for one year.

Electrolyte Correction

Imbalance in electrolytes particularly Na^+ , K^+ , Cl^- , Ca^{2+} , Mg^{2+} and Ph^{2+} are closely monitored. Sodium and potassium are more commonly fluctuate in early postoperative period, particularly in patients with poor renal function.

In **Asian countries**, use of LMWH, PGE1 and Gabexate mesylate is routine in many transplant programs during early post-transplant period for all LDLTs to avoid thrombotic complications.

Low Molecular Weight Heparin (LMWH)

50 Units/kg/day is given postoperatively as continuous infusion as a prophylactic measure to prevent vascular thrombotic complications. This has important role in pediatric patients where the incidence of hepatic artery thrombosis is more common. PT, ACT and APTT is monitoring closely in patients on heparin and dose is adjusted accordingly. PT at 15-20 sec and ACT (activated clotting time) at 150-200 sec is maintained. After 7 days, heparin is discontinued and dipyridamole are used (Dose Adults: 300 mg/kg/day, children 4 mg/kg/day) for 1 to 3 months depending on the center protocols. Platelet counts are closely monitored and anticoagulation therapy is withheld if the platelet count is below 30-50,000/ mm^3 .

Heparin induced thrombocytopenia (HIT) is an adverse immune-mediated drug reaction, resulting in a platelet count decrease of >50% within 5 to 10 days after heparin administration. HIT is associated with paradoxical thrombosis during heparinization, such as

deep vein thrombosis, pulmonary embolism, and arterial thrombosis.¹³ HIT is caused by the platelet factor 4/heparin-reactive antibody. Heparin produces mild platelet activation, resulting in the release of platelet factor 4 from platelet alpha-granules and the formation of immunogenic platelet factor 4 and heparin complexes. HIT antibodies, B lymphocyte-generated immunoglobulins that recognize multimolecular complexes of heparin and platelet factor 4, strongly activate platelets, monocytes, and endothelial cells, which accelerate thrombin generation, leading to the development of HIT.¹⁴ Kaneko et al. reported that HIT is uncommon following liver transplantation. But careful monitoring of platelet counts and possible thrombosis is necessary when heparin therapy is prolonged or patients have a history of heparin therapy.¹⁷

Prostaglandin E1 (PGE1)

Intravenous therapy with a prostaglandin E1 analogue (Alprostadil), dose: 0.5 $\mu\text{g/kg/h}$ or 0.01 $\mu\text{g/kg/min}$ seems to be effective in ameliorating ischemia-reperfusion injury to the hepatic allograft in patients with elevated arterial vascular resistance and early depressed graft function after liver transplantation. It is usually administered for 1-3 weeks.^{8,9}

Gabexate Mesylate (Foy)

It is given at a rate of 1 mg/kg/hour. Less commonly used.

Blood Components

Transfusion with FFP is needed, if the prothrombin time is more prolonged and vitamin K is added basing on the coagulation profile specifically INR. In some centers, routine use of FFP at a rate of 0.5-1.0 ml/kg/hour is standard practice. Platelet transfusion is required, if the platelet count goes down. There are no clear cut levels beyond which platelet transfusion should be given. However 20,000-30,000/ mm^3 may be taken as cut-off and platelet transfusion indicated below this level. Packed RBC is given so as to maintain the hemoglobin level around 10 gm%. The indication for transplantation, platelet transfusion, and red blood cell transfusion were identified as important risk factors predicting 1-year patient survival.¹⁸

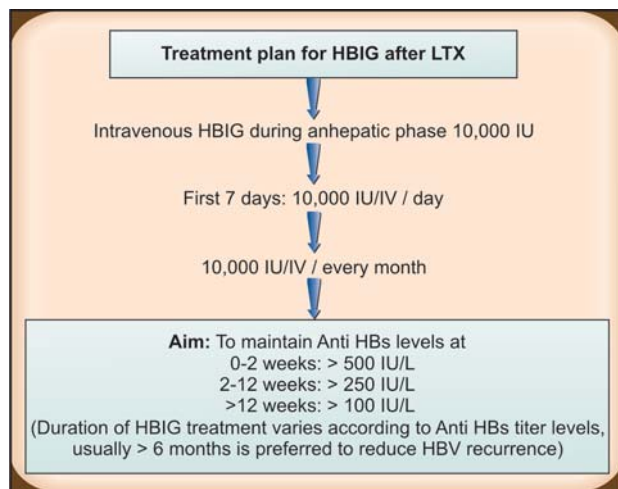
Nutrition

Early enteral nutrition is the golden rule in liver transplantation and commenced as per the advice of dietician.

ANTIVIRAL TREATMENT

HBV POSITIVE RECIPIENT

Aim is to maintain Anti Hbs Ab titer at least 100 IU/L at the end of 3 months



Lamivudine 100 mg /day started 3-4 weeks before transplantation in elective cases and continued post-operatively for long term. **Entecavir** (0.5 mg/day) now a days used as first line antiviral drug for HBV patients. **Adefovir dipivoxil** 10 mg/day is used in case of HBV mutants. Telbivudine is also another option.

Taiwan National Policy for HBV prophylaxis after LTX

HBIG (Hepatitis B immune globulin)*

Anhepatic phase	10,000 IU iv
Day 1-7	2,000 IU daily
Day 8-28 (1-3 weeks)	2,000 IU once a week for 3 weeks
2-12 months	2,000 IU once a month or 800 IU im

* Cost is an important factor while using HBIG. (Source: Lee PH, NTUH)

CORE ANTIBODY POSITIVE DONORS (HBV -ve RECIPIENT RECEIVING GRAFT FROM HBcAb +ve AND HBsAg -ve DONOR)

Post-transplant HBV prophylaxis depends on the HBV DNA status of donor and anti HBsAb titers of the recipient. In pre-transplant period anti HBsAb titers are checked in the recipient. If Anti HBsAb titers are very low or absence of antibody titers, recipient is immunised with 3 doses of HBV recombinant vaccine at an interval of 1 month. During anhepatic phase 2000 U/kg HBIG

is given intravenously. Lamivudine/entecavir is started in post-transplant period. Anti HbsAb titers are usually maintained at least 200 U/L by once a monthly dosage of HBIG 2000 units IV for longer time. Cost factor is a concern with HBIG therapy. So many centers stop HBIG after 6 months of maintenance of adequate Anti HbsAb level. In post-transplant period, if the Anti HBsAb titers are high (>1000 IU/L) for a long time, antiviral treatment may be discontinued. Exact duration of antiviral treatment in such recipients is a matter of debate.

HCV POSITIVE RECIPIENT

Early initiation of HCV antiviral treatment is not recommended. HCV treatment is started in 4-8 weeks depending upon the clinical and laboratory evidence of HCV recurrence. Interferon and ribavarin combination is recommended. Treatment is discussed in detail in recurrent diseases after liver transplantation. According to National Taiwan Policy, fibrosis score F1 (Ishak score) on liver biopsy is an indication for treatment hepatitis C infection.

Pegylated interferon (Peg.IFN) α-2a: 180 µg once weekly, subcut. or Pegylated Interferon α-2b 1-1.5 µg/kg/week, subcutaneously or in combination with oral ribavirin 800-1200 mg/day. Duration of treatment is for 48 weeks for genotype 1 and 4, and for other upto 24 weeks depending upon the patient tolerance. Ribavirin is continued for another 6 months after discontinuation of interferon.

DUS

Doppler ultrasound is routinely done everyday in the first week followed by once in 2 days in the 2nd week to verify the graft flow and for early diagnosis of:

- Vascular (HA/PV) thrombosis
- Bilioma/intra-abdominal collection
- Signs of rejection
- Biliary obstruction.

Role of RRT (Renal Replacement Therapy)

Poor renal function is a common problem in early post-transplant period. Early initiation of RRT in the form of CVVHD or hemodialysis is the key to success. CVVHD is preferred as the most of the patients requiring RRT are hemodynamically unstable. Intermittent hemodialysis can be used in stable patients.

UDCA

In case of cholestasis UDCA 8-10 mg/kg in 2-3 divided doses given for 6 months to 1 year.

Dry Cough, Constipation and Insomnia

Dry cough, constipation and insomnia are common problems in ICU patients, which are treated symptomatically with cough suppressants, laxatives, and mild sedation respectively.

Multivitamin Infusions

Multivitamin infusions are given in early post transplant period.

Psychological Support

Psychological to the patient and family is very important in early post-transplant period. Nurse coordinators interacts along with the ICU staff to support the both the patient and family. Psychiatrist opinion is needed sometimes. ICU psychosis is a problem in patients who stay in ICU for long time. But before diagnosing it, CINs neurotoxicity is to be ruled out. Opinion of psychiatrist is needed in such cases.

Postoperative Bleeding

Approximately 5% of patients during early post-transplant period need re-exploration to control bleeding. This decision depends on excessive blood in the drains, hemodynamic instability and drop in hemoglobin level. Other indication for re-exploration is early HAT or PVT.

Bowel Perforation

Bowel perforation is an infrequent complication and should be kept in mind particularly in pediatric patients. Pyrexia and a sudden increase in heart rate, abdominal distension, free gas in abdomen may signal perforation.

Liver Biopsy

Liver biopsy is avoided in early postoperative period, but may be needed to confirm the diagnosis in controversial cases.

Close monitoring of liver function is critical to diagnose PNF, DGF, early infection, rejection, HA/PV/HV thrombosis. Close monitoring of graft function and regeneration, immunosuppression levels and medical compliance every 3-4 weeks until the corticosteroids are completely stopped (6 months).

Discharge

Patient is usually discharged in the end of 2nd week, but the patient should stay close to the hospital for another 3-4 weeks.

POST-TRANSPLANT FOLLOW-UP

The follow-up OPD visits after discharge from the hospital vary from 2 weeks to 3 months. During the first 3 months after transplantation the recipient can be reviewed in OPD once in 2 weeks, later once a monthly visit is usually followed. Patients who are doing well after transplantation with good compliance can be followed in OPD once in 2-3 months. Follow-up is for life long. OPD follow-up visits are always flexible depending upon the clinical status of the recipients.

Advice to the patient at the time of discharge**General care**

- Regular visit to transplant OPD as per the advice
- Regular use of medication without any missing doses
- Bring update list to OPD.
- Frequent hand washing and maintenance of hygiene to avoid infection
- General abdominal wound and drain care
- Check body weight once a week
- Temperature measurement everyday
- Return to work after 2-3 months, not to lift weights for 3 months
- Heavy vehicle driving restricted for 2 months
- Return to sexual activity after 1-2 months
- Use of contraceptives and birth control measures in females
- Avoid partially cooked foods.

Report to transplant OPD in any of the signs and symptoms

- Fatigue/weakness
- Fever $> 100^{\circ}\text{F} \pm$ chills
- Vomiting or diarrhea
- Itching/Jaundice/clay colored stool
- Wound discharge or pain
- Right upper quadrant pain
- Cough $\pm$ expectoration
- Urinary symptoms like dysurea/frequency.

COMMON IMMUNOSUPPRESSIVE DRUGS USED IN LTX

Because the majority of acute rejections occur within the first few months after liver transplantation, most centers try to taper off steroids and minimize maintenance trough levels of calcineurin inhibitors within the first 6 months after LTX.^{1,2} Recently, more rapid steroid withdrawal programs (within 2 week) were introduced.^{3,4} The aim of steroid withdrawal is to reduce long-term complications, such as diabetes mellitus, hyperlipidemia, and opportunistic infections. The shorter steroid regimen increases the possibility of late-onset acute rejection, which might result in graft loss and serious morbidity.⁵

TACROLIMUS / FK-506

Available as **Prograf**: Given as twice daily dose and **Advagraf**: Prolonged release tablets, given as once daily dose.

PROGRAF

Prograf: available as 0.5 mg, 1 mg, and 5 mg capsules. Injections are available at 5 mg/ml (equivalent of 5 mg of anhydrous tacrolimus per ml) diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to decreased stability and the potential for extraction of phthalates. Tacrolimus injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g. drugs solutions such as ganciclovir or acyclovir).

Laboratory investigations during post-transplant follow up during OPD visit

Routine: (During every visit)

Hb, Hematocrit, Differential Count (% of Bands)
TWBC, TRBC, Platelet count, MCV, MCH, MCHC
Liver function tests: S.Bilirubin, AST, ALT
Total protein, albumin, globulin, Alk. pH, GGT, LDH
Coagulation profile: PT, APTT, INR,
Renal function tests: BUN, S.Creatinine
Serum electrolytes: Na⁺, K⁺, Cl⁻
Blood sugar (AC and PC)
Cholesterol, Triglyceride
Urine analysis and Sp. gravity
Serum amylase, Lipase,
Immunosuppression levels: Cs A /Tacrolimus/sirolimus trough level

Specific

HBV positive recipients: Anti HbsAb (during every visit)

HBsAg, HBeAg and Anti HBeAb (once in 3 months)

HBV DNA and Mutants (once in 3-6 months)

HCV + recipients: HCV RNA once in 3-6 months

HCC patients: AFP (during every visit)

Ultrasonography: Once in every 3-6 months.

(HCC +ve recipients: once in 3 months)

CMV infection: CMV IgG and IgM (depending on the clinical status)

EBV infection: EBV IgG and IgM (depending on the clinical status)

ABO incompatible LTX patients:

Immunological studies (during every visit)

T-CD₃, B-CD₁₉, CD₄ T-cell and CD₈ T-cell

IgG and IgM titer (during every visit)

AIH/PBC: Antinuclear antibody/Antimitochondrial antibody (Once in 6 months)

Recipients with **Diabetes mellitus:** HbA1c (once in 3-6 months).

ADVAGRAF

Approved for use by European Union (EU). The EU approval of Advagraf is based on the results of Phase II trials in liver, kidney and heart transplant patients (n=613) and a phase III trial 4 (n=638). Further shorter studies were also carried out in 119 kidney transplant patients and 129 liver transplant patients, looking at how Advagraf is absorbed by the body in comparison to Prograf. These studies have confirmed the safety and efficacy of once-daily Advagraf to be similar to that of twice-daily Prograf. It is a prolonged-released capsule containing tacrolimus (0.5 mg: yellow and orange; 1 mg: white and orange; 5 mg: greyish-red and orange). 'Prolonged-release' means that tacrolimus is released slowly from the capsule over a few hours. In liver transplant, the starting dose is 0.10 to 0.20 mg/kg.

Tacrolimus should not be taken with grapefruit or grapefruit juice as this may cause blood levels of tacrolimus to increase. It may be taken with food or on an empty stomach, but one should try to be consistent (e.g. always with food or always on an empty stomach). Capsules are stored at 59° to 86°F and injections are stored at 41° to 77°F.

CYCLOSPORINE

Cyclosporine is available as **Sandimmune** available as soft gelatin capsules: 25 mg and 100 mg, oral solution (50 ml) and injection form (5 ml, 50 mg/ml). **Neoral** available as 25 mg, 50 mg and 100 mg capsules, oral solution (50 ml, 100 mg/ml). It may be taken on an empty stomach or with food to reduce stomach irritation. The capsules should be swallowed whole and not opened, crushed or chewed. It should not be mixed with grape juice.

MYCOPHENOLATE MOFETIL

Available as **Cellcept** (MMF) and **Myfortic** (mycophenolate sodium).

CELLCEPT

Cellcept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/ml mycophenolate mofetil. Cellcept intravenous is the hydrochloride salt of mycophenolate mofetil. Cellcept Intravenous is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of cellcept intravenous contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. Reconstitution and dilution with 5% Dextrose injection

yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL.

MYFORTIC

This is a form of delayed release tablets, available as 180 mg and 360 mg tablets. It is taken in an empty stomach, 1 hour before or 2 hours after food intake. Use of myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. 250 mg of MMF is equal to 180 mg of myfortic and 500 mg of MMF equal to 360 mg of Myfortic. Margaret et al²¹ reported that MMF is both effective and safe as add-on therapy to rescue liver grafts with steroid resistant rejection in children under CIN-based immunosuppressive regimens, with good long-term patient and graft outcome.

SIROLIMUS

Available as **Rapamune** as tablets, 1 mg, 2 mg and solution (1 mg/ml) Sirolimus is a second-generation immunosuppressive agent, which provides an alternative to standard immunosuppressive regimens. Voriconazole is contraindicated for use along with sirolimus.⁷ Side effects are hepatic artery thrombosis, graft loss and mortality. Hence, it is less commonly used in liver transplantation. The most notable and concerning adverse effect of sirolimus is hyperlipidemia, involving both hypercholesterolemia and hypertriglyceridemia, also causes pneumonitis.

Yang et al¹⁹ reported that sirolimus is a safe, effective replacement agent as primary immunosuppressive therapy following withdrawal of CNIs in liver transplant recipients with CNI-induced chronic nephrotoxicity. Nocera et al.²⁰ recently reported in his series of HCC patients, that sirolimus based immunosuppression is effective, even as monotherapy, in liver transplant patients without any increased risk for rejection. Sirolimus is seemed to be safe, with an acceptable side effect profile, as long as there was tight patient screening for predisposing factors to sirolimus related side effects, namely, are pre-existent dyslipidemia, anemia or low peripheral blood white cell or platelet counts. However, Large randomized trials investigating sirolimus use in HCC liver transplant patients is awaited.

AZATHIOPRINE

Azathioprine is available as **Imuran**; 50 mg tablet and 100 mg (as the sodium salt) for IV injection. Store at 59 to 77°F, in a sealed, light-resistant, container, avoid moisture. Always to be taken with food and is secreted in breast milk. It causes serious lowering of the white blood cell count, resulting in an increased risk of infections. This can reverse when the dose is reduced or temporarily discontinued. GI side effects are nausea, vomiting, and loss of appetite.

TOLERANCE

The literature research on tolerance is beset with contradiction and part of this confusion arises from the definition of tolerance. Perhaps from a clinician's point of view the long-term function of a graft without the need for maintenance immunosuppression would be a reasonable definition and tolerance could be looked upon rather like happiness, as something that we recognize when it is not present and there are varying degrees when it is present that are not always perceived. We found in kidney-allografted pigs that a 7-day course of high-dosage intravenous cyclosporine A could result in tolerance and this occurred in approximately 50% of animals when a gap of 48–72 hour was left after the first dose before the next six doses were given.¹⁰

TOLERANCE AND THE LIVER IN THE CLINIC

The spontaneous tolerance to liver grafts in some pigs and rodents without immunosuppression is not fully understood. However, a clinical experiment conducted on a number of Dr Starzl's patients showed that many years of 'operational tolerance' can occur after a successful liver graft following initial standard immunosuppression. Some patients stopped taking their drugs without telling their doctors. Others were taken off immunosuppression because of viral infections. A surprising number of patients continued to survive with good liver function for years.¹¹

Kyoto University¹² has developed protocol for withdrawal of immunosuppression based on the following criteria

1. 2 years or more passed after LTX.
2. Normal liver function tests.
3. No history of acute cellular rejection within 1 year.
4. No evidence of progressive bile duct damage on liver biopsy.

They succeeded in creating immune tolerance in 35 children out of 67. But to date, we cannot predict which patients can be safely weaned off immunosuppression.

GRAFT FUNCTION AND GRAFT REGENERATION IN RECIPIENT

POSTOPERATIVE EVALUATION OF GRAFT FUNCTION¹⁵

Serum total bilirubin, AST, ALT, PT, INR, serum albumin levels were examined postoperatively at 1 and 2 weeks as well as one, three and twelve months after LDLT. CT Scan is done at 1, 3 and 12 months to evaluate the liver regeneration and volume assessment. (**Figures 20.1 to 20.6** shows the graft regeneration and volumetry in a right lobe graft after one month of LTX).

Right lobe recipient's follow up after one month of transplantation (**Figures 20.1 to 20.6**).

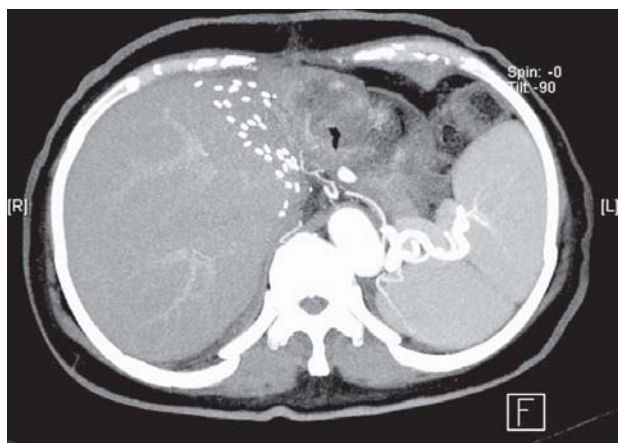


Figure 20.1: Right lobe graft with hemoclips on the cut surface

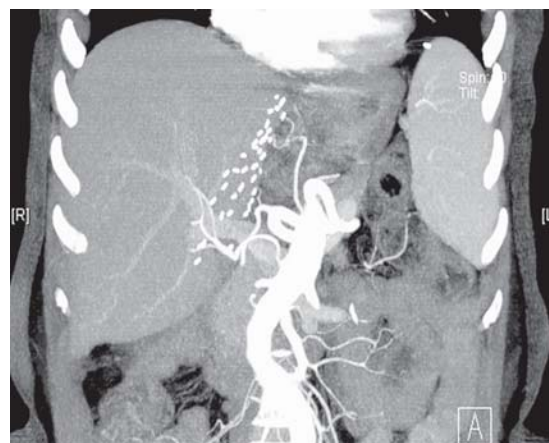


Figure 20.4: Arterial phase showing arterial anatomy (after 1 month)

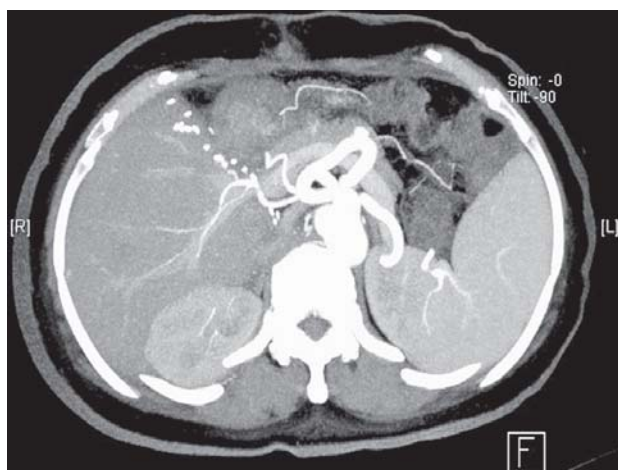


Figure 20.2: Arterial phase

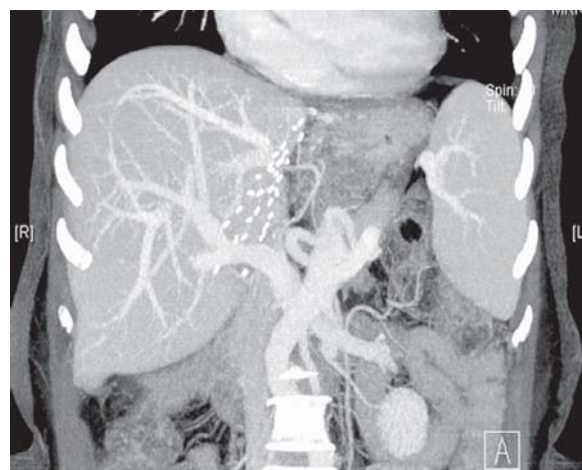


Figure 20.5: Both portal and hepatic veins are shown (after 1 month)

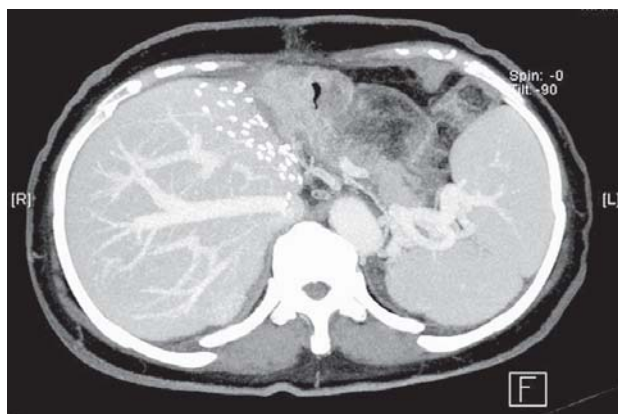


Figure 20.3: Venous phase showing portal venous anatomy (after 1 month)

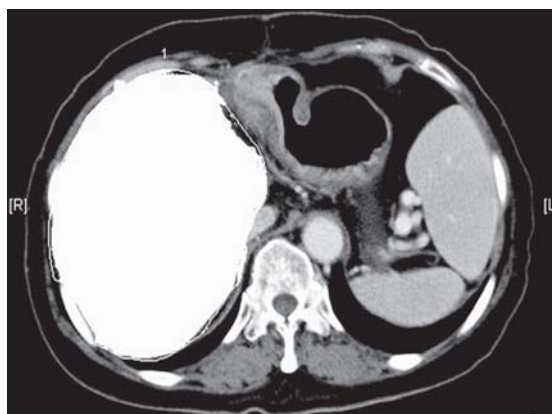


Figure 20.6: CT volumetry in a RLG recipient after one month

EVALUATION OF GRAFT REGENERATION¹⁵

The calculated GV itself and regeneration rate (RR) were compared between groups.

$$RR = \frac{GVn - GV0}{GV0} \times 100(\%)$$

[RR, regeneration rate; GV0, Initial graft volume measured just after harvesting (ml = mg); and GVn, volume of the graft on computed tomography at *n* months after LDLT (mL)]

Another index of graft regeneration was defined as the volume ratio to the recipient SLV, because regeneration of the graft size converged toward the SLV. The volume ratio of the whole graft to SLV at *n* months after LDLT was calculated as follows:

$$RSLVn = \frac{GVn}{SLVn} \times 100(\%)$$

(SLVn, SLV calculated at *n* months after LDLT; and RSLVn, volume ratio of the graft to the recipient SLV *n* months after LDLT).

REFERENCES

- Greig P, Lilly L, Scudamore C, et al. Early steroid withdrawal after liver transplantation: the Canadian tacrolimus versus microemulsion cyclosporine A trial: 1-year follow-up. *Liver Transpl* 2003; 9:587-95.
- Pirenne J, Aerts R, Koshiha T, et al. Steroid-free immunosuppression during and after liver transplantation—a 3-year follow-up report. *Clin Transplant* 2003;17:177-82.
- Pageaux GP, Calmus Y, Boillot O, et al. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. *Liver Transpl* 2004;10:1454-60.
- Boillot O, Mayer DA, Boudjema K, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: A large randomized clinical study. *Liver Transpl* 2005;11:61-67.
- Mazariegos GV, Reyes J, Starzl TE, et al. Weaning of immunosuppression in liver transplant recipients. *Transplantation* 1997;63:243-49.
- SJ Kim, KW Lee, DS Lee, et al. Randomized Trial of Tacrolimus Versus Cyclosporine in Steroid Withdrawal in Living Donor Renal Transplant Recipients *Transplant Proceed* 2004;36:2098-00.
- AS Mathis, NK Shah, GS Friedman. Combined use of sirolimus and voriconazole in renal transplantation: A report of two cases. *Transplant Proceed* 2004;36(9):2708-09.
- Kornberg A, Schotte U, Kupper B, et al. Impact of selective prostaglandin E1 treatment on graft perfusion and function after liver transplantation. *Hepatogastroenterology* 2004;51(56):526-31.
- Kornberg A, Grube T, Wagner T, et al. Differentiated therapy with prostaglandin E1 (alprostadil) after orthotopic liver transplantation: The usefulness of procalcitonin (PCT) and hepatic artery resistive index (RI) for the evaluation of early graft function and clinical course. *Clin Chem Lab Med* 2000;38(11):1177-80.
- Calne RY, Watson CJ, Brons IG, et al. Tolerance of porcine renal allografts induced by donor spleen cells and 7 days treatment of cyclosporine. *Transplantation* 1994;57:1433-35.
- Mazariegos GV, Reyes J, Marino I, et al. Risks and benefits of weaning immuno-suppression in liver transplant recipients: Longterm follow-up. *Trans Proc* 1997;29:1174-77.
- M Shimada, M Fuji, Y Morine, et al. Living donor liver transplantation: Present status and future prospective. *Journal of medical investigations* 2005;52:22-32.
- Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. *Br J Haematol* 2003;21:535.
- Warkentin TE, Sheppard JA, Moore JC, et al. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? *J Lab Clin Med* 2005;146:341.
- N Akamatsu, Y Sugawara, M Makuuchi, et al. Impact of Live Donor Age (>50) on Liver Transplantation. *Transplant Proceed* 2007;39:3189-93.
- J Viganò, S Gruttadauria, L Mandalà, et al. The role of basiliximab induction therapy in adult-to-adult living-related transplantation and deceased donor liver transplantation: A comparative retrospective analysis of a single-center series. *Transplant Proceed* 2008;40:1953-55.
- J Kaneko, Y Sugawara, Makuuchi M, et al. Heparin-Induced Thrombocytopenia After Liver Transplantation. *Transplant Proceed* 2008;40:1518-21.
- Ilona T, A Pereboom, Ton Lisman, et al. Platelets in Liver Transplantation: Friend or Foe? *Liver transplantation* 2008; 14:923-31.
- YJ Yang, DZ Chen, LX Li, et al. Sirolimus-based immunosuppressive therapy in liver transplant recipient with tacrolimus-related chronic renal insufficiency. *Transplant Proceed* 2008;40:1541-44.
- A Nocera, E Andorno, A Tagliamacco, et al. Sirolimus Therapy in Liver Transplant Patients: An Initial Experience at a Single Center. *Transplant Proceed* 2008;40:1950-52.
- Marion MAW, A Verma, M Rela, et al. Long-Term Outcome of Mycophenolate Mofetil Rescue Therapy for Resistant Acute Allograft Rejection in Pediatric Liver Transplant Recipients. *Liver transplantation* 2008;14:1303-08.

Immunosuppression Drugs

INTRODUCTION

Immunosuppression plays an important role in solid organ transplantation in patient and graft survival. 25-80% of patients present with acute cellular rejection¹ and 5-10% will develop chronic rejection in liver transplantation.² Adequate immunosuppression will control these episodes of rejection.

IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

Immunosuppression in liver transplantation is classified into three different phases:

- Induction (initial) phase
- Maintenance phase
- Treatment of rejection.

INDUCTION/INITIAL PHASE

It includes events immediately associated with implantation and reperfusion of the liver allograft. High level of immunosuppression is maintained during this phase. Goal of induction phase is to induce a state of acute immunologic nonresponsiveness or immunoparalysis to prevent early cell-mediated rejection. Initial immunosuppression therapy includes a combination of high dose glucocorticoids and calcineurin inhibitors to protect the allograft from acute cellular rejection (ACR) that is comparable with the protection achieved with induction antilymphocyte based therapy.³

Benefits of not using antilymphocyte therapy is to⁴

- Decrease in opportunistic infections
- Decrease the cost of therapy
- Lower incidence of post-transplant lymphoproliferative disease, (PTLD)
- Reserve this therapy for treatment for steroid-resistant rejection episodes.

MAINTENANCE PHASE

Change from induction therapy to maintenance immunosuppression therapy should be gradual. Calcineurin inhibitors (Cyclosporine and Tacrolimus) are usually the basis for the most of maintenance immunosuppression protocols. Trough level of maintenance immunosuppression is adjusted according to the needs of the patient like history of rejection in patient or underlying liver disease. Patients who experience frequent episodes of ACR are maintained on higher blood levels of immunosuppression for longer periods of time. On the other hand some patients do well with low blood levels of immunosuppression. So blood level and patient's immunological response to allograft varies from patient to patient. As patients show stable graft function without episodes of rejection, most transplant centers make every effort to gradually reduce and maintain low levels of immunosuppression to avoid immunosuppression related side effects and at the same time to avoid episodes of rejection. If necessary required modifications are made depending upon the side effects in the patients like neurotoxicity or nephrotoxicity (calcineurin-associated).^{5,6} Few patients have benefited from reduction in dose of calcineurin inhibitors or from switching to alternative drug of same group or treating with a different immunosuppressive agents.

TREATMENT OF REJECTION

Rejection in liver transplant is divided into 3 types (discussed in detail in respective chapters)

- Hyperacute rejection
- Acute cellular rejection
- Chronic rejection

Hyperacute rejection/Antibody mediated rejection is mediated is difficult to treat, once it is established and leads to high mortality rates. The mainstay of therapy is treatment of acute cellular rejection is to treat with

Classification of Immunosuppressive drugs in LTX

1. Corticosteroids

2. Cell cycle inhibitors

Early cell cycle inhibitors: Calcineurin Inhibitors (CIN)

Cyclophilin-binding drugs: Cyclosporine (Cs A)

FKBP12-binding drugs: Tacrolimus (FK-506)

Late cell cycle inhibitors: Transduction via IL-2R: Sirolimus (Rapamycin) (SRL)

3. Inhibitors of nucleotide synthesis: Purine synthesis (IMPDH) inhibitors: Mycophenolate mofetil (MMF)

4. Antimetabolites: Azathioprine (AZA), 6-Mercaptopurines

5. Antibody therapy

Compound	Antibody source	Brand name	Target
Antilymphocyte Globulin (ALG)	Horse Polyclonal	MALG	Antigens on lymphocyte cells
Antithymocyte Globulin (ATG)	Horse	ATGAM	Antigens on lymphocyte cells
Antithymocyte Globulin (ATG)	Rabbit Polyclonal	Thymoglobulin	Antigens on lymphocyte cells
Monoclonal Anti CD ₃ Ab (Muromonab-CD ₃)	Murine Monoclonal	Orthoclone OKT3	CD ₃ complex on T-cells

6. Anti-interleukin-2 receptor antibodies

Basiliximab	Mouse/Human	Simulect	CD ₂₅ Interleukin 2 receptors
Chimeric monoclonal			
Daclizumab	Human	Zenapax	CD ₂₅ Interleukin 2 receptors

high-dose glucocorticoids which are used as high dose bolus dose or pulse therapy followed by tapering. In majority of cases, mild to moderate ACR responds steroid therapy. Treatment for severe ACR or steroid-resistant rejection may require use of antilymphocyte antibody therapy.⁷ Tacrolimus (FK-506) is very effective drug to reverse mild, moderate, and severe ACR⁸ and steroid-resistant rejections.^{9,10} Treatment of established chronic allograft rejection is very limited.

David et al. classified both older and newer immunosuppression agents in one group.

CORTICOSTEROIDS

Corticosteroids play key role both in induction therapy and ACR. The adverse effects of this group on long-term used have led to early withdrawal in LTX.

Route of Administration

Intravenous form: Methylprednisolone given during surgery and early postoperative period. Oral form: Prednisolone given after 4-5 days post-transplant continued 3-6 months with gradual tapering of dose.

Pharmacokinetics

Prednisone rapidly reaches peak plasma level within 1-2 hours of oral administration. It is metabolized in liver to prednisolone and then to inactive compounds. In hepatic insufficiency, increased levels are marked due in

insufficient metabolism. It is excreted in urine. Hemodialysis does not really affect the clearance of this drug. Secreted in breast milk and can cross placental barrier.

Adverse effects of corticosteroids

- Hyperglycemia
- Increased appetite and weight gain
- Insomnia
- Osteoporosis
- Cataract
- Myopathy
- Neurological impairment—psychosis, insomnia
- Skin changes
- Adrenal insufficiency (if tapered suddenly)

Mechanism of corticosteroids

- Decrease the cytotoxic T-cell proliferation and cytotoxicity
- Inhibit the production and expression of cytokines like IL-1, IL-2, IL-6, TNF
- Block the ability of macrophages to respond to lymphocyte derived signals
- Depress delayed hypersensitivity
- To some extent inhibits antibody-dependent cytotoxicity
- Inhibit production γ -interferon
- Decreases local inflammation by decreasing migration of neutrophils and inhibiting lysosomal enzyme released by neutrophils.

Use in Transplantation

Initial therapy and maintenance therapy for 3-6 months.

Treatment of ACR

500-1000 mg of methylprednisolone for 3 days or 1000 mg of methylprednisolone single dose followed by taper within 6 days. Early suppression of corticosteroids is advised in HCV related transplants with increased viral load and to avoid early reactivation of HCV.

EARLY CELL CYCLE INHIBITORS

CALCINEURIN INHIBITORS (CINS)

This group provides the immunosuppressant base for most antirejection therapies in all solid and cellular organ transplants. The discovery of cyclosporine, the first calcineurin inhibitor used for immunosuppression, defined a new revolution in solid organ transplantation. Cyclosporine and tacrolimus both agents act in a similar fashion, each possess many unique qualities that have clinical relevance. Patients on tacrolimus have fewer episodes of ACR, steroid-resistant rejection, less exposure to Muromonab-CD₃ therapy, and lower cumulative steroid exposure.^{5,6} Tacrolimus is effectively to treat ACR as a single drug or in combination with glucocorticoids.⁸ Tacrolimus has been shown to reverse steroid-resistant rejection¹¹ and reverse chronic allograft rejection in selected liver transplant recipients.¹² Both tacrolimus and cyclosporine show similar graft and patient survival in LTx.^{5,6,13} Tacrolimus is also useful in chronic rejection.

Mechanism of Action

Inhibition of cytokine gene transcription, primarily interleukin-2 (IL-2) in T-lymphocytes. Inhibition of calcineurin (calmodulin-dependent serine-threonine protein phosphatase) occurs when it is bound to either tacrolimus-FK binding protein (FKBP) complex or the cyclosporine-cyclophilin complex.¹⁴ This interferes with the dephosphorylation of nuclear factor of activated T-cells (NF-AT). Potency of tacrolimus at calcineurin inhibition is 10 to 100 times greater than cyclosporine.¹⁵ Tacrolimus interferes with the transcription of a variety of other cytokines, IL-3, IL-4, interferon- α (IFN- α), tumor necrosis factor- α (TNF- α), and granulocyte-macrophage colony-stimulating factor (GM-CSF).¹⁶⁻¹⁸ Tacrolimus is hepatotropic a property not shown by cyclosporine. This

tissue-specific distribution may partially explain the lower rates of allograft rejection obtained with tacrolimus.

Cyclosporine (Cs A)

Available as **Neoral** and **Sandimmune**: liquid and liquid filled gel capsules. It is a fungal polypeptide extracted from *Cylindrocarpus lucidum*. It is insoluble in water, soluble in organic solvents and lipids. Neoral is a micro emulsion formulation, less dependent on the presence of intestinal bile for absorption than Sandimmune.¹⁹ Oral bioavailability ranges from 17 to 68%. Food decreases the rate absorption. External biliary drainage has little impact on the extent and degree of absorption of Neoral but significantly decreases bioavailability of Sandimmune.²⁰ Initial dosage pharmacokinetics of cyclosporine demonstrated a large volume of distribution (13 L/kg). But on chronic dosing, however, results in a steady state volume of distribution of 3 to 5 L/kg. Tacrolimus and cyclosporine are partitioned into plasma, serum, and erythrocytes. Cyclosporine undergoes extensive hepatic metabolism primarily by the P450-3A cytochrome mediated by GI and liver microsomal enzyme system generating more than 17 metabolites. Pediatric patients seem to have a higher rate of drug clearance, which is ascribed to increased cytochrome activity in the gastrointestinal tract.²¹

It is excreted in the bile. Less than 0.1% of cyclosporine is excreted unchanged in the urine. Dose reduction is required if the renal toxicity is due to Cs A. In case of Cs A induced nephrotoxicity, other drugs like aminoglycosides, Amphotericin B, acyclovir and NSAIDs should be cautiously used. Half life is around 15 hours (10-40 hours). Microemulsion and nonemulsion formulation of cyclosporine demonstrate wide variability in different patients and in the same patient also. Clinically, this variability is reflected in a wide range of trough values for the same dose exposure in a patient and different patients. When Cs A is given parentally, it should be mixed in a glass container because its lipophilic nature causes it to bind to plastics. Cs A trough levels are monitored by immunoassay and High pressure liquid chromatography assay (HPLC) methods. HPLC assay is preferable in many centers. The mode of action of Cs A disrupts HCV RNA synthesis resulting in potent inhibition of HCV replication. Tacrolimus did not affect the HCV RNA level.^{22,23} Graft survival in liver transplant recipients with HCV may be greater with CsA-based immunosuppression.²⁴

Trough levels to be maintained after liver transplantation²⁵

Time period	Range of trough level (ng/ml)	
	Cyclosporine	Tacrolimus
1st week	300–350	12–15
1st week to 1 month	200–300	10–12
1 to 3 months	150–250	8–10
> 3 months	100–200	6–8

After 6 months to 1 year of transplantation, if the graft function and liver functions are within normal limits, then low trough levels are acceptable.

All drugs except Prednisolone and Sirolimus are available in both oral and parenteral forms.

Methylprednisolone is used when parenteral corticosteroids are given in early post-transplantation. Cs A, Tacrolimus and MMF are taken 1 hr before or 2 hours after a meal.

Sirolimus is taken consistently in relation to eating.

Adverse effects more common with Tacrolimus

Post-transplant diabetes mellitus
Gastrointestinal symptoms

Headache

Adverse effects more common with Cyclosporine

Hirsutism
Gingival
Hyperplasia
Hyperlipidemia
Hypertension

Tacrolimus

Synonym: FK-506 or Fujimycin.

Available as: **Prograf** and **Advagraf** (sustained release capsules for once daily dose).

Tacrolimus was discovered in 1987 by a Japanese team headed by T. Goto, T. Kino and H. Hatanaka. It is a Macrolide antibiotic found in a soil fungus, although it is produced by a type of bacteria, *Streptomyces tsukubaensis*.² The name tacrolimus is reportedly derived from "Tsukuba", macrolide immunosuppressant. It was first approved by the Food and Drug Administration

Pharmacokinetics of immunosuppressant drugs

Drug	Dose	Metabolism	Excretion	Dose reduction		Secreted in breast milk	Removed by dialysis	Monitor trough level
				Renal failure	Hepatic failure			
Prednisolone	5-20 mg/day	Liver	Kidney	—	Yes	Yes	No	No
Cyclosporine	8±4 mg/kg/day	Liver	Bile, Kidney	Yes	Yes	Yes	No	Yes
Tacrolimus	0.1-0.3 mg/kg/d	Liver	Bile	Yes	Yes	Yes	No	Yes
Sirolimus	2 mg/day	Liver	Bile	—	Yes	Yes	No	Yes
MMF	500-1000 mg bid	Liver	Kidney	Yes	—	—	No	No
AZA	1-2 mg/kg/day	Liver	Kidney	Yes	—	Yes	Yes	Yes

Side effects of immunosuppressants²⁶

Drug	Prednisolone	Cyclosporine	Tacrolimus	Sirolimus	MMF	AZA
Year	—	1976	1987	1975	1991	1963
Side effects	Hyperglycemia HTN Neurotoxicity Hyperlipidemia Osteoporosis Myopathy Cataract Weight gain Gastritis	Nephrotoxicity Neurotoxicity Hyperkalemia Hypomagnesemia HTN Hyperlipidemia Hyperglycemia Hepatotoxicity Hirsutism Gingival hyperplasia Skin changes Gynecomastia Fibroadenoma	Nephrotoxicity Neurotoxicity Hyperglycemia Hyperkalemia Hypomagnesemia HTN Hyperlipidemia Cardiomyopathy (in children) Hirsutism Gingival hyperplasia	Anemia Leucopenia Thrombocytopenia Headache HTN Hyperlipidemia Hypokalemia Hepatic art. thrombosis	Anemia Leucopenia Thrombocytopenia GI: Nausea Vomiting Anorexia Diarrhea Esophagitis Gastritis CMV inf.	Bone marrow depression Pancreatitis Toxic hepatitis Veno-occlusive disease

Cs A induced gynecomastia is reversible on changing to Tacrolimus

(FDA) in 1994 for use in liver transplantation. It is available in oral and parenteral forms. Oral form commonly used. Oral bioavailability is 5 to 67% with a marked variability in the rate of absorption.^{27,28} Bioavailability was significantly higher after partial liver transplantation using the right hepatic lobe compared with full-size transplants.²⁹

Absorption is reduced by food but seems less dependent on the presence of bile.²⁸ Tacrolimus metabolized in the liver by the mixed function oxidase system, primarily the cytochrome P450-3A subset and also to some extent metabolized in small intestine by small bowel cytochrome system.³⁰ Pediatric patients clear tacrolimus at a faster rate than adults do on a body-weight basis. Most tacrolimus is excreted as a conjugate in the bile (>95%), with less than 1% excreted unchanged in the urine.²⁸ Terminal elimination half-life of tacrolimus is approximately 12 hours. Measurement of trough levels is useful in dosage adjustment. Unlike cyclosporine, tacrolimus has a strong trough area-under-the-curve (AUC) correlation. As a result, trough levels are used to guide immunosuppressive effect and monitor toxicity.³¹

Adverse effects: Hypertension common in both drugs,^{5,6} primarily a manifestation of nephrotoxicity on long term use. Acute exposure can cause in both hypertension and hypotension and is blood level related. Hyperglycemia is more common with tacrolimus than Cs A due to its effect on cells of the pancreas.³²⁻³⁴

Nephrotoxicity is dose related and reversible when dose is reduced. It is due to vasoconstriction of the afferent arterioles and decreased GFR.^{5,6} Manifested by elevated blood urea nitrogen (BUN) and serum creatinine. The effect is usually reversible with cessation or lowering of the dose of the agent. Chronic use can result in more permanent changes in the kidney and include arteriolar hyalinosis, tubular vacuolization, and atrophy.³⁵ Progressive deterioration in renal function has prompted some programs to use alternative immunosuppressants in order to lower or avoid further exposure to calcineurin inhibitors.³⁶

Other side effects are³⁷⁻³⁹:

- Electrolyte disturbances
- Hyperkalemia,
- Hyponatremia,
- Hypomagnesemia
- Lower level of serum bicarbonate levels.

Neurotoxicity: Tremor and headache are common (50%)^{5,6} during initiation of therapy and are when high trough levels are maintained. Seizures, coma and grey-white matter changes in the brain.⁴⁰⁻⁴² Increased risk of cyclosporine-induced neurotoxicity in patients with low

perioperative serum cholesterol levels.⁴³ No such correlation has been established for tacrolimus.

Gastrointestinal disturbances are diarrhea, dyspepsia, bloating, vague abdominal pain and discomfort.^{5,6} Mostly symptoms resolve by decreasing the dose, or alteration in the dosing interval, occasionally withdrawal of these agents is necessary. GI symptoms are more with combination of mycophenolate mofetil and calcineurin inhibitor.

Gingival hyperplasia and hypertrichosis are more common with cyclosporine than Tacrolimus.⁴⁴

Risk of infection: The overall increased risk of viral, bacterial, and fungal infectious complications exist with both drugs.

Post-transplant lymphoproliferative disease (PTLD) is more with Tacrolimus than Cyclosporine.⁴⁵

Most of the transplant centers at present favour tacrolimus based immunosuppression in all adult recipients of both LDLT and DDLT. Tacrolimus is usually given preoperatively around 2-4 hrs before induction at a dose of 0.075mg/kg and continued enterally thereafter. In the immediate posttransplant period the dose of tacrolimus is adjusted to maintain a target trough level of between 10-20 ng/mL. Methylprednisolone is given as an intraoperative bolus and tapered rapidly to maintenance within 1st week and replaced with prednisolone dose of 20 mg/day by postoperative day seven. Acute rejection in the early post-operative period can be treated with an increase in dose of tacrolimus or glucocorticoid bolus therapy, or both. In the first 3 months target trough level of tacrolimus is maintained between 8-12 ng/mL. Most patients are maintained long-term on tacrolimus maintain a trough level of 5 ng/mL to 7 ng/mL. During the 1st 3 months, steroid dose is gradually tapered to the lowest possible dose and are withdrawn completely within 3-6 months. In the pediatric transplantation, cyclosporine is preferred to very young patients and Tacrolimus is preferred in older pediatric patients due to concerns about the potential increase in PTLD with tacrolimus exposure in this high-risk population. If pediatric patients develop chronic rejection or steroid resistant rejection, Tacrolimus is preferred irrespective of the age.

LATE CELL CYCLE INHIBITORS

SIROLIMUS (SRL)

Synonym: Rapamycin. (Rapamune)

A mTOR (mammalian target of rapamycin) inhibitor, available as **Rapamune**. SRL is an immunosuppressive drug that inhibits the immune system and at the same

Drug interaction of calcineurin inhibitors**Drugs that increase the levels of CINs****Antibiotics**

Erythromycin
 Clarithromycin
 Azithromycin
 Josamycin
 Ponsinomycin
 Metronidazole

Calcium channel blockers

Verapamil
 Diltiazem
 Amlodipine
 Nicardipine

Immunosuppressive agents

Sirolimus

Other drugs

Methylprednisolone
 Ethinyl Estradiol

Antifungal agents

Fluconazole
 Ketoconazole
 Itraconazole
 Clotrimazole

Protease inhibitors

Saquinavir
 Indinavir
 Nelfinavir
 Ritonavir

Foods

Grape fruit and juice

Omeprazole
 Allopurinol

Drugs that decrease the levels of CINs**Antibiotics**

Nafcillin
 Cephalosporins
 Ciprofloxacin
 Terfenadine
 IV Trimethoprim
 IV Sulfadimidine

Anticonvulsants

Barbiturates
 Phenytoin
 Carbamazepine

Antitubercular drugs

Rifampicin
 Isoniazid
 Imipenems

Others

Octreotide
 Ticlopidine

Drugs that potentiate the toxic effects of CINs

Nephrotoxicity: Aminoglycosides, NSAIDs,
 Amphotericin B

Hyperkalemia: K+sparing diuretics

Bone marrow suppression and Rhabdomyolysis:

Antacids containing magnesium and aluminium

time is not nephrotoxic, neurotoxic, or diabetogenetic. It is a macrolide antibiotic first discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from an Ester island called Rapa Nui.⁴⁶ SRL can also be used alone or in conjunction with calcineurin inhibitors and/or MMF to provide steroid-free immunosuppression regimes. It is structurally similar to Tacrolimus. Even though sirolimus binds to the FK-binding protein⁴⁸ similar to tacrolimus and cyclosporine, immunosuppressant activity is different from them.⁴⁸ The FKBP-sirolimus complex mediates a series of intracellular

events that result in the inhibition of both T-cell and thymocytes proliferation and B-cell activation. It inhibits the response of lymphocytes (both T and B cells) to cytokine stimulation and inhibits antibody production by B cells.⁴⁹ It inhibits intracellular signal transduction and subsequent proliferation mediated by IL-2 receptor stimulation of at least two cell-cycle kinases, 70-kD S6 kinase^{50,51} and p34.^{52,53}

It inhibits late in the G₁ phase of the cell cycle,⁴⁷ later than tacrolimus or cyclosporine. Activation stimuli that are resistant to calcineurin inhibition or cytokine stimulation are sensitive to sirolimus. This late-stage inhibition allows greater lymphocyte activation than previously possible with calcineurin inhibitors. Pharmacokinetics: Oral bioavailability is variable and is increased with high-fat diet.⁵⁴ It is metabolized through the cytochrome P450-3A system like tacrolimus and cyclosporine.⁵⁵ Terminal half-life is 63 to 68 hours and is given as a single dose /day. Most of the drug is sequestered in erythrocytes.⁵⁶ This factor must be considered when interpreting the SRL blood or serum trough levels.

Side Effects

Incidence and severity of the side effects are related to trough levels.⁵⁷⁻⁶⁰

- Hyperlipidemia (elevated cholesterol and triglycerides)
- Leucopenia, thrombocytopenia
- Pulmonary disease
- Joint pain

Side effects of cyclosporine such as hypertension, nephrotoxicity are not augmented by combination with sirolimus.^{58,59} Efficacy of sirolimus as an immunosuppressant is derived from renal transplant recipients and approved by FDA in 1999. Sirolimus in combination with cyclosporine and steroids results in a lower incidence of ACR.⁶¹⁻⁶² Experience with sirolimus in liver transplantation is limited. Few studies have reported use of cyclosporine and sirolimus provide adequate steroid-free immunosuppression. Sirolimus used as the sole agent in maintenance therapy is adequate and well tolerated.⁶³ Early results with combination therapy using sirolimus and tacrolimus in liver transplant recipients are encouraging. The side effect profiles do not overlap, and the addition of sirolimus provides a steroid and tacrolimus sparing effect. Patients with hepatorenal syndrome or poor renal function are suitable candidates for sirolimus-based immunosuppression. With improvement in renal function, tacrolimus may be gradually added to the postoperative immunosuppression cocktail and the sirolimus dose is gradually

lowered. Rapamycin can be safely used in OLT recipients with severe neurological symptoms ascribed to or exacerbated by CINs. Rapamycin monotherapy may be inadequate to control rejection early after transplantation. Rapamycin can be combined with low doses of CIN to prevent rejection.⁶⁴ SRL can also be used in LTX recipients of hepatocellular carcinoma due to its antitumor effect.

SRL can be used in 2 different ways. First dose is started as loading dose of 0.10 mg/kg, and consequent decrement of SRL to 0.05 mg/kg daily for the next few days, with dose adjustments until a trough level between 8 and 10 ng/mL is achieved. The other method of using SRL is introduction of SRL with low dose and contemporaneous decrement of CIN dose.⁶⁵ SRL is avoided in the first three months after LTX to avoid hepatic arterial complications. Benedetto et al. reported use of Sirolimus monotherapy in selective cases of the recipients developing complications due to calcineurin inhibitors or in Kaposi's sarcoma.⁶⁵

ANTIMETABOLITES

MYCOPHENOLATE MOFETIL (MMF)

Mycophenolate is derived from the fungus *Penicillium stoloniferum*. It was initially marketed as the prodrug mycophenolate mofetil to improve oral bioavailability. More recently, the salt mycophenolate sodium has also been introduced. It is available as **Cellcept** (MMF) and **Myfortic** (mycophenolate sodium). Mycophenolate is potent and can be used in place of the older antiproliferative azathioprine. It is usually used as part of a three compound regimen of immunosuppressants, also including a calcineurin inhibitor (cyclosporine or tacrolimus) and prednisolone. Myfortic (Entericoated Mycophenolate Sodium) appears to have a similar efficacy and safety profile as MMF in OLT when added to the current immunosuppressant regimens or as a substitute for MMF. Hematologic and gastrointestinal adverse events were infrequent.⁶⁶

Pharmacology

It is an esterified prodrug of mycophenolic acid. It acts selectively on T and B lymphocytes.⁶⁷ It acts by its antiproliferative effect by reversible noncompetitive inhibition of inosine monophosphate dehydrogenase (IMPDH), which is responsible for de novo purine synthesis.⁷⁰ As the lymphocytes lack the salvage pathway for purine synthesis, they are dependent on the de novo pathway and are sensitive to the antiproliferative effects of MMF.⁶⁸ Its more specific enzyme inhibition offer advantage over azathioprine, which also inhibits 5-phosphoribosyl-1-pyrophosphate-amidotransferase and adenylosuccinate synthetase.⁶⁹

Pharmacokinetics

MMF, a prodrug is hydrolyzed to the active agent mycophenolic acid (MPA) in the liver. MPA is further metabolized to the inactive glucuronide conjugate (MPAG). MPAG is excreted into bile and subsequently deconjugated in the gut into MPA and reabsorbed into the enterohepatic circulation. MPA and MPAG are both highly protein bound, and high levels of MPAG can displace MPA, thereby increasing free drug and potential toxicity and volume distribution. Most of the dose of MMF is excreted in the urine as MPAG with less than 1% as MPA. Plasma half-life is approximately 18 hours.⁶⁹ A patient who is planning a pregnancy should not use MMF unless she cannot be successfully treated with other immunosuppressant drugs, due to increased risk of pregnancy loss and congenital malformations.

Side Effects

GI symptoms are dose related - diarrhea, nausea, abdominal pain, and constipation. These are more severe in recipients receiving both Tacrolimus and MMF.^{71,72} Leukopenia is a common side effect of MMF. Opportunistic infections are common in patients receiving high dose.^{73,74}

Indications of MMF in Liver transplantation⁷⁵⁻⁸¹

- Steroid reduction
- Calcineurin toxicity
- Treatment of steroid-resistant rejection
- Chronic rejection.

MMF is potent and safe immunosuppressive agent, and replacement of CIN by MMF in liver transplant patients with renal dysfunction may improve not only kidney function but also other CIN-associated side-effects, such as hypertension and hyperuricemia, with a low risk of rejection.⁸² MMF monotherapy in liver transplant recipients has improved renal function and its use is not associated with a significant risk of acute or chronic allograft rejection. Side effects were mild with dose regimens upto 750 mg twice daily.^{83,84}

AZATHIOPRINE (AZA)

It is available as **Imuran** and Azathioprine sodium. First synthesized as prodrug of 6-Mercaptopurine (6-MP). It is an imidazole derivative of 6-MP. Mechanism of action is by inhibiting de novo purine synthesis, thus inhibiting DNA and RNA synthesis. It also inhibits T and B lymphocyte proliferation, decreasing immunoglobulin secretion and IL-2 secretion. It complements the activity of steroids and calcineurin inhibitors. It is available as oral and parenteral forms. Oral and parenteral dosage is same. Dose is 1-3 mg/kg/day usually single dose. It

is available as 50 mg tablets. Absorption is not affected by food. Peak plasma level is 2 hrs. Half life is 0.7-3 hrs. Metabolized in liver and excreted by kidneys. Dose reduction is reduced in renal insufficiency. It can be removed by dialysis. AZA cross placental barrier and secreted in breast milk. So breast feeding is not recommended in mothers on this drug. Plasma drug concentration monitoring is required for AZA. Side effects: Dose dependent bone marrow depression leading to pancytopenia and increased infection rate, pancreatitis, idiosyncratic toxic hepatitis and venoocclusive disease.

ANTIBODY THERAPY

Antilymphocyte antibody (ALG) is a polyclonal antibodies derived from immunizing horses against human lymphocytes. Antithymocyte globulins (ATG) is a polyclonal antibodies derived from immunizing horses or rabbits against human thymocytes respectively. It is a very potent immunosuppression in the allograft recipients and also effective as induction therapy and management of steroid-resistant rejection.⁸⁴⁻⁸⁶ Antilymphocyte antibodies do not provide benefit over standard calcineurin-based therapy.⁸⁷ Polyclonal antibody products are primarily used in renal transplantation.^{87,88} The polyclonal antibody products have much broader antigen specificity. They are given for 7-14 days at a fixed dose depending on the preparation. When used in combination with calcineurin inhibitors, they decrease the incidence of rejection in first 30 days and a delay in the onset of first rejection episode. They bind to various cellular antigens on both T and B lymphocytes in addition to cellular antigens on platelets, erythrocytes, and leukocytes.⁹⁰⁻⁹² Mechanism of immunosuppression is mediated primarily by IgG antibody binding resulting in opsonization or antibody-mediated complement lysis of the target cells. Adverse affects are fever, chills, arthralgia, nausea, vomiting, leukopenia and thrombocytopenia.

MUROMONAB-CD₃

It is a murine monoclonal antibody. It is specific for the ϵ chain of the TCR/CD₃ complex expressed on mature T cells and medullary thymocytes.⁹³ It exerts its immunosuppressive effect by binding to and modulating the CD₃ complex on T cells. Within minutes of infusion of this drug, CD₃₊ lymphocytes are cleared from the circulation. During this therapy, CD₃₊ lymphocytes remain undetectable unless neutralizing antibodies develop. This antibody T-cell interaction results in trafficking of the T lymphocytes out of the circulation and down regulation of TCR mediated signaling.^{93,94}

Additionally, binding of the antibody to the CD₃ complex results in liberation of a vast array of cytokines contributing to the cytokine release syndrome experienced by many patients treated with this agent.

Side Effects

*Cytokine release syndrome*⁹⁵⁻⁹⁹

Usually occurs with the first dose in patients with large number of T cells and usually manifests within one hour of administration of this drug. It manifests as fever, rigors, chills, malaise, nausea, vomiting and diarrhea. Less frequently, patients experience pulmonary edema, cardiovascular collapse, seizures, and renal failure.

This syndrome can be prevented by pretreatment with acetaminophen, antihistamines and steroid pretreatment.

- Neuropsychiatric toxicity: present as headache, seizures, confusion and aseptic meningitis.
- Use of Muromonab-CD₃ in steroid-resistant rejection is a risk factor for CMV infection and in hepatitis C related transplants predisposes the patients to early and severe recurrence of hepatitis C infection.
- In pediatric transplants use Muromonab-CD₃ increases the risk of EBV and CMV infection and PTLD.

Prophylaxis with Muromonab-CD₃ in liver transplant patients offers no advantage over standard calcineurin-based therapy nor is Muromonab-CD₃ the only effective agent for rescue therapy for refractory rejection after liver transplant.

ANTI-INTERLEUKIN-2 RECEPTOR ANTIBODIES (BASILIXIMAB, DACLIZUMAB)

These are commonly used in liver transplantation. These are antibodies directed against α subunit of the IL-2 receptor (CD₂₅).¹⁰⁰ Both are IgG 1 monoclonal antibodies. Mostly they are used for induction therapy. These monoclonal antibodies are specific for the IL-2R (CD₂₅, IL-2R- α) expressed only on activated T-cells. Immunosuppression is mediated by binding to the IL-2 receptor in a non activating fashion, competing with IL-2 and thereby inhibiting IL-2 driven proliferation of the activated T lymphocyte. Interleukin-2 induced proliferation of activated (antigen stimulated) T-lymphocytes is a critical step in clonal proliferation and acquisition of effector function. Both agents appear to lessen the incidence of ACR among recipients of cadaveric renal allografts when added to baseline immunosuppression.¹⁰⁰ Addition of anti-IL-2-receptor blockade to baseline immunosuppression can safely decrease the incidence of ACR early after liver transplantation. In the liver transplant recipient, unlike the renal transplant recipient, administration of the antibody must be delayed until reperfusion of the graft has been established because

of the large volume of blood replacement associated with liver transplantation. Antibody may also be lost in ascites fluid.¹⁰¹ These are commonly indicated in multiorgan transplants.

Pharmacokinetics

They have different pharmacokinetic patterns. Basiliximab demonstrates a volume of distribution equivalent to blood and plasma (4 to 5 L). At steady state, the volume of distribution increases suggesting distribution outside the vascular compartment. Daclizumab demonstrates a smaller volume of distribution than Basiliximab at steady state but it still exceeds the vascular compartment. Increased volume of distribution at steady state may be partially explained by redistribution of the antibodies into ascites fluid. Basiliximab clearance is not well correlated with body weight and age, terminal half-life of 4 to 14 days. Daclizumab has a clearance proportional to body weight, terminal half-life of 20 days and both agents when used in proper dosage, provide saturation binding of IL-2 R for greater than 1 month after dosing.^{102,103}

Daclizumab

Daclizumab (Zenapax)¹⁰⁴ - Humanized anti-IL-2 receptor monoclonal antibody (mAb)

Dose: 1 mg/ kg every 14 days for 5 doses. Figueras et al. reported that steroid-free immunosuppressive regime using Daclizumab, MMF and tacrolimus is effective for prevention of acute rejection after LT, without an increase either in infection rates or in adverse effects.

Basiliximab

Basiliximab (Simulect)¹⁰⁵-Chimeric anti-IL-2 receptor mAb.

Dose: 20 mg within 6 hrs of reperfusion and on day 4 of post-transplantation. Gruttadauria et al. reported the use of Basiliximab in association with tacrolimus and steroids in early post-transplant period is an effective prophylaxis of ACR in liver transplant recipients and does not increase the incidence of infections or adverse effects. Induction with Basiliximab in combination with tacrolimus-based immunosuppressive regimen reduces the incidence of rejection and improves rejection-free survival rate after LT without increasing the incidence of CMV, PTLT, or HCV recurrence.¹⁰⁶

Side Effects¹⁰⁷

Both monoclonal antibody preparations are well tolerated. Side effects are opportunistic infections (viral or bacterial), malignancy and posttransplant lymphoproliferative disease.

Long term adverse effects of immunosuppressive therapy

- Hypertension
- Diabetes mellitus
- Renal toxicity
- Hyperlipidemia
- Osteopenia and osteoporosis
- Obesity
- Hyperuricemia

Disorders that require modification of immunosuppression

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune hepatitis
- Fulminant hepatic failure
- Retransplantation

Patients transplanted for end-stage primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis are at increased risk for rejection and disease recurrence. Cellular rejection is more in patients transplanted for fulminant hepatic failure and retransplantation patients.

Autoimmune hepatitis

It recurs in 33 % of patients after transplantation and risk is increased as immunosuppression dose is reduced, and longer follow-up was required to assess the impact of recurrent disease upon patient and graft survival. Difference in the immunosuppressive regime and length of follow-up influences the recurrence rates. Weaning of immunosuppression should be approached with caution, but recurrent disease appears to respond to an increase in corticosteroids (continued for long time) with or without antimetabolites. Benefit of tacrolimus over cyclosporine in the prevention of recurrent disease is not clear.

Primary biliary cirrhosis

Recurrent PBC after transplant may be dependent on the immunosuppressive regimen and method of weaning. Long-term immunosuppression therapy may modify expression of recurrent disease within the graft. These patients have increased chance of rejection. Cyclosporine may be preferable to tacrolimus in patients transplanted for PBC.

Primary sclerosing cholangitis

The recurrence of PSC after LT is controversial. Recurrence was based upon clinical symptoms and signs of cholestasis, nonanastomotic strictures within intrahepatic or extrahepatic bile ducts, and periductal

inflammation with fibrosis at least 6 months after transplantation.¹⁰⁸ Jeyarajah et al. found recurrent disease in 15.7% and chronic rejection in 13%.¹⁰⁹ In order to accurately diagnose PSC recurrence, well-defined cholangiographic and histologic criteria are mandatory. Effect of immunosuppression may modify or delay disease expression within the graft.

*Fulminant hepatic failure*¹¹⁰

The outcome of transplantation in patients with fulminant hepatic failure (FHF) has been generally inferior to that of transplantation performed electively for patients with chronic liver disease reflecting the impact of severe complications such as severe cerebral edema, on survival. Graft dysfunction and infections are also more prevalent in patients transplanted for FHF. Primary immunosuppression tacrolimus may be preferable to cyclosporine in this group.

Retransplantation

Patients undergoing retransplantation have a significantly inferior result compared with patients receiving a first graft; overall 1-year survival is 50% to 70%.^{111,112} Markmann et al. reported that pre-operative criteria predictive factors of poor outcome after LTX are older patient age, donor organ ischemia, requirement for preoperative mechanical ventilation, elevated total bilirubin, and elevated creatinine.¹¹³

Steroid withdrawal

Posttransplant metabolic complications like hyperglycemia, hyperlipidemia, osteoporosis and hypertension are related to corticosteroids. At present most of the transplant centers believe in early withdrawal of steroids ranging from 3-6 months.

Early withdrawal of prednisone was well tolerated by patients and was associated with fewer metabolic complications.^{114,115} Withdrawal of steroids in patients with stable graft function appears to be safe, with no significant increased risk of rejection.¹¹⁶ Prime concern with steroid withdrawal is the potential for precipitating rejection. Most cases of chronic rejection and episodes of acute rejection occurred in patients on calcineurin inhibitors. This can be avoided by using combination of calcineurin inhibitors preferably tacrolimus and antimetabolites (MMF).

PEDIATRIC IMMUNOSUPPRESSION

INITIAL IMMUNOSUPPRESSION

Direct comparisons between pediatric patients receiving cyclosporine and tacrolimus have demonstrated similar graft and patient survival, but patients receiving

tacrolimus had less acute, chronic, and steroid-resistant rejection.^{117,118} Advantage of tacrolimus is steroids can be withdrawn much more rapidly than in cyclosporine-based immunosuppression thereby limiting the complications associated with long-term steroid use.¹¹⁹ When we compare the tacrolimus and cyclosporine, there was no significant difference in patient and graft survival. But recipients respond well to tacrolimus in steroid resistant rejection.¹²⁰ Incidence of nephrotoxicity and hypertension are similar in tacrolimus and cyclosporine, but the rate of hyperkalemia requiring treatment and the rate of insulin-dependent diabetes is slightly higher in tacrolimus than cyclosporine.^{117,118} The most worrisome side effect in pediatric patients receiving tacrolimus is on increased incidence of post-transplant lymphoproliferative disease (PTLD). In cyclosporine-based immunosuppression the rate is 4% and the rate on tacrolimus is 6% to 13%.¹²¹

Neoral has better absorption and bioavailability than Sandimmune due to its micro emulsified form.¹²² Sandimmune is poorly absorbed after LTX because bile flow is diminished; therefore, in the early postoperative period and when patients have graft dysfunction with cholestasis the cyclosporine needs to be given intravenously.¹²³ Infants with smaller bowel length have poorer Sandimmune absorption. Neoral gives the advantage of being given orally regardless of bile flow. But in studies comparing pediatric patients taking Sandimmune and Neoral directly there was no significant difference in the rates of rejection, or of graft or patient survival.¹²⁴ 70% to 74% of pediatric patients on tacrolimus can be maintained on single drug therapy 1 year after transplant.¹²⁵ Current immunosuppression in pediatric transplantation includes triple regime including corticosteroids, calcineurin inhibitors and Interleukin-2 receptor antibodies.

NEWER IMMUNOSUPPRESSION DRUGS

RAD (EVEROLIMUS)

RAD^{126-131,140} is a novel macrolide with potent immunosuppressive and antiproliferative activities. It is related to, but structurally different from, sirolimus and, by virtue of its hydroxyethyl side chain, has enhanced bioavailability. RAD exerts its immunosuppressive activities to inhibit mTOR and inhibit growth factor-dependent proliferation of vascular smooth muscle cells. In clinical trials, RAD has shown its efficacy in reducing the incidence of rejection in kidney transplant recipients, and the severity and incidence of cardiac-allograft vasculopathy in heart transplant recipients. In a phase I

trial of liver transplant recipients, a single dose of RAD was well tolerated and safe. Additional trials assessing the efficacy of RAD in liver transplant patients are ongoing. Recently Masetti et al.¹⁴¹ reported that de novo anemia in OLT patients treated with Everolimus monotherapy showed the same incidence as in patients treated with CsA. Hemoglobin values remained similar during the entire follow-up. In his report, the overall myelosuppression in the Everolimus Group was not significantly different from patients in the CsA Group.

FTY 720

FTY 720^{132,133,140} has a unique anti-rejection property characterized by selective reduction of circulating mature lymphocytes, particularly T cells, in peripheral blood. The reduction is induced either by induction of apoptosis of lymphocytes or by acceleration of lymphocyte homing to lymph nodes and Peyer's patches. The immunosuppressive effect of FTY 720 has been evaluated in transplant models in animals. A multicenter, randomized, phase I study demonstrated a dose-dependent, reversible decline in peripheral blood lymphocytes without an enhanced incidence of side effects, except possibly bradycardia. FTY 720 is expected to be used in combination with calcineurin inhibitors or other immunosuppressants to prevent acute and chronic rejection, because of its unique capacity to reduce peripheral blood lymphocytes.

FK 778

FK 778^{134,135,140} is a synthetic malononitrilamide (MNA) derived from A77 1726, an active metabolite of leflunomide. FK 778 inhibits de novo pyrimidine synthesis and tyrosine kinase activity of T- and B-lymphocytes. It prolongs the survival of skin and heart grafts in rodents and of kidneys in dogs. The half-life of FK 778 is 5.9 hours in rodents and 21 to 45 hours in dogs, which is shorter than that of leflunomide (15 to 18 days). Given in combination with standard immunosuppressive drugs, FK 778 improved graft survival in a canine kidney transplant model. Its vasculoprotective properties, with inhibition of several growth factor receptor tyrosine kinases (RTK), may make it a candidate for the treatment of restenosis and chronic allograft rejection.

Tolerance Induction Therapy

Tolerance induction therapy was introduced by Starzl et al. who tailored their protocol according to two principles:

recipient pretreatment and minimum use of posttransplant immunosuppression.^{126, 140}

CAMPATH 1-H

CAMPATH 1-H,¹³⁶⁻¹³⁸ a humanized anti-CD₅₂ antibody, is a powerful lytic agent for both T and B lymphocytes that does not affect bone-marrow stem cells. CAMPATH 1-H was used in 31 renal transplant recipients among whom 30 patients are alive at 15–28 months follow-up, and 29 patients have intact grafts under treatment with low-dose cyclosporine. There have been six episodes of steroid responsive rejection, and opportunistic infections in two recipients. CAMPATH 1-H and tacrolimus were used in 16 cases of intestinal and multi visceral transplantation without steroids. Twelve of the 16 patients are alive with functioning grafts. CAMPATH 1-H allows the patient to be steroid-free and to be maintained on low dose of immunosuppressive monotherapy.¹⁴⁰

Other newer immunosuppression drugs under Pre-clinical and clinical trials are:

- Phase 1 trial
 - BCX 4208
 - TAFA 93
- Phase 2 trial
 - CP690
 - CP550
 - AEB 071
 - ISA 247
- Phase 3 trial
 - Balatacept (LEA 29Y)
- Pre clinical trial
 - CRB 15
 - Anti CD 40 mAb

THYMOGLOBULIN

Starzl et al.¹³⁹ reported that in 82 patients waiting for kidney, liver, pancreas, or intestinal transplants who were pretreated with a polyclonal rabbit antithymocyte globulin (Thymoglobulin). Post-transplant immunosuppression used tacrolimus. One-year patient and graft survivals were 95% and 89%, respectively. Of the 72 with surviving grafts, 43 are on spaced doses of tacrolimus monotherapy: every other day (n=6), three times per week (n=11), twice per week (n=15), or once per week (n=11). Tremendous dose reductions, close to tolerance, were achieved with thymoglobulin pretreatment.¹⁴⁰

REFERENCES

- Adam DH, Neuberger JM. Treatment of acute rejection. *Semin liver dis* 1992;12:80-88.
- Soin AS, Rasmussen A, et al. Cs A level in early transplant period – predictive of chronic rejection in liver transplantation? *Transplantation* 1995;59:1119-23.
- Balan V, Abu-Elmagd K, Demetris AJ: Autoimmune liver diseases: recurrence after liver transplantation. *Surg Clin North Am* 1999;79:147.
- Woodle ES, Bruce DS, Josephson M, et al. FK 506 therapy for refractory renal allograft rejection: Lessons from liver transplantation. *Clin Transplant* 1996;10:323.
- Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. European FK506 Multicentre Liver Study Group [see comments]. *Lancet* 1994;344(8920):423.
- The US Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994;331:1110.
- Solomon H, Gonwa TA, Mor E, et al. OKT3 rescue for steroid-resistant rejection in adult liver transplantation. *Transplantation* 1993;55:87.
- Jonas S, Bechstein WO, Tullius SG, et al. Indications for tacrolimus anti-rejection therapy in liver allograft recipients. *Transpl Int* 1996;9 Suppl 1:S164.
- Millis JM, Bruce DS, Newell KA, et al. Treatment of steroid-resistant rejection with tacrolimus prior to OKT3 in liver transplant recipients. *Transplant Proc* 1996;28:1014.
- Millis JM, Woodle ES, Piper JB, et al. Tacrolimus for primary treatment of steroid-resistant hepatic allograft rejection. *Transplantation* 1996;61:1365.
- Platz KP, Mueller AR, Zytowski M, et al. Management of acute steroid-resistant rejection after liver transplantation. *World J Surg* 1996;20:1052.
- Sher LS, Cosenza CA, Michel J, et al. Efficacy of tacrolimus as rescue therapy for chronic rejection in orthotopic liver transplantation: A report of the U.S. Multicenter Liver Study Group. *Transplantation* 1997;64:258.
- Wiesner RH. A long-term comparison of tacrolimus (FK506) versus cyclosporine in liver transplantation: A report of the United States FK506 Study Group. *Transplantation* 1998;66:493.
- Cacciarelli TV, Green M, Jaffe R, et al. Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. *Transplantation* 1998;66:1047.
- Wiederrecht G, Lam E, Hung S, et al. The mechanism of action of FK-506 and cyclosporin A. *Ann NY Acad Sci* 1993;696:9.
- Dumont FJ, Staruch MJ, Koprak SL, et al. Distinct mechanisms of suppression of murine T cell activation by the related macrolides FK-506 and rapamycin. *J Immunol* 1990;144:251.
- Mattila PS, Ullman KS, Fiering S, et al. The actions of cyclosporin A and FK506 suggest a novel step in the activation of T lymphocytes. *E MBO J* 1990;9:4425.
- Tocci MJ, Matkovich DA, Collier DA, et al. The immunosuppressant FK506 selectively inhibits expression of early T-cell activation genes. *J Immunol* 1989;143:718.
- Mueller EA, Kovarik JM, van Bree JB, et al. Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. *Pharm Res* 1994;11:301.
- Otto MG, Mayer AD, Clavien PA, et al. Randomized trial of cyclosporine microemulsion (neoral) versus conventional cyclosporine in liver transplantation: MILTON study. Multicentre International Study in Liver Transplantation of Neoral. *Transplantation* 1998;66:1632.
- Whittington PF, Emond JC, Whittington SH, et al. Small-bowel length and the dose of cyclosporine in children after liver transplantation. *N Engl J Med* 1990;322:733.
- Watashi K, Hijikata M, Hosaka M, et al. Cyclosporin A suppresses replication of hepatitis C virus genome in cultured hepatocytes. *Hepatology*. 2003;38(5):1282-8.
- Firpi RJ, Zhu H, Morelli G, et al. Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virological response after liver transplantation. *Liver Transpl*. 2006;12(1):51-7.
- SC Rayhill, R Barbeito, W Schmidt, et al. A Cyclosporine-Based Immunosuppressive Regimen May Be Better Than Tacrolimus for Long-Term Liver Allograft Survival in Recipients Transplanted for Hepatitis C. *Transplant Proceed* 2006;38:3625-28.
- SJ Kim, KW Lee, DS Lee, HH Lee, SK Lee, et al. Randomized Trial of Tacrolimus Versus Cyclosporine in Steroid Withdrawal in Living Donor Renal Transplant Recipients *Transplant Proceed* 2004;36:2098-100.
- G. Iaria, L. Urbani, G. Catalano, et al. R. Liermann, F. Mosca, and F. Filippini. Switch to Tacrolimus for Cyclosporine-Induced Gynecomastia in Liver Transplant Recipients. *Transplant Proceed* 2005;37:2632-33.
- Venkataramanan R, Jain A, Warty VS, et al. Pharmacokinetics of FK 506 in transplant patients. *Transplant Proc* 1991;23:2736.
- Venkataramanan R, Jain A, Warty VW, et al. Pharmacokinetics of FK 506 following oral administration: a comparison of FK 506 and cyclosporine. *Transplant Proc* 1991;23:931.
- J Wilberg, B Küpper, et al. Oral Tacrolimus Bioavailability Is Increased After Right Split Liver transplantation. *Transplant Proceed* 2007;39:3237-38.
- Milkiewicz P, Hubscher SG, Skiba G, et al. Recurrence of autoimmune hepatitis after liver transplantation. *Transplantation* 1999;68:253.
- Pichlmayr R, Winkler M, Neuhaus P, et al. Three-year follow-up of the European Multicenter Tacrolimus (FK506) Liver Study. *Transplant Proc* 1997;29:2499.
- Drachenberg CB, Klassen DK, Weir MR, et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. *Transplantation* 1999;68:396.
- Hirano Y, Fujihira S, Ohara K, et al. Morphological and functional changes of islets of Langerhans in FK506- treated rats. *Transplantation* 1992;53:889.
- Tamura K, Fujimura T, Tsutsumi T, et al. Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. *Transplantation* 1995;59:1606.
- Andoh TF, Burdmann EA, Lindsley J, et al. Functional and structural characteristics of experimental FK 506 nephrotoxicity. *Clin Exp Pharmacol Physiol* 1995;22:646.
- Chan CK, Head GA. Relative importance of central imidazoline receptors for the antihypertensive effects of moxonidine and rilmenidine. *J Hypertens* 1996;14:855.
- Canzanello VJ, Textor SC, Taler SJ, et al. Renal sodium handling with cyclosporin A and FK506 after orthotopic liver transplantation. *J Am Soc Nephrol* 1995;5:1910.

38. McDiarmid SV, Colonna JOd, Shaked A, et al. A comparison of renal function in cyclosporine- and FK-506-treated patients after primary orthotopic liver transplantation. *Transplantation* 1993;56:847.
39. O'Gorman MA, Fivush B, Wise B, et al. Proximal renal tubular acidosis secondary to FK506 in pediatric liver transplant patients. *Clin Transplant* 1995;9:312.
40. Fryer JP, Fortier MV, Metrakos P, et al. Central pontine myelinolysis and cyclosporine neurotoxicity following liver transplantation. *Transplantation* 1996;61:658.
41. Jain A, Brody D, Hamad I, et al. Conversion to neoral for neurotoxicity after primary adult liver transplantation under tacrolimus [in process citation]. *Transplantation* 2000;69:172.
42. Torocsik HV, Curless RG, Post J, et al. FK506-induced leukoencephalopathy in children with organ transplants. *Neurology* 1999;52:1497.
43. Cooper DK, Novitzky D, Davis L, et al. Does central nervous system toxicity occur in transplant patients with hypercholesterolemia receiving cyclosporine? *J Heart Transplant* 1989;8:221.
44. Tejani A, Butt KM, Khawar MR, et al. Cyclosporine experience in renal transplantation in children. *Mt Sinai J Med* 1987;54:467.
45. Ciancio G, Siquijor AP, Burke GW, et al. Post-transplant lymphoproliferative disease in kidney transplant patients in the new immunosuppressive era. *Clin Transplant* 1997;11:243.
46. Pritchard DI. "Sourcing a chemical succession for cyclosporin from parasites and human pathogens". *Drug Discovery Today* 2005;10 (10):688-91.
47. Vilella-Bach M, Nuzzi P, Fang Y, et al. The FKBP12-rapamycin-binding domain is required for FKBP12-rapamycin-associated protein kinase activity and G1 progression. *J Biol Chem* 1999;274:4266.
48. Bierer BE, Mattila PS, Standaert RF, et al. Two distinct signal transmission pathways in T lymphocytes are inhibited by complexes formed between an immunophilin and either FK506 or rapamycin. *Proc Natl Acad Sci U S A* 1990;87:9231.
49. Luo H, Chen H, Daloze P, et al. Inhibition of in vitro immunoglobulin production by rapamycin. *Transplantation* 1992;53:1071.
50. Chung J, Kuo CJ, Crabtree GR, et al. Rapamycin-FKBP specifically blocks growth-dependent activation of and signaling by the 70 kd S6 protein kinases. *Cell* 1992;69:1227.
51. Kuo CJ, Chung J, Fiorentino DF, et al. Rapamycin selectively inhibits interleukin-2 activation of p70 S6 kinase. *Nature* 1992;358(6381):70-3.
52. Morice WG, Wiederrecht G, Brunn GJ, et al. Rapamycin inhibition of interleukin-2-dependent p33cdk2 and p34cdc2 kinase activation in T lymphocytes. *J Biol Chem* 1993;268:22737-45.
53. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998;31: 335.
54. Zimmerman JJ, Ferron GM, Lim HK, et al. The effect of a high-fat meal on the oral bioavailability of the immunosuppressant sirolimus (rapamycin). *J Clin Pharmacol* 1999;39:1155.
55. Sattler M, Guengerich FP, Yun CH, et al. Cytochrome P-450 3A enzymes are responsible for biotransformation of FK506 and rapamycin in man and rat. *Drug Metab Dispos* 1992;20:753.
56. Yatscoff R, LeGatt D, Keenan R, et al. Blood distribution of rapamycin. *Transplantation* 1993;56:1202.
57. Groth CG, Backman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group [see comments]. *Transplantation* 1999;67:1036.
58. Kahan BD, Julian BA, Pescovitz MD, et al. Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: a phase II trial. Rapamune Study Group. *Transplantation* 1999;68:1526.
59. Kahan BD, Podbielski J, Napoli KL, et al. Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. *Transplantation* 1998;66:1040.
60. Kahan BD, Rajagopalan PR, Hall M: Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation* 1999;67:276.
61. Kahan BD, Wong RL, Carter C, et al. A phase I study of a 4-week course of SDZ-RAD (RAD) quiescent cyclosporine-prednisone-treated renal transplant recipients. *Transplantation* 1999;68:1100.
62. McAlister V, Gao Z, Pltekian K, et al. Sirolimus-tacrolimus combination immunosuppression. *Lancet* 2000;355:9201.
63. Watson CJ, Friend PJ, Jamieson NV, et al. Sirolimus: a potent new immunosuppressant for liver transplantation. *Transplantation* 1999;67:505.
64. Forgacs, HJ Merhav, J Lappin, L Miesles. Successful Conversion to Rapamycin for Calcineurin Inhibitor-Related Neurotoxicity Following Liver Transplantation. *Transplant Proceed* 2005;37:1912-14.
65. F Di Benedetto, S Di Sandro, N De Ruvo, et al. Sirolimus Monotherapy in Liver Transplantation *Transplant Proceed* 2007;39:1930-32.
66. GPC Cantisani, ML Zanotelli, ALM Gleisner, et al. Enteric-Coated Mycophenolate Sodium Experience in Liver Transplant Patients. *Transplant Proceed* 2006;38:932-33.
67. Allison AC, Eugui EM. Immunosuppressive and other effects of mycophenolic acid and an ester prodrug, mycophenolate mofetil. *Immunol Rev* 1993;136:5.
68. Allison AC, Kowalski WJ, Muller CD, et al. Mechanisms of action of mycophenolic acid. *Ann NY Acad Sci* 1993;696:63.
69. Sievers TM, Rossi SJ, Ghobrial RM, et al. Mycophenolate mofetil. *Pharmacotherapy* 1997;17:1178.
70. TS Mele, PF Halloran, et al. The use of mycophenolate mofetil in transplant recipients. *Immunopharmacology* 2000;47:215-2.
71. Hebert MF, Ascher NL, Lake JR, et al. Four-year follow-up of mycophenolate mofetil for graft rescue in liver allograft recipients. *Transplantation* 1999;67:707.
72. Jain A, Reyes J, Kashyap R, et al. Liver transplantation under tacrolimus in infants, children, adults, and seniors: long-term results, survival, and adverse events in 1000 consecutive patients. *Transplant Proc* 1998;30:1403.
73. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group [see comments]. *Lancet* 1995;345(8961):1321.
74. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 1995;60:225.

75. Ringe B, Braun F, Lorf T, et al. Tacrolimus and mycophenolate mofetil in clinical liver transplantation: experience with a steroid-sparing concept. *Transplant Proc* 1998;30:1415.
76. Stegall MD, Wachs ME, Everson G, et al. Prednisone withdrawal 14 days after liver transplantation with mycophenolate: a prospective trial of cyclosporine and tacrolimus. *Transplantation* 1997;64:1755.
77. Eckhoff DE, McGuire BM, Frenette LR, et al. Tacrolimus (FK506) and mycophenolate mofetil combination therapy versus tacrolimus in adult liver transplantation. *Transplantation* 65:180, 1998.
78. Papatheodoridis GV, O'Beirne J, et al. Mycophenolate mofetil monotherapy in stable liver transplant patients with cyclosporine-induced renal impairment: A preliminary report. *Transplantation* 1999;68:155.
79. Fisher RA, Ham JM, Marcos A, et al. A prospective randomized trial of mycophenolate mofetil with neoral or tacrolimus after orthotopic liver transplantation. *Transplantation* 1999;66:1616.
80. Kato T, Ruiz P, DeFaria W, et al. Mycophenolate mofetil rescue therapy in patients with chronic hepatic allograft rejection. *Transplant Proc* 1999;31:396.
81. Klupp J, Glanemann M, Bechstein WO, et al. Mycophenolate mofetil in combination with tacrolimus versus Neoral after liver transplantation. *Transplant Proc* 1999;31(1-2):1113.
82. TM Manzia, N De Liguori Carino, G. Orlando, et al. Use of Mycophenolate Mofetil in Liver Transplantation: A Literature Review. *Transplant Proceed* 2005;37:2616-17.
83. A. Pierini, S. Mirabella, A. Brunati, et al. Mycophenolate Mofetil Monotherapy in Liver Transplantation. *Transplant Proceed* 2005;37 :2614-15.
84. M Jiménez-Pérez, J.M. Lozano Rey, et al. Efficacy and Safety of Monotherapy With Mycophenolate Mofetil in Liver Transplantation. *Transplant Proceed* 2006;38:2480-81.
85. Gordon RD, Tzakis AG, Iwatsuki S, et al. Experience with Orthoclone OKT3 monoclonal antibody in liver transplantation. *Am J Kidney Dis* 1998;11:141.
86. Wall WJ, Ghent CN, Roy A, et al. Use of OKT3 monoclonal antibody as induction therapy for control of rejection in liver transplantation. *Dig Dis Sci* 1995;40:52.
87. Wall WJ: Use of antilymphocyte induction therapy in liver transplantation. *Liver Transpl Surg* 1999;54(suppl 1):S64.
88. Brennan DC, Flavin K, Lowell JA, et al. A randomized, double-blinded comparison of Thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. *Transplantation* 1999;67(7):1011-18.
89. Gaber AO, First MR, Tesi RJ, et al. Results of the double-blind, randomized, multicenter, phase III clinical trial of Thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation* 1998;66:29.
90. Bonnefoy-Berard N, Flacher M, Revillard JP: Antiproliferative effect of antilymphocyte globulins on B cells and B-cell lines. *Blood* 1992;79:2164.
91. Bonnefoy-Berard N, Revillard JP: Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. *J Heart Lung Transplant* 1996;15:435.
92. Bonnefoy BN, Verrier B, Vincent C, et al. Inhibition of CD25 (IL-2R alpha) expression and T-cell proliferation by polyclonal anti-thymocyte globulins. *Immunology* 1992;77:61.
93. Wilde MI, Goa KL: Muromonab CD3: A reappraisal of its pharmacology and use as prophylaxis of solid organ transplant rejection. *Drugs* 1996;51:865.
94. Buysmann S, Bemelman FJ, Schellekens PT, et al. Activation and increased expression of adhesion molecules on peripheral blood lymphocytes is a mechanism for the immediate lymphocytopenia after administration of OKT3. *Blood* 1996;87:404.
95. Lee CW, Logan JL, Zukoski CF: Cardiovascular collapse following orthoclone OKT3 administration: a case report. *Am J Kidney Dis* 1991;17:73.
96. Spieker C, Zidek W, Barenbrock M, et al. Cardiovascular side effects after renal allograft rejection therapy with Orthoclone: prevention with nitrendipine. *J Cardiovasc Pharmacol* 1991;18 Suppl 1:S79.
97. Costanzo-Nordin MR: Cardiopulmonary effects of OKT3: Determinants of hypotension, pulmonary edema, and cardiac dysfunction. *Transplant Proc* 1993;25:21.
98. Abramowicz D, De Pauw L, Le Moine A, et al. Prevention of OKT3 nephrotoxicity after kidney transplantation. *Kidney Int* 1996;53(suppl):S39.
99. Klintmalm GB, Goldstein R, Gonwa T, et al. Use of Prograf (FK 506) as rescue therapy for refractory rejection after liver transplantation. US Multicenter FK 506 Liver Study Group. *Transplant Proc* 1993;25(1 Pt 1):679.
100. Waldmann TA, O'Shea J. The use of antibodies against the IL-2 receptor in transplantation. *Curr Opin Immunol* 1998;10:507.
101. Kovarik J, Breidenbach T, Gerbeau C, et al. Disposition and immunodynamics of basiliximab in liver allograft recipients. *Clin Pharmacol Ther* 1998;64:66.
102. Lampen A, Christians U, Gonschior AK, et al. Metabolism of the macrolide immunosuppressant, tacrolimus, by the pig gut mucosa in the Ussing chamber. *Br J Pharmacol* 1996;117:1730.
103. Vincenti F, Lantz M, Birnbaum J, et al. A phase I trial of humanized anti-interleukin 2 receptor antibody in renal transplantation. *Transplantation* 1997;63:33.
104. J Figueras, A Bernardos, et al. Steroid-Free Regimen With Daclizumab, Mycophenolate Mofetil and Tacrolimus in Liver Transplant Recipients. *Transplant Proceed* 2002;34:1511-13.
105. S Gruttadauria, F Vasta, L Mandalà, et al. Basiliximab in a Triple-Drug Regimen With Tacrolimus and Steroids in Liver Transplantation. *Transplant Proceed* 2005;37:2611-13.
106. CB Ramirez, C Doria, et al. Basiliximab Induction in Adult Liver Transplant Recipients With 93% Rejection-Free Patient and Graft Survival at 24 Months. *Transplant Proceed* 2006 38:3633-35.
107. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group [published erratum appears in *Lancet* 1997 Nov 15;350(9089):1484]. *Lancet* 1997;350(9086):1193.
108. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis: A 12-year single center experience. *Ann Surg* 1997;225:472.
109. Jeyarajah DR, Netto GJ, Lee SP, et al. Recurrent primary sclerosing cholangitis after orthotopic liver transplantation. *Transplantation* 1998;66:1300.
110. Van de Stadt J, Gelin M, Bourgeois N, et al. Liver transplantation for fulminant and subacute viral hepatic failure in adults. *Transplant Proc* 1990;22:1505.
111. Doyle HR, Morelli F, McMichael J, et al. Hepatic retransplantation: an analysis of risk factors associated with outcome. *Transplantation* 1996;61:1499.

112. Kumar N, Wall WJ, Grant DR, et al. Liver retransplantation. *Transplant Proc* 1999;31:541.
113. Markmann JF, Gornbein J, Markowitz JS, et al. A simple model to estimate survival after retransplantation of the liver. *Transplantation* 1999;67:422.
114. Charco R, Cantarell C, Vargas V, et al. Serum cholesterol changes in long-term survivors of liver transplantation: A comparison between cyclosporine and tacrolimus therapy. *Liver Transplant Surg* 1999;5:204.
115. De Carlis L, Belli LS, Rondinara GF, et al. Early steroid withdrawal in liver transplant patients: final report of a prospective randomized trial. *Transplant Proc* 1997;29:539.
116. Ramirez CB, Sebayer MI, Kizilisik T: Early steroid withdrawal after liver transplantation. *Transplant Proc* 1998;30:3182.
117. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. The U.S. Multicenter FK506 Liver Study Group [see comments]. *N Engl J Med* 1994;331:1110.
118. Reding R, Wallemacq PE, Lamy ME, et al. Conversion from cyclosporine to FK506 for salvage of immunocompromised pediatric liver allografts. Efficacy, toxicity, and dose regimen in 23 children. *Transplantation* 1994;57:93.
119. Tzakis AG, Fung JJ, Todo S, et al. Use of FK 506 in pediatric patients. *Transplant Proc* 1991;23:924.
120. Kelly DA, Jara P, et al. Tacrolimus and steroids versus cyclosporine microemulsion, steroids and azathioprine in children undergoing liver transplantation: randomized European multicenter trial. *Lancet* 2004;363:1354-57.
121. Jain A, Reyes J, Kashyap R, et al. What have we learned about primary liver transplantation under tacrolimus immunosuppression? Long-term follow-up of the first 1000 patients. *Ann Surg* 1999;230:441.
122. Freeman D, Grant D, Levy G, et al. Pharmacokinetics of a new oral formulation of cyclosporine in liver transplant recipients. *Ther Drug Monit* 1995;17:213.
123. Mirza DF, Gunson BK, Soonawalla Z, et al. Reduced acute rejection after liver transplantation with Neoral-based triple immunosuppression [letter]. *Lancet* 1997;349:701.
124. Loss GE, Jr, Brady L, Grewal HP, et al. Cyclosporine versus cyclosporine microemulsion in pediatric liver transplant recipients. *Transplant Proc* 1998;30:1435.
125. McKee M, Mattei P, Schwarz K, et al. Steroid withdrawal in tacrolimus (FK506)-treated pediatric liver transplant recipients. *J Pediatr Surg* 1997;32:973.
126. Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation* 1997;64:36.
127. Neumayer HH, Paradis K, Korn A, et al. Entry-into-human study with the novel immunosuppressant SDZ-RAD in stable renal transplant recipients. *Br J Clin Pharmacol* 1999;48:694.
128. Sehgal SN: Rapamune (sirolimus, rapamycin): An overview and mechanism of action. *Ther Drug Monit* 1995;17:660.
129. Kahan BD, Kaplan B, Lorber M, et al. Multicenter, randomized, double-blind, dose-finding study evaluating the efficacy and safety of RAD001 (RAD) in de novo renal transplant recipients. *Transplantation* 2000;70 (Abstract 954).
130. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac transplant recipients. *N Engl J Med* 2003;349:847.
131. Levy GA, Grant D, Paradis K, et al. Pharmacokinetics and tolerability of 40-0-[2-hydroxyethyl]rapamycin in de novo liver transplant recipients. *Transplantation* 2001;71:160.
132. Suzuki S, Enosawa S, Kakefuda T, et al. A novel immunosuppressant, FTY720, with a unique mechanism of action, induces long-term graft acceptance in rat and dog allotransplantation. *Transplantation* 1996;61:200.
133. Kahan BD, Karlix JL, Ferguson RM, et al. Pharmacodynamics, pharmacokinetics, and safety of multiple doses of FTY720 in stable renal transplant patients: a multicenter, randomized, placebo-controlled, phase study. *Transplantation* 2003;76:1079.
134. Jin MB, Nakanishi M, Ogata T, et al. A novel leflunomide derivative, FK778, for immunosuppression after kidney transplantation in dogs. *Surgery* 2002;132:72.
135. Savikko J, Willebrand EV, Hayry P: Leflunomide analogue FK 778 is vasculoprotective independent of its immunosuppressive effect: Potential applications for restenosis and chronic rejection. *Transplantation* 2003;76:455.
136. Calne R, Friend P, Moffat S, et al. Prope tolerance, perioperative campath 1h, and low-dose cyclosporin monotherapy in renal allograft recipients. *Lancet* 1998;351:1701.
137. Calne R, Moffatt S, Friend PJ, et al. Campath 1h allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. *Transplantation* 1999;68:3161.
138. Tzakis AG, Kato T, Nishida S, et al. Alemtuzumab (Campath 1h) combined with tacrolimus in intestinal and multivisceral transplantation. *Transplantation* 2003;75:1512.
139. Starzl TE, Murase N, Abu-Elmagd K, et al. Tolerogenic immunosuppression for organ transplantation. *Lancet* 2003;361:1502.
140. H Furukawa, S Todo. Evolution of Immunosuppression in Liver Transplantation: Contribution of Cyclosporine. *Transplant Proceed* 2004;36(Suppl 2S):274S-284S.
141. M Masetti, G Rompianesi, R Montalti, et al. Effects of Everolimus Monotherapy on Hematological Parameters and Iron Homeostasis in De Novo Liver Transplant Recipients: Preliminary Results. *Transplant Proceed* 2007;40:1947-49.

Hepatic Hemodynamics and Role of Doppler Ultrasonography

(A) HEPATIC HEMODYNAMICS

Hemodynamics of a patient with advanced liver disease is characterized by high portal outflow resistance and by an increase in portal inflow resulting from splanchnic arterial vasodilation. Earlier reports showed an increase in hepatic and portal blood flow after OLT.¹⁻³ After OLT, the normalization of portal resistance in the presence of an increased splanchnic flow, is followed by an increase in portal blood flow. An increase in hepatic blood flow,^{1-3,5} portal blood flow (PBF), mean velocity^{6,7} and portal blood flow volume^{1,2} has been reported in cirrhotic patients after OLT by most authors, whereas conflicting results have been reported on hepatic artery blood flow.^{1,2,8,9} The denervation of the transplanted liver³ and the persistence of portal-systemic collateral circulation, which after OLT disappears very slowly^{3,4,5} have both been considered as possible causes for the persistence of an increased hepatic blood flow after OLT. Whether and when this particular post-OLT hyperdynamic circulatory syndrome improves is controversial.^{4,5}

In patients transplanted for liver cirrhosis, superior mesenteric artery pulsatility index (PI) values and flow return to normal range in 3 to 6 months after OLT, whereas an increase in PBF persists for years after OLT, probably because of the persistence of splenomegaly. An increase in hepatic RI (resistance index) can be considered a normal finding the first few days after OLT. It is transient and is related to the increase in PBF.

PORTAL FLOW AND PORTAL VENOUS PRESSURE (PVP) MEASUREMENT

LDLT is an established procedure worldwide, allowing a wider organ pool.¹⁰ The successful use of smaller grafts

led to a revolution to alleviate mortality on the waiting list¹¹ but the consequences of using a small graft in a cirrhotic patient with severe portal hypertension are unpredictable.¹² Small-for-size syndrome (SFSS) occurs in the presence of a reduced liver mass that is insufficient to maintain normal liver function.¹³

Quality assurance of LDLT depends on

- Flow measurement of PV, HA and HV
- Vascular graft patency verification
- PVP measurement
- Inflow modulation (if any required)

In DDLT using a whole liver graft, the mean PVF has been reported to be around 130 mL/min/100 g graft weight¹⁴. It has been speculated that graft exposure to excessive portal vein flow (PVF) plays a major role in the development of SFSS. Poor graft outcome has been reported in patients with PVF values of more than 260 mL/min/100 gm graft weight in LDLT¹⁶ and elevated portal venous pressure.¹⁴ Busani et al used octreotide and esmolol infusion to decrease portal vein pressure in left lobe transplantation with a small-for-size graft.¹⁵

In order to alleviate graft over perfusion, intraoperative modulation of graft portal inflow using different techniques such as splenic artery ligation, splenectomy and portosystemic shunting have been attempted.

Troisi et al claimed that the PVF should be reduced to < 250 mL/min/100 gm of graft weight using graft inflow modification.¹⁷ Graft dysfunction is principally associated with graft exposure to excessive portal perfusion due to increased PVF, portal venous pressure and hepatic venous pressure gradient.¹⁸ Intraoperative measurement of portal vein pressure and vascular flow during LDLT allow evaluation of perfusion to separate

lobes of the living donor in order to select appropriate harvesting procedure and any necessity of portal flow modulation in the recipient depending on the flow measurement result. At the same time primary graft dysfunction due to technically flawed reperfusion of the graft in the recipient can be identified and alleviated.

Partial liver grafts are exposed to even higher portal inflow.^{19,20} Konishi et al²⁴ reported that hemodynamic changes are much more pronounced in left lobe grafts than those occurring in DDLT, and are inversely correlated with the GV/SLV (graft volume/ Standard liver volume) ratio. Shimamura et al.¹⁶ in his study classified patients into two groups: First group with a PVF > 260 mL/min/100 gm of graft weight (twice the mean PVF of whole liver graft) and the other group with PVF < 260 mL/min/100gm. They reported that patients with a PVF exceeding 260 mL/min/100 g graft weight were characterized by a smaller GV/SLV ratio and a significantly higher peak total bilirubin level with a consequently poor outcome, compared with the control group.¹⁶ **Figures 22.1 and 22.2** show the measurement of flow with TTFM flow meter.

GRAFT PORTAL FLOW ESTIMATION

$$\frac{\text{Total volume of portal flow measured by flow meter}}{\text{Weight of the hepatic allograft}} \times 100$$

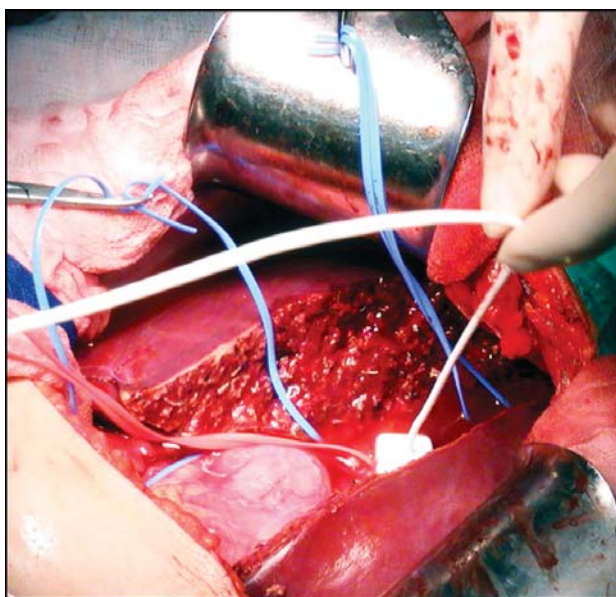


Figure 22.1: Intraoperative portal flow measurement in a donor right lobe graft using transient time flow meter (TTFM) with a flexible probe



Figure 22.2: Intraoperative hepatic artery flow measurement in a recipient after DDLT

Intractable ascites is one of the complications related to SFSS. Portal venous pressure (PVP) showed a significant correlation with daily production of ascites during the first 2 weeks. It is well known that leakage of ascites into the peritoneal space occurs as a result of sinusoidal hypertension.²² An increase in PVP may cause elevation of hydrostatic pressure within the liver sinusoids. Early elevation of postoperative PVP > 20 mmHg was associated with a poor outcome and graft dysfunction with hyperbilirubinemia, coagulopathy and severe ascites.²³ Intraoperative PVP measurement (**Figures 22.3 and 22.4**) before and after the allograft implantation is a useful in predicting such complications and need for some form of portal flow modulation. When PVP exceeds 25 mm Hg after transplantation, some attempt to modulate portal venous circulation might be required in order to improve the early postoperative course.²⁴

MEASUREMENT OF PORTAL FLOW

Before recipient hepatectomy and after the reperfusion of the allograft, portal flow measurement is important to estimate the amount of flow through the portal vein, hepatic artery and to confirm the patency of the vascular grafts, if used for reconstruction of V5 and V8.

DIFFERENT METHODS OF FLOW MEASUREMENT

1. **Finger palpation method:** It is subjective, no correlation with flow, no documentation and no evidence.

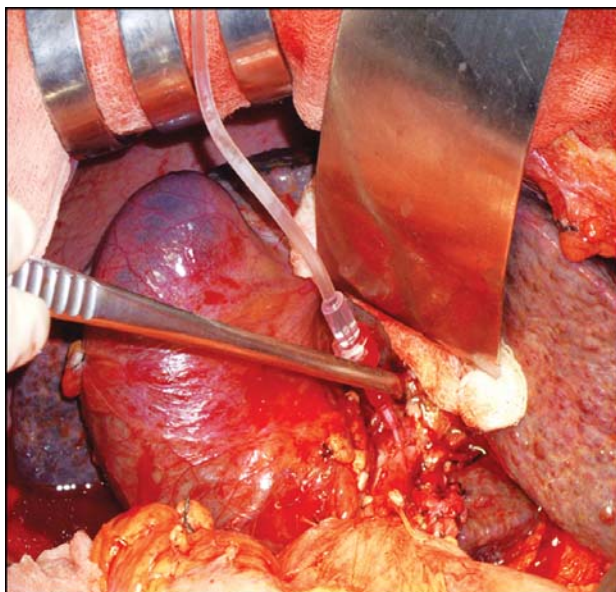


Figure 22.3: Intraoperative portal venous pressure measurement in the recipient prior to recipient hepatectomy

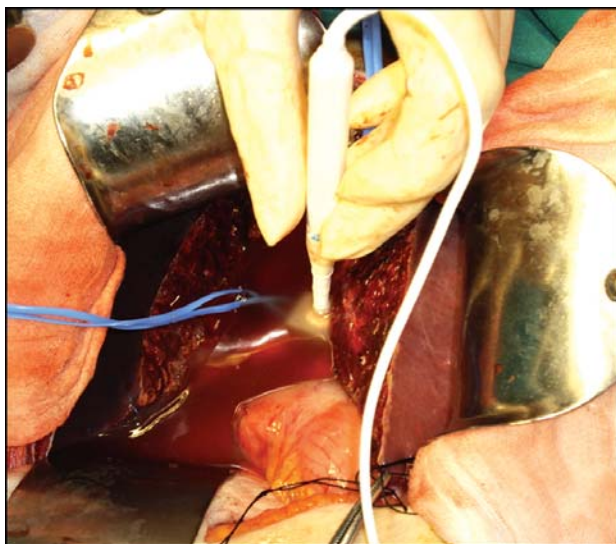


Figure 22.4: Intraoperative portal flow measurement in the recipient prior to recipient hepatectomy

2. **DUS** is the most popular and commonly used method for verification of flow. Drawbacks of DUS are: It is operator dependent, time consuming in verifying the routine patency, limited accuracy of flow volume estimation. Using the DUS, narrowest diameter of the portal vein is recorded along with the diameter at sites proximal and distal to this point, and the maximum flow velocity (Vmax) is measured at each point. The

portal vein blood flow is calculated from recordings in the proximal portal vein and at the narrowest point according to the formula mentioned below.²¹

Portal blood flow (L/minute) = Area $\times$ 0.57 $\times$ Vmax (Maximum flow velocity).

3. **Transit time flow meter probes** are the recent ones which provide easy way of flow estimation, less time consuming and not operator dependent. Ultrasonic **Transit time flow measurement (TTFM)** probes use transit time ultrasound technology (**Figure 22.5**) which is accurate and fast method of measuring flow. Probe size for hepatic artery is 3- 6 mm and for portal vein is 10-14 mm (**Figures 22.6 and 22.7**). Probe and vessel contact using isotonic saline in transit time flow meter. Probe with or without handle can be used. Probes without handle are more flexible in detecting flow in deeply located vessels. **Figures 22.8 to 22.12** show the recording of flow in portal vein and hepatic artery in the donor and recipient.
4. **Angiography** is more invasive and used less frequently.



Figure 22.5: Transit time flow meter (TTFM)



Figure 22.6: TTFM Probes with handle; Left: Size 10 mm for Portal vein flow; Right: Size 3 mm for hepatic artery flow

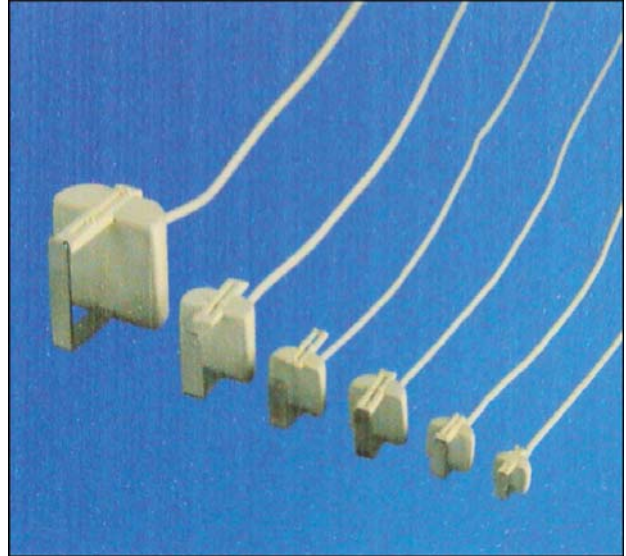


Figure 22.7: TTFM Probes without handle (different sizes)

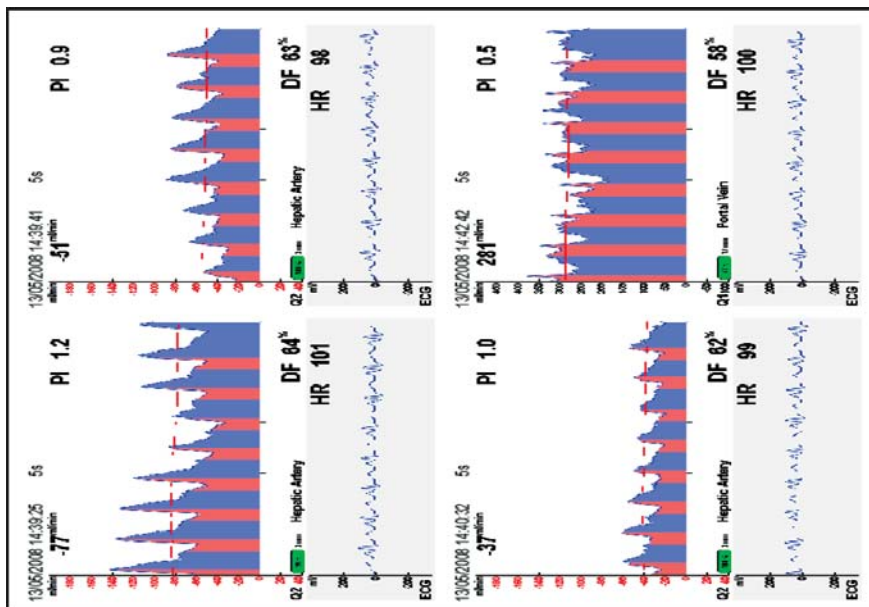


Figure 22.8: Normal donor hepatic artery and portal vein flow

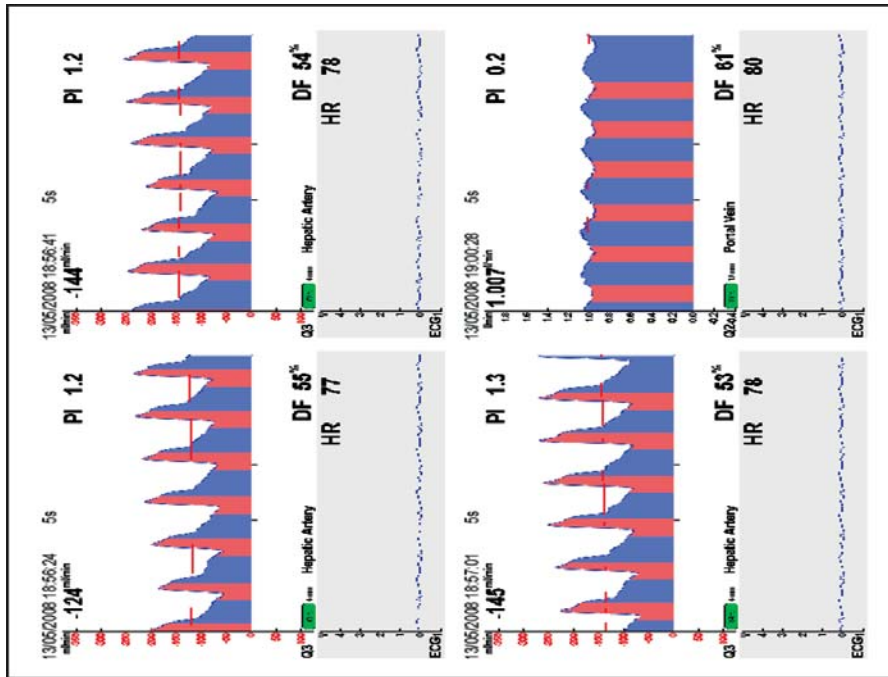


Figure 22.9: Normal recipient hepatic artery and portal vein flow

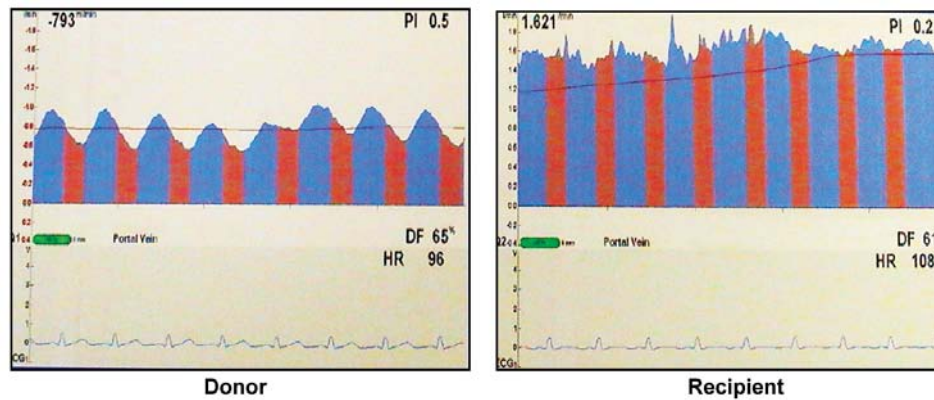


Figure 22.10: Normal portal vein flow in donor and recipient

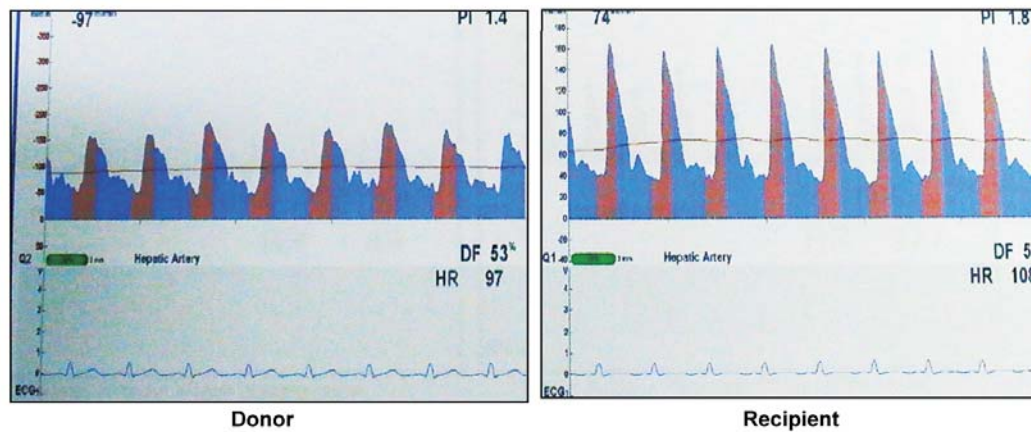


Figure 22.11: Normal hepatic artery flow in donor and recipient

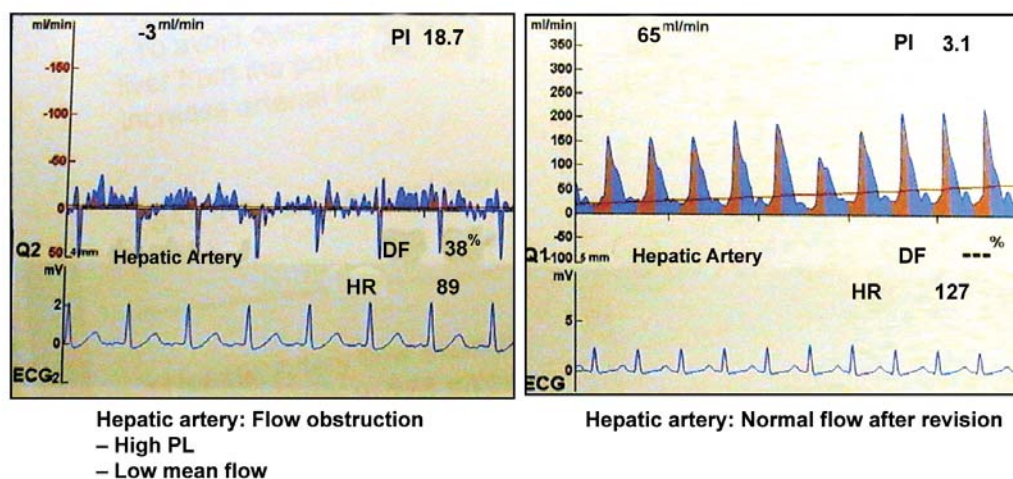


Figure 22.12: Hepatic artery flow occlusion and flow after revision of anastomosis

REFERENCES

- Paulsen AW, Klintmalm GB. Direct measurement of hepatic blood flow in native and transplanted organs, with accompanying systemic hemodynamics. *Hepatology* 1992;16:100-11.
- Henderson JM, Gilmore GT, Mackay GJ, Galloway JR, Dodson TF, Kutner MH. Hemodynamics during liver transplantation: the interactions between cardiac output and portal venous and hepatic arterial flows. *Hepatology* 1992;16:715-18.
- Hadengue A, Lebrech D, Moreau R, et al. Persistence of systemic and splanchnic hyperkinetic circulation in liver transplant patients. *Hepatology* 1993;17:175-78.
- Navasa M, Feu F, Garcia-Pagan JC, et al. Hemodynamic and humoral changes after liver transplantation in patients with cirrhosis. *Hepatology* 1993;17:355-60.
- Gadano A, Hadengue A, Widmann JJ, et al. Hemodynamics after orthotopic liver transplantation: Study of associated factors and long-term effects. *Hepatology* 1995;22:458-65.
- De Gaetano AM, Boldrini G, Agnes S, et al. Duplex Doppler in the postoperative monitoring of liver transplant recipients. *Transplant Proc* 1989;21:2319-21.
- Sukigara M, Iwatsuki S, Stieber A, et al. Changes of portal venous flow velocity after liver transplantation. *Transplant Proc* 1994; 26:2261-62.
- Houssin D, Fratacci M, Dupuy P, et al. One week of monitoring of portal and hepatic arterial blood flow after liver transplantation using implantable pulsed Doppler microprobes. *Transplant Proc* 1989; 21:2277-78.
- M Bolognesi, D Sacerdoti, G Bombonato, et al. Change in Portal Flow After Liver Transplantation: Effect on Hepatic Arterial Resistance Indices and Role of Spleen Size. *Hepatology* 2002; 35(3):601-08.
- Miller CM, Gondolesi GE, Florman S, et al: One hundred and nine living donor liver transplants in adults and children: a single-center experience. *Ann Surg* 2001;234:301.
- Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant* 2005;5:2605.
- Garcia-Valdecasas JC, Fuster J, Charco R, et al. Changes in portal vein flow after adult living-donor liver transplantation: Does it influence postoperative liver function? *Liver Transpl* 2003;9:564.
- Tucker ON, Heaton N. The "small for size" syndrome. *Curr Opin Crit Care* 2005;11:150.
- Ito T, Kiuchi T, Yamamoto H, et al. Changes in portal vein pressure in the early phase after living donor liver transplantation: Pathogenesis and clinical implications. *Transplantation* 2003; 75:1313.
- S Busani, G Marconi, L Schiavon L, et al. Living donor liver transplantation and management of portal venous pressure. *Transplant Proceed* 2006;38:1074-75.
- Shimamura T, Taniguchi M, Jin MB, et al. Excessive portal venous flow as a cause of allograft dysfunction in small-for-size living donor liver transplantation. *Transplant Proc* 2001;33:1331.
- Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. *Am J Transplant* 2005; 5:1397-404.
- Troisi R, Cammu G, Militerno G, et al. Modulation of portal graft inflow: A necessity in adult living-donor liver transplantation? *Ann Surg* 2003;3:429.
- Paulsen AW, Klintmalm GB. Direct measurement of hepatic blood flow in native and transplanted organs, with accompanying systemic hemodynamics. *Hepatology* 1992;16:100-11.
- Marcos A, Olzinski AT, Ham JM, et al. The interrelationship between portal and arterial blood flow after adult to adult living donor liver transplantation. *Transplantation* 2000;70:1697-703.
- N Konishi, Y Ishizaki, S Kawasaki, et al. Impact of a left-lobe graft without modulation of portal flow in adult-to-adult living donor liver transplantation. *Am J of Transpl* 2008;8:170-74.
- Garcia-Tsao G. Ascites. In: Boyer TD, Wright TL, Manns MP, eds. *Zakim and Boyer's hepatology: A textbook of liver disease*, 5th Ed. Philadelphia, PA: Saunders; 2006:333-46.
- Yagi S, Iida T, Taniguchi K, et al. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. *Liver Transpl* 2005;11:68-75.
- Moriyasu F, Ban N, Nishida O, et al. Clinical application of an ultrasonic duplex system in the quantitative measurement of portal blood flow. *J Clin Ultrasound* 1986;14:579-88.

(B) DOPPLER ULTRASONOGRAPHY IN LIVER TRANSPLANTATION

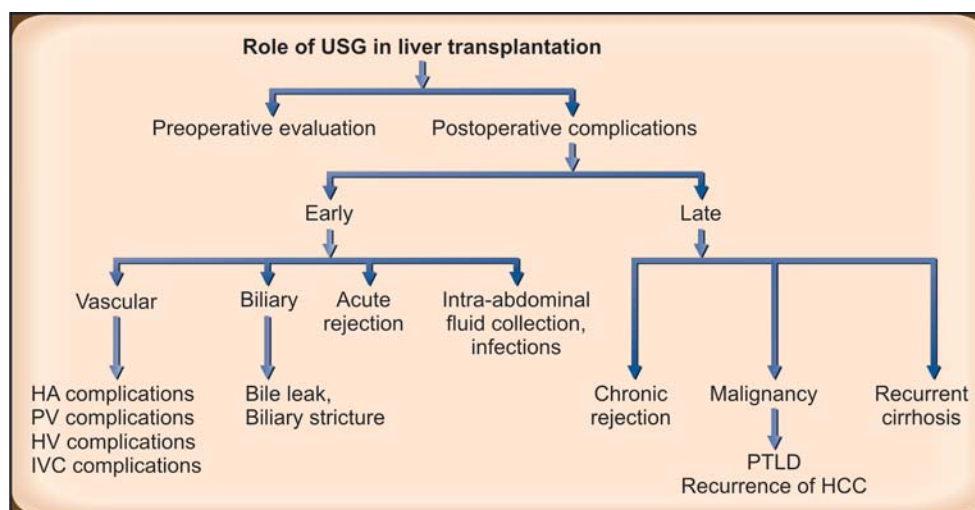
Prognosis in liver transplantation is closely related to postoperative vascular patency. Early detection and treatment of vascular complications reduces morbidity and mortality. Role of USG in liver transplantation is depicted in **Flow chart 22.1**. Doppler ultrasonography (DUS) provides an accurate diagnosis of complications after LTX and plays a very important role in post-transplant monitoring and is essential in guiding treatment.¹ It is used as a screening test in liver transplant patients due to its noninvasive imaging technique for evaluating the patency of the hepatic vasculature.²⁻⁶ MR angiography is performed to confirm abnormalities demonstrated in DUS or in patients in whom the DUS study is suboptimal. Conventional vascular studies are currently reserved for endovascular treatment of these complications.

Intra- and postoperative DUS is routinely performed in transplant units. Intraoperative DUS is widely used to determine intraoperative vascular patency. The diagnosis of vascular patency often relies only on quantitative and qualitative assessment of intraoperative Doppler signals. Intraoperative DUS is performed directly on the liver after completion of vascular anastomosis. It is usually performed with duplex Doppler system equipped with more than 6 MHz convex-array transducer for better visualization of vascular structures. The colour velocity scale is set to the lowest possible level that avoided aliasing, gain is adjusted to the maximum value without background noise and wall-motion high-pass filter is set at 50 Hz. When an arterial signal is detected,

the pulsed Doppler mode is activated. The insonation angle ranged from 30° to 60° during each examination. Postoperative DUS, a triplex DUS with a convex probe of 2-5 MHz is used. Color DUS examination includes a real-time morphologic evaluation of the liver parenchyma and color mapping of the hepatic artery, portal vein, hepatic veins, and IVC. Spectral analyses of the HA, PV, HV and IVC are also obtained. Hepatic artery, portal veins and hepatic veins are evaluated for patency, stenosis of anastomosis and presence of any thrombosis. Vascular graft flow and patency is also assessed by DUS in case of LDLT where V5 and V8 are reconstructed by using a vascular graft.

POSTOPERATIVE DUS PROTOCOLS

Postoperative DUS protocols after LTX differs from center to center. Meticulous monitoring of hepatic hemodynamics using DUS is required after LTX in the 1st two weeks for early detection of vascular complications is essential. Nishida et al. suggested that protocol DUS every 12 hrs in the 1st week followed by once daily in the 2nd week is useful in early detection and treatment of HAT.⁷ Others reported that once daily in the 1st week followed by once in 2 days in the 2nd week or daily in the initial period followed by once in 2 days in the first week. Kok et al. suggested DUS once in every 3 days in the first 2 weeks.⁸ Follow up DUS examination is usually done at 1, 3, 6, and 12 months after transplantation.



Flow chart 22.1: Role of USG in liver transplantation

Postoperative DUS measures the different parameters such as:

- Size, configuration and echo of graft
- Diameter of the hepatic veins, PV and hepatic artery
- Vascular anastomotic stoma, presence of thrombosis, blood flow and spectrum
- Presence of biliary obstruction
- Presence of perihepatic collection, hydrothorax and ascites

Complications affecting the portal vein after LTX include portal venous thrombosis and anastomotic stenosis, both of which are detected by the absence or acceleration of portal blood flow on DUS.⁹⁻¹¹ Hepatic venous occlusion or stenosis can occur after liver transplantation; the latter is usually accompanied by alterations in the modulation of the Doppler waveform.¹⁵⁻¹⁹

HEPATIC ARTERY

Hepatic artery is evaluated by placing the Doppler sample volume just proximal to the arterial bifurcation at the porta hepatis. The hepatic arterial Doppler velocity waveform is classified as a tardus-parvus pattern if the early systolic peak is absent or dampened and/or if the SAT is lengthened and/or if the RI is decreased.²¹ The sensitivity and specificity of DUS in detecting HA complications (thrombosis or stenosis) is 92% and 64% respectively.²⁰

DUS indicators of abnormalities in hepatic artery are:^{2,12-14}

- Resistive index (RI): Normal range between 0.6 and 0.8 (Peak systolic velocity - end diastolic velocity) / peak systolic velocity.
- Pulsatility index (PI): (peak systolic velocity - minimum velocity) / mean of maximal velocities.
- Systolic acceleration time (SAT): Normal range is < 80 ms
- Peak systolic velocity (PSV): Normal range is 40-80 cm/s
- Diastolic velocity (EDV)
- Mean velocity (Vm)
- Qualitative evaluation of the morphologic characteristics of the spectral waveform.

DUS Findings for HA Stenosis^{6,22}

- RI < 0.6
- SAT > 0.08 seconds
- Tardus-parvus pattern
- Focal PSV increase > 2 m/second

A low hepatic artery resistive index is a reliable predictor of hepatic artery thrombosis and stenosis

DUS Findings for Hepatic Artery Thrombosis (HAT)²³

- Total absence of hepatic arterial blood flow and hepatic artery signal
- Absence of extrahepatic signal with intrahepatic low amplitude
- Delayed upstroke signal suggesting thrombosis with collateralization
- Direct visualization of abrupt loss of arterial signal in the extrahepatic arterial branches
- Visualization of arterial collaterals in the porta hepatis.

Combination of abnormal RI, SAT, or peak velocity or no flow has a 97% sensitivity and 64% specificity for the diagnosis of marked arterial complications in transplanted livers.² Low hepatic artery resistive index in the early post-transplantation period is a sensitive (100%) and specific (80%) predictor of arterial and venous vascular complications.²² Arterial edema and vasospasm may explain some false positive results of intraoperative DUS for the detection of HAS during the early post-operative course (within 2 days), because they can alter the Doppler waveform and simulate stenosis.⁶ Therefore, follow-up DUS examinations and hepatic function evaluations are highly recommended. HAS may develop later on and could be missed on early.

PORTAL VEIN

DUS provides an ideal specificity on diagnosing PVT ranging from 97% to 100%.^{5,23} A small (2-5-mm) Doppler sample volume is used to exclude the signal from the portal vein; the smaller Doppler velocity scale is initially chosen and is increased when necessary. The portal venous flow is also measured at the porta hepatis. Normal range of portal venous velocity in LTX is not clearly established.

Huang et al suggested that in uncomplicated cases of vascular reconstruction:²⁴

- Portal venous flow velocity (PVFVe) : 25-60 cm/second (mean, 41 cm/second)
- Portal venous flow volume (PVFVo) : 15-33 ml/minute/kg (mean, 24 ml/minute/kg)

Blood flow velocity is calculated from recordings in the proximal portal vein and at the narrowest point. Recordings from the distal portal vein are not used as turbulent blood flow produced a wider range of flow velocities.

DUS Criteria for PV Stenosis

- Visualized narrowing of the luminal diameter to 2.5 mm or less
- Acceleration of flow at the stricture
- Post-stenotic jet of portal vein flow associated with or without post stenotic dilatation.

DUS Findings for Diagnosis of PV Aneurysm

Presence of a saccular dilatation of the portal vein adjacent to the anastomotic site with turbulent venous flow on colour DUS. High-flow velocities in these recipients may be caused by a combination of splanchnic hyperdynamic circulation and portal venous narrowing.

HEPATIC VEINS

The hepatic veins were examined at a distance of 1–3 cm from their outlet into the inferior vena cava.

The Doppler velocity waveforms of hepatic veins are classified as 1 of 3 patterns:

- Triphasic pattern (a waveform consisting of large antegrade systolic and diastolic waves and a small retrograde wave)
- Biphasic pattern in the absence of retrograde wave
- Flat waveform without any cardiac modulation.

The Doppler waveform of HVs is triphasic because right atrial pressure changes during the cardiac cycle are transmitted backward to the inferior vena cava and its tributaries.

DUS Findings for HV Stenosis

- Loss of triphasic wave pattern
- Persistent monophasic wave pattern.
- Accelerated flow velocities, ranging from 4–7 times the normal flow.

DUS Findings for HV Outflow Obstruction²⁵:

- Dilation of the hepatic veins
- Flattened hepatic vein velocity waveform
- Slowed hepatic vein flow velocity (<10 cm/second)
- Extreme decrease in portal inflow velocity (<14 cm/second)

Flow velocity of hepatic veins may be affected by many parameters like patency of the outflow vein and inflow vessels (HA and PV). Thus, the flow velocities and waveforms of the HV, PV and HA should be thoroughly evaluated to diagnose hepatic venous obstruction. Diagnostic validity of contrast-enhanced ultrasound (CEUS) was comparable to that of angiography, and CEUS shortened study time markedly.

REFERENCES

1. Yi-Ping Jia, Qiang Lu, Shu Gong, et al. Postoperative complications in patients with portal vein thrombosis after liver transplantation: Evaluation with Doppler ultrasonography. *World J Gastroenterol* 2007;13(34):4630–40.
2. Dodd GD 3rd, Memel DS, Zajko AB, et al. Hepatic artery stenosis and thrombosis in transplant recipients: Doppler diagnosis with resistive index and systolic acceleration time. *Radiology* 1994;192:657.
3. Platt JF, Yutzy GG, Bude RO, et al. Use of Doppler sonography for revealing hepatic artery stenosis in liver transplant recipients. *Am J Roentgenol* 1997;168:473.
4. Stell D, Downey D, Marotta P, et al. Prospective evaluation of the role of quantitative Doppler ultrasound surveillance in liver transplantation. *Liver Transpl* 2004;10:1183.
5. Tamsel S, Demirpolat G, Killi R, et al. Vascular complications after liver transplantation: evaluation with Doppler US. *Abdom Imaging* 2007;32(3):339–47.
6. Vit A, De Candia A, Como G, et al. Doppler evaluation of arterial complications of adult orthotopic liver transplantation. *J Clin Ultrasound* 2003;31:339.
7. Nishida S, Kato T, et al. Effect of protocol Doppler ultrasound and urgent revascularisation on early hepatic artery thrombosis after pediatric liver transplantation. *Arch Surg* 2002;137:1279–83.
8. Kok T, Slooff MJH, et al. Routine Doppler ultrasound for detection of clinically unsuspected vascular complications in the early postoperative phase after orthotopic liver transplantation. *Transpl Int* 1998;11:272–76.
9. Tang SS, Shimizu T, Kishimoto R, et al. Analysis of portal venous waveform after living-related liver transplantation with pulsed Doppler ultrasound. *Clin Transplant* 2001;15:380.
10. Berrocal T, Parron M, Alvarez-Luque A, et al. Pediatric liver transplantation: a pictorial essay of early and late complications. *Radiographics* 2006; 26:1187.
11. Crossin JD, Muradali D, Wilson SR. US of liver transplants: normal and abnormal. *Radiographics* 2003;23:1093.
12. Nghiem HV et al. Imaging of hepatic transplantation. *Radiol Clin North Am* 1998;36:429.
13. Vassiliades VG, Ostrow TD, Chezmar JL, et al. Hepatic arterial resistive indices: correlation with the severity of cirrhosis. *Abdom Imaging* 1993;18:61–65.
14. Hubner GH, Steudel N, Kleber G, Behrmann C, Lotterer E, Fleig WE. Hepatic arterial blood flow velocities: assessment by transcutaneous and intravascular Doppler sonography. *J Hepatol* 2000;32:893–99.
15. Cheng YF, Huang TL, Chen CL, et al. Intraoperative Doppler ultrasound in liver transplantation. *Clin Transplant* 1998;12:292.
16. Gondolesi GE, Florman S, Matsumoto C, et al. Venous hemodynamics in living donor right lobe liver transplantation. *Liver Transpl* 2002;8:809.
17. Huang TL, Chen TY, Chen CL, et al. Hepatic outflow insults in living-related liver transplantation: by Doppler sonography. *Transplant Proc* 2001;33:464.
18. Ko EY, Kim TK, Kim PN, et al. Hepatic vein stenosis after living donor liver transplantation: evaluation with Doppler US. *Radiology* 2003;229:806.
19. Yamagiwa K, Yokoi H, Isaji S, et al. Intrahepatic hepatic vein stenosis after living-related liver transplantation treated by insertion of an expandable metallic stent. *Am J Transplant* 2004; 4:1006.
20. De Gaetano AM, Cotroneo AR, Maresca G, et al. Color Doppler sonography in the diagnosis and monitoring of arterial

- complications after liver transplantation. *J Clin Ultrasound* 2000; 28:373-80.
21. Kotval PS. Doppler waveform parvus and tardus. A sign of proximal flow obstruction. *J Ultrasound Med* 1989;8:435.
22. Uzochukwu LN, Bluth EI, Smetherman DH, et al. Early postoperative hepatic sonography as a predictor of vascular and biliary complications in adult orthotopic liver transplant patients. *AJR Am J Roentgenol* 2005;185:1558.
23. Hom BK, Shrestha R, Palmer SL, et al. Prospective evaluation of vascular complications after liver transplantation: comparison of conventional and microbubble contrast-enhanced US. *Radiology* 2006;241:267-74.
24. Huang TL, Cheng YF, Chen TY, et al. Portal hemodynamics in living-related liver transplantation: quantitative measurement by Doppler ultrasound. *Transplant Proc* 1998;30:3186.
25. Someda H, Moriyasu F, Fujimoto M, et al. Vascular complications in living related liver transplantation detected with intraoperative and postoperative Doppler US. *J Hepatol* 1995;22:623.

ABO-Incompatible Liver Transplantation

INTRODUCTION

Living donor liver transplantation has been established as a treatment for patients with ESLD. But as donor selection is limited to mostly to relatives and spouses, concept of ABO-incompatibility is developed to meet the demands of donor shortage. In the 1970s, the liver was considered a privileged organ because no hyperacute rejections had been observed when the ABO barrier was crossed.¹ But later the concept about ABO barrier in LTX has changed with advances in understanding the immunology of liver transplantation.

Demetris et al² showed that ABO-incompatible (ABO-I) liver allografts may be susceptible to antibody-mediated (hyperacute) rejection from preformed antibodies (isoagglutinins). He described a high incidence of early graft failure (46% during the first 30 days) and severe hemorrhagic necrosis shown histologically with intra-organ thrombosis, as well as prominent arterial deposition of antibody and complement.

LDLT using an ABO-I donor has been reserved as the only available option for saving the life of a patient who only has ABO-I donors. The first ABO-I LDLT was performed in November 1991 in Japan.³⁴ In Japan national registry for ABO-incompatible transplantation was established in 2001. According to this registry, 291 (136 adults) ABO-I LDLTs have been performed till March 2006 in Japan from 28 institutions.³⁴ In the last decade, the initial results of ABO-I LDLT were dismal. 5-year patient survival was 22%.³ The main reason for these poor results is the severe hyperacute rejection due to anti-donor antibodies during the early postoperative period. The impact of preformed anti-donor antibodies and the strategy to reduce their titers play key roles in the success of this form of transplantation.⁴ Liver transplantation (LTX) across the ABO blood type barrier (ABO-

incompatible) is usually contraindicated earlier or is exceptionally performed only as a rescue option in an emergency situation because of the possibility of graft loss caused by antibody mediated rejection (AMR).

Organ transplantation based on blood type and immunological response is divided into three groups as shown in the box below:

- **Identical:** Similar blood type in donor and recipient such as:
A to A / B to B / AB to AB / O to O.
- **Compatible:** Compatible blood type in donor and recipient such as:
O to A / O to B / A to AB / B to AB, etc.
(O blood type: Universal donor; AB blood type: Universal recipient)
- **Incompatible:** Incompatible blood type between donor and recipient.
(A to B / B to A / A to O / B to O / AB to B / AB to A, etc.)

IgG and IgM anti-donor blood type antibodies are estimated preoperatively and postoperatively in the recipient. The titers are expressed in terms of 1:1, 1:2, 1:4, 1:8, 1:16, 1:32.....1:1024, etc. IgM titer more than 1024 is considered as a high-risk patient. Every effort is made to reduce the antibody titer to less than 1:16 throughout the course of transplantation to avoid humoral rejection.

T-cell cross-match test⁵: Pretransplant T-cell cross-match tests are performed. The test is interpreted as:

T-cell cross match test⁵

- **Positive:** When $\geq 41\%$ of donor lymphocytes are killed
- **Weakly positive:** 21 to 40% of donor lymphocytes are killed
- **Negative:** < 20% of donor lymphocytes are killed

Risk factors for antibody mediated (AMR) in ABO-I LTX³³

- Older age group
- Presence of autoimmune liver disease
- High IgG titer in postoperative period.
- IgM titer greater than 1024 preoperatively is a high-risk patient

(Children <2 years are less susceptible to humoral rejection due to incomplete development of immune system)

Gugenheim et al reported that systemic antirejection alone is not sufficient to control rejection after ABO-I liver transplantation. The frequency of major postoperative complications such as vascular complications and intrahepatic biliary complications are increased in ABO-I liver transplantation.⁷

DIFFERENT TREATMENT MODALITIES USED FOR IN ABO-INCOMPATIBLE TRANSPLANTATION⁸⁻¹⁰

Different treatment modalities to control AMR in ABO-I LTX

- Plasmapheresis (before and after transplantation)
- Anti CD₂₀ Antibody (Rituximab)
- Splenectomy
- Local infusion therapy.
 - Portal infusion therapy (PVI) (introduced in 2000)
 - Combined hepatic artery infusion (HAI) with PVI (introduced in 2001)
 - HAI without PVI (introduced in 2003)
- Intravenous immunoglobulin (IVIG)
 - Low-dose IVIG: 0.15 g/kg
 - High-dose IVIG: 0.6 g/kg
- Immunosuppression
 - Tacrolimus or cyclosporine + steroids and
 - Antimetabolites like MMF, azathioprine and cyclophosphamide

Until 2000, the gold standard for ABO incompatibility was plasmapheresis, systemic use of multiple immunosuppressive drugs and splenectomy; the 5-year survival was poor (22%). Later local administration of Prostaglandin E1 (PGE1), Corticosteroids, and Gabexate mesylate via portal vein (PV) catheter, as introduced by Keio University remarkably improved the results (60%). HAI therapy in addition to PVI improved the 1-year survival to 85.7%.

PLASMAPHERESIS / PLASMA EXCHANGE

Several studies have demonstrated the effects of plasmapheresis in the reduction of anti-donor antibody titers such as anti-A or anti-B antibody.³ Plasma exchange with blood-type AB fresh-frozen plasma (0.5 unit /kg) is performed, aiming at an antibody titer 1:16 or less before transplantation. After transplantation, plasma exchange is basically sustained until the antibody titer increased to 1:256 or more. Kozaki et al. suggested that anti-IgM and anti-IgG antibody titers sustained intrahepatic biliary complications and hepatic necrosis in ABO-I LTX in their experience at Kyoto University. Plasmapheresis is usually started atleast one week prior to transplantation. This procedure may increase the possibility of portal vein thrombosis. So after the procedure, usually portal flow is verified by Doppler US.

Plasmapheresis plays an important role in ABO-I LDLT. Multiple plasmapheresis courses (4-9 courses) are performed pre- and postoperatively to reduce the recipient's IgM and/or IgG antibody titers, such as anti-A or anti-B anti-donor antibody against the donor's blood type, to 1:16 or lower. The titers are measured on a regular basis after transplantation, every day during the first 2 weeks and during follow up OPD visits thereafter. Although multiple plasmapheresis courses are performed postoperatively, there are differences in elevation of IgM and/or IgG peak titers after transplantation.¹¹ Despite of the preoperative plasmapheresis and reduction in IgG and IgM antibody titers, postoperatively there is every possibility of increase in antibody titer in recipient of ABO-I LDLT. Ashizawa et al. reported the overall patient survival at 1 yr in ABO-I LDLT is 80%. There was no difference in transplant outcomes between the patients with incompatible blood types and identical or compatible blood types.¹¹ Multiple plasmapheresis therapy plays an important role in liver transplantation across ABO blood group barriers and that elevation of anti-ABO titers after transplantation may be a predictive risk factor for increased mortality and morbidity. In order to perform adult LDLT in a safer manner, plasmapheresis is an indispensable treatment to improve the outcome of ABO-I LTX. (11) Tanabe et al. described that multiple plasmapheresis before transplantation effectively reduced preformed antibody, which is the key to avoid humoral rejection. He recommended that a strong immunoinflammatory reaction and agents with vast spectra of action must be used to control single organ disseminated intravascular coagulation (DIC) after ABO-I LTX.¹²

SPLENECTOMY

Salomon et al. had reported that the spleen plays a clinically important role in the production of anti-A and anti-B antibodies.¹³ Previously splenectomy was performed in adult ABO-I transplantation with post-operative PVI therapy. But after the introduction of HAI therapy and Rituximab, splenectomy can be avoided, thus avoiding complications like portal vein thrombosis. Spleen preservation decreased the incidence of portal vein thrombosis but there is every possibility of increased the antibody titer.¹⁴

Indications for splenectomy during LDLT

- ABO-I LDLT
- Future anti-hepatitis C viral treatment of patients with thrombocytopenia
- Massive splenomegaly affecting quality of life and/or thrombocytopenia
- Portal flow modulation for small graft.

LOCAL INFUSION THERAPY

Tanabe et al. from Keio university (2000) first reported the use of local infusion treatment with intraportal or intra-arterial infusion of Prostaglandin E1 (PG E1-0.01 µg/kg/min for 3 weeks), Gabexate mesylate (20 to 30 mg/kg/d for 3 weeks) and Methyl prednisolone (100-125 mg/day first week and 50 mg/day in the next 2 weeks) for 3 weeks and the survival rate has increased to 60 to 70% although catheter related PV thrombosis was observed in 8 to 37.5% of cases.¹²

Gabexate mesylate is a protease inhibitor that commonly used for systemic DIC, inhibits platelet aggregation, thrombin, and other coagulation factors. PGE1 had the effect of improving microcirculation through vasodilatation, stabilizing lysosomal membranes, and inhibiting platelet aggregation as well as enhancing the effect of immunosuppression.^{15,16}

Yamada et al.¹⁷ reported that in pediatric liver transplants (biliary atresia) with ABO incompatibility, splenectomy and intraportal infusion therapy protocol consisting of continuous local administration of Prostaglandin E₁ (0.005-0.01 µg/kg per minute), methylprednisolone (2-3 mg/kg per day), and Gabexate mesylate (1 mg/kg/hour) via a portal vein catheter for 2 weeks. Even after the application of local infusion treatment, a considerable number of ABO-I LDLT grafts have been lost due to total graft necrosis associated with the rebound elevation of the isoagglutinins, for which plasma exchange seemed to be ineffective.¹⁸

HEPATIC ARTERY INFUSION THERAPY

After hepatic artery anastomosis, an 18-G catheter (designed for a central venous line) is placed in the hepatic arterial branch of the recipient, which is not used for reconstruction. Methylprednisolone, PG E1 and Gabexate mesylate are administered (as per the dosage mentioned earlier) immediately through the hepatic artery catheter adding to the basic immunosuppression. The catheter is removed 3 weeks after transplantation.

Complications of PV/HA infusion therapy

- Thrombosis of PV, SMV and HA
- Bleeding from the hepatic artery
- Accidental dislocations
- Sepsis
- Hepatic embolism

PV thrombosis was thought due to PV cannulation and splenectomy. Incidence of PV thrombosis (37.5%) can be reduced by inserting a catheter into a peripheral branch of the middle colic vein and keeping the tip of the catheter peripheral to the SMV.

ANTI CD₂₀ AB (RITUXIMAB)

It is a chimeric monoclonal gamma globulin (mouse / human) available as Rituxan. The antibody binds to the cluster of differentiation 20 (CD₂₀) widely expressed on B-cells.^{23,24} It is given as IV infusion at a dose of 375 mg/m². Half life is around 30-400 hours depending on the dose and length of treatment. Mechanism of action: The antibody binds to CD₂₀ and induces apoptosis of CD₂₀ positive cells. It has a general regulatory effect on the cell cycle. It induces complement mediated cell lysis and antibody-dependent cytotoxicity on CD₂₀ positive cells.^{19,20} The Fc portion mediates antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). It can reduce complement-dependent and antibody-dependent cellular cytotoxicity induced by antidonor blood type antibodies via B-cells.²¹ It down regulates the B-cell receptor. Adverse events are severe infusion reactions, cardiac arrest, leukopenia, renal dysfunction, and pulmonary edema, infections like HBV reactivation, progressive multifocal leukoencephalopathy (PML) and immune toxicity due to depletion of B-cells.

Uses of Anti-CD₂₀ Antibody therapy

- ABO-I transplantation
- B-cell non-Hodgkin's lymphoma
- B-cell leukemia
- Autoimmune disorders like Rheumatoid arthritis and SLE.

Other anti-CD₂₀ monoclonals: They are not recommended for use in transplantation.

- Ocrelizumab, humanized (90-95% human) B-cell agonist.
- Ofatumumab (HuMax-CD₂₀) a fully-human B-cell agonist.
- Belimumab

Rituximab can be used for rescue treatment or preoperative prophylaxis or for both. Usui et al. reported successful suppression of the isoagglutinin titer with the use of anti-CD₂₀ antibody (Ab) for 3 weeks before LDLT.²² In the ABO-I kidney field, Sonnenday et al. showed no correlation between clinical humoral rejection and positive C4d or high isoagglutinin titers. Further investigation is necessary in this field. He mentioned the possible avoidance of splenectomy for ABO-I cases with the use of anti-CD₂₀ Ab and Intravenous immunoglobulins.²³

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

It is used as treatment for evoked humoral responses. In the field of kidney transplantation, the effective use of IVIG for the control of acute humoral rejections in highly sensitized candidates was practiced as early as 1994.²⁴

Morioka et al. reported a case with the use of IVIG with local graft infusion treatment for a rebound elevation of the isoagglutinin titer after LDLT.²⁵ In ABO-I LDLT, early reports have described its ineffectiveness to control the rebound elevation of the isoagglutinin titer and the occurrence of total graft necrosis with its use after LDLT. In 2004, Morioka et al.²⁵ used IVIG for ABO-I LDLT. Even though the immunomodulatory mechanisms of IVIG are described as B-cell apoptosis, Fc-receptor dependent pathway, induction of the inhibitory receptor on the B-cell, inhibition of complement-mediated allograft injury, but the mechanism in ABO incompatibility is still unclear.^{24,25} Ikegami et al.²⁶ reported successful use of preoperative rituximab single dose and PE (twice daily for 3 days) and postoperative high-dose IVIG in combination with PE without the use of local infusion therapy in a case of ABO-I LDLT with humoral rejection. This strategy should therefore be another management option for ABO-I LDLT.

TRIPLE IMMUNOSUPPRESSION THERAPY

Systemic immunosuppression consists of Tacrolimus (10-15 ng/ml) or cyclosporine (300-350 ng/ml), corticosteroids, and antimetabolites like MMF (500-1000 mg bid) or azathioprine are used as per the normal protocol. Corticosteroids are tapered as per the routine protocol for compatible transplantation. The strategies developed for adult ABO-I LTX should be applied to the

child age group to further improve outcomes. High preoperative antibody titer did not have a significant effect on the frequency of AMR. Even if the antibody titer is decreased by preoperative plasmapheresis, patients are at increased risk for AMR. Conversely, a postoperative anti-donor blood-type antibody titer of 1:256 or greater is a significant risk factor for AMR. Every effort should be made to prevent a postoperative increase in anti-donor blood-type antibody titer. In Japan, survival rates and incidence of AMR in patients of blood type A mismatch and type B mismatch are similar. Blood type O is a significant risk factor for AMR in adults.⁶ Immune response is weak in blood type A2 than to type A1 leading to a better outcome of transplant with organs from A2 donors than from A1 donors.²⁷

Kyoto group²⁹ reported that rituximab administered earlier than 7 days before transplantation combined with HAI without splenectomy terminated clinical and pathological AMR and increased the 1-year survival rate to 80%.²⁸

Plasma exchange is performed three times before transplantation to remove the antidonor antibody to below an eight-fold dilution (1:8). The final plasma exchange is done in the early morning of the transplantation day. Oral administration of cyclophosphamide and tacrolimus is started 3 days before transplantation. Splenectomy is performed to suppress anti-donor antibody. A single-lumen catheter (16G) is inserted through the splenic artery in to the proper hepatic artery. The catheter is fixed with rubber used for ligation esophageal varices. PGE₁ is immediately and continuously infused at a dose of 0.01 µg/kg min. Immunosuppression with tacrolimus, steroid, and cyclophosphamide is administered as usual for ABO-compatible transplantation. When the donor antibody dilution was positive at =16 fold, plasma exchange is aggressively enforced to remove antidonor antibody, occurring twice after the operation with double-filtration plasmapheresis.

Kyoto university reported about ABO-incompatible liver transplantation and the immunosuppression used in their center:²⁹

1. Perioperative plasmapheresis using plasma exchange and the aim is to maintain antidonor blood group A/B antibody IgG and/or IgM titers at or below 1:16.
2. Pretransplantation immunosuppression: Cyclophosphamide 2 mg/kg/day (-3 day to 14 days) and Tacrolimus 0.05 mg/kg/day (-2 day on)
3. Intraoperatively methylprednisolone 500 mg IV during the anhepatic phase and splenectomy.
4. Post-transplantation immunosuppression includes 4 drug combination such as Tacrolimus trough level maintained at 10-15 ng/mL (first 3 weeks) followed

by 7-10 ng/mL from 4th week onwards; Methylprednisolone at a dose of 48-40-32-24-16-12 mg (taper); MMF at a dose of 250-1000 mg BID; Cyclophosphamide and Azathioprine are used only for 2 weeks in the post-transplant period. Cyclophosphamide-2 mg/kg/day, IV and Azathioprine-50 mg/day, PO.

5. Local antirejection therapy in post-transplant period by intrahepatic artery infusion of Prostaglandin E₁ 0.005-0.01

Recently Egawa et al.³⁴ reported Splenectomy and PV infusion therapy with triple-agent immunosuppression regimen consisting of tacrolimus, steroids, and MMF or cyclophosphamide is the most effective treatment to prevent AMR after ABO incompatible transplantation. Careful selection of patients is an essential component of improving outcomes of ABO-Incompatible LDLT, but the most important is to reduce the incidence of fatal infections and of AMR. The treatment strategy can be divided in to 3 groups such as:

A. Preoperatively:

Rituximab 1 week prior to surgery

Plasmapheresis one day prior to surgery

- B. Intraoperatively:** Splenectomy (may be avoided if rituximab is used)

C. Postoperatively:

- i. Local infusion therapy with PGE₁, Gabexate mesylate and Methylprednisolone for 3 weeks.
- ii. Immunosuppression: 3 drugs were used such as Corticosteroids (6 months), MMF or Cyclophosphamide (1 year) and Tacrolimus continued as standard protocol.

Egawa et al., in his series, used local infusion therapy in 133 patients.

- A. Portal infusion therapy (PVI) (41 patients of > 1 year age group) (introduced in 2000): prostaglandin E₁ (PGE₁), methyl prednisolone, and mesylates were used.
- B. Hepatic arterial infusion (HAI)+ PVI (23 patients of > 8 years age group): PGE₁ and steroids were administered through a catheter into the hepatic artery and mesylates through a catheter into the portal vein.
- C. HAI without PVI (68 patients of > 1 year age group): PGE₁ and steroids were used.

Egawa et al.⁴ reported that all long-term survivors showed low levels of IgM titers.⁴ Between PV and HA infusion, it is not yet concluded that which local infusion therapy is better and should be included in standard practice methods. Recently, the Kyoto group has reported that the CD₈⁺ T-cell phenotype can be used to predict the postoperative course and that the frequency of effector CD₈⁺ cells changed with the postoperative course.³⁰

Complications in ABO-I LDLT

- Humoral rejection 18%
- Hepatic necrosis 10%
- Intrahepatic biliary complications 8%
- Bacterial infections 29%
- Fungal infections 15%
- Viral infections 51%
- Thrombotic microangiopathy (TMA)

*Thrombotic microangiopathy (TMA):*³¹ It is diagnosed by sudden and severe thrombocytopenia, followed by hemolytic anemia with fractionated erythrocytes in the blood smear. It is manifested by thrombocytopenia, hemolytic anemia, renal dysfunction with marked elevation in fibrinolytic function markers such as plasminogen activator inhibitor type 1 (PAI-1). TMA occurred at a higher prevalence in ABO-I graft recipients. Early recognition of thrombocytopenia and elevation of PAI-1 is crucial to diagnose TMA and plasma exchange is started as soon as TMA is suspected.

Diagnosis of Antibody mediated rejection (AMR): Increase in of CD₁₉-positive lymphocytes observed in the peripheral blood will give a clue about humoral rejection. Hepatic necrosis and intrahepatic biliary complications can be diagnosed by CT scan. Biliary complication rate is more in ABO-I liver transplants. Percutaneous liver biopsy from specimen helps in confirming the humoral rejection showing signs of periportal edema, haemorrhage and necrosis. C4d staining shows apparent deposition in the portal area. Haga et al. reported that a positive C4d is the hallmark of acute humoral rejection and is associated with high isoagglutinin titers.³²

Prophylaxis for infection in ABO-I LDLT: Postoperative prophylaxis for the infection of patients with ABO-I transplantation consists of 3rd or 4th generation cephalosporins during operation and for the first 3-4 days postoperatively, antifungal agents like fluconazole or micafungin for 10 days, gancyclovir for 3 months, and trimethoprim/sulphamethoxazole for 1 year. Cytomegalovirus antigenemia is assessed every week for 6 weeks. A bacterial, viral, or fungal infection was assumed if clinical or laboratory signs of acute infection, positive serologic markers or culture are found.

ABO-I LDLT in pediatric patients: Keio university has reported ABO-incompatible liver transplantation in pediatric population⁶ which can be performed with a low risk of humoral rejection or late biliary complications using the combined antirejection strategy as discussed earlier in this chapter.

Kasahara et al. reported that in their LDLT program, an ABO-I graft was unavoidable in 12% of the recipients. Despite the application of preoperative plasma exchange, splenectomy and enhanced immunosuppression, the 5-year graft survival was less than 50% in an adult population.³³

REFERENCES

- Starzl TE, Ishikawa M, Putnam CW, et al. Progress in and deterrents to orthotopic liver transplantation, with special reference to survival, resistance to hyperacute rejection, and biliary duct reconstruction. *Transplant Proc* 1974;6:129.
- Demetris AJ, Jaffe R, Tzakis A, et al. Antibody-mediated rejection of human orthotopic liver allografts A study of liver transplantation across ABO blood group barriers. *Am J Pathol* 1988; 132:489.
- Kozaki K, Egawa H, Ueda M, et al. The role of apheresis therapy for ABO incompatible living donor liver transplantation: the Kyoto University experience. *Ther Apher Dial* 2006;10:441.
- Egawa H, Oike F, Buhler L, et al. Impact of recipient age on outcome of ABO-incompatible living-donor liver transplantation. *Transplantation* 2004;77:403.
- Demetris AJ, Nakamura K, Yagihashi A, et al. A clinicopathological study of human liver allograft recipients harboring preformed IgG lymphocytotoxic antibodies. *Hepatology* 1992;16:671-81.
- Y Yamada, K Hoshino, Y Morikawa, et al. Successful liver transplantation across the ABO incompatibility barrier in 6 cases of biliary atresia. *Journal of Pediatric Surgery* 2006;41:1976-79.
- Gugenheim J, Samuel D, Reynes M, et al. Liver transplantation across ABO blood group barriers. *Lancet* 1990;336:519.
- Pescovitz MD. B-cells: A rational target in alloantibody-mediated solid organ transplantation rejection. *Clin Transplant* 2005;10:48-54.
- Hanto DW, Fecteau AH, et al. ABOincompatible liver transplantation with no immunological graft losses using total plasma exchange, splenectomy, and quadruple immunosuppression: evidence for accommodation. *Liver Transplant* 2003;9:22-30.
- Troisi R, Noens L, et al. ABO-mismatch adult living donor liver transplantation using antigenspecific immunoadsorption and quadruple immunosuppression without splenectomy. *Liver Transpl* 2006;12:1412-17.
- T Ashizawa, N Matsuno, K Tanaka, et al. The Role of Plasmapheresis Therapy for Perioperative Management in ABO-Incompatible Adult Living Donor Liver Transplantation. *Transplant Proceed* 2006;38:3629-32.
- Tanabe M, Shimazu M, Wakabayashi G, et al. Intraportal infusion therapy as a novel approach to adult ABO-incompatible liver transplantation. *Transplantation* 2002; 73:1959.
- Salamon DJ, Ramsey G, Nusbacher J, et al. Anti-A production by a group O spleen transplanted to a group A recipient. *Vox Sang* 1985;48:309.
- A Yoshizawa, S Sakamoto, K Tanaka, et al. New protocol of immunosuppression for liver transplantation across ABO Barrier: The use of rituximab, hepatic arterial infusion, and preservation of spleen. *Transplant Proceed*. 2005;37:1718-19.
- Takaya S, Iwaki Y, Starzl TE. Liver transplantation in positive cytotoxic crossmatch case using FK 506, high-dose steroids, and prostaglandin E1. *Transplantation* 1992;54:927.
- Kamada N, Ozawa T, Ashizawa T, et al. Effects of combined therapy with prostaglandin E1 and cyclosporine A on rat heart allograft survival. *Transplant Proc* 1991;23:2213.
- Y Yamada, K Hoshino, Y Morikawa, et al. Successful liver transplantation across the ABO incompatibility barrier in 6 cases of biliary atresia. *Journal of Pediatric Surgery* 2006;41(12):1976-79.
- Kozaki K, Egawa H, Ueda M, et al. The role of apheresis therapy for ABO incompatible living donor liver transplantation: the Kyoto University experience. *Ther Apher Dial* 2006;10:441.
- Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006;6:859.
- Cartron G, Watier H, Golay J, et al. From the bench to the bedside: ways to improve rituximab efficacy. *Blood* 2004;104:2635.
- Vieira CA, Agarwal A, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. *Transplant* 2004; 77:542.
- Usui M, Isaji S, Mizuno S, et al. Experiences and problems pre-operative anti-CD20 monoclonal antibody infusion therapy with splenectomy and plasma exchange for ABO-incompatible living-donor liver transplantation. *Clin Transplant* 2007;21:24.
- Sonnenday CJ, Warren DS, Cooper M, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. *Am J Transplant* 2004; 4:1315.
- Jordan SC, Vo AA, Peng A, et al. Intravenous gammaglobulin (IVIG): A novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. *Am J Transplant* 2006;6:459.
- Morioka D, Sekido H, et al. Antibody-mediated rejection after adult ABO-incompatible liver transplantation remedied by gamma-globulin bolus infusion combined with plasmapheresis. *Transplantation* 2004;78:1225.
- T Ikegami, A Taketomi, Y Soejima, et al. Successful ABO Incompatible Living Donor Liver Transplantation in a Patient With High Isoagglutinin Titer Using High-Dose IVIG. *Transplant Proceed* 2007;39:3491-94.
- Rydborg L. ABO-incompatibility in solid organ transplantation. *Transfus Med* 2001;11:325-42.
- Egawa H, Ohmori K, et al. B-cell surface marker analysis for improvement of rituximab prophylaxis in ABO-incompatible adult living donor liver transplantation. *Liver Transplant* 2007;13:579-88.
- Y Nakamura, N Matsuno, K Tanaka, T Nagao, et al. Successful case of adult ABO-incompatible liver transplantation: Beneficial effects of intrahepatic artery infusion therapy: A case report. *Transplantation Proceedings* 2004;36(8):2269-73.
- Tanaka K, Uemoto S, et al. Antiinfectious defense by CD8+ cytotoxic T cells in human liver transplant recipients. *Liver Transplantation* 2006;12:792-800.
- R Miyata, I M Shimazu, M Tanabe, et al. Clinical characteristics of thrombotic microangiopathy following ABO-incompatible living donor liver transplantation. *Liver Transpl* 2007;13:1455-62.
- Haga H, Egawa H, Fujimoto Y, et al. Acute humoral rejection and C4d immunostaining in ABO blood type-incompatible liver transplantation. *Liver Transpl* 2006;12:457.
- M Kasahara, Y Takada, H Egawa, et al. Auxiliary Partial Orthotopic Living Donor Liver Transplantation: Kyoto University Experience *Am J of Transplant* 2005;5(3):558-65.
- Egawa H, Satoshi T, Hironori H, et al. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology* 2008;47(1):143-52.

Electrolyte Abnormalities in ESLD

INTRODUCTION

Electrolyte and acid base disturbances are often seen in end stage liver disease (ESLD).

OLT is divided into three phases:

- Phase I (Pre-anhepatic phase/Dissection phase): Begins with the introduction of anesthesia and concludes upon occlusion of blood flow to the patient's diseased liver (anhepatic time)
- Phase II (Anhepatic phase): Begins at the anhepatic time and terminates with reperfusion of the donor liver by the patient's circulating blood
- Phase III (Postanhepatic or Reperfusion phase): Begins

at the time of reperfusion and continues until the end of the surgical procedure.¹

ELECTROLYTE DISTURBANCE

SODIUM

Normal plasma sodium—135 to 145 mEq/L

Hyponatremia

Pre-transplant hyponatremia is common in ESLD patients, especially in those with cirrhosis and ascites, because of impaired free water excretion.

Hypotonic hyponatremia (S _{osm} < 280 mOsm/kg H ₂ O)			
	Hypervolemia	Isovolemia	Hypovolemia
$U_{Na} > 20 \text{ mEq/L}$	① Acute renal failure ② Chronic renal failure ③ Dilutional hyponatremia	① Endocrine ① Hypothyroidism ② Glucocorticoid deficiency ③ SIADH ② Drugs ① Sulfonylureas ② NSAID ③ TCA and Haloperidol ④ Cyclophosphamide ⑤ Opiates and Nicotine ③ Psychogenic polydipsia	① Salt-losing nephritis ① Medullary cystic disease ② Polycystic disease ③ Obstructive nephropathy ④ Analgesic nephropathy ⑤ Chronic pyelonephritis ② RTA type I ~ IV ③ Diuretics and osmotic diuresis ④ Mineralocorticoid deficiency ⑤ Metabolic alkalosis
$U_{Na} < 10 \text{ mEq/L}$	① Congestive heart failure ② Liver cirrhosis ③ Nephrotic syndrome		① Skin loss ① Burns ② Excessive sweating ② GI loss ① GI suction ② Pancreatitis ③ Vomiting ④ Diarrhea ③ Third space loss ④ Traumatized muscle ⑤ Post-diuretic therapy
Isotonic pseudohyponatremia ① Hyperproteinemia ② Hyperlipidemia			
Hypertonic hyponatremia (S _{osm} > 295 mOsm/kg H ₂ O) ① Hyperglycemia ② Mannitol excess ③ Glycerol therapy			

Different mechanisms for free water retention:

- Nonosmotic hypersecretion of antidiuretic hormone (ADH)
- Altered prostaglandin metabolism
- Reduced delivery of filtrate to the ascending limb of the loop of Henle for free water production because of decreased filtered sodium and excessive proximal sodium reabsorption.²

Intraoperatively, hyponatremia may be reversed and patients may even become hypernatremic due to large amount of sodium infusion through blood products, sodium bicarbonate and isotonic or hypertonic saline.

Simultaneous infusion of potassium may lead to enhanced cellular uptake of potassium and contribute to the rise in extracellular sodium concentration.³

Rapid reversal of hyponatremia and the development of hypernatremia should be avoided because of the risk of central pontine myelinosis.^{3,4}

Recently, it has been shown that pretransplant hyponatremia is associated with significant complications during the first month after orthotopic liver transplantation (OLT). Hyponatremia should be considered not only a risk factor for death before OLT but also a risk factor for impaired early post-OLT outcomes.¹⁷

MAINTENANCE OF SODIUM LEVEL

HYPONATREMIA

Replacement therapy is by infusion of isotonic or hypertonic saline. Replacement therapy is guided by the formula

$$\text{Sodium deficit (mEq)} = \text{Normal total body water} \times (130 - \text{Current plasma sodium})$$

Total body water (In liters): 60% of lean body weight in males and 50% of lean body weight in females.

Plasma sodium of 130 mEq/L is taken as desired end point of replacement therapy.

To limit the risk of demyelinating encephalopathy, the rate of rise of plasma sodium should not exceed 0.5 mEq/L/hour and the final plasma sodium concentration should not exceed 130 mEq/L.

Central Pontine Myelinosis (CPM)

It is a symmetric noninflammatory demyelinating disorder in the brainstem pons. It is a complication of severe and prolonged hyponatremia. Cirrhotic patients on potent diuretic therapy are at risk of developing CPM.

Risk factors:

- Serum sodium < 120 mEq/L for more than 48 hrs.

- Aggressive IV fluid therapy with hypertonic saline and hypernatremia during treatment

With correction of the hyponatremia use of intravenous hypertonic saline, the correction can be too quick, not allowing enough time for the brain's cells to adjust to the new tonicity. With a rise in extracellular tonicity, the cells compensate by losing a small amount of water. This loss will continue until the intra- and extracellular tonicities are equal. If hypertonic therapy continues or is too rapid, the extracellular tonicity will continue to drive water out of the brain's cells, leading to cellular dysfunction and CPM.

Clinical manifestations include delirium, pseudo-bulbar palsy, dysphasia, dysarthria and spastic quadriplegia leading to permanent neurological damage. Individuals with hyponatremia should receive no more than 8-10 mmol of sodium per day to prevent central pontine myelinosis.

Hypernatremia

<i>Hypovolemia</i> (hypotonic fluid loss)	<i>Isoolemia</i> (pure water loss)	<i>Hypervolemia</i> (hypertonic fluid gain)
1. Renal losses *Osmotic diuresis a. hyperglycemia b. mannitol c. postacute tubular necrosis d. relief of obstruction *Diuretics	1. Renal losses *Central DI *Nephrogenic DI	1. Iatrogenic *Hypertonic saline *Hypertonic sodium bicarbonate
2. Extrarenal losses *Skin *Respiratory tract *Gastrointestinal tract	2. Extrarenal losses *Respiratory *Skin	2. Mineralocorticoid excess

Treatment of hypernatremia depends on the cause of hypernatremia. If it is hypovolemic hypernatremia, replace the volume deficit with isotonic saline (0.9% NaCl) and control cardiac output. If the hypernatremia is due to hypervolemia, diuretics are used to control it.

POTASSIUM

Normal value – 3.5 to 5.5 mEq/L

Hypokalemia

Mild hypokalemia is common in patients awaiting liver transplantation.

Etiology of hypokalemia

- Potassium loss from the intestines
 - Vomiting
 - Diarrhea

- Ileostomy: In some patients who have had bowel surgery and an Ileostomy formed, significant potassium loss can occur.
- Villous adenoma (a type of colon polyp that can cause the colon to leak potassium)
- Laxative use
- Potassium loss from the kidney
 - Diuretics like hydrochlorothiazide (HCTZ) or furosemide (Lasix)
 - Elevated corticosteroid levels, either from medication like prednisone or from Cushing's Syndrome
 - Elevated levels of aldosterone, a hormone that can increase with renal artery stenosis or adrenal tumors
 - Renal tubular acidosis
 - Low body magnesium levels
- Side effects of some medications
 - Aminoglycosides like gentamicin or tobramycin
 - Amphotericin B
 - Prednisone

Intraoperatively, during phases I and II, the potassium concentration remains relatively stable. Following reperfusion, however, there may be a transient 10 to 15 minute sharp rise in potassium levels if the potassium-rich perfusate is allowed to enter the circulation or if venovenous bypass is not used.^{5,6}

Rapid resolution of the rise in potassium concentration has been attributed to re-entry of potassium into hepatocytes. Still many patients require potassium supplementation.

Fluctuations in potassium concentration may be secondary to:

- Kidney dysfunction^{1,5}
 - Acute and chronic renal failure,
 - Glomerulonephritis,
 - Lupus nephritis,
 - Transplant rejection, and
 - Obstructive diseases of the urinary tract, such as urolithiasis (stones in the urinary tract).
- Diseases of the adrenal gland: Addison's disease
- Potassium shifts
 - Diabetic ketoacidosis
 - Trauma,
 - Burns,
 - Surgery,
 - Hemolysis (disintegration of red blood cells),
 - Massive lysis of tumor cells, and
 - Rhabdomyolysis (a condition involving destruction of muscle cells that is sometimes associated with muscle injury, alcoholism, or drug abuse)
- Medications
 - ACE inhibitors,
 - ARBs,

- NSAIDs,
- Potassium-sparing diuretics

When potassium has to be supplemented in great quantity with high sodium-containing fluid, hypernatremia may follow potassium supplementation because of an extracellular movement of sodium in association with cellular sodium and potassium exchange and an extracellular sodium concentrating effect caused by enhanced cellular free water uptake in association with cellular uptake of both potassium and chloride.

Control of hyperkalemia in patients with poor renal function may require dialysis.

Acute hyperkalemia caused by influx of potassium from the liver at the beginning of reperfusion during orthotopic liver transplantation (OLT) may induce various arrhythmias and myocardial depression, or "cardioplegia."¹⁶

MAINTENANCE OF POTASSIUM LEVELS

Hypokalemia

Treat the condition that promotes transcellular potassium shift (e.g. Alkalosis)

If the hypokalemia is due to potassium depletion, then potassium replacement is required.

Potassium deficit of 10% is expected for every 1 mEq/L of decrease in the serum potassium.

Replacement therapy:

- a. Potassium chloride: Available as a concentration of 1-2 mEq/L in ampoules containing 10,20,30 and 40 mEq of potassium.
- b. Potassium phosphate solution (4.5 mEq of potassium and 3 mM phosphate/mL)

Intravenous potassium replacement: Add 20 mEq of potassium to 100 ml of isotonic saline and infuse over 1 hour. Maximum rate of infusion is 20 mEq/hour. Preferably central line should be used for infusion due to irritating property of hyperosmotic potassium solution.

If the hypokalemia is refractory, check for serum magnesium as magnesium deficit promotes urinary potassium loss.

Hyperkalemia

Hyperkalemia occurs after early post-transplant period in recipients with decreased renal functions.

Treatment of Hyperkalemia:

- Stop all potassium intake (IV and PO)
- Monitor EKG
- Check pH, correct acidosis (if present)
- Calcium gluconate (10%) 10 ml intravenous over 3 mins and can be repeated in 5 mins. Response lasts for 20-30 mins. Avoid bicarbonate after calcium dose.

- Calcium chloride (10%) contains 3 times more calcium than calcium gluconate and rate of infusion is 10 ml intravenous over 3 mins.
- Kayexalate (oral dose of potassium) 30 gm in 50 ml of 20% sorbitol or rectal dose of 50 gm in 200 ml of 20% sorbitol as retention enema.
- 10 units of regular insulin in 500 ml of 20% dextrose solution, infused over 1 hour.
- Loop diuretics like frusemide can be used.
- Hemodialysis or CRRT is the most effective method of lowering potassium level in patients with renal compromise after liver transplantation.

CALCIUM

Normal value – 9 to 10 mg/dl

Hypocalcemia

Decreased total and ionized calcium is common in ESLD patients.

Intraoperatively, calcium levels may fall to life-threatening levels.

During phases I and II of liver transplantation, the free calcium level may fall when calcium is chelated by the citrate in any blood products the patients receive.^{1,6-8}

During the phase III (postanhepatic phase) this chelation process may be reversed when the functioning liver is able to metabolize citrate to bicarbonate.⁹

Excessive administration of blood products and calcium supplementation during phases I and II can predispose patients to hypercalcemia and metabolic alkalosis postoperatively.

Less commonly, hypercalcemia may occur in patients awaiting liver transplantation. Reports of hypercalcemia

have been documented in patients with renal failure and hepatocellular carcinomas independent of skeletal metastatic disease.¹⁰ When hypercalcemia does occur, control of both calcium and phosphate levels are crucial to avoid metastatic calcification.

Causes of Hypercalcemia

- Primary hyperparathyroidism
 - Sporadic
 - Familial
- Hypercalcemia of malignancy
 - Osteolytic hypercalcemia
 - Humoral hypercalcemia of malignancy
 - Ectopic production of calcitriol (by lymphoma)
- Hypercalcemia of granulomatous disease
- Chronic renal failure with aplastic bone disease
- Tertiary hyperparathyroidism
- Acute renal failure
- Familial hypercalcemic hypocalciuria
- Lithium-associated hypercalcemia
- Vitamin D intoxication
- Other causes
 - Increased calcium intake
 - Pheochromocytoma
 - Congenital lactase deficiency
 - Hyperthyroidism
 - Vitamin A intoxication
 - Thiazides
 - Milk-alkali syndrome
 - Immobilization
 - Theophylline

Etiology of hypocalcemia

<i>Decreased entry of calcium into the circulation</i>	<i>Increased loss of calcium from the circulation</i>	<i>Other causes</i>
• Hypoparathyroidism (absence of PTH secretion) – Postoperative – Autoimmune (isolated or part of polyglandular autoimmune syndrome) – Congenital (mutations of CaSR, PTH, and parathyroid aplasia) – Pseudohypoparathyroidism, types 1a and 1b, and type 2 • Magnesium depletion • Severe hypermagnesemia • Deficiency of vitamin D	• Hyperphosphatemia – Renal failure – Rhabdomyolysis – Tumor lysis – Phosphate administration • Acute pancreatitis • Hungry bone syndrome • Chelation – Citrate – EDTA – Lactate – Foscanet • Widespread osteoblastic metastases – Prostate cancer – Breast cancer	• Sepsis • Fluoride administration • Surgery • Chemotherapy – Cisplatin – 5-fluorouracil – Leucovorin

(Source: www.clevelandclinicmeded.com)

Calcium Replacement Therapy

10% Calcium chloride or 10% Calcium gluconate.

Bolus dose of 100 mg of elemental calcium diluted in 100 ml of isotonic saline given over 5-10 mins, followed by continuous infusion of 0.5-2 mg/kg/hr for at least 6 hours. Calcium chloride is preferably given in central line and calcium gluconate is given via peripheral vein.

PHOSPHATE

Normal value – 2.5 to 5 mg/dl

Hypophosphatemia is due to:

- Rapid redistribution of phosphate from the extracellular fluid into bone or soft tissue
- Inadequate intestinal phosphate absorption
- Excessive renal phosphate excretion

Hypophosphatemia is not uncommon in ESLD patients without renal failure. Intraoperative phosphate levels have been reported to rise. Postoperative hypophosphatemia is typically observed secondary to extracellular volume expansion, the use of diuretic, cyclosporine, and phosphate-binding medications.⁹

Treatment of Hypophosphatemia

Severe Hypophosphatemia (serum pH <1 mg/dl): IV phosphorus replacement is recommended at a rate of 0.6 mg/kg/hr

Hypophosphatemia (<2 mg/dl): IV phosphorus 0.9 mg/kg/hr

Once 2 mg/dl serum phosphorus is achieved, the oral replacement should be started at a dose of 1200-1500 mg phosphorus per day.

MAGNESIUM

Normal value – 1.4 to 2 mEq/L

HYPOMAGNESEMIA

Patients with ESLD may present with hypomagnesemia for the same reasons as for hypokalemia.

- Intraoperative hypomagnesemia is due to transfusion of citrated blood products.
- Postoperatively hypomagnesemia is due to
 - Enhanced renal loss
 - Use of cyclosporine
 - Recovering diuretic phase of pretransplant acute renal failure
 - Excessive gastrointestinal loss

Early replacement of magnesium is necessary to prevent cardiac arrhythmias and neurologic complications because calcineurin inhibitor neurotoxicity is more common in the presence of hypomagnesemia.¹¹

Magnesium Replacement Therapy

50% Magnesium sulfate (500 mg/ml) is diluted to 10% (100 mg/ml) or 20% (200 mg/ml) solution for intravenous use. Isotonic saline is used for dilution.

Dose – 1 to 5 mEq/kg/ 12- 24 hrs infusion depending on the severity of hypomagnesemia, later at a lower dose of 1 mEq/L/day for 3-5 days.

Oral preparations in the form of magnesium chloride, magnesium oxide (140 mg, 400 mg) and magnesium gluconate (500 mg) are available.

ACID-BASE DISTURBANCES**RESPIRATORY ALKALOSIS**

It is the most common acid-base disturbance seen in ESLD patients.

Possible factors in the hyperventilation that results in this alkalosis include

1. Increased CNS drive for respiration
 - Anxiety
 - CNS infection, infarction, trauma
 - Drugs: salicylates, nicotine, aminophylline
 - Fever, sepsis: especially gram-negative sepsis
 - Pregnancy, progesterone
 - Liver disease
2. Increased stimulation of chemoreceptors
 - Hypoxia
 - Anemia
 - Carbon monoxide toxicity
 - Pulmonary edema, pneumonia
 - Pulmonary emboli
 - Reduced inspired O₂ tension: high altitude
3. Increased mechanical ventilation — iatrogenic

METABOLIC ALKALOSIS

It is another common finding among ESLD patients and is due to

1. Chloride-responsive (urinary chloride < 10 mEq/L)
 - Vomiting
 - Nasogastric suction
 - Diuretics (urinary chloride > 20 mEq/L)
 - Post-hypercapnic alkalosis
 - Stool losses (laxative abuse, cystic fibrosis, villous adenoma)
 - Massive blood transfusion: Intraoperative infusion of citrated blood products and sodium bicarbonate solutions
 - Exogenous alkali administration
 - Reduced oral intake/inadequate fluid administration
 - Reduction of sufficient chloride delivery to the distal tubule to allow adequate bicarbonate excretion.¹⁴

2. Chloride-resistant (urinary chloride > 20 mEq/L)
 - Hyperadrenocorticoid states (Cushing's syndrome, primary hyperaldosteronism, secondary mineralocorticoidism [licorice, chewing tobacco] – Hypoalbuminemia^{12,13})
 - Hypomagnesemia
 - Hypokalemia
 - Bartter's syndrome
3. Milk-alkali syndrome

METABOLIC ACIDOSIS

It can occur as a result

- Metabolic acidosis with an increased anion gap
 - K. Diabetic ketoacidosis
 - U. Uremia
 - S. Salicylate intoxication
 - S. Starvation ketosis
 - M. Methanol
 - A. Alcohol ketoacidosis
 - U. Unmeasured osmoles: ethylene glycol, paraldehydes
 - L. Lactic acidosis
- Metabolic acidosis with a normal anion gap (hyperchloremic metabolic acidosis)
 - Renal loss of bicarbonate
 - a. Renal tubular acidosis
 - b. Hypoaldosteronism
 - c. Carbonic anhydrase inhibition: acetazolamide
 - GI loss of bicarbonate
 - a. Diarrhea
 - b. Pancreatic fistulas
 - c. Ureterosigmoidostomy
 - Mineral acid administration
 - a. Ammonium chloride
 - b. Arginine hydrochloride
 - c. Calcium chloride (oral only)

Renal tubular acidosis has been reported in patients with cholestatic liver disease and ethanol-induced chronic liver disease.¹⁵

RESPIRATORY ACIDOSIS

It is rare, but the presence of respiratory acidosis portends an ominous prognosis.¹⁵

Causes

1. Decreased alveolar ventilation and CO₂ removal
 - Obstruction (e.g. bronchospasm, emphysema, aspiration, foreign body or laryngospasm)
 - Primary depression of respiratory center (e.g. anesthesia, narcotics, sedatives, increased

intracranial pressure (IICP), vertebral artery embolism or thrombosis, trauma, neoplasm or infection)

- Mechanical or structural defect (eg. pneumothorax, hemothorax, ARDS, flail chest or kyphoscoliosis)
 - Mechanical or neuromuscular defect (eg. primary muscular disease, neuromuscular diseases, drugs, botulism, tetanus, organophosphate poisoning or spinal cord injury)
 - Decreased stimulation of respiratory center (sleep apnea)
2. Decreased capillary exchange of CO₂
 - Cardiac arrest
 - Circulatory shock
 - Severe pulmonary edema

Treatment of acidosis and alkalosis (metabolic/respiratory) is according to the etiology and the conditions precipitating the acid base disturbances.

REFERENCES

1. Rettke SR, Janossy TA, Chantigian RC, et al. Hemodynamic and metabolic changes in hepatic transplantation. *Mayo Clin Proc* 1989;64:232–40.
2. Arroyo V, Claria J, Salo J, et al. Antidiuretic hormone and the pathogenesis of water retention in cirrhosis with ascites. *Semin Liver Dis* 1994;14(1):44.
3. Rose BD. In Rose BD (ed). *Clinical Physiology of Acid-Base and Electrolyte Disorders*, ed 4. New York, McGraw-Hill, 1994:679.
4. Laurenro R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatremia. *Lancet* 1988;1:1439–41.
5. Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation: Cardiovascular and metabolic alterations and their management. *Anesth Analg* 1985;64:108–16.
6. Ring-Larsen H, Palazzo U. Renal failure in fulminant hepatic failure and terminal cirrhosis: A comparison between incidence, types, and prognosis. *Gut* 1981;22:585.
7. Bertholf RL, Bertholf MF, Brown CM, et al. Ionized calcium buffering in the transfused anhepatic patient: Ab initio calculations of calcium ion concentrations. *Ann Clin Lab Sci* 1992;22:40–50.
8. Wu AH, Braccy A, Bryan-Brown CW, et al. Ionized calcium monitoring during liver transplantation. *Mayo Clin Proc* 1989;64:232–40.
9. Gonwa TA, Wilkinson AH. Liver transplantation and renal function: Results in patients with and without hepatorenal syndrome. In Epstein M (ed): *The Kidney in Liver Disease*, ed 4. Philadelphia, Hanley and Belfus, 1996:529–42.
10. Sealy MM. Severe hypercalcemia due to a parathyroid-type hormone secreting tumour of the liver treated by hepatic transplantation. *Anaesthesia* 1985;40:170–77.
11. Gijtenbeek JM, van den Bent MJ, Vecht CJ, et al. Cyclosporine neurotoxicity: A review. *J Neurol* 1999;246(5):339–46.
12. McAuliffe JJ, Lind LJ, Leith DE, et al. Hypoproteinemic alkalosis. *Am J Med* 1986;81:86–90.
13. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983;61:1444–61.

14. Oster JR, Perez GO. Acid-base homeostasis and pathophysiology in liver disease. *In* Epstein M (ed): The Kidney in Liver Disease, ed 3. New York, Elsevier Biomedical 1983:119-31.
15. Oster JR. Acid-base homeostasis and liver disease. *In* Epstein M (ed): The Kidney in Liver Disease, ed 2. New York, Elsevier Science, 1983:147-82.
16. Aggarwal S, Bloom M, Kang Y, et al. EEG and AVDO₂ monitoring: Adjuncts in the management of acute hepatic encephalopathy during liver transplantation. *Transplant Proc* 1991;23(3):1922-23.
17. Londono MC, Guevara M, Rimola A, et al. Hyponatremia impairs early post-transplantation outcome in patients with cirrhosis undergoing liver transplantation. *Gastroenterology* 2006;130:1135.

Immunology of Transplantation

CELLULAR BASIS OF REJECTION

Liver is one of the most immune-tolerant of all solid organ transplants. Histological criteria for diagnosis of ACR in liver depends on the presence of large portal based inflammatory infiltrate with injury to hepatic components. Early target tissue for ACR is the bile duct epithelium and venous endothelium leading to injury to hepatocytes either by direct immunological injury or due to the effect of vascular injury and ischemia.

ROLE OF CD₄⁺ AND CD₈⁺ LYMPHOCYTES IN ACR

Lymphocytes are the predominant of cells involved in ACR. Hepatic allograft rejection is mediated by a primary response of T-lymphocytes, followed by a mixed inflammatory infiltrate. Lymphocyte population contains both CD₄⁺ and CD₈⁺ lymphocytes, when activated, these cells proliferate, differentiate and secrete cytokines. The appearance of CD₄⁺ lymphocytes within the portal tracts predicts rejection even before the biochemical evidence is present. ACR and chronic rejection correlate with the presence of CD₈⁺ rather than CD₄⁺ cells within the portal tracts.¹ It is believed that CD₈⁺ T-cells that cause the graft injury via cytolytic activity directed against donor alloantigen. Clinical observations suggest that CD₄⁺ cells have a central role in allograft rejection by acting through CD₈⁺ effector cells.

Mc Caughan et al² using frozen tissues from 18 cases with ACR, reported that CD₄⁺ and CD₈⁺ cells were present in approximately equal numbers in the portal tracts and that the CD₈⁺/CD₄⁺ ratio in bile ducts was approximately 6:1, whereas slightly more than 50% of T-cells attached to portal and central veins indicating endothelitis were CD₈⁺ cells. Ibrahim et al.³ using frozen liver tissues, found the number of portal CD₃-positive T-lymphocytes to be significantly higher in 20 patients showing rejection than in 30 without evidence of rejection. This was primarily

the result of a significant increase in CD₈⁺ cells. Ibrahim et al. comparing subjects with and without transplanted liver rejection, concluded that rejection was most associated with a marked increase in the number of CD₈⁺ T-cells. Dollinger et al.⁴ using formalin fixed and paraffin-embedded liver tissues, reported that CD₄⁺ T-lymphocytes were located predominantly inside the portal tracts and were significantly more numerous, accounting for 59.0-66.2% of lymphocytes and CD₈⁺ T-cells were located predominantly within the liver parenchyma, based on observation of 10 liver tissues with ACR.

Kuboto et al⁵ reported that the number of CD₈⁺ lymphocytes increased while CD₄⁺ lymphocytes decreased, according to the degree of ACR. This resulted in positive and inverse correlations between portal infiltration of CD₈⁺ and CD₄⁺ T-lymphocytes and ACR severity, respectively. CD₈⁺ lymphocytes were also demonstrated to be present in the bile duct epithelia and subendothelial portions of portal veins, sites used pathologically to diagnose ACR, indicating that CD₈⁺ cells participate in tissue injury.

From all earlier studies it is clear, morphologically, that CD₈⁺ rather than CD₄⁺ T-lymphocytes play an important role in tissue damage, which corresponds to the severity of ACR inflammation.

Identification of tissue CD₈⁺ levels in the portal tract to be useful for objectively evaluating the degree of ACR in LRLT. It was also suggested that cytotoxic T-cells play an important role in ACR.⁵ Other studies reported that rejection demonstrates higher expression of CD₄⁺, CD₇⁺ and CD₈⁺, CD₃₈⁺ T-lymphocytes in liver in comparison to peripheral blood. In patients without acute rejection, CD₄⁺, CD₇⁺ T-lymphocytes were found in higher number in peripheral blood than in the liver. This indicates that T1-helper cell immune mechanism operates in a local fashion and may be involved in acute rejection. CD₄⁺ cells

are important in initiating and amplifying the immune response and the CD₈₊ cells are involved in rejection process.

Helper T-lymphocytes and Rejection

It is generally accepted that helper T-lymphocytes play a central role in the triggering of allograft rejection,⁶ especially by the secretion of cytokines, that provide help for the activation, proliferation, and differentiation of other lymphocytes.⁷ After activation, helper T-lymphocytes are polarized into two major subsets, T-helper 1 cells (Th₁) and T-helper 2 cells (Th₂), based on their cytokine production.⁸⁻¹⁰ Similarly, cytotoxic T (Tc) lymphocytes may differentiate into Tc₁ and Tc₂ populations with cytokine profile analogous to those seen in Th subpopulations.¹¹

Th₁ cells produce interleukin- γ (IL-2), interferon- α (IFN- γ), tumor necrotic factor α and β and promote immunopathologic functions by mediating delayed-type hypersensitivity (DTH),¹ and frequently his type of immune activation is usually manifested during allograft rejection.⁹ Th₁ type cytokines have been correlated with acute graft rejection severity as well as a kind of selective recruitment of Th₁ cells into sites of DTH reactions,⁷ probably due to the expression of selectin ligands in cell surface. Drugs that suppress the IL-2 production and release like cyclosporine and tacolimus play a vital role in the inhibition of rejection response.

Kim et al reported that measurement of serum IFN- α and sCD₃₀ during the pre- and post-LDLT periods may be helpful to evaluate the risk for liver allograft rejection.¹³ CD₃₀ is a 120-kDa transmembrane glycoprotein member of the tumor necrosis factor-nerve growth factor receptor family. A soluble form of CD₃₀ (sCD₃₀), which is released into the bloodstream, can be used as a marker for an activation state of Th₂ cytokine-producing T-cells.¹² Th₂ cells produce IL-3, IL-4, IL-5, IL-6 and IL-10, among others,⁸ provide B cell help, and could inhibit Th₁ proliferation and cytokine secretion. Th₂ cells may modulate acute rejection and the development of allograft tolerance.¹⁴ Also Th₂ cytokine transcripts correlate with milder rejection episodes and support humoral/antibody mediated response mediated by Ig G1 and Ig E1.¹⁵ These findings led to the hypothesis that immune deviation from a Th₁ to a Th₂ cytokine profile could play a crucial role in long-term graft survival.⁹ Th₂ type cytokines have been correlated to a certain tolerance induction and a promoting graft survival.¹⁶

ROLE OF REGULATORY T-CELLS (TREGS)

Early studies in rats suggested that tolerance to liver grafts involves immune suppression, as splenocytes of

recipients were able to suppress an allo-MLR.⁶⁸ These experiments showed that there were two spleen cell populations involved in the suppressive activity, an early-acting population enriched in macrophages that was nonspecific and mediated by prostaglandins and a late-acting population developing after 35 days that was specific and depended on T-cells. Subsequent studies confirmed the presence of suppressor T-cells after LTX.⁶⁹⁻⁷¹

In recent years, the descended concept of suppressor T-cells has undergone renewal and T-cells with immunosuppressive function have become renamed as Tregs. The predominant Treg cell subset, initially identified by Hall et al⁷² and later studied by Sakaguchi et al.⁷³ is included among CD₄₊ CD₂₅₊ T-cells and is marked by the expression of the transcription factor Foxp3. In addition to this subset, there is a variety of other T-cell subsets with regulatory properties and varied phenotypes, including CD₈₊, CD₈₊ CD₂₈-, TCR₊ CD₄- CD₈- double negative, and NK receptor expressing T-cells.⁷⁴ The CD₄₊ CD₂₅₊ regulatory T-cells are dividable into natural thymus-dependent Tregs and into peripherally induced Tregs that develop inter alia during an allospecific immune response.⁷⁴ Therefore, in transplantation, natural Tregs might be carried by the liver allograft or may develop as peripherally induced regulatory T-cells in the recipient during the immune response against the graft. Where and how Tregs exert their function during the induction and maintenance phases of spontaneous liver allograft tolerance are unclear, but there is evidence for their existence.

A recent study addressed the question of the specific role of the CD₄₊ CD₂₅₊ Treg subset in spontaneous liver tolerance in mice, using a CD₂₅ depleting antibody.⁷⁵ Liver acceptance was not affected when CD₂₅₊ cells were depleted in the donor prior to or in the recipient 20 days after the transplantation; however, the antibody injected into recipient mice at the time of transplantation resulted in liver rejection. Therefore, CD₂₅₊ and, presumably CD₄₊, Tregs seem to be necessary in the induction but not the maintenance phase of allogeneic tolerance in this model. This finding has been indirectly confirmed in humans among whom peripheral blood CD₄₊ T-cells completely weaned from immunosuppression displayed donor-specific hyporesponsiveness in vitro, which was not affected when the CD₂₅₊ subset was depleted.⁷⁶ However Demirkiran et al⁷⁷ reported a drop in CD₄₊ CD₂₅₊ T-cells in peripheral blood directly after human liver transplantation, and low levels were sustained in patients who experienced acute rejection episodes, whereas a relative recovery of this subset was observed in patients with stable allograft function.

These studies indicate that the cells with regulatory function do seem to participate in both the induction and

the maintenance phase of liver transplant tolerance. Although the recipient CD₄₊ CD₂₅₊ Treg subset seems to be critical in the induction phase, other types of regulatory cells of undetermined phenotype and mode of action might function during the maintenance phase.⁷⁸

ROLE OF OTHER CELLS IN ACR

Other types of cells present within the portal tracts are noninflammatory response. Their appearance reflects the influence of local cytokines in the inflammatory response.

Neutrophils

They are seen in rejection, acute cholangitis and CMV infection. They are usually seen in partially treated or late rejection.

Eosinophils

Peripheral eosinophilia usually <5% is seen in allograft rejection. CD₄₊ Th₂ cells secrete IL-5 which attract eosinophils causing further injury and inflammation. Eosinophil count has a predictive value in the diagnosis of ACR and a marker of treatment response. Normal count of eosinophils rules out the moderate to severe rejection and elevated count has a positive predictive value for ACR. They can be used to differentiate recurrent HCV infection and ACR.

Peripheral Blood Lymphocytes

Peripheral blood lymphocytes have a limited value in predicting ACR. Macrophages are considered as a part of nonspecific inflammatory response and Plasma cells are not tested for antibody specificity.

ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

MHC plays an important role immune system. MHC in humans is divided into class I, II and III. These molecules are expressed on macrophages and dendritic cells.

- MHC Class I: They present antigen fragments to cytotoxic T-cells and will bind to CD₈₊ receptors on cytotoxic T-cells. HLA- A, B, and C genes belong to this class I.
- MHA class II: They present antigen fragments to T-helper cells by binding to the CD₄₊ receptor on T-helper cells. HLA-DP (A1 and B1), DQ (A1 and B1), and DR (A1 and B1) genes belong to this class.
- MHC III expression is variable.

The initiation of ACR is recipient T-cell recognition of allo-MHC-peptide complex on donor macrophages and dendritic cells. Transplanted livers contain large number of donor macrophages and dendritic cells, which serve as a primary stimulation to the recipient alloreactive T-cells.

HUMAN LEUCOCYTE ANTIGEN (HLA) AND REJECTION

Previous studies about the impact of HLA on the outcome of a liver allograft have yielded contradictory results. Some workers report a beneficial effect of HLA matching, whereas others observe no effect or even a negative impact of the HLA compatibility.^{1,17} Some HLA alleles, such as HLA-DQB1*0302, in the recipient have been associated with a higher risk of early acute rejection in LTX.²⁰

LTX is successful despite human leukocyte antigen (HLA) histocompatibility barriers. It has been reported that HLA influences the outcome of hepatic allografts.

MHC Class I and II antigens	
Class I antigens	Class II antigens
Structure	
Encoded by HLA-A, -B, -C loci in humans	Encoded by HLA-D locus (DP, DR, DQ)
Single polymorphic heavy chain (45 kd)	Two chains a (29 kd) and b (34 kd)
Expressed on all nucleated cells	Expressed on B cells, antigen-presenting cells, and vascular endothelium
Functions	
Activator and target for cytotoxic T (CD ₈₊) lymphocytes	Activator of helper T-cells (CD ₄₊) and stimulator in mixed lymphocyte reaction
Target for antibody-mediated rejection	Possible target for antibody-mediated
Stimulator of antibody response unknown	Significant stimulator of antibody response

HLA antigens are involved in cellular immune response¹⁸ and the expression of HLA class I as well as specific HLA-class II alleles may determine liver graft tolerance versus rejection.^{19,20} Polymorphisms of the HLA-DQA1 and -DPB1 loci do not seem to be primarily associated with the occurrence of acute rejection among liver allograft recipients.²¹

ROLE OF HLA-C

Immunoregulatory functions of HLA-C molecules to interact with inhibitory receptors expressed on natural killer cells and on some T-cell subsets suggests that involvement of the HLA-C locus may affect the outcome of liver allografts.²² Partial class I (HLA-A and HLA-B) compatibility may increase the incidence of acute rejection among recipients with preoperative viral infections.²³ and HLA-C may play a role in LTX and should not be ignored in elucidating the mechanisms leading to the induction of liver graft tolerance.²⁴

Inflammatory response seen in rejection is localised to portal tracts (is one of the venue, not only localized to portal tract) where a mixed inflammatory infiltrate is seen with damage to bile duct epithelium and venous endothelium and this site is a rich source of MHC class I and II antigens. This damage causes elevated alkaline phosphatase level. Central vein is another target for rejection response and these cells also express class I and II antigens. Conversely hepatocytes are rarely the target of ACR, except in late rejection. Human hepatocytes express less amount of class I antigen on their surface and do not express class II antigens during an episode of ACR. The expression of HLA antigens some way triggers the rejection response and the HLA disparity between the donor and recipient correlates with rejection. HLA related rejection is well established in kidney transplants, but in liver transplantation results of HLA related rejection is still controversial. Till present era, no attempt is made to match the HLA antigens in LTX.

Pittsburg group showed that class I and II compatibility was associated with decreased graft survival, although few grafts were lost secondary to rejection. This probably explains the increased susceptibility to CMV infection when donor and recipient HLA DR is well matched. Wisconsin group reported that matching of MHC class I antigens predict the graft survival. Donor type MHC class I antigens have been identified in the serum of liver transplant recipients, but they decrease with the removal of liver. Solid phase ELISA can be used to detect HLA class I antigen in the serum. Liver transplant patients show a higher level of HLA class I antigen after transplantation with a transient increase in rejection and infection.

Hanvesakul et al⁷⁹ reported that KIR ligand-dependent mechanisms play a major role in long-term allograft survival after LTX, natural killer (NK) cells play a critical role in determining the degree of chronic rejection and subsequent fibrosis in the allograft. An important observation in this study is that both heterozygous and homozygous HLA-C₂ allografts, which together represent approximately 60% of transplanted organs. It might therefore be appropriate to allocate HLA-C₂ homozygous allografts to high-risk recipients, such as those receiving a second transplant, in order to maximize the chance of long-term graft function. The remaining 40% of allografts will possess the HLA-C₁/C₁ genotype associated with impaired graft survival and this should be taken into account when planning future immunosuppressive regimens.

IMMUNE TOLERANCE

Bellingham, Brent and Medawar in 1953 showed that tolerance can be acquired. Tolerance was inferred from a rapidly declining need for maintenance of immunosuppression after success treatment of rejection. Later in 1970s, Henry Garnier reported that a significant percentage of untreated pig liver recipients did not reject their allografts during this time they were using azathioprine and antilymphocyte globulin.²⁵ Previous findings suggest that the induction of liver transplant tolerance relies on active suppression of immune reactivity, possibly mediated by regulatory T-cells (Treg).^{26,27} Introduction of immune tolerance in liver transplantation is associated with increased rate of apoptosis of T-lymphocytes in the portal inflammatory infiltrate and presence of intra graft T-helper 2 cells (it is one of the possible mechanisms to induce tolerance).

ROLE OF KUPFFER CELLS

Kupffer cells in the hepatic sinusoids

- Can directly interact with T-lymphocytes
- Play a vital role in immunomodulation
- Can suppress T-cell proliferation in mixed leukocyte reactions
- Express functional Fas ligand and can induce apoptosis of Fas-positive cells.
- Kupffer cells recovered from chronically accepted hepatic allografts have increased Fas ligand mRNA and protein expression
- Have more ability to induce apoptosis of alloreactive T-cells.
- Regulate cytokine production and T-helper 2/T-helper 3 cell like cytokine mRNA expression in allogenic mixed lymphocyte reaction.

CHIMERISM

Migration of donor-derived cells to recipient tissues after LTx has been suggested to be a mechanism to induce and maintain allograft tolerance^{28,29} although evidence for the presence of cells of recipient origin within the transplanted liver is limited. Liver has been shown to be particularly capable of inducing tolerance. A number of hypotheses have been advanced to explain this immunoprivileged state, one of which is the presence of chimerism. Other factors are the regenerative capacity and the production of soluble major histocompatibility complex antigens.³⁰

Chimerism is the presence of donor-derived cells found in the recipient's peripheral tissues years and even decades after transplantation.^{29,331-33} Chimerism may be defined as a phenomenon in which cells from one individual are present in another individual. These cells can either be circulating or they can be integrated into the parenchyma. Migration of donor-derived cells to recipient tissues after liver transplantation is called peripheral chimerism,³¹ which may be a mechanism to induce and maintain allograft tolerance.²⁹ Human hepatic intra-graft chimerism, namely, migration of recipient-derived cells to the transplanted liver ranges from no chimerism to low or even high levels of chimeric cells.³⁴⁻³⁶

It was questioned whether the transplanted organs could not already have been chimeric before transplantation, due to circulating fetal cells or cells derived from previous blood transfusions.^{36,37} Koopmans et al. observed that chimerism is not related to child bearing or blood transfusion.³⁶ It might be useful to perform pretransplant biopsies to establish whether chimeric cells were present before transplantation.³⁶ HLA tissue compatibility did not influence the occurrence of acute rejection and presence of chimerism.^{28,38}

ROLE OF NITRIC OXIDE IN ACR

Nitric oxide (NO) is an immunomodulatory molecule acts as mediator in ACR in liver allograft. NO is produced by NO synthetase, a group of P-450 like enzymes which convert L-arginine and oxygen into L-citrulline and NO. Hepatocytes are the main source of production of NO. Plasma levels are increased during ACR as compared to normal or chronic rejection patients. NO levels correspond to the severity of rejection. Calcineurin inhibitors reduce the NO synthesis. Nitric oxide level is not increased after liver resection.

ROLE OF CYTOKINES AND CHEMOKINES IN REJECTION

Various cytokines such as IL-1, IL-2, IL-2 receptor, IL-4, IL-6, IL-10, IL-15 Tumor necrotic factor and IFN- α have

a definite role in the hepatic allograft rejection. Identification of systemic cytokine levels is a method of directly identifying the pathological changes and a noninvasive method of diagnosing rejection. TNF is also found to be elevated in bacterial and viral infections. IL-6 enhances the differentiation of B-cells and cytotoxic T-cells and induces IL-2 receptor expression. A high IL-6 level during intraoperative period is a predictive of bacterial or viral infection. TNF- α may promote the binding of the host lymphocytes to the graft endothelium or induce expression of MHC antigens in the graft. Elevated levels of IL-2 receptor in seen in rejection indicates their vital role. Eosinophils in the allograft site produce IL-5 which enhances the development of cytotoxic T-cells. To my knowledge, the level of these cytokines could not predict the outcome of the graft. If it is true, you might mention this point here. Chemokines are chemotactic cytokines with a low molecular weight. They are responsible for the recruitment of leukocytes.³⁹ Release of chemokines by hepatocytes is supposed to trigger rejection.⁴⁰ Data on chemokine expression after transplantation is limited.^{41,42} Chemokine ligand 3 and 4 (CCL3 and CCL4) are significantly increased during allograft rejection. The sensitivity of CCL3 for rejection was 98%. Remarkably, the increase of serum chemokines precedes the acute rejection by several days. High sensitivity of CCL3 (and CCL4) seems to allow for a reliable diagnosis of rejection. In addition, CCL3 and CCL4 decreased in CMV infection.

ROLE OF MONOCYTES AND TOLL-LIKE RECEPTORS 2 AND 4 IN ACR

Innate immunity plays an important role in the immune recognition of solid organ allografts.^{43,44} Toll-like receptors (TLRs) are a group of innate immune receptors that are expressed on a variety of cell types, including antigen-presenting cells (APC) and epithelial and endothelial cells.⁴⁵ This group has recently emerged as a critical component to activate dendritic cell (DC) maturation programs to induce adaptive immune responses.⁴⁶⁻⁴⁸ TLRs may be activated by some endogenous agonists thereby participating in allograft responses. Role of TLR-4 has been demonstrated in acute allograft rejection after lung and cardiac transplantation.^{49,50}

Monocytes, another important component of the innate immune system, also play more important role in allograft rejection than previously suspected. Indeed, rejection does not occur until monocytes are available in the peripheral circulation. Graft dysfunction occurs upon infiltration of activated monocytes even without a prominent T-cell infiltration (usually, the monocytes will become macrophage or dendritic cell when the migrate

to tissue, please check it). Signaling through TLRs is believed to be the critical first step in monocytes activation.

Deng et al reported that a significant association between TLR-4 and TLR-2 expression on circulating monocytes and acute rejection episodes in liver transplantation and they observed that steroid pulse therapy which is considered to be effective for acute rejection, reduced TLR-4 and TLR-2 expressions in acute rejection patients and then improve the patients conditions.⁶⁷ Signals mediated by TLR-4 and TLR-2 may be one mechanism of acute rejection in liver transplantation. The expression of TLR-4 and TLR-2 on monocytes may be early predictive candidate of acute rejection after liver transplantation.⁶⁷

ROLE OF C4d IN ACUTE REJECTION

C4d is a product of the complement pathway and is deposited in humoral rejection.²² Earlier it was believed that the acute rejection was mainly cellular rejection. But et al suggested that C4d deposition in the vascular walls of portal area might be used to determine the presence of acute cellular rejection. Compared with acute rejection in a transplanted kidney, positive reactions of C4d deposition in the hepatic sinusoidal walls was weak but did exist in their study. In acute rejection, the sites of C4d deposition are mainly in the vascular walls of portal areas and hepatic sinusoids.⁶⁶

PSYCHOLOGICAL FACTORS IN REJECTION

Accumulating evidence suggests that psychosocial factors may impinge on immune-related events such as modulation of T-cell responses⁵¹ or exacerbation of immune-related disorders.⁵² Distress as well as depressive moods have been shown to correlate with the modulation of distinct immune responses⁵³ and therefore, may contribute to transplant rejections as well.⁵⁴

ANTIBODY MEDIATED/HYPERACUTE REJECTION

Earlier reports suggested that successful LTX can be done in presence of anti donor HLA antibody.^{55,56} But other studies have shown inferior graft and patient survival in presence of positive cross match.^{57,58} Liver allograft failure rate is high in the first 4 weeks after transplantation when there was a positive T-cell cross match and these patients are more likely to suffer from sepsis after transplantation. Relative resistance of the liver to antibody mediated rejection can be explained in terms of its dual blood supply and less vasoreactive venous system.⁵⁹ But still this is a subject of research and yet to be determined. Transplanted liver is capable of resisting antibody

mediated rejection and capable of absorbing antibodies from the circulation.⁶⁰

Clinical pattern of ABO incompatible grafts may represent an important antibody mediated rejection. Even though the short term results in these grafts are satisfactory, long term results are poor particularly in adult patients. ABO-I LTX is more successful and better outcome in pediatric patients, particularly those who are younger than 3 years due to the lack of antibodies against ABO antigens. Several reports from Japan suggest that intra arterial infusion of methyl prednisolone; PG E₁ and Gabexate mesylate have reduced the biliary and vascular complications following ABO incompatibility. Kasahara et al. found that the overall 1 and 5 year graft survival was 85.7% and 84.1% respectively and 5 year survival in HLA 0, I, II and III mismatched groups were not significantly different.⁶¹

ABO-INCOMPATIBLE LTX

ABO blood group antigens and HLA antigens are the major hurdles in organ transplantation.⁶⁵ They are distributed in most of the cells and antibodies directed against these antigens cause severe damage to the allograft, thus influencing the outcome of transplantation. Recipients, with antidonor HLA antibodies at the time of transplantation will suffer from hyperacute rejection.^{62,63} Individuals develop natural antibodies against A and B structures that differ from their own.

Different Blood types producing different antibodies shown below:

- Blood type A and O have antibodies against B type antigen
- Blood type B and O will have antibodies against A type antigen
- Blood type O can have antibodies against both blood type A and B antigens as they display neither A nor B
- Blood type AB can't produce antibodies against A or B antigens as they display both.
- Patients with blood type A2 can't produce Anti A antibodies even though the expression of antigen is limited

ABO-I LTX is performed in emergency when compatible donor organ is not available. The incidence and severity of hyperacute rejection in LTX is less than the other solid organ transplantation. Children <3 years with an immature immune system is more favorable for ABO-I LTX. Majority of the complications occur in the first year of transplantation. There is an increase in the incidence of rejection, avascular and biliary complications. UNOS and European transplant society suggested a restricted ABO matching policy to provide optimal

balance for both urgent and elective patients from the allocation prospective.

The graft versus host blood group reactions are often self limiting because the antibody producing plasma cells transplanted with the graft have a limited life span and are not replaced. Interestingly Anti ABO blood group antibodies may return to high levels without causing any damage to the graft, a phenomenon called accommodation. GVHD (Graft versus host disease) following LTX is rare but often fatal complications that result the engraftment of alloreactive donor T-lymphocytes carried in the graft.

As the ABO blood group antigens, circulating antidonr HLA antibodies represent a risk to the graft. Unlike the natural ABO blood group antigen, anti HLA antibodies are produced as a result of direct immunization with allogenic HLA molecules. This commonly occurs in pregnancy, blood transfusion or previous transplantation. Early analysis of HLA matching in liver recipients failed to demonstrate any survival advantage among recipients of better HLA matched grafts. Poorer survival among those patients with who received a liver with no mismatches at any of the individual HLA-A, B or DR loci and more poorly HLA matched grafts were more likely to fail because of rejection. Better matched grafts suffer higher rate of graft loss due to primary nonfunction or other causes.⁶⁴ Increased incidence of CMV infection is noted in patients matched for one or more HLA-DR antigens with their donors.

REFERENCES

- Donaldson P, Underhill J, Doherty D, et al. Influence of human leukocyte antigen matching on liver allograft survival and rejection: "the dualistic effect". *Hepatology* 1993;17(6):1008-15.
- McCaughan GW, Davies JS, Waugh JA, et al. A quantitative analysis of T lymphocyte populations in human liver allografts undergoing rejection: The use of monoclonal antibodies and double immunolabeling. *Hepatology* 1990;12(6):1305-13.
- Ibrahim S, Dawson DV, Killenberg PG, et al. The pattern and phenotype of T-cell infiltration associated with human liver allograft rejection. *Human Pathol* 1993;24(12):1365-70.
- Dollinger MM, Howie SE, Plevris JN, et al. Intrahepatic proliferation of 'naive' and 'memory' T cells during liver allograft rejection: Primary immune response within the allograft. *FASEB J* 1998;12(11):939-47.
- N Kubota, M Sugitani, S Takano, et al. Correlation between acute rejection severity and CD8-positive T cells in living related liver transplantation. *Transplant Immunology* 2006;16:60-64.
- García-Alonso AM, Minguela A, Muro M, et al. CD28 expression on peripheral blood T lymphocytes after orthotopic liver transplant: upregulation in acute rejection. *Hum Immunol*. 1997; 53(1):64-72.
- Vierling JM. Immunology of acute and chronic hepatic allograft rejection. *Liver Transpl Surg* 1999;5(4 Suppl 1):S1-S20.
- Van den Berg AP, Twihaar WN, Corver K, et al. Cyclosporine A is associated with a shift of the Th1/Th2 balance in liver transplant patients. *Transplant Proc* 1998;30(5):2378-79.
- Strom TB, Roy-Chaudhury P, Manfro R, et al. The Th1/Th2 paradigm and the allograft response. *Curr Opin Immunol* 1996; 8(5):688-93.
- Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* 1996;17(3):138-46.
- Mosmann TR, Li L, Hengartner H, et al. Differentiation and functions of T cell subsets. *Ciba Found Symp* 1997;204:148-54.
- Durkop H, Latza U, Hummel M, et al. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease *Cell* 1992;68:421.
- KH Kim, E-J Oh, E-S Jung, et al. Evaluation of Pre- and Posttransplantation Serum Interferon-Gamma and Soluble CD30 for Predicting Liver Allograft Rejection. *Transplant Proceed* 2006; 38:1429-31.
- TaKeuchi T, Lowry RP, Konieczny B, et al. Heart allografts in murine systems. The differential activation of Th2-like effector cells in peripheral tolerance. *Transplantation*. 1992;53(6):1281-94.
- Stinn JL, Taylor MK, Becker G, et al. Interferon-gamma-secreting T-cell populations in rejecting murine cardiac allografts: assessment by flow cytometry. *Am J Pathol* 1998;153(5):1383-92.
- Sankaran D, Asderakis A, Ashraf S, et al. Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. *Kidney Int* 1999;56(1):281-88.
- Markus BH, Duquesnoy RJ, Gordon RD, et al. Histocompatibility and liver transplant outcome. Does HLA exert a dualistic effect? *Transplantation* 1988;46(3):372-77.
- Fung JJ, Zeevi A, Starlz TE, et al. Functional characterization of infiltrating T lymphocytes in human hepatic allografts. *Hum Immunol* 1986;16(2):182-99.
- Minguela A, Torio A, Marin L, et al. Implication of soluble and membrane HLA class I and serum IL-10 in liver graft acceptance. *Hum Immunol* 1999;60(6):500-09.
- Muro M, A'lvarez-Lo'pez MR, Torio A, et al. HLA-DRB1 and -DQB1 polymorphism in liver recipients: relationship between HLA-DQB1*0302 allele frequency and acute rejection. *Hum Immunol*. 1997;56(1-2):70-76.
- M Muro, F Sa' nchez-Bueno, L Marý'n, et al. DQA1 and DPB1 Genes Polymorphism on Acute Rejection Development in Liver Transplantation. *Transplant Proceed* 2002;34:3302-03.
- Lanier LL, Gumperz JE, Parham P, et al. The NKB1 and HP-3E4 NK cells receptors are structurally distinct glycoproteins and independently recognize polymorphic HLA-B and HLA-C molecules. *J Immunol* 1995;154(7):3320-27.
- Ontan'on J, Muro M, Garcý'a-Alonso AM, et al. Effect of partial HLA class I match on acute rejection in viral pre-infected human liver allograft recipients. *Transplantation* 1998;65(8):1047-53.
- MR Moya-Quiles, A Torý'o, M Muro, et al. Impact of HLA-C on Acute Rejection in Liver Transplantation. *Transplant Proceed* 2003;35:1892-93.
- Clordier G, Garnier H, Clot JP, et al. La greffe de foie orthotopique chez le porc. *Men acad Chir(paris)* 1967;92:799-807.
- Qian S, Demetris AJ, Murase N, et al. Murine liver allograft transplantation: tolerance and donor cell chimerism. *Hepatology* 1994;19:916.

27. Li W, Zheng XX, Kuhr CS, et al. CTLA4 engagement is required for induction of murine liver transplant spontaneous tolerance. *Am J Transplant* 2005;5:978.
28. Araujo MB, Leonardi LS, Boin IFSF, et al. Development of donor-specific microchimerism in liver transplant recipient with HLA-DRB1 and -DQB1 mismatch related to rejection episodes. *Transplant Proc* 2004;36:953.
29. Starzl TE. Chimerism and tolerance in transplantation. 2004; 101(Suppl 2):14607-14.
30. Hove WR, Hoek B, Bajema IM, et al. Extensive chimerism in liver transplants: vascular endothelium, bile duct epithelium, and hepatocytes. *Liver Transplant* 2003;9:552.
31. Jonsson JR. Peripheral blood chimerism following human liver transplantation. *Hepatology* 1997;25:1233.
32. Kleeberger W, Rothamel T, Glöckner S, et al. High frequency of epithelial chimerism in liver transplants demonstrated by microdissection and STR-analysis. *Hepatology* 2002;35:110.
33. Ng IOL, Chan KL, Shek WH, et al. High frequency of chimerism in transplanted livers. *Hepatology* 2003;38:989.
34. Fogt F, Beyser KH, Poremba C, et al. Recipient-derived hepatocytes in liver transplants: a rare event in sex-mismatched transplants. *Hepatology* 2002;36:173.
35. Idilman R, Erden E, Kuzu I, et al. Recipient-derived hepatocytes in sex-mismatched liver allografts after liver transplantation: early versus late transplant biopsies. *Transplantation* 2004;78:1647.
36. Koopmans M, Hovinga ICLK, Baelde HJ, et al. Chimerism in kidneys, livers and hearts of normal women: implications for transplantation studies. *Am J Transpl* 2005;5:1495.
37. Stevens AM, McDonnell WM, Mullarkey ME, et al. Liver biopsies from human females contain male hepatocytes in the absence of transplantation. *Lab Invest* 2004;84:1603.
38. B Bilezikci, FS, ahin, M Haberal, et al. Frequency of Recipient-Derived Chimerism and Relationship With Acute Rejection and HLA Tissue Typing in Transplanted Livers. *Transplant Proceed* 2006;38:598-601.
39. Thelen M. Dancing to the tune of chemokines. *Nat Immunol* 2001; 2(2):129-34.
40. Gerard C, Rollins BJ: Chemokines and disease. *Nat Immunol* 2001; 2(2):108-15.
41. Hancock WW, Gao W, Faia KL, et al. Chemokines and their receptors in allograft rejection. *Curr Opin Immunol* 2000;12(5):511-16.
42. Melter M, McMahon G, Fang J, et al. Current understanding of chemokine involvement in allograft transplantation. *Pediatr Transplant* 1999;3(1):10-21.
43. Van den Berg TK, Yoder JA, Litman GW. On the origins of adaptive immunity: innate immune receptors join the tale. *Trends Immunol* 2004;25:11.
44. Goldstein DR, Tesar BM, Akira S, et al. Critical role of the Toll-like receptor signal adaptor protein MyD88 in acute allograft rejection. *J Clin Invest* 2003;111:1571.
45. Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. *Nat Immunol* 2004;5:987.
46. Khush RS, Leulier F, Lemaitre B. Immunology. Pathogen surveillance—the flies have it. *Science* 2002;296:273.
47. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. *Nature* 1997;388:394.
48. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol* 2001;2:675.
49. Tesar BM, Zhang J, Li Q, et al. TH1 immune responses to fully MHC mismatched allografts are diminished in the absence of MyD88, a toll-like receptor signal adaptor protein. *Am J Transplant* 2004;4:1429.
50. Palmer SM, Burch LH, Davis RD, et al. The role of innate immunity in acute allograft rejection after lung transplantation. *Am J Respir Crit Care Med* 2003;168:628.
51. Tournier JN, Mathieu J, Mailfert Y, et al. Chronic restraint stress induces severe disruption of the T-cell specific response to tetanus toxin vaccine. *Immunology* 2001;102(1):87-93.
52. Levenstein S, Prantera C, Varvo V, et al. *Am J Gastroenterol* 2000; 95:1213.
53. Arck PC, Rose M, Hertwig E, et al. Stress and immune mediators in miscarriage. *Hum Reprod* 2001;16(7):1505-11.
54. M Walter, M Hildebrandt, J Ruter, et al. Evidence of Psychosocial Influences on Acute Rejection After Liver Transplantation. *Transplant Proceed* 2002;34:3298-301.
55. Iwatsuki S, Iwaki Y, Kano T, et al. Successful liver transplantation from cross match-positive donors. *Transpl proceed* 1981;13:286.
56. Gordon RD, Fung JJ, Markus B, et al. The antibody cross match in liver transplantation. *Surgery* 1986;100:705.
57. Takaya S, Bronsther O, Iwaki Y, et al. The adverse effect of using positive cytotoxic cross match donors. *Transplantation* 1992; 53:400.
58. Batts KP, Moore SB, Perkin JD, et al. Effect of positive lymphocyte cross match and HLA mismatching on vanishing bile duct syndrome in human liver allografts. *Transpl* 1988;45:376.
59. Fly MW, Byffy BF, Phelan DL, et al. Protective effects of liver transplantation on a simultaneously transplanted kidney in a highly sensitized patient. *Transpl* 1990;50:1051.
60. Fung J, Makowka L, Tzakis A, et al. Combined liver-kidney transplantation: Analysis of patients with preformed lymphocytotoxic antibodies. *Transplant proceed* 1988;20:88.
61. Kasahara M, Tanaka K, Uryuhara K, et al. Role of HLA compatibility in pediatric living related liver transplantation. *Transplantation* 2002;74:1175.
62. Patel R, Terasaki PI. Significance of the positive cross match test in kidney transplantation. *N Eng J Med* 1969;280:735-39.
63. KF Neilsen, Oslen S, et al. Hyperacute rejection of kidney allografts associated with pre-existing humoral antibodies against donor cells. *Lancet* 1966;2:662-65.
64. Markus BH, Gordon RD, et al. Histocompatibility and liver transplant outcomes: Does HLA exert a dualistic effect? *Transplantation* 1988;46:372-377.
65. Nikaein A, Backman L, et al. HLA compatibility and liver transplant outcomes: improved survival by HLA and cross matching. *Transplantation* 1994;58:786-92.
66. X Bu, Z Zheng, Y Yu, et al. Significance of C4d Deposition in the Diagnosis of Rejection After Liver Transplantation. *Transplant Proceed* 2006;38:1418-21.
67. JF Deng, L Geng, Y-G Qian, et al. The Role of Toll-Like Receptors 2 and 4 in Acute Allograft Rejection After Liver Transplantation. *Transplant Proceed* 2007;39:3222-24.
68. Yoshimura S, Gotoh S, Kamada N. Immunological tolerance induced by liver grafting in the rat: splenic macrophages and T cells mediate distinct phases of immunosuppressive activity. *Clin Exp Immunol* 1991;85:121-27.
69. Gassel HJ, Hutchinson IV, Engemann R, Morris PJ. The role of T suppressor cells in the maintenance of spontaneously accepted orthotopic rat liver allografts. *Transplantation* 1992;54:1048-53.

70. Knoop M, Pratt JR, Hutchinson IV. Evidence of alloreactive T suppressor cells in the maintenance phase of spontaneous tolerance after orthotopic liver transplantation in the rat. *Transplantation* 1994;57:1512-15.
71. Olver S, Goto S, Chiba S, et al. Persistence of donor-reactive CD4⁺T cells in liver and spleen of rats tolerant to a liver allograft. *Transplantation* 1998;66:132-35.
72. Hall BM, Pearce NW, Gurley KE, Dorsch SE. Specific unresponsiveness in rats with prolonged cardiac allograft survival after treatment with cyclosporine: III. Further characterization of the CD4⁺ suppressor cell and its mechanisms of action. *J Exp Med* 1990;171:141-57.
73. Sakaguchi S, Sakaguchi N, Asano M, et al. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25): breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* 1995;155:1151-64.
74. Wood KJ, Sakaguchi S. Regulatory T cells in transplantation tolerance. *Nat Rev Immunol* 2003;3:199-210.
75. Jiang X, Morita M, Sugioka A, et al. The importance of CD25⁺CD4⁺regulatory T cells in mouse hepatic allograft tolerance. *Liver Transpl* 2006;12:1112-18.
76. Yoshizawa A, Ito A, Li Y, et al. The roles of CD25⁺CD4⁺ regulatory T cells in operational tolerance after living donor liver transplantation. *Transplant Proc* 2005;37:37-39.
77. Demirkiran A, Kok A, Kwekkeboom J, et al. Low circulating regulatory T-cell levels after acute rejection in liver transplantation. *Liver Transpl* 2006;12:277-84.
78. Benseler V, McCaughan GW, Schlitt HJ, et al. The liver: a special case in transplantation tolerance. *Semin Liver Dis* 2007; 27(2):194-213.
79. R Hanvesakul, N Spencer, M Cook, et al. Donor HLA-C Genotype Has a Profound Impact on the Clinical Outcome Following Liver Transplantation. *Am J of Transplant* 2008;8:1931-41.

Early Complications of Liver Transplantation

(A) PRIMARY NONFUNCTION

INTRODUCTION

Expanding the donor pool is now the focus of every organ transplant center in the United States due to organ shortage. In recent years, modification of the criteria for donors to increase donor pool, like expanding the range of donor age and donation after cardiac death, along with use of living donors, split or partial grafts. Overall, long-term graft and patient survival appear to be similar following split-liver and living donor transplantation¹⁻⁵ but the outcomes of cases in which livers from expanded criteria donors (ECD) were used are contradictory.^{6,7} Early graft function is essential in liver transplantation unlike the kidney and pancreas transplantation.

Primary nonfunction (PNF) is defined as primary graft failure that resulted in death or retransplantation within 30 days of the primary transplantation. Primary graft failure is one of the UNOS categories of graft failure that excludes other causes such as recurrent disease, graft versus host disease, rejection, and vascular thrombosis. UNOS definition of PNF restricts the duration to within 7 days of transplantation. Recent report from European Liver Transplant Registry restricted PNF to within 30 days of transplantation. Using UNOS data, Amin et al.⁶ in a recent Markov analysis defined primary graft failure as a “non-functioning graft within 1 month after receiving deceased liver transplantation.” Incidence of PNF among liver transplant recipients is 2-14%. Precise cause of PNF is not known.

UNOS/OPTN database data (1990–2004) reports that the overall incidence of PNF in liver transplant recipients was 3.5%. European Liver Transplant Registry (ELTR) reports the incidence of PNF at 90 days post-

transplantation was 6%.⁸ It is well recognized that the overall graft and patient survival rates without retransplantation are extremely low.

Graft survival time in recipients with PNF is defined as the time that elapsed from retransplantation to graft failure.

Patient survival in recipients with PNF is defined as the time that elapsed from retransplantation to patient death.

Primary liver transplantation (PLT) is defined as first liver transplantation and only considered when patient did not have a PNF event. PLT also was also referred to as those without PNF—‘no PNF’.

Graft survival time in recipients with PLT was defined as the time that elapsed from transplantation to graft failure.

Patient survival in recipients with PLT was defined as the time that elapsed from transplantation to patient death.

Delayed graft function (DGF) is defined as impaired liver function responding to support therapy.

Risk factors contributing to PNF^{9,10}

Donor factors

- Marginal donor: Age > 50 years
- Macrovesicular steatosis (>30%) in donor liver
- Serum Na⁺ level >160 m mol/L
- CIT > 12 hours
- Organ preservation method.
- Donation after cardiac death (DCD)
- Seropositive Hepatitis B and C.
- Split livers

Recipient factors

- Poor medical condition
- Presence of renal failure

PNF was the most frequent indication for retransplantation. Overall patient and graft survivals after retransplantation were inferior to those of primary liver transplant recipients. There was a decreased incidence of PNF since 2000.^{12,13} Decrease in PNF rate, despite the overall increasing utilization of ECD (expanded criteria for donors) organs, may be due to the matching of donors to recipients with less severe liver disease (low MELD scores), as has been described in two recent reports.^{14,15}

INITIAL POOR FUNCTION

Initial poor function describes a marginally functioning graft that recovers adequate function only after few days to weeks after liver transplantation. Sometimes these grafts fail, and end up in retransplantation. In such circumstances, there is an increased risk of death from sepsis due to bacterial or fungal infections. The risk factors for initial poor function are similar to those for primary nonfunction. Graft with initial poor function has greater than the normal graft failure rate in first 3 months after OLT.¹¹

ASSESSMENT OF GRAFT FUNCTION

Hepatic allograft dysfunction is indicated like AST, ALT, albumin, PT and INR and cholestasis is indicated by measurement of Bilirubin, alkaline phosphatase and GGT. Recovery of cytochrome P-450 dependent microsomal enzyme activity starts immediately after reperfusion of the graft. By the end of 2nd week, allograft synthetic function and coagulation profile returns to normal. AST, alkaline phosphatase and GGT may remain mildly elevated for longer time.

REFERENCES

- Cardillo M, De Fazio N, et al. Split and whole liver transplantation outcomes: A comparative cohort study, *Liver Transpl* 2006;12:402.
- H Yersiz, JF Renz, et al. One hundred in situ split-liver transplantations: A single-center experience, *Ann Surg* 2003;238:496.
- DG Maluf, RT Stravitz, et al. Adult living donor versus deceased donor liver transplantation: A 6-year single center experience, *Am J Transplant* 2005;5:149.
- KM Olthoff, RM Merion Ghobrial, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: A report from the A2ALL Consortium, *Ann Surg* 2005;242:314.
- CL Liu, ST Fan, et al. Operative outcomes of adult-to-adult right lobe live donor liver transplantation: a comparative study with cadaveric whole-graft liver transplantation in a single center, *Ann Surg* 2006;243:404.
- MG Amin, MP Wolf, et al. Expanded criteria donor grafts for deceased donor liver transplantation under the MELD system: A decision analysis, *Liver Transpl* 2004;10:1468.
- JF Renz, C, et al. Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation, *Ann Surg* 2005;242:556.
- AK Burroughs, CA Sabin, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome, *Lancet* 2006;367:225.
- Ploeg RJ, et al. Risk factors for primary dysfunction after liver transplantation-a multivariate analysis. *Transpl* 1993;55(4):807-13.
- Avolio AW, et al. Primary dysfunction after liver transplantation: donor or recipient fault? *Transpl proceed* 1993;31(1-2):434-36.
- Strasberg SM, Howard TD, et al. Selecting the donor liver: Risk factors for poor function after orthotopic liver transplantation. *Hepatology* 1994;20:829-38.
- M Facciuto, D Heidt, et al. Retransplantation for late liver graft failure: predictors of mortality, *Liver Transpl* 2000;6:174.
- Kemmer N, Secic M, et al. Long-term analysis of primary nonfunction in liver transplant recipients. *Transplant proceed* 2007;39:1477-80.
- S Feng, NP Goodrich, JL Bragg-Gresham, et al. Characteristics associated with liver graft failure: The concept of a donor risk index, *Am J Transplant* 2006;6:783.
- R Mateo, Y Cho, G Singh, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: An analysis of OPTN/UNOS data, *Am J Transplant* 2006;6:791.

(B) ALLOGRAFT REJECTION

Hepatic allograft rejection is divided into

- Hyperacute (antibody mediated) rejection
- Acute cellular rejection
- Chronic (ductopenic) rejection

ACUTE CELLULAR REJECTION

In general, organ allograft rejection can be defined as, “an immunological reaction to the presence of a foreign tissue or organ, which has the potential to result in graft dysfunction and failure.”¹ Acute rejection, defined by the Banff international consensus document on terminology for hepatic allograft rejection² as, “inflammation of the allograft, elicited by a genetic disparity between the donor and recipient, primarily affecting interlobular bile ducts and vascular endothelia, including portal veins and hepatic venules and occasionally the hepatic artery and its branches.”¹

Acute cellular rejection (ACR) is the most common explanation for early allograft dysfunction after liver transplantation [median, 8 days; 48% by 6 weeks; 65% by 1 year.⁴⁹⁻⁵¹ The incidence of ACR in LDLT is reportedly 36-63%, in 1st year after transplantation with a peak incidence in 7-10 days. Majority of these episodes occur in the 1st 2-3 months after transplantation. Incidence of chronic rejection is 2-3%.⁴⁻⁶ The type of immunosuppression used after transplantation greatly affects the likelihood of developing ACR.^{7,8} The incidence of both acute and chronic rejection (defined as graft failure due to chronic rejection) has declined over the last few decades, from 60-75% to 40-50% and 10-15% to around 2%, respectively.^{2,9} Single episodes of acute rejection will not have any impairment of hepatic dysfunction, but recurrent episodes may leave some permanent damage in the allograft leading to chronic rejection. Previous studies suggest that there is a minimal impact of ACR on either mortality or late graft function.¹⁰⁻¹²

ACR is divided into two subgroups:

1. *Early acute rejection*: Rejection appearing in < 28 days after transplantation and is not associated with any adverse impact on patient and graft survival.^{13,14}
2. *Late acute rejection*: Rejection appearing in > 28 days after transplantation and is due to under dosage of immunosuppression. It is associated with worse prognosis, with reports of nearly half of patients developing graft loss.¹⁵

PATHOGENESIS OF ACR

ACR is primarily T-cell mediated response, where the targets of the response are the major and minor histocompatibility antigen (HLA) on cells. Factors influencing the cell-mediated immunity may also influence the incidence of rejection. Cell characterization studies have documented that the cells in the portal triads are primarily T-cells, with fewer macrophages and neutrophils. Bile duct epithelial cells appear to be a prime target of immune attack, and they are known to express large amounts of class II HLA antigen. Graft failure from ACR occurs primarily because of ischemic necrosis of the organ. The severity of ACR based primarily on the necroinflammatory activity and evidence of acute vascular compromise. A positive pretransplant complement dependent cytotoxicity cross match is associated with rejection episodes.¹⁶ A critical issue of rejection is related to the balance of T-helper 1 (Th₁) and T-helper₂ (Th₂) lymphocytes in the discrimination of self-antigens and generation of anti-inflammatory T-cells for the maintenance of “self-tolerance.”¹⁷ Acute rejection is characterized by predominant intrahepatic Th₁ cell immune response and High level of activated CD₈⁺ T-cells are present in liver tissue.¹⁸ No significant difference is noticed in either naive or memory T-cells during acute rejection.¹⁸

ROLE OF C4d IN ACUTE REJECTION

Theoretically, C4d is a product of the classic complement pathway. Its deposition means the occurrence of humoral rejection.¹⁹ Recent studies in kidney transplants have shown that C4d deposition in the walls of renal interstitial capillaries of the transplanted kidney is a more specific immunohistochemical indication of rejection.^{20,21} In the past it was believed that the acute rejection was mainly cellular rejection.²² Bu et al. suggested that C4d deposition in the vascular walls of portal area might be used to determine the presence of acute cellular rejection. Compared with acute rejection in a transplanted kidney, positive reactions of C4d deposition in the hepatic sinusoidal walls was weak but did exist in their study. In acute rejection, the sites of C4d deposition are mainly in the vascular walls of portal areas and hepatic sinusoids.²³ C4d deposition is also observed in patients with Hepatitis B, indicating that hepatitis B is also associated with humoral immunity. However, in

Hepatitis B patients, C4d deposition is found mainly in the vascular walls of the portal area with more cellular infiltration, no C4d deposition was detected in the hepatic sinusoids.²³

Risk factors for ACR³

- Young age of the recipient
- Black patient
- Creatinine level < 2.0 mg/dL without dialysis
- High AST levels
- Cold ischemia time > 15 hours
- Few HLA-DR matches
- Donor age > 30 years
- Transplantation indications
 - Autoimmune disease
 - Fulminant hepatic failure
 - Hepatitis C related cirrhosis

Incidence of rejection is less in alcoholic liver disease than in PBC, which may be related to nutritional status of the patient, as alcoholics are often malnourished. Larger bleeding volumes experience rejections later and had significantly fewer steroid resistant rejections than patients with smaller bleeding, volumes due to temporary immunosuppressive effect of bleeding.¹⁴ Greater amount of blood transfusions were associated with decreased occurrence of early ACR.²⁴ Blood transfusions have been suggested to have immunomodulatory effects and to induce tolerance in LTX patients.¹⁶ Development of microchimerism and anti-idiotypic antibodies was suggested to explain these immunomodulatory effects of blood transfusions.²⁴

Tzimas et al. reported that implementation of leukoreduction (effectively reduce the leukocyte count of transfused products to less than 5.0×10^6 WBCs/U or to remove more than 99.99% of donor leukocytes) had a favorable effect to lowering the early ACR rate among adult liver transplant recipients.²⁵ Induction with Basiliximab, in combination with tacrolimus based immunosuppressive regimen, reduces the incidence of rejection and improves rejection-free survival rate after OLT, without increasing the incidence of CMV, PTLT, or HCV recurrence.²⁶

SYMPTOMS AND SIGNS OF ACUTE CELLULAR REJECTION

Usually symptoms and signs are nonspecific and none of them is diagnostic of rejection. Fever, malaise, weakness and abdominal pain are the common symptoms and hepatosplenomegaly may be seen on clinical examination. Few patients may present without signs and symptoms. High suspicion is required. If there is a T-tube,

bile output may decrease or change from thick dark green color to thin light colored bile.

DIAGNOSIS

Sometimes it is very difficult to differentiate rejection from other causes like infection and biliary obstruction. USG will exclude biliary obstruction. Infection and rejection are difficult to differentiate. White cell count will misguide the diagnosis in presence of immunosuppression.

Laboratory evaluation

- Peripheral blood leukocytosis and occasional eosinophilia
- Biochemical changes: elevated levels of AST, ALT, Alk. Ph. and GGT
- Elevated bilirubin levels should be ruled out for biliary obstruction
- Prolonged PT and an abnormal elevation of serum bilirubin also suggest the possibility of ACR, but frequently these parameters are normal if ACR is detected early.

Doppler Ultrasonography (DUS)

Klar et al (1999) studied that significant reduction of liver microperfusion during early acute rejection, as measured by thermodiffusion method. The disturbance of hepatic microcirculation preceded the increase of transaminases by 36 hours and the subsequent liver biopsy by 60 hours. The extent of microcirculatory impairment correlated with the degree of rejection. It facilitates early diagnosis and treatment of early rejection.²⁷

Bolognesi et al (2005) reported that measurement of portal blood velocity (PBV) and splenic pulsatility index (SPI) in diagnosis of clinically relevant acute rejection could represent an additional noninvasive test. ACR is suspected, when a marked unexpected decrease in PBV and an increase in SPI are found during the first weeks after liver transplantation. This finding on DUS will prompt the physician to perform a liver biopsy to confirm and treat early ACR.²⁸

Liver Biopsy

Liver biopsy is the gold standard for the diagnosis of ACR. Biopsy can be collected percutaneously or transjugular route or fine needle aspiration biopsy. It can also be used as a response to treatment with immunosuppression by identification of mononuclear cells. In a liver biopsy sample, examine at least two hematoxylin and eosin stained sections from at least two different levels, of a core needle biopsy containing at least five triads to

confirm rejection. Bile cytology can be used to diagnose ACR, by the presence of high cell density within the bile sediment and polymorphonuclear leukocytes.

Demirhan et al reported that patients with pericentral inflammation and marked portal eosinophilia during an initial episode of acute rejection might be more likely to develop subsequent episodes of ACR.⁵³ Sectioning is recently reported to be possible within a few hours using a rapid tissue processor.³¹ Immunostaining, including CD4 and CD8 using an automatized process, has become widespread, now being done in most pathology laboratories, thereby increasing reproducibility and objectivity. ACR on H and E sections of liver needle biopsies can be diagnosed pathologically on the same day even in formalin-fixed and paraffin-embedded tissues, and CD8 analysis is possible the next day. ACR pathological diagnosis is based on H and E findings, according to the Banff schema.³¹

Histological hallmarks of acute cellular rejection (Snover's triad)^{29,30}

- Portal inflammation
- Nonsuppurative obstructive cholangitis
- Endotheliitis (attachment of inflammatory cells to the endothelial surface of portal or terminal hepatic veins)

There are various systems of grading of hepatic allograft rejection such as Banff schema, European grading system and Birmingham system. (Mentioned in liver biopsy and histology chapter) A number of studies have shown the Banff schema to be useful in the diagnosis and staging of ACR.³²⁻³⁴ The most accepted scoring system for rejection is the grading suggested by Banff schema of grading suggested by international consensus document. Although the Banff RAI score is a useful marker of the severity of rejection, neither the total RAI score nor any of the individual components correlated with response to steroids or graft survival.³⁵

REACTIVATION OF HCV AND REJECTION

In HCV positive recipients, it is critical to differentiate recurrent Hepatitis C from ACR. At times, the difference can be subtle, and a pathologist with experience in the interpretation of allograft biopsies is extremely valuable. Enhanced immunosuppression is associated with accelerated rates of HCV replication; it is, therefore, important that immunosuppression be kept to a minimum for HCV positive patients. It is well known that treated rejection episodes make grafts more susceptible to earlier recurrence of HCV post-OLT.^{36,54} Reactivation of HCV is almost universal after transplantation. Antiviral treatment (Interferon and Ribavirin) is required to

prevent progression and recurrence of HCV infection. Histological recurrence develops at least in 50% of the transplants within the first year of transplantation. ACR and recurrent HCV infection can occur simultaneously in the graft and can be detected by liver biopsy.

Criteria for diagnosis of HCV recurrence

- Spotty necrosis
- Lobular inflammation
- Steatosis
- Sinusoidal dilatation
- Kupffer cell activation

Histological features common in both HCV recurrence and ACR

- Portal inflammation
- Ductal damage
- Apoptosis of hepatocytes

Endotheliitis, a sign of rejection may also be present in HCV recurrence.

HCV RNA load is used to confirm the diagnosis of HCV recurrence, when the histological findings of liver allograft biopsy are confusing. HCV RNA levels are higher in HCV recurrence in comparison to rejection. Rejection in a HCV positive recipient results in increase in IL-4 and IL-10 gene expression rather than IL-2, Interferon and TNF seen in chronic HCV infection. Incidence and severity of HCV recurrence is related to use of increased dose of corticosteroids for immunosuppression or to control rejection.

LATE ONSET OF ACUTE REJECTION (LAR)

Recently, more rapid steroid withdrawal programs (within 2 weeks) were introduced.^{37,38} The shorter steroid regimen increases the possibility of late-onset acute rejection (LAR), which might result in graft loss and serious morbidity.³⁹ Incidence of late onset of acute rejection is 7-23%.⁴⁰⁻⁴⁴ Neither HLA compatibility nor lymphocytotoxic crossmatch are associated with LAR. Episodes of early ACR are not related to LAR.⁴⁰

Risk factors for LAR⁴¹⁻⁴⁴

- Cyclosporine A based immunosuppressive therapy
- Lower recipient age
- Subtherapeutic levels of calcineurin inhibitors

TREATMENT

Treatment of acute rejection with enhanced immunosuppressive therapy is highly effective, and an episode of rejection does not affect long-term graft survival. Never

treat rejection without any histological evidence. ACR, unresponsive to increased immunosuppression can progress to chronic rejection. About 10% of ACR progress to chronic rejection.²⁴ Confirmation of ACR is not always possible. So many times clinician starts treatment of rejection on clinical suspicion and liver biochemical data.

High dose steroid pulse therapy is the first line treatment for ACR, which improves the liver function and prevent ACR recurrence.¹⁵

- In mild rejection, increase of the tacrolimus dose when a low trough level is regarded as contributory to the ACR or changed to mycophenolate mofetil (MMF = 30 mg/kg/d) where appropriate.³⁵ Usually optimization of the serum tacrolimus level to 8-12 µg/L is necessary.
- First episode of ACR: Methyl prednisolone, dose: 10 mg/kg/day (or 500-1000 mg/day) iv for 3 days or Prednisolone, dose 200 mg orally for 3 days. Gradually taper prednisolone to 20 mg/day.³⁵
- Repeated episodes: Methylprednisolone, dose: 10 mg/kg/day (or 500-1000 mg/day) intravenous for 3-5 days followed by steroid recycle therapy.

Steroid Resistant Rejection

28-35% of patients do not respond to high-dose steroid therapy and require further intervention with anti T-cell antibodies.^{46,47}

- Rabbit antithymocyte globulins (ATG), Dose: 1.5 mg/kg/day intravenous for 3-7 days. Closely monitor for side effects such as leucopenia and thrombocytopenia, consider dose reduction if these side effects appear.
- Murine monoclonal antibodies: OKT3 is rarely required. Dose: 5 mg/day, iv for 5-10 days. Disadvantage of this is that it drastically reduces the T-cell counts and increases the chances of infection.⁴⁸ Clinically significant infections may require antibiotic or antiviral therapy within 1 month of anti-IL-2r antibody administration.
- Anti-IL-2 receptor antibodies are effective and well tolerated in the treatment of moderate to severe steroid resistant rejection in patients with ACR without histologic evidence of chronic rejection.
- Basiliximab, dose: 20 mg per dose, with a repeat infusion 3 to 5 days later.
- Daclizumab, dose: 1 mg/kg intravenously, with repeat infusions 7 to 14 days later.

RESPONSE TO TREATMENT OF ACR

An episode of ACR is usually defined as responsive when 2 out of 3 laboratory parameters [serum transaminases (AST and ALT), alkaline phosphatase, or bilirubin] fell

to values less than twice the upper limits of normal within 2 weeks of the start of the treatment or diagnosis. Routine diagnosis rejection is performed by liver biopsies but follow-up liver biopsies are usually not indicated to confirm histological resolution.⁵²

REFERENCES

1. International Working Party. Terminology for hepatic allograft rejection. *Hepatology* 1995;22:648-54.
2. International Panel. Banff schema for grading liver allograft rejection: An international consensus document. *Hepatology* 1997;25:658-63.
3. Wiesner RH, Demetris AJ, Belle SH, et al. Acute hepatic allograft rejection: Incidence, risk factors and impact on outcome. *Hepatology* 1998;28:638-45.
4. Minamiguchi S, Sakurai T, Fujita S, et al. Living related liver transplantation: histopathologic analysis of graft dysfunction in 304 patients. *Hum Pathol* 1999;30(12):1479-87.
5. Chen CL, Fan ST, Lee SG, et al. Living-donor liver transplantation: 12 years of experience in Asia. *Transplantation* 2003;15;75(3 Suppl):S6-S11.
6. Sugawara Y, Makuuchi M, Kaneko J, et al. Living-donor liver transplantation in adults: Tokyo University experience. *J Hepatobiliary Pancreat Surg* 2003;10(1):1-4.
7. Mirza DF, Gunson GB, Soonawalla Z, et al. Reduced acute rejection after liver transplantation with Neoral-based triple immunosuppression. *Lancet* 1997;349:701-02.
8. Neuberger J. Incidence, timing, and risk factors for acute and chronic rejection. *Liver Transpl Surg* 1999;5:S30-6.
9. Gouw ASH, van den Heuvel MC, van den Berg AP, et al. Significance of parenchymal changes of acute cellular rejection in predicting chronic liver graft rejection. *Transplantation* 2002;73:243-47.
10. Dousset B, Conti F, Cherruau B, et al. *J Hepatol* 1998;29:660.
11. Demetris AJ, Belle SH, Seaberg EC, et al. *Hepatology* 1998;28:638.
12. Avolio AV, Agnes S, Chirico ASA, et al. *Transplant Proc* 1998;30:3962.
13. Berenguer M, Prieto M, Cordoba J, et al. Early development of chronic active hepatitis in recurrent hepatitis C after liver transplantation: Association with treatment of rejection. *J Hepatol* 1998;28:756.
14. Chaudry IH, Ayala A, Ertel W, et al. Hemorrhage and resuscitation: immunological aspects. *Am J Physiol* 1990;259:R663.
15. Anand A, Hubscher S, Gunson B, et al. Timing, significance and prognosis of late acute liver allograft rejection. *Transplantation* 1995;60:1098-103.
16. Bishara A, Brautbar C, Eid A, et al. Is presensitization relevant to liver transplantation outcome? *Hum Immunol* 2002;63:742.
17. Hori S, Kitagawa S, Iwata H. *J Exp Med* 1992;28:84.
18. O Cuomo, C Sbriglia, G Militerno, et al. T-Lymphocyte Kinetics in Acute Rejection After Orthotopic Liver Transplantation. *Transplant Proceed* 2001;33:3303.
19. H Haga, H Egawa, Y Fujimoto, et al. Acute humoral rejection and C4d immunostaining in ABO blood type-incompatible liver transplantation. *Liver transpl* 2006;12:457-64.
20. Regele H, Bohmig GA, Habicht A, et al. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and

- glomerular capillaries: A contribution of humoral immunity to chronic allograft rejection. *J Am Soc Nephrol* 2002;13:2371.
21. Herzenberg AM, Gill JS, Djurdjev O, et al. C4d deposition in acute rejection: an independent long-term prognostic factor. *J Am Soc Nephrol* 2002;13:234.
 22. Mauiyyedi S, Pelle PD, Saidman S, et al. Chronic humoral rejection: Identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. *J Am Soc Nephrol* 2001;12:574.
 23. X Bu, Z Zheng, Y Yu, et al. Significance of C4d deposition in the diagnosis of rejection after liver transplantation. *Transplant Proceed* 2006;38:1418-21.
 24. IH Matinlauri, MM Nurminen, KA Höckerstedt, et al. Changes in liver graft rejections over time. *Transplant Proceed* 38:2663-66.
 25. GN Tzimas, M Deschenes, JS Barkun, et al. Leukoreduction and acute rejection in liver transplantation: An interim analysis. *Transplant Proceed* 2004;36:1760-62.
 26. CB Ramirez, C Doria, F DiFrancesco, et al. Basiliximab induction in adult liver transplant recipients with 93% rejection-free patient and graft survival at 24 months. *Transplantation Proceed* 2006;38:3633-35.
 27. E Klar, M Angelescu, C Zapletal, et al. Impairment of hepatic microcirculation as an early manifestation of acute rejection after clinical liver transplantation. *Transplant Proceed* 1999;31:385-87.
 28. M Bolognesi, D Sacerdoti, C Mescoli, et al. Acute liver rejection: Accuracy and predictive values of doppler US measurements—Initial experience. *Radiology* 2005;235:651-58.
 29. Demetris AJ, Seaberg EC, Batts KP, et al. Reliability and predictive value of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database nomenclature and grading system for cellular rejection of liver allografts. *Hepatology* 1995;21(2):408-16.
 30. Demetris AJ, Batts KP, Dhillon AP, et al. Banff schema for grading liver allograft rejection: An international consensus document. *Hepatology* 1997;25(3):658-63.
 31. N Kubota, M Sugitani, S Takano, et al. Correlation between acute rejection severity and CD8-positive T-cells in living related liver transplantation. *Transplant Immunology* 2006;16:60-64.
 32. Ormonde DG, de Boer WB, Kierath A, et al. Banff schema for grading liver allograft rejection: utility in clinical practice. *Liver Transpl Surg* 1999;5:261-67.
 33. Blakolmer K, Jain A, Ruppert K, et al. Chronic liver allograft rejection in a population treated primarily with tacrolimus as baseline immunosuppression: long-term follow-up and evaluation of features for histopathological staging. *Transplantation* 2000;69:2330-36.
 34. Demetris A, Rupert K, Dvorchik I, et al. Realtime monitoring of acute liver allograft rejection using the Banff schema. *Transplantation* 2002;9:1290-96.
 35. BS Ho'roldt, M Burattin, BK Gunson, et al. Does the banff rejection activity index predict outcome in patients with early acute cellular rejection following liver transplantation? *Liver Transpl* 2006;12:1144-51.
 36. Tisone G, Laria G, Orlando G, et al. Effect of steroid amount on hepatitis C recurrence following orthotopic liver transplantation. *Transplant Proc* 1999;31:3167.
 37. Pageaux GP, Calmus Y, Boillot O, et al. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. *Liver Transpl* 2004;10:1454-60.
 38. Boillot O, Mayer DA, Boudjema K, et al. Corticosteroid-free immunosuppression with tacrolimus following induction with daclizumab: a large randomized clinical study. *Liver Transpl* 2005;11:61-67.
 39. Mazariegos GV, Reyes J, Marino IR, et al. Weaning of immunosuppression in liver transplant recipients. *Transplantation* 1997;63:243-49.
 40. Ramji A, Yoshida EM, Bain VG, et al. Late acute rejection after liver transplantation: the Western Canada experience. *Liver Transpl* 2002;8:945-51.
 41. Anand AC, Hubscher SG, Gunson BK, et al. Significance, and prognosis of late acute liver allograft rejection. *Transplantation* 1995;60:1098-03.
 42. Yoshida EM, Shackleton CR, Erb SR, et al. Late acute rejection occurring in liver allograft recipients. *Can J Gastroenterol* 1996;10:376-80.
 43. Florman S, Schiano T, Kim L, et al. The incidence and significance of late acute cellular rejection (>1000 days) after liver transplantation. *Clin Transplant* 2004;18:152-55.
 44. N Akamatsu, Y Sugawara, M Makuuchi, et al. Late-onset acute rejection after living donor liver transplantation. *World J Gastroenterol* 2006;12(41):6674-77.
 45. J Ziolkowski, L Paczek, M Niewczasz, et al. Acute liver transplant rejection: Incidence and the role of high-doses steroids. *Transplant Proceed* 2003;35:2289-91.
 46. Conti F, Dousset B, Archambeau D, et al. Enhanced risk of steroid-resistant acute rejection following pretransplant steroid therapy in liver graft recipients. *Transplantation* 1995;60:1104.
 47. Andreu H, Rimola A, Bruguera M, et al. Acute cellular rejection in liver transplant recipients under cyclosporin immuno-suppression: predictive factors of response to antirejection therapy. *Transplantation* 2002;74:1936.
 48. DW. Orr, BC Portmann, ASKnisely, et al. Anti-interleukin 2 receptor antibodies and mycophenolate mofetil for treatment of steroid-resistant rejection in adult liver transplantation. *Transplant Proceed* 2005;37:4373-79.
 49. Minamiguchi S, Sakurai T, Fujita S, et al. Living related liver transplantation: histopathologic analysis of graft dysfunction in 304 patients. *Hum Pathol* 1999;30(12):1479-87.
 50. Chen CL, Fan ST, Lee SG, Living-donor liver transplantation: 12 years of experience in Asia. *Transplantation* 2003;15;75(3 Suppl):S6-S11.
 51. Sugawara Y, Makuuchi M, Kaneko J, et al. Living-donor liver transplantation in adults: Tokyo University experience. *J Hepatobiliary Pancreat Surg* 2003;10(1):1-4.
 52. Sheiner PA, Schwartz ME, Mor E, et al. Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. *Hepatology* 1995;21:30.
 53. B Demirhan, B Bilezikci, M Haberal, et al. Hepatic Parenchymal Changes and Histologic Eosinophilia as Predictors of Subsequent Acute Liver Allograft Rejection. *Liver Transpl* 2008;14:214-19.
 54. MT Killackey, GE Gondolesi, LU Liu, et al. Effect of ischemia-reperfusion on the incidence of acute cellular rejection and timing of histologic hepatitis C virus recurrence after liver transplantation. *Transplant Proceed* 40:1504-10.

CHRONIC REJECTION

In liver transplantation, incidence of chronic rejection (CR) is less common than acute cellular rejection. Clinically, the pattern is one of gradual elevation of alkaline phosphatase and bilirubin, in the absence of obstruction of the large bile ducts. Incidence of CR has been declining from 15-20% to 2-3% as a consequence of effective immunosuppression and early detection.^{1,2,4} Chronic rejection currently occurs in less than 5% of adult liver transplants.^{5,6,34} The reported incidence of chronic rejection in pediatric series is between 4% and 8%.^{8,9} It is one of the most frequent cause of graft loss after one year of transplantation. This is due to better recognition and control of ACR and early chronic rejection, as well as the use of better immunosuppressive drugs.

Chronic rejection is characterized by¹⁻³

- Progressive jaundice unresponsive to immunosuppression
- Histologically by the obliterative vasculopathy affecting large and medium-sized muscular arteries
- Loss of small bile ducts.

CR may occur as early as 2 to 5 weeks after transplantation, with a peak incidence of graft failure occurring at 3 months after transplantation and more than 85% of cases occurring in the first within 6 months.^{10,11} Previously used terms such as "ductopenic rejection" and "vanishing bile duct syndrome" are no longer used as loss of bile ducts is only one recognized aspect of chronic rejection.¹⁰

Most cases occur after an episode of ACR unresponsive to corticosteroids or Muromonab-CD3 (OKT3) or after repeated episodes of ACR with persistent elevation of AST and ALT levels and progressive rise in alkaline phosphatase and bilirubin levels.¹² Some cases, often late cases (>1 year after LTX), evolve indolently without preceding clinically recognized episodes of ACR.^{5,9,12} This type of chronic rejection is due to inadequate monitoring of the patient or poor compliance or an inadequate immunosuppression presenting as an asymptomatic increase in alkaline phosphatase levels followed by progressive elevation of bilirubin levels and clinical jaundice.¹⁴ A reduced probability of chronic rejection has been demonstrated when both donor and recipient were CMV-positive.¹⁵ Langrehr et al. reported that IL-2 receptor antibody induction therapy increases the risk of chronic rejection after transplantation.^{16,17}

Risk factors for development of CR^{13,14,18}

- Late onset of rejection
- Repeated episodes of ACR
- Poor compliance
- Inadequate monitoring of immunosuppressive drugs

Risk factors for CR in patients treated with cyclosporine^{13,19-22}

- Younger recipient age
- Primary diagnosis of autoimmune hepatitis
- Biliary disease
- Baseline immunosuppression
- Male-to-female gender mismatch
- Nonwhite race

Risk factors for CR in patients treated with tacrolimus.¹⁴

- Number and severity of ACR episodes
- Donor age > 40 years

PATHOPHYSIOLOGY

The pathophysiologic mechanism of CR is not fully understood. Both humoral and cell mediated alloimmune mechanisms have an important role in CR. It is defined as a type of immunemediated allograft damage.^{1,3} The pathognomonic vascular lesions seen in the rejected liver allograft are intimal aggregates, that is, homing of foamy macrophages results in luminal occlusion. The loss of small bile ducts is partly the result of lymphocyte-directed attack on biliary epithelium. Direct lymphocytic inflammation of allogenic endothelium in the liver allograft can cause endothelial damage leading to vasculopathy.^{2,24} Relative to other cells in the liver, biliary epithelium tends to express more class I antigen. Thus, biliary epithelial cells are vulnerable targets for host attack because of their antigenicity. Loss of bile ducts may also occur indirectly as the result of ischemia secondary to immunemediated obliteration of small to medium arteries. It has been thought that obliterative arteriopathy is related to the presentation of donor antigens on the arteries and is probably a consequence of a response to endothelial injury.^{23,35} Thickening of intimal lesion seen in obliterative arteriopathy in liver allograft consists of the foamy macrophages and mesenchymal cells of recipient origin.²⁴

DIAGNOSIS

The diagnosis of chronic rejection can be difficult in needle-biopsy specimens, because a minimum of 20 portal tracts is necessary for a figure of 50% bile duct loss to be significant.¹²

HISTOLOGIC FEATURES

Histologic features of chronic rejection on liver biopsy:

- **Bile duct loss:** Progressive bile duct destruction that leads to a decrease in the number of interlobular and septal bile ducts, the process is irreversible (paucity or disappearance in at least 50% of portal tracts).³⁴ Severe centrilobular cholestasis from bile duct loss and ischemic parenchymal necrosis.

- **Obliterative endarteritis in medium and large sized arterioles:** Progressive intimal and subintimal inflammation of the 2nd and 3rd order hepatic arterial branches.
- **Ischemia of zone 3 hepatocytes and interlobular bile ducts.**

In the era of cyclosporine, management of chronic rejection often required retransplantation; however, with newer immunosuppressant medications such as tacrolimus, mycophenolate mofetil, and sirolimus, chronic rejection can be reversed, if identified and treated early before becoming severe. There is a close association between CMV infection and chronic rejection,^{25,26} but the role of CMV remains controversial.²⁷⁻²⁹

TREATMENT

Tacrolimus

Tacrolimus is more effective in treating chronic rejection in the early stage (mild-moderate cholestasis with bilirubin < 10 mg/dl and < 50% loss of bile ducts) and the patients on tacrolimus are less likely to develop chronic rejection than in cyclosporine. The benefits of tacrolimus conversion are maintained over the long term. In a study of 51 pediatric patients with chronic rejection converted to tacrolimus, 8 years survival was 65.3%.³⁰

Sirolimus

Sirolimus is also found to be effective in the treatment of chronic rejection.³² Nishida et al. reported that 50% (8/16 cases) of biopsy proven chronic rejection responded to sirolimus without need for retransplantation.³²

MMF

MMF is also a potent and safe immunosuppressive agent for rescue therapy in patients with acute and ongoing chronic rejection after liver transplantation.³³

Retransplantation

It is the definitive treatment in established CR. After retransplantation for chronic rejection the chances of recurrent chronic rejection is high.³⁴ Due to risk of infections, high dose of immunosuppression is avoided in patients, likely requiring retransplantation.

REFERENCES

1. Demetris A, Adams D, Bellamy C, AP, et al. Update of the International Banff Schema for Liver Allograft Rejection: Working recommendations for the histopathologic staging and reporting of chronic rejection. An International Panel. Hepatology 2000;31:792-99.
2. Wiesner RH, Batts KP, Krom RA. Evolving concepts in the diagnosis, pathogenesis, and treatment of chronic hepatic allograft rejection. Liver Transpl Surg 1999;5:388-400.
3. Vierling JM. Immunologic mechanisms of hepatic allograft rejection. Semin Liver Dis 1992;12:16-27.
4. Jain A, Mazariegos G, Pokharna, et al. The absence of chronic rejection in pediatric primary liver transplant patients who are maintained on tacrolimus-based immunosuppression: A long-term analysis. Transplantation 2003;75:1020-25.
5. Anand A, Hubscher S, Gunson B, et al. Timing, significance and prognosis of late acute liver allograft rejection. Transplantation 1995;60:1098-103.
6. Mirza DF, Gunson GB, Soonawalla Z, et al. Reduced acute rejection after liver transplantation with Neoral-based triple immunosuppression. Lancet 1997;349:701-02.
7. Demetris AJ, Murase N, Lee RG, et al. Chronic rejection. A general overview of histopathology and pathophysiology with emphasis on liver, heart and intestinal allografts. Ann Transplant 1997;2:27-44.
8. Alonso EM, Piper JB, Echols G, et al. Allograft rejection in pediatric recipients of living related liver transplants. Hepatology 1996;23:40.
9. Gupta P, Hart J, Cronin D, et al. Risk factors for chronic rejection after pediatric liver transplantation. Transplantation 2001;72:1098.
10. Demetris A, Adams D, Bellamy C, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic stages and report of chronic rejection. An international panel. Hepatology 2000;31:792-99.
11. Neil DAH, Adams DH, Gunson B, et al. Is chronic rejection of liver transplants different to graft arteriosclerosis (chronic rejection) of kidney and heart transplants? Transplant Proc 1997;29:2533-34.
12. Neil DAH, Hubscher SG. Histologic and biochemical changes during the evolution of chronic rejection of liver allografts. Hepatology 2002;35:639-51.
13. Freese DK, Snover DC, Sharp HL, et al. Chronic rejection after liver transplantation: a study of clinical, histopathological and immunological features. Hepatology 1991;13:882-91.
14. Blakolmer K, Jain A, Ruppert K, et al. Chronic liver allograft rejection in a population treated primarily with tacrolimus as baseline immunosuppression: long-term follow-up and evaluation of features for histopathological staging. Transplantation 2000;69:2330-6.
15. Candinas D, Gunson BK, Nightingale P, et al. Sex mismatch as a risk factor for chronic rejection of liver allografts. Lancet 1995;346:1117.
16. Langrehr JM, Klupp J, Pfitzmann R, et al. Transplant Proc 2001;33:1520.
17. Langrehr JM, Lohmann R, Guckelberger O, et al. IL-2 Receptor antibody induction increases the risk for chronic rejection after liver transplantation. Transplant Proc 2001;33:1433.
18. Candinas D, Gunson BK, Nightingale P, et al. Sex mismatch as a risk factor for chronic rejection of liver allografts. Lancet 1995;346:1117-21.
19. Blakolmer K, Seaberg EC, Batts K, et al. Analysis of the reversibility of chronic liver allograft rejection and implications for a staging schema. Am J Surg Pathol 1999;23:1328-39.
20. Hayashi M, Keeffe EB, Krams SM, et al. Allograft rejection after liver transplantation for autoimmune liver diseases. Liver Transpl Surg 1998;4:208-14.

21. European FK. 506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporine in prevention of liver allograft rejection. *Lancet* 1994;344:423-8.
22. Devlin JJ, O'Grady JG, Tan KC, et al. Ethnic variations in patient and graft survival after liver transplantation. Identification of a new risk factor for chronic allograft rejection. *Transplantation* 1993;56:1381-4.
23. Demetris AJ, Murase N, Lee RG, et al. Chronic rejection. A general overview of histopathology and pathophysiology with emphasis on liver, heart and intestinal allografts. *Ann Transplant* 1997;2:27-44.
24. AM Hayashino, T Tsuruyama, H Haga, et al. Arteriopathy in Chronic Allograft Rejection in Liver Transplantation. *Liver Transplant* 2004;10(4):513-19
25. Arnold JC, Portmann BC, O'Grady JG, et al. Cytomegalovirus infection persists in the liver graft in the vanishing bile duct syndrome. *Hepatology* 1992;16:285-92.
26. Lautenschlager I, Hockerstedt K, Jalanko H, et al. Persistent cytomegalovirus in liver allografts with chronic rejection. *Hepatology* 1997;25:190-04.
27. Waldman WJ, Adams PW, Knight DA, et al. CMV as an exacerbating agent in transplant vascular sclerosis: potential immune-mediated mechanisms modeled in vitro. *Transplant Proc* 1997;29:1545-46.
28. Manez R, White LT, Linden P, et al. The influence of HLA matching on cytomegalovirus hepatitis and chronic rejection after liver transplantation. *Transplantation* 1993;55:1067-71.
29. Paya CV, Wiesner RH, Hermans PE, et al. Lack of association between CMV infection, HLA matching and the vanishing bile duct syndrome after liver transplantation. *Hepatology* 1992;16:66-70.
30. Sher LS, Cosenza CA, Michel J, et al. Efficacy of tacrolimus as rescue therapy for chronic rejection in orthotopic liver transplantation: A report of the US Multicenter Liver Study Group. *Transplantation* 1997;64:258-63.
31. Reyes J, Jain A, Mazariegos G, et al. Long-term results after conversion from cyclosporine to tacrolimus in pediatric liver transplantation for acute and chronic rejection. *Transplantation* 2000;69:2573-80.
32. S. Nishida, A. Pinna, R. Verزارo, et al. Sirolimus (Rapamycin)-Based Rescue Treatment Following Chronic Rejection After Liver Transplantation. *Transplant Proceed* 2001;33:1495.
33. R Pfitzmann, J Klupp, P Neuhaus, et al. Mycophenolate Mofetil for Treatment of Ongoing or Chronic Rejections After Liver Transplantation. *Transplant Proceed* 2002;34:2938-39.
34. Neuberger J. Incidence, timing, and risk factors for acute and chronic rejection. *Liver Transpl Surg* 1999;5:S30-36.
35. LH Gao, SS Zheng, YF Zhu, et al. A Rat Model of Chronic Allograft Liver Rejection *Transplant Proceed* 2005;37:2327-32.

HYPERACUTE REJECTION

Synonym: Antibody mediated rejection/ Humoral Rejection

In Asian countries particularly Japan, where the deceased donor availability is limited ABO-incompatible LDLT has emerged as an elective option to meet the demand. Hyperacute rejection is rarely observed among ABO-compatible liver transplant patients, in contrast to kidney transplants.^{1,2} Liver is relatively resistant to injury from recipient antibodies, regardless of whether they are

present at the time of transplant or develop later. This is very different compared with other solid organ transplants like renal and cardiac recipients who experience rapid graft destruction, termed hyperacute rejection, if performed in a patient who has complement fixing antibodies directed against the donor organ in significant concentrations at the time of transplantation.

The mechanism of low antibody-mediated destruction in the liver than in the kidney is not clearly understood. One factor may be the vastly different microcirculation that the liver has compared with the kidney, with a preponderance of sinusoidal channels and a smaller capillary network. It is probable that antibody-mediated injury affects blood flow through the delicate capillary network of the kidney more than it does liver sinusoids. In addition, each hepatocyte is exposed to two sinusoidal channels, presumably permitting survival if only one sinusoid is occluded. Finally, differences in HLA antigen expression are known to exist in the two organs, with the kidney the more antigenic of the two.

Hyperacute rejection is usually related to ABO-incompatible liver transplants, occurring in up to 60% of cases. It is the most serious form of rejection. Hence previously it was thought that the use of these grafts should be avoided except in small children less than 3 years or in patients previously treated with splenectomy, cellular reduction therapy, or plasmapheresis. But recent use of plasma exchange, anti CD₂₀ antibodies, intravenous immunoglobulins, and intra arterial infusion of PG E1, Gabexate mesylate, and Corticosteroids has improved the survival rates in LDLT following ABO incompatible liver transplants. Hepatic graft injury from preexisting antidonor antibodies against ABO blood types in ABO-incompatible liver transplantation is much less than in renal transplantation.

MECHANISM OF INJURY

Hepatic lesions in hyperacute rejection are caused by preformed antibodies that are deposited in the hepatic sinusoids and vascular endothelium of the graft, activating the complement system and the procoagulant cascade with thrombosis and hemorrhagic necrosis of the allograft.

PRE-TRANSPLANT CONDITIONING

ABO incompatible transplant recipients are usually performed after conditioning the recipient to reduce the likelihood of early antibody mediated rejection. Goal of conditioning is to reduce the antidonor antibody titer to < 1:8 to 1:16 by various methods like plasma exchange, anti-CD₂₀ antibody therapy, splenectomy or postoperative intra-arterial injections of Methylprednisolone,

PG E1 and Gabexate mesylate. Despite of these preparations, there remains a higher risk of hyperacute rejection after ABO- incompatible liver transplantation. Mild to serious hemolytic reactions may develop in some patients because of antibodies produced by passenger lymphocytes in the graft against the recipient's blood group antigens.

Descriptions of cases of hyperacute rejection among ABO-compatible liver transplants are dramatic, with loss of the graft within a few days with an estimated incidence of one to two cases in among 100 transplants performed by a transplant team in 1 year.³ The relationship among HLA matching and liver transplantation is controversial in the literature, while it is performed routinely for recipients of kidney and pancreas allografts. At present no attempt has been made to match donors and recipients of liver transplantation according to shared MHC antigens.

Among ABO-compatible liver transplant patients, a positive lymphocyte cross match result has been described in 8 to 12% of cases, but only 30% show titers sufficiently high to cause hyperacute rejection. Therefore, the population of liver transplant patients susceptible to this complication is small. That is probably due the natural resistance of the liver to preformed antibodies, consequent to the phagocytosis of the antibodies by hepatic Kupffer cells, to the dual blood supply, and to the presence of class I histocompatibility complex antigens secreted by the donor liver, which neutralize these antibodies.³

ROLE OF C4d IN THE HUMORAL REJECTION

Complement system plays an important role in humoral rejection. When humoral rejection occurs, the recipient produces specific antibodies against the graft, which recognize and bind to antigens in the vascular endothelium of the graft. Once antibody combines with antigen specifically, the classical complement pathway is activated and activated C4 protein is hydrolyzed into C4d. C4d binds to the endothelial cells of interstitial capillaries which may be detected by immunohistochemical staining. C4d deposition means the occurrence of humoral rejection.^{10,11} Therefore C4d may serve as a marker of humoral rejection.¹⁰

Due to the gravity of hyperacute rejection cases in ABO-compatible LTX and the possibility of resolution with early retransplantation, the diagnosis should be considered even in the absence of preformed anti-HLA antibodies when the diagnoses of hepatic artery thrombosis and primary graft dysfunction have been excluded by diagnostic tests.¹³

CLINICAL PRESENTATION

Asthenia, fever, hypotension, oliguria, coagulopathy, fulminant hepatic failure and acidosis. Usually humoral rejection episodes appear in the 1st week of transplantation.

DIAGNOSIS

- Sudden rise of liver function tests
- **Liver biopsy:** Periportal edema, hemorrhage and necrosis are histological indicators of the early phase of severe humoral rejection resulting in massive parenchymal or biliary necrosis.⁶ Portal hemorrhagic edema without significant necroinflammation may represent a milder degree of humoral rejection.⁷
- **Immunostaining of immunoglobulins or complements, including C4d:** Immuno-histochemical detection of C4d has both diagnostic and prognostic value and could be a hallmark of antibody mediated rejection in liver biopsy.¹²
- Elevated antidonor antibody titer (IgG and IgM) (Measured by micro-hemagglutination assay)⁵
- **CT Scan:** Hepatic necrosis demonstrated on CT Scan as diffusely spreading low-density lesions in the graft.
- **MRCP:** Intrahepatic biliary complications such as irregularity and beading throughout the intrahepatic biliary tree.

Decrease in graft survival rate is seen as ABO-incompatible transplants are usually performed in emergency circumstances where the patient is so critical that he or she may not survive till the compatible donor is available. Because preformed antibodies do not seem to be clinically important, most transplantation programs do not perform prospective cross-matches between recipient serum and donor cells before transplantation and determination of recipient and donor HLA type is no longer considered mandatory.

DIFFERENTIAL DIAGNOSIS

- Primary nonfunction
- Hepatic artery thrombosis

TREATMENT

- Antihumoral rejection therapy such as the arterial/portal infusion of prostaglandin E1, methylprednisolone, gabexate mesylate, use of anti-CD₂₀ antibody (Rituximab), intravenous immunoglobulins and preoperative and/or plasma exchange.
- Emergency retransplantation is required in most of the cases of hyperacute rejection and is the definitive treatment.

SURVIVAL RESULTS

Overall results of ABO-incompatible liver transplants are somewhat inferior to those of ABO-compatible transplantations. 10 to 20% decrease in 1-year graft survival rates as compared to ABO-compatible grafts. Significant decrease in longterm survival has discouraged many transplant programs like Tokyo and Juntendo universities to abandon ABO-incompatible transplantation. However it has a place in emergency situation where there is no alternative compatible donor is available or in very young children less than 2 years, where the immune system is weak.

REFERENCES

1. Hale DA. Basic transplantation immunology. *Surg Clin North Am* 2006;86:1103.
2. Burton-Jr JR, Rosen HR. Diagnosis and management of allograft failure. *Clin Liver Dis* 2006;10:407.
3. Lipshutz GS, Ascher NL, Roberts JP. Rejection after transplantation. In: Busuttil RW and Klintmalm GK (eds): *Transplantation of the Liver*. 2nd ed. Philadelphia: Elsevier Saunders 2005.
4. Egawa H, Oike F, Haga H, et al. Impact of recipient age on outcome of ABO incompatible living-donor liver transplantation. *Transplantation* 2004;77:403-11.
5. Haga H, Egawa H, Shirase T, et al. Periportal edema and necrosis as diagnostic histological features of early humoral rejection in ABO-incompatible liver transplantation. *Liver Transpl* 2004;10:16-27.
6. Haga H, Egawa H, Shirase T, et al. Periportal edema and necrosis as diagnostic histological features of early humoral rejection in ABO-incompatible liver transplantation. *Liver Transpl* 2004;10:16-27.
7. Morioka D, Sekido H, Kubota K, et al. Antibody-mediated rejection after adult ABO-incompatible liver transplantation remedied by gammaglobulin bolus infusion combined with plasmapheresis. *Transplantation* 2004;78:1225-28.
8. Magro CM, Pope Harman A, Klinger D, et al. Use of C4d as a diagnostic adjunct in lung allograft biopsies. *Am J Transplant* 2003;3:1143-54.
9. Ruiz P, Garcia M, Pappas P, et al. Mucosal vascular alterations in isolated smallbowel allografts: Relationship to humoral sensitization. *Am J Transplant* 2003;3:43-49.
10. Regele H, Bohmig GA, Habicht A, et al. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: A contribution of humoral immunity to chronic allograft rejection. *J Am Soc Nephrol* 2002;13:2371.
11. Ai-bing Z. The mechanism of acute rejection in graft. *Foreign Medical Sciences of Immunology* 2004;27:4.
12. H Haga, H Egawa, Y Fujimoto, et al. Acute Humoral Rejection and C4d Immunostaining in ABO Blood Type-Incompatible Liver Transplantation. *Liver transpl* 2006;12:457-64.
13. BD Guardia, MD Almeida, SP Meira-Filho, et al. Antibody-Mediated Rejection: Hyper-acute rejection reality in liver transplantation? A Case Report. *Transplant Proceed* 2008;40:870-71.

LYMPHOCYTE CROSS MATCH TEST

The targets of activated lymphocytes in ACR are bile duct epithelial cells and the endothelium of vein and artery within the liver. The portal infiltrates contain activated lymphoblastoid cells, both B and T-cells and plasma cells. These cells are thought to be the primary source of cytokines, which act to upregulate HLA expression, increase cytotoxic T-lymphocyte differentiation, and increase alloantibody production.² This test is performed to detect antidonor lymphocytotoxic antibody.³

PROCEDURE

Lymphocytotoxic cross-match is performed according to the standard National Institutes of Health (NIH) technique.⁴ The recipient serum obtained immediately before LDLT was tested for cytotoxic antibody against donor T or B lymphocytes. Donor lymphocytes were isolated from peripheral blood, and 1 μ L of the patient's serum is added for 30 minutes at room temperature. Rabbit complement (5 μ L) is added for 1 additional hour at room temperature, and ethidium bromide and acridine orange are added to stain the cells. The cross-match test was interpreted as positive when more than 20% of the donor lymphocytes were killed by the recipient serum.

Gordon, et al. reported that there is no difference in either graft survival or in the rate of retransplantation between cross-match—positive and cross-match—negative patients.⁵ Other studies also suggest that antibody-mediated damage is not important in liver transplantation and that a successful outcome is possible despite a positive pretransplantation cross-match.^{6,7} In contrast, Takaya, et al. showed that highly sensitized cross-match—positive grafts had a poor prognosis and function in tacrolimus-based immunosuppression.⁸ Other reports indicated the higher incidence of vanishing bile duct syndrome⁹ or the severity of the acute rejection episodes^{4,10} or adverse effect on patient or graft survival^{1,11-14} in lymphocytotoxic cross-match—positive grafts.

All the above studies are in DDLT. Studies regarding lymphocytotoxic cross-match in graft survival or acute rejection after LDLT are limited. The Pittsburgh group studied the influence of cross-match on survival and reported that early graft survival rates were lower in the positive cross-match group than in the negative group (65% vs. 72% at 1 year).¹⁵ Doran et al. reported that 1-year graft survival of a positive T lymphocytotoxic cross-match was only 51%, in contrast to 82% for that of negative cross-match.¹⁴ Sugawara et al. reported that a positive T-lymphocytotoxic cross-match is associated with a higher incidence of acute rejection that did not adversely affect patient survival.¹⁶

REFERENCES

1. Hathaway M, Gunson BK, Neuberger JM. A positive cross-match in liver transplantation—No effect or inappropriate analysis? A prospective study. *Transplantation* 1997;64:54-59.
2. Lilly LB, Ding J, Levy GA. The immunology of hepatic allograft rejection. In: Maddrey WC, Schiff ER, Sorrell MF, eds. *Transplantation of the Liver*. 3rd ed. Philadelphia: Lippincott Williams and Wilkins 2001;211-27.
3. Takakura K, Kiuchi T, Kasahara M, et al. Clinical implications of flow cytometry crossmatch with T or B cells in living donor liver transplantation. *Clin Transplant* 2001;15:309-16.
4. Bathgate AJ, McColl M, Garden OJ, et al. The effect of a positive T-lymphocytotoxic crossmatch on hepatic allograft survival and rejection. *Liver Transpl Surg* 1998;4:280-84.
5. Gordon RD, Fung JJ, Markus B, et al. The antibody cross-match in liver transplantation. *Surgery* 1986;100:705-15.
6. Iwatsuki S, Rabin BS, Starzl TE, et al. Liver transplantation against T-cell-positive warm cross-matches. *Transplant Proc* 1984;16:1427-29.
7. Fujita S, Rosen C, Reed A, et al. Significance of preformed anti-donor antibodies in liver transplantation. *Transplantation* 1997;63:84-88.
8. Takaya S, Bronsther O, Iwaki Y, et al. The adverse impact on liver transplantation of using positive cytotoxic cross-match donors. *Transplantation* 1992;53:400-06.
9. Donaldson PT, Alexander GJ, O'Grady J, et al. Evidence for an immune response to HLA class I antigens in the vanishing-bile duct syndrome after liver transplantation. *Lancet* 1987;8539:945-51.
10. Katz SM, Kimball PM, Ozaki C, et al. Positive pretransplant cross-matches predict early graft loss in liver allograft recipients. *Transplantation* 1994;57:616-20.
11. Demetris AJ, Murase N, Nakamura K, et al. Immunopathology of antibodies as effectors of orthotopic liver allograft rejection. *Semin Liver Dis* 1992;12:51-59.
12. Nikaein A, Backman L, Gonwa T, et al. HLA compatibility and liver transplant outcome. Improved patient survival by HLA and cross-matching. *Transplantation* 1994;58:786-92.
13. Charco R, Vargas V, Balsells J, et al. Influence of anti-HLA antibodies and positive T-lymphocytotoxic cross-match on survival and graft rejection in human liver transplantation. *J Hepatol* 1996;24:452-59.
14. Doran TJ, Geczy AF, Painter D, et al. A large, single center investigation of the immunogenetic factors affecting liver transplantation. *Transplantation* 2000;69:1491-98.
15. Doyle HR, Marino IR, Morelli F, et al. Assessing risk in liver transplantation. Special reference to the significance of a positive cytotoxic cross-match. *Ann Surg* 1996;224:168-77.
16. Y Sugawara, M Makuuchi, J Kaneko, et al. Positive T Lymphocytotoxic Cross-Match in Living Donor Liver Transplantation. *Liver Transplantation* 2003;9(10):1062-66.

(C) BILIARY COMPLICATIONS

INCIDENCE

The incidence of biliary tract complication after orthotopic liver transplantation varies from 11 to 25%.^{1-5,13} These high rates may signify an inherently sensitive nature of the biliary epithelium to ischemic damage in comparison with hepatocytes and vascular endothelium. Biliary strictures and bile leaks are the most common biliary complications following liver transplantation, although a decreasing trend has been noted in recent years. The reported incidence of biliary strictures is 5-15% after deceased donor liver transplantation (DDLT) and 28-32% after right-lobe live donor liver transplantation (LDLT).⁸⁻¹²

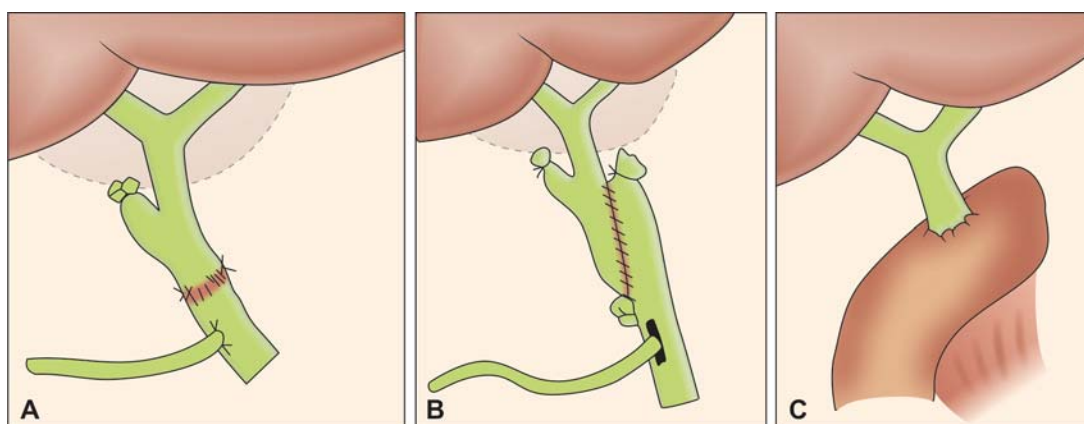
The frequency of biliary complications is higher in LDLT than DDLT.^{6,7} Potential background of post-transplant biliary complications are technical, anatomical, ischemic, and immunological factors including arterial thrombosis, CMV infection, rejection and preservation injury. These complications not only affect graft survival but also have a major impact on the quality of life for a liver allograft recipient, as they entail frequent readmission, reoperation, hospital stays, and escalating costs and add to the emotional trauma that patients suffer. Majority of biliary complications are now amenable to endoscopic interventions and the role of surgery mainly confined to treatment failures as a second-line backup option. Right lobe has more anatomical variations in the vascular and biliary tract; this may be explained by the relative consistency between the left umbilical vein and the liver. Multiple biliary orifices are encountered in 26.0

to 39.6% of the cases, which make the reconstruction in right lobe LDLT technically difficult,¹³⁻¹⁵ making more vulnerable to biliary complications.

TECHNICAL ISSUES RELATED TO BILIARY COMPLICATIONS IN DDLT

Duct-to-duct anastomosis is used in 80-90% of adult liver transplantations (**Figures 26.1A and B**).^{16,17} Roux-en-Y Hepaticojejunostomy is used only under specific conditions, including gross disparity between the sizes of the ducts and diseased or unavailable ducts, and for revision surgery (**Figure 26.1C**).^{18,19} T-tubes were widely used in the past but recent studies failed to show any benefit due to the use of T-tubes, and at the same time, a higher incidence of complications (bacterial colonization of the biliary tract and bile leaks) and higher costs were noted in the T-tube group.^{20,21} 50% of complications were related to the biliary drainage: bile leakage close to the T-tube or after removal of the drain.^{22,23} It seems obvious that abandonment of the use of drainage eliminates the possibility of these complications.²⁴⁻²⁷

The use of an internal stent theoretically eliminates the possible complications related to T-tubes and at the same time offering the potential benefits of a splint, has not shown uniformly reproducible results. Both increased incidence and decreased incidence of complications have been reported with the use of internal stents in comparison with T-tubes.^{28,29} Their role of internal stents in biliary reconstruction is yet to be fully determined.



D-D anastomosis—2 types (end-to-end and side-to-side with a T-Tube)

Hepaticojejunostomy

Figures 26.1A to C: Different types of biliary anastomosis (Reproduced from slides of Makuuchi M)

Technical factors leading to biliary complications

- Placement of too many sutures
- Uneven distribution and tension of the sutures
- Less number of sutures resulting in inadequate mucosal apposition leading to leaks.

A recent report described the use of spatulation of the donor and recipient bile ducts and the use of continuous sutures as methods to increase the luminal diameter of the anastomosis and provide even distribution of the tension along the suture walls. The anastomotic stricture incidence rate was 2.5% versus 12.5% without spatulation.³⁰

TECHNICAL ISSUES RELATED TO BILIARY COMPLICATIONS IN LDLT

Growing experience in LDLT and improved surgical skills has resulting in duct-to-duct anastomosis favorable over Roux-en-Y anastomosis, and it has become the standard of care as it maintains the physiologic bilioenteric continuity.^{31,32} In some cases there is discrepancy in the size of the ducts of allograft and recipient. Usually recipient's duct size is larger than the graft duct. It may be necessary to partially close the common hepatic duct, which should not be done exactly same size of the graft duct as it may narrow the antero-posterior diameter causing the CHD smaller than the desired size. Occasionally graft duct size is more than the recipient's duct size. In such cases if the confluence of the RHD and LHD if preserved, is opened to form a single duct opening which is larger than the individual ducts.

Roux-en-Y Hepaticojejunostomy is preferred in patients with PSC, biliary atresia, secondary biliary cirrhosis and when the allograft contains 2 or more bile ducts that are far apart and not suitable for ductoplasty. In case of 2 ducts, reconstructing by Roux-en-Y anastomosis, the distance between the openings of the jejunum should be at least 3 times the distance between the hepatic ducts openings on the graft side, as the bowel contracts after openings are made in the jejunum which will cause difficulty in anastomosis.

Obtaining a single healthy vascularised right duct and avoiding injury to the left hepatic duct is crucial step in LDLT.³³ It is always better to leave the donor stump as short as possible and the recipient stump as long as possible to maintain adequate blood supply on both ends. Too short a donor stump makes the anastomosis technically demanding, and maintaining a fine balance is critical. A single right duct is identified in only 50% of donors, and even in those cases in which a single duct is identified, it frequently subdivides into anterior and

posterior parts fairly quickly; this leaves very little margin for error.³⁴ Careful preoperative planning and maintaining flexibility are the critical components of effective prevention. The value of preoperative MRCP and intraoperative cholangiogram in delineating the anatomy and identifying any aberrations is crucial.^{35,36} Repeating the cholangiogram after completion of parenchymal transection and immediately before the ductal transection guides the precise site and angle of the transection.³⁷ Further surgical techniques that have been hypothesized to reduce the incidence of biliary strictures include minimal dissection of the hilar plate to prevent devascularization of the right duct and perpendicular division of the right duct to prevent ischemia to the lateral edges of the duct.³⁷

Presence of more than one duct in the allograft increases the complexity of biliary anastomosis and the leak rate, but the effects on the incidence of biliary strictures have not been conclusively demonstrated. In the absence of a sufficient length of the ducts or when the ducts are separated too much or placed at sharp angles, the use of ductoplasty (use of combined ducts for a single anastomosis) is an option with a possible risk of putting tension on the anastomosis and reducing the vascularity. Ductoplasty although increases the luminal diameter of the anastomosis, but has shown conflicting results as far as the leak rates are concerned.^{38,39}

SUTURES AND TECHNIQUES OF ANASTOMOSIS

Use of synthetic monofilament nonabsorbable sutures (polypropylene) has recently become preferred because of their feasibility and supposedly less induction of the tissue reaction and less bacterial colonization, as compared to PDS sutures. There is every probability that in presence of corticosteroids, PDS sutures will not hold the tissue together for long duration leading to impaired wound healing and leakage.^{40,41} Interrupted sutures have shown higher leak rates, whereas continuous sutures are associated with a higher stricture rate. Using the benefits of both, the technique includes the continuous posterior wall and interrupted anterior wall in biliary reconstruction with the use of 6-0 or 7-0 monofilament nonabsorbable suture and the distance between each suture is 1 mm.³⁹ Biliary reconstruction is usually performed under 2.5 times loupe magnification. Use of microsurgical techniques in biliary reconstruction (ducts <2 mm) similar to hepatic arterial anastomosis has recently been discussed in literature and it has shown a reduction in the incidence of biliary strictures.⁴³

Steps in the recipient hepatectomy to avoid biliary complications^{44,120}

- High hilar dissection using the intrahepatic Glissonian approach
- Dissection between the bile duct and the hepatic artery is kept minimal to prevent the disruption of the ductal vascularity
- Dissecting the artery and the duct as one unit,
- Dividing the ducts at a point that is distal to bifurcation of CHD in order to preserve a long length of the vascularized recipient duct
- Use of microsurgical techniques for smaller ducts
- Use of ductoplasty, and flexibility in the performance of double ductal anastomosis

Steps in live donor to harvest allograft with a vascularised bile duct¹²⁰

- Judicious use of intraoperative cholangiogram
- Minimal dissection of the hilar plate
- Avoid skeletonisation of bile duct
- Perpendicular transection of the duct

COMPLICATIONS IN THE RECIPIENT

In the absence of any attachments in transplanted liver recipients, the blood supply to the graft bile duct is derived solely from the hepatic artery. Preservation of periductal microcirculation in the recipient duct and excellent hepatic artery reconstruction might be a key factor for successful bile duct reconstruction. Common biliary complications are due to technical problems, ischemia or anatomic variations.⁴⁶

Biliary complications

- Anastomotic biliary leak
- Biliary strictures
 - Anastomotic stricture
 - Nonanastomotic stricture
- Bile leak from cut surface of graft or T-tube exit
- Cholangitis after T-tube cholangiography or obstruction
- Sludge and stone formation
- Extrahepatic bile duct necrosis
- Sphincter of oddi dysfunction

There is a considerable disparity reported in literature regarding the incidence of biliary complications after LDLT, ranging from 24 to 60%.⁴⁷⁻⁴⁹ Duct-to-duct anastomosis is currently the standard technique of choice for biliary reconstruction in right lobe LDLT.^{50,51} The benefits include preservation of the sphincter of Oddi, less frequent colonization of the biliary tract, less

operative time, fewer anastomoses, and the availability of endoscopic treatment as a back-up option if strictures develop.⁵²

Advantages of D-D anastomosis over Roux-en-Y choledochojejunostomy^{50,51}

- Technically faster, less time consuming and less number of anastomoses.
- It is more physiologic biliaryenteric continuity and sphincter of oddi function is preserved.
- Intestinal handling is avoided, thus acting as an anatomical barrier to reflux of enteric contents into the biliary tract and this may theoretically decrease the risk of ascending cholangitis.
- Provides an easy access for endoscopic treatment of postoperative biliary complications.
- Morbidity is reduced when there is a biliary leak.
- Early oral feeding and drug administration possible.

PRESENTATION OF BILIARY COMPLICATIONS

First sign of bile leak is increased bile content in abdominal drain or detection of bilioma on the cut surface of the graft by routine Doppler USG study for portal flow measurement. Stricture or obstruction or stones may present as pruritus, abdominal pain, fever and signs of cholangitis or biliary peritonitis.^{53,54} Cholestatic liver picture: elevated bilirubin, AST, ALT, alkaline phosphatase and increased WBC counts Liver biopsy findings rarely suggestive of obstructive pathology.⁵⁵ Serum bilirubin >1.5 mg/dL is a better indirect marker of biliary stasis than alkaline phosphatase in LDLT as alkaline phosphatase is overly sensitive.⁵⁶

Differential diagnosis

Preservation/perfusion injury
Graft injury due to ischemia
Sepsis
Rejection
Reactivation of original disease such as
Hepatitis due to HBV and HCV, Autoimmune etiology

BILE LEAK

It is one of the most common biliary complications. It is related to anastomotic complications resulting in focal or generalized biliary peritonitis depending on the amount of bile leak. A bilioma is a source of infection in the recipient and can compromise the healing of biliary anastomosis and can cause pseudoaneurysm of hepatic artery leading to dangerous complication like sepsis and rupture of pseudoaneurysm of HA. Sources of bile leak

are from anastomotic site, T-tube exit site, aberrant bile duct and cut surface of the graft.

BILIARY STRICTURES

Biliary strictures can present at any time after the surgery, the mean interval at the time of presentation is 5-8 months after OLT⁵⁸ and the majority present within 1 year, but recent studies suggest that their prevalence continue to increase with the time after transplantation.

Types of Biliary Strictures^{59,60}

Two types, anastomotic and nonanastomotic strictures, based on their inherent differences in their pathology, time of presentation, treatment, and response to treatment (as shown in the table below)

1. **Anastomotic strictures (AS)**^{57, 66-69}
2. **Nonanastomotic strictures (NAS)**:^{58,60-65} These are further classified into 2 subgroups based on etiology.
 - Hepatic artery thrombosis (HAT) leading to microangiopathy.
 - Non-HAT etiology, i.e. due to microangiopathy and immunogenicity.

CLASSIFICATION OF BILIARY STRICTURE

Type of stricture	Anastomotic stricture (AS)	Nonanastomotic stricture (NAS)
Number	Isolated and single	Multiple
Length	Short	Long
Site of stricture	Anastomotic site	Intrahepatic duct and/or donor ducts proximal to anastomosis
Incidence	4-9%	1-19%
Graft loss	Rare	Often causes graft loss, if untreated
Appearance after transplantation	5 to 8 months	3.3 to 5.9 months
Etiology	Bile leak Poor vascularity, duct ischemia and fibrosis due to poor technique	HAT causing microangiopathy Non HAT (Microangiopathy and immunogenicity)*

*NAS secondary to ischemia and microangiopathy, present within 1 year after transplant, whereas the occurrence after 1 year is more often related to immunological cause.

CAUSES OF MICROANGIOPATHY AND IMMUNOGENICITY

Microangiopathy	Immunogenicity
HAT Preservation injury Prolonged cold and warm ischemia time	Chronic rejection, ABO incompatibility, Autoimmune hepatitis,
DCD donors Prolonged use of vasopressors in the donor	Primary sclerosing cholangitis

Risk factors for development of biliary strictures in DDLT and LDLT⁷⁰⁻⁸³

- Bile leaks
- Hepatic artery thrombosis
- ABO incompatibility
- DCD donors
- Marginal donors (old age): Degenerative age-related changes in the microcirculation of the biliary tract leading to more biliary complications
- Preservation injury
- Prolonged cold and warm ischemia time
- Severe acute and chronic rejection
- Technical factors leading to duct ischemia caused by poor vascularity and fibrosis
- Small size of the duct (<4 mm)
- Multiple bile duct anastomoses
- Viral and bacterial infections particularly CMV infection
- Prolonged use of vasopressors in the donors
- Primary sclerosing cholangitis.

Kyoto group reported large series showing that the overall incidence of biliary complications was 24.0 and 74.5% of these complications are managed by endoscopic treatment.³⁹ Duct-to-duct choledocho-choledochostomy has a lower incidence of bile leak and a higher incidence of stricture.^{39,84}

Biliary complications in right lobe LDLT:

Author	Type of biliary complications	Roux-en-Y anastomosis	Duct-to-duct anastomosis
Gondolesi et al.	Bile leak Stricture	18.2% 7.3%	16.3% 31.7%
Kasahara et al.	Bile leak Stricture	12.4% 8.3%	4.7% 26.6%
Fan et al.	Bile leak Stricture	7.3% 30.5%	5.5% 20.1%

Biliary complications in right lobe DDLT^{86,87}

Author	Bile leak	Stricture
Davidson et al.	17.5%	13.5%
Rabkin et al.	19%	12%

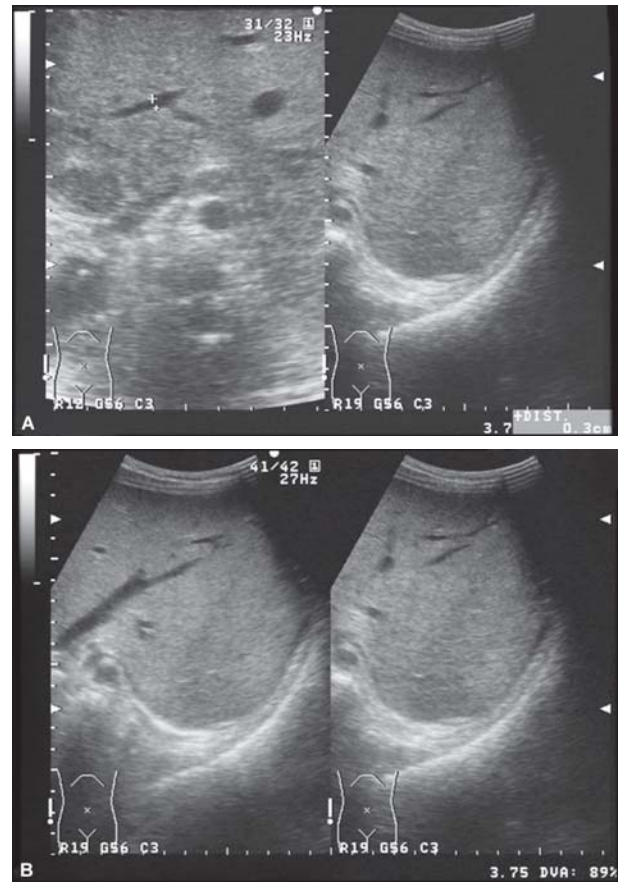
Biliary complications are usually diagnosed clinically and radiologically. Biliary leakage is defined by bilirubin level in the bilious ascites higher than the serum level and stricture is diagnosed by dilated intrahepatic bile ducts with USG, hepatobiliary scan with Tc-99m Sn-N-pyridoxyl-5- methyltryptophan (99 mTc-PMT).⁸⁸

DIAGNOSIS OF BILIARY COMPLICATIONS

USG (Figures 26.2A and B) is the first noninvasive modality to be used, when a biliary complication is suspected. Its sensitivity is 38-66% and its value is limited in treatment planning.⁸⁹⁻⁹¹ A negative USG examination does not rule out the biliary complications in liver transplant recipients. **CT scan** is important in detecting biliary tract dilatation and presence of bilioma. It allows the evaluation of vascular supply and indirect evaluation of intra and extra hepatic biliary tree. **Gadolinium enhanced MRI** is very useful for diagnosis and treatment planning for biliary stricture with a sensitivity and specificity close to 90%.^{92,93} but the lack of therapeutic ability is the main disadvantage. **Cholangio-graphy:** It is considered by all to be the gold standard not only in establishing the diagnosis but also for therapeutic intervention.⁹⁶ T-Tube cholangiogram is obsolete in the present days as most of the transplant programs do not use T-tube. The role of MR cholangiography is the best option to study the biliary complications.

Endoscopic retrograde cholangiography (ERC) and **Percutaneous transhepatic cholangiography (PTC)** have both diagnostic and therapeutic value, but with a higher operational risk. ERC is the first choice, as it is not only more physiological but also less invasive. But it can't be used in patients with Hepaticojejunostomy or choledochojejunostomy. Double balloon enteroscopic technique has been made it possible to reach this difficult area. The ERCP findings in NAS consist of mucosal abnormalities, narrowing, and prestenotic dilatation, whereas the findings in AS include narrowing at the anastomosis or bifurcation. PTC is invasive but very useful. ERCP failed cases and inpatients of proximal biliary strictures can be treated by PTC.

Hepatobiliary scintigraphy of the biliary tree using 99-technetium-labeled iminodiacetic acid identifies strictures with 75% sensitivity and 100% specificity^{94,95} but the absence of any therapeutic benefit offsets its noninvasive advantage. Leak appears as trace activity



Figures 26.2A and B: Biliary stricture leading to proximal biliary dilatation shown in an USG examination after 3 weeks of LTX in a child with left lateral segment graft

outside the biliary tree and stricture appears as failure of the tracer to pass down the distal biliary tree and duodenum. Its sensitivity and specificity for diagnosis of biliary complications approaches to 100% overall, 93% for bile leak and 88% for biliary obstruction.⁹⁷ But in the present era of transplantation, its use has been replaced by ERC and PTC in most of the transplant centers.

Liver biopsy: The importance of liver biopsy is to rule out other differential diagnosis like rejection or reactivation of original disease.

Treatment of biliary complications is performed more frequently by nonoperative endoscopic approach rather than the operative approach. ERCP is a safe treatment modality, with a low risk of complications (2.4%) and an absence of mortality. Cholangiography was feasible in about 80% patients and, after access to the bile duct; treatment of the lesion was possible in 82% of cases. The overall success of ERCP, including those resulting in a normal cholangiogram, is 64%.⁴⁵ Thuluvath et al.

described a response rate of strictures to endoscopic management of 68%.⁹⁸ Overall success of ERCP varies according in different studies (ranging between 50 and 80%).¹⁰⁰ Biliary enteric anastomosis is an alternative for patients with late biliary complications after HAT that were not solved by endoscopic or percutaneous treatment and that required an urgent intervention.¹⁰¹

BILE LEAK

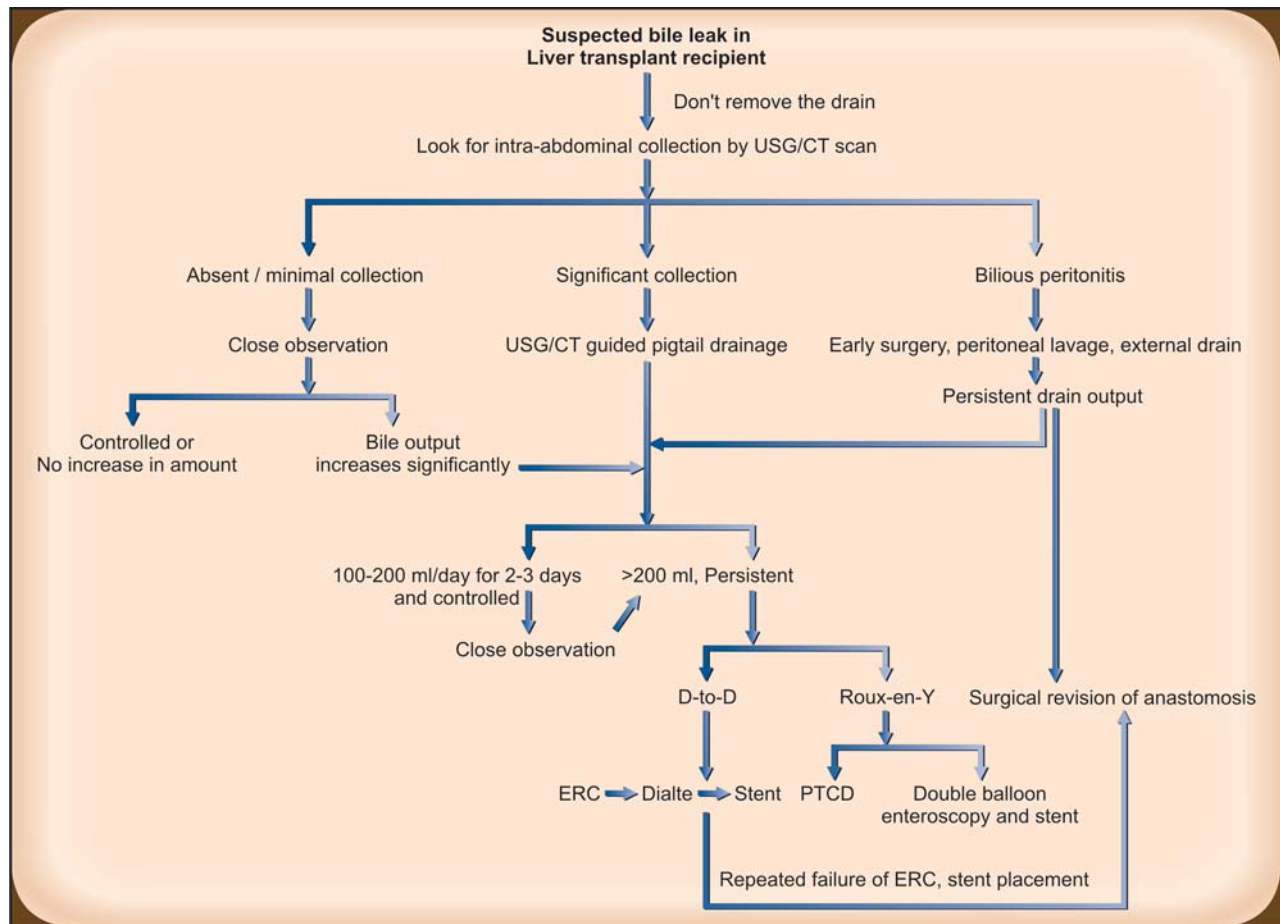
The algorithm for the management of biliary leak in liver transplant recipients is shown in the **Flow chart 26.1**.

BILIARY STRICTURE

The goal of treating biliary strictures is to prevent complications of biliary-outflow obstruction, including jaundice, cholangitis, choledocholithiasis, postobstructive biliary cirrhosis, and liver failure requiring retransplan-

tation. The treatment of plan of different biliary strictures in LDLT and DDLT is shown in the **Flow chart 26.2**.

Previously, biliary strictures following OLT managed by surgical reconstruction in the form of Roux-en-Y Hepaticojejunostomy. But the endoscopic techniques are the first choice now a days.¹⁰² ERCP is the first choice for treatment of biliary complications before performing a surgical intervention.¹⁰² PTC has a success rate of 40-85%, is considered the second-line option because of the invasive nature of the procedure and the associated complications of hemorrhage, bile leaks and morbidity. Davidson et al¹⁰³ described that after surgical choledochojejunostomy, a 6% rate of perioperative deaths, 26% early complications, and 22% late complications. Prior nonsurgical intervention (ERCP or PTC) did not adversely influence the outcome of subsequent surgical reconstruction, concluding to recommend surgery to treat biliary complications after OLT in patients in whom an endoscopic or percutaneous approach fails.



Flow chart 26.1

Potential risks of percutaneous treatment (PTC)

Minor complications

Biloma
Transient hemobilia
Puncture site hematoma
Drainage obstruction
Dislocation abscess

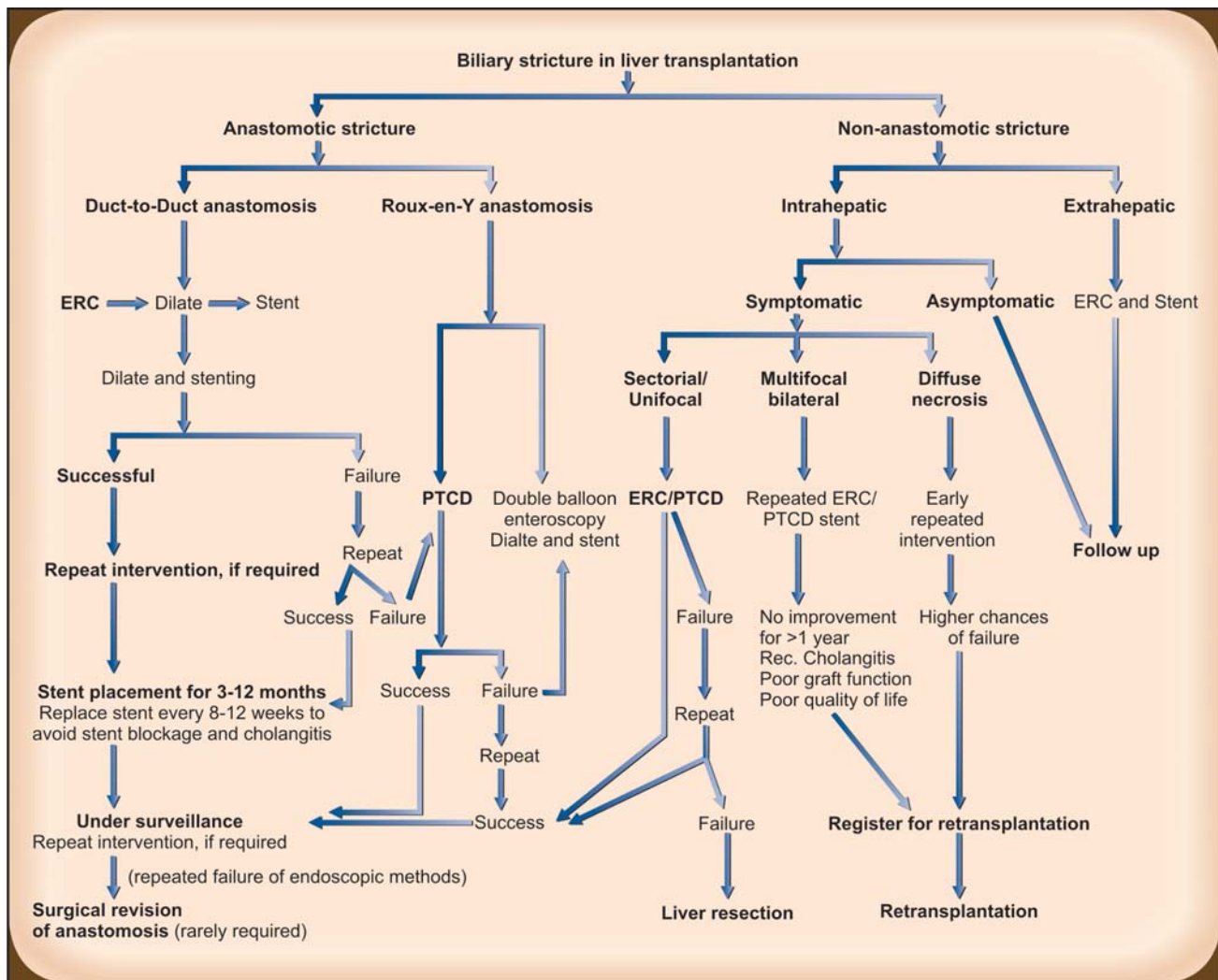
Major complications

Sepsis
Hemorrhage
Fistulas
Subcapsular hematoma
Peritonitis
Pancreatitis
Cholangitis
Pseudoaneurysm

Sepsis and hemorrhage represent the most important complications, and the reported rates are 2.5%.⁸⁵ The recommended overall procedure threshold for all major complications is 10%.

ANASTOMOTIC BILIARY STRICTURE IN DDLT

Anastomotic biliary stricture in DDLT (Figures 26.3 to 26.10) constitutes one of the most common biliary complications and is a major cause of morbidity after DDLT.¹⁰⁴ Anastomotic strictures constitute as much as 87% of biliary strictures and involve the choledochojejunostomy or the choledochocholedochostomy site in DDLT.¹⁰⁵ Aggressive endoscopic therapy with combined biliary dilation and maximal stent placement achieves successful resolution of anastomotic biliary strictures occurring after DDLT through a relatively short treatment course that achieves sustained success with minimal complications.¹⁰⁶ During ERC, cannulation of the biliary tree with a guide wire and contrast is injected into the biliary tree to stricture under fluoroscopy and the stricture



Flow chart 26.2

Treatment course of biliary stricture in DDLT and LDLT (Endoscopic treatment)

Anastomotic biliary strictures in DDLT

(Figures 26.3 to 26.10: Course of treatment over 1 year period)

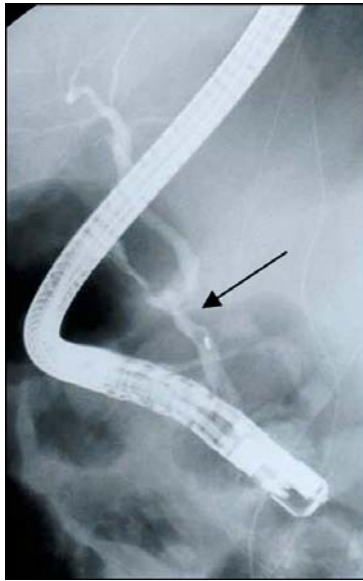


Figure 26.3: Stricture



Figure 26.4: Single stent (10 Fr.)

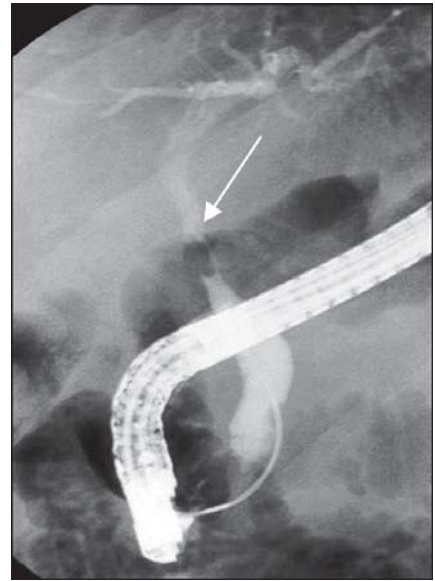


Figure 26.5

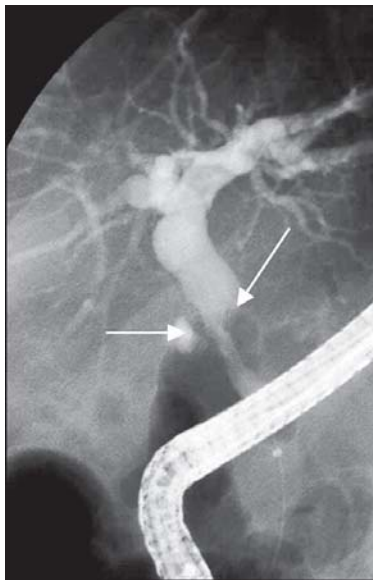


Figure 26.6: Dilatation of stricture

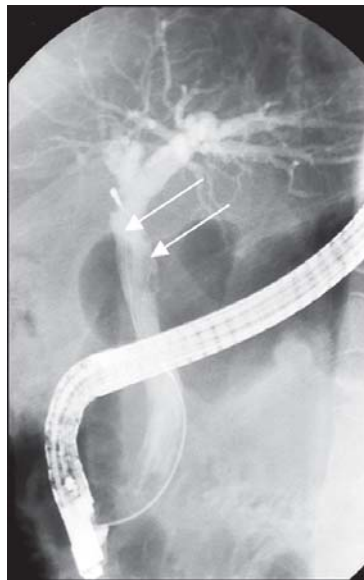


Figure 26.7

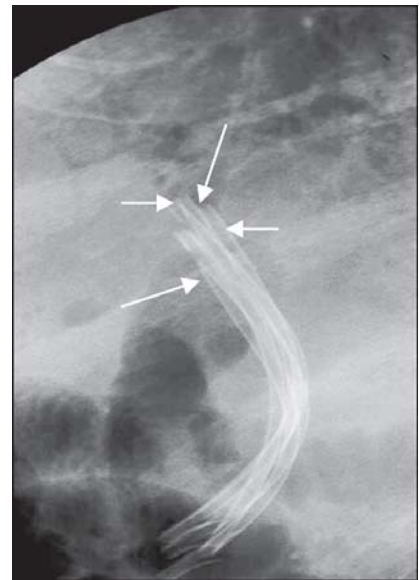


Figure 26.8: Four stents



Figure 26.9: Four plastic stents



Figure 26.10: Five plastic stents

Figures 26.3 to 26.10: Progressive increasing stent number to dilate the strictures every 3 months (5 stents)
(Contributed and reproduced with permission of Nai-Jen Liu, CGMH, Taiwan)

is dilated with a balloon and a plastic stent of size 8-10 FG size is placed at the stricture site. Sometimes 2-4 stents are placed in a single stricture so as to allow maximum dilatation. The stents are progressively replaced by larger stents every 8-12 weeks to prevent the complication of obstruction, cholangitis, or stone formation. The treatment is usually completed in 6 months 1 year with an average of 3-4 stent exchange sessions.⁵³ It has been conclusively seen that the use of stents in addition to balloon dilatation achieves higher success rates and less recurrence in comparison with balloon dilatation alone.⁵³ Stent positioning seems to be the best and durable treatment of anastomotic biliary strictures, as demonstrated by Morelli et al. with long-term stricture resolution in 80% of patients.¹⁰⁷ The overall success rate of ERCP treatment for AS is 70-100%, depending on the experience of the team.⁵³

Poor results are seen in^{11,19,55}

- Delayed presentation post-transplant (>6 months)
- Presence of tight strictures.

Sharma et al recently used the Spyglass direct visualization system as the guidance system for the passage of the guide wire through a tight stricture where conventional ERCP failed. The system, by providing direct visual access to the biliary tract for guidance, can be an important assisting device in this subset of patients. It helps in cannulating the tight strictures.⁹⁹

Risk factors for recurrence of biliary strictures.⁸¹

- Late initial presentation, presence of bile leaks
- Use of T tubes

Anastomotic strictures that are identified within 1 year show excellent responses to short-term stenting (3 to 6 months), while late-appearing anastomotic strictures (after 12 months) require long-term stenting (12 to 24 months).¹⁰⁹

When AS are treated appropriately, the long-term results in terms of patient and graft survival are equivalent to those for matched controls without AS. The management for AS complicating a hepaticojejunostomy includes the use of PTC with success rates of 50-75% or stent placement with the help of double balloon enteroscopy.¹¹⁰⁻¹¹² Surgical revision is confined to endoscopic failures, and the long-term results are good, with no effect on patient or graft survival.¹¹³⁻¹¹⁴

NON-ANASTOMOTIC STRICTURES IN DDLT¹¹⁵

According to the site of obstruction, NAS in DDLT (**Figure 26.11**) can be divided into 2 groups:

I. Intrahepatic⁵²

- Unifocal
- Confluence type
- Bilateral multifocal
- Diffuse necrosis type.

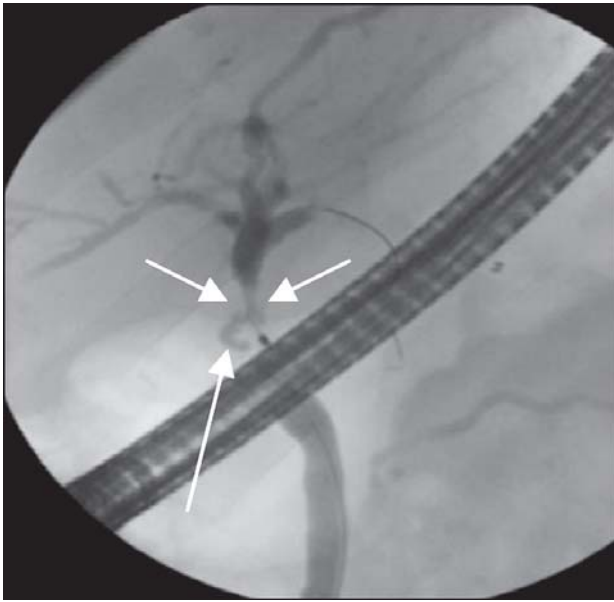


Figure 26.11: ERCP image showing a long non-anastomotic stricture extending proximally from the site of the anastomosis.¹²⁰ ("Reprinted with permission of John Wiley and Sons, Inc.")

II. Extrahepatic

NAS are difficult to treat and any generalized treatment recommendations are difficult to make. NAS secondary to early HAT usually require urgent revascularization or retransplantation. Late HAT, causing NAS can be treated by more aggressive endoscopic procedures and require long duration of treatment. Intrahepatic strictures not only are difficult to dilate but also respond poorly to endoscopic treatment. Success rate is 50-75%.

Factors influencing the success of endoscopic procedures in NAS:

- Severity of the stricture
- Number of strictures
- Location of the stricture

Inadequate treatment of these strictures leads to development of frequent episodes of cholangitis, biliary cirrhosis or atrophy of the involved segment or lobe. 50% of the patients with NAS either die in need of a liver or require retransplantation secondary to graft loss.¹¹⁵

ANASTOMOTIC BILIARY STRICTURES IN LDLT (FIGURES 26.12 TO 26.33)

Endoscopic approach has the potential to be a first-line therapy for the management of biliary complications after LDLT.¹¹⁶ however the role of endoscopic procedures in AS of LDLT is still under evaluation.

Anastomotic biliary strictures in LDLT (right lobe) (Figures 26.12 to 26.23 course of treatment over 10 months period)

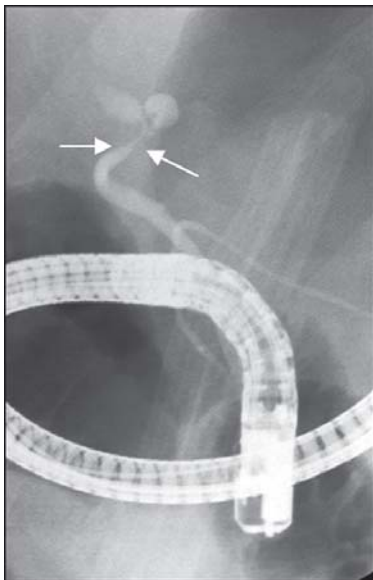


Figure 26.12

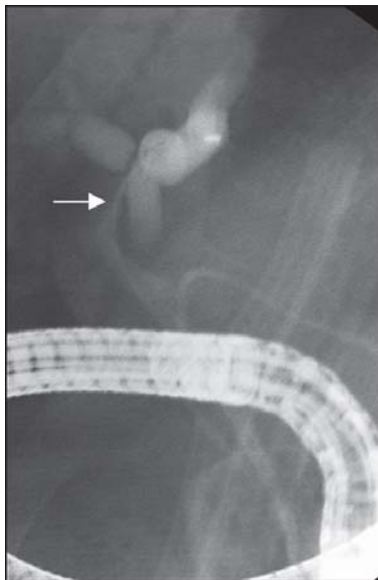


Figure 26.13

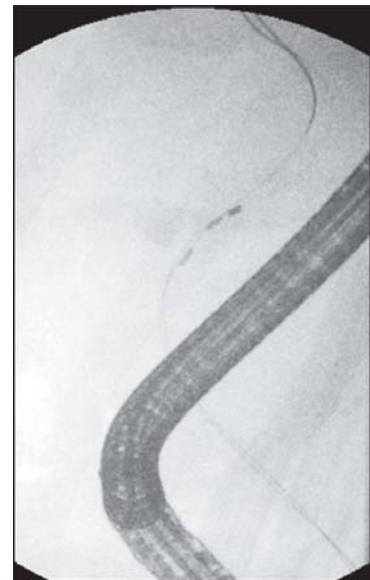


Figure 26.14

Figures 26.12 to 26.14: Angulated strictures in both right anterior and posterior branches. Special Haber catheter was used to negotiate both ducts

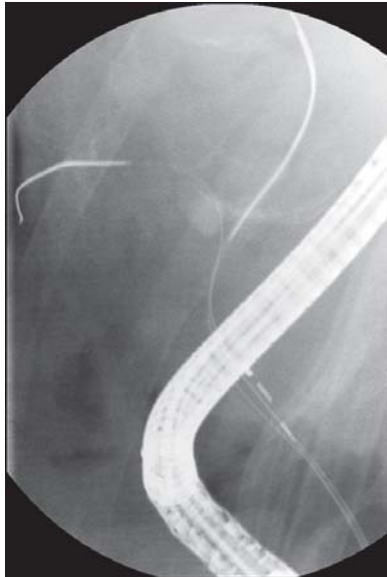


Figure 26.15

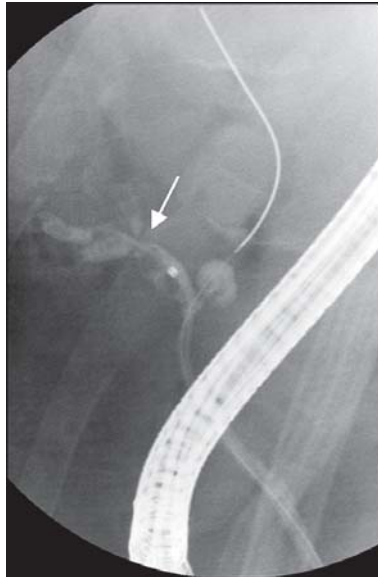
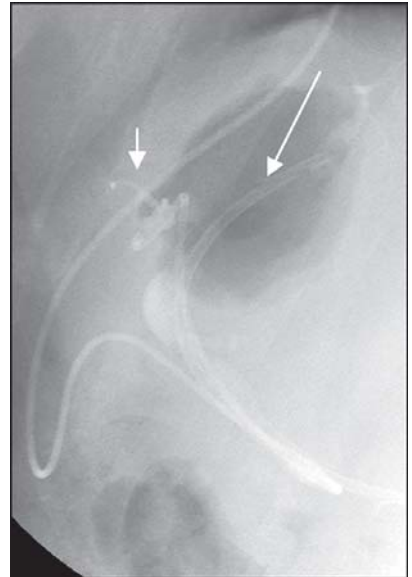


Figure 26.16

Figure 26.17: Short arrow-ENBD catheter
Long arrow-stent

Figures 26.15 to 26.17: A 10 Fr. Stent was placed in right anterior IHD,
a 6 Fr. ENBD catheter was placed in right posterior sectorial branch

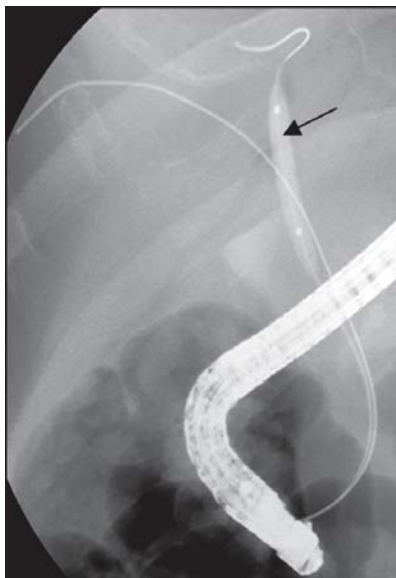


Figure 26.18: Balloon dilatation



Figure 26.19: 2 plastic stents

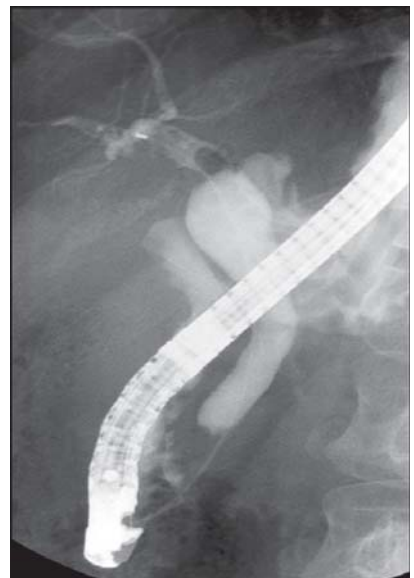


Figure 26.20

Figures 26.18 to 26.20: Two 10 Fr. Stents were placed 4 weeks after first treatment

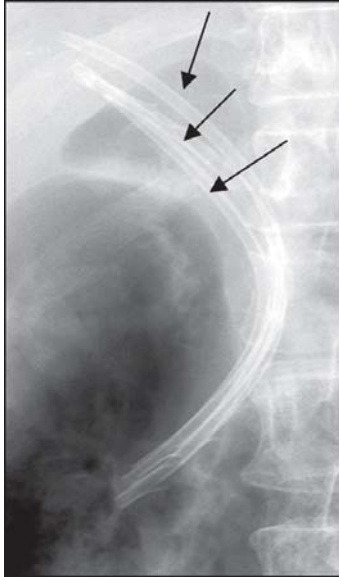


Figure 26.21: 3 plastic stents

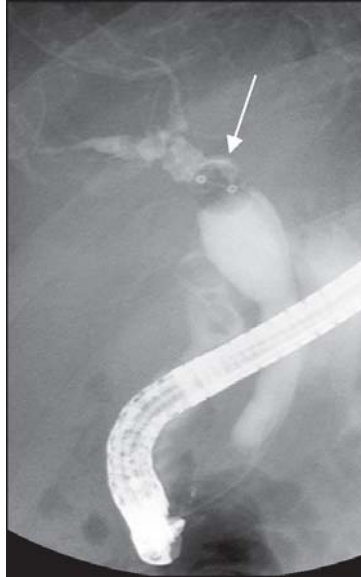


Figure 26.22



Figure 26.23

Figures 26.18 to 26.23: Progressive increasing stent number to dilate the strictures every 3 months (4 stents) No waist demonstrated by balloon catheter at the end of treatment (10 months)] (Contributed and reproduced with permission of Nai-Jen Liu, CGMH, Taiwan)

Problems leading to less success rate of endoscopic procedures in treating AS in LDLT:

- Smaller size/tight stricture
- Peripheral location
- Multiple ductal anastomosis
- Increased risk of devascularization and ischemia

Very few published trials have evaluated the efficacy of endoscopic approaches in AS secondary to LDLT.^{117,118} Kyoto group has described crane neck deformity of AS in LDLT, in which the biliary anastomosis is located at a point that is far below the highest portion of the recipient duct. The occurrence of this event is probably related to compensatory hypertrophy of the donor lobe, causing a sharp angulation of the bile duct and hence a difficult endoscopic approach. These strictures have been reported to be resistant to endoscopic treatment.¹¹⁸ Success rate for endoscopic procedures in AS in LDLT is 60-75% as compared to DDLT rate of 80-90%.^{117,118} Commonest reason for failure of endoscopic treatment is the inability to cannulate the stricture. As in DDLT, the combination of balloon dilatation and stenting was more effective than either modality alone. Stent placement is difficult due to complex and peripheral anastomosis.¹¹⁸

Anastomotic biliary stricture in a right lobe LDLT, treated by PTC drainage for a failed ERC treatment (Figures 26.24 to 26.27).

Anastomotic biliary stricture in a left lateral segment graft in a child (Figures 26.28 to 26.33).

NON-ANASTOMOTIC BILIARY STRICTURES IN LDLT

Results of endoscopic procedures are very disappointing in the treatment of NAS in LDLT. Average success rate ranges from 25 to 33%, which is way below the 60% success rate seen with NAS in DDLT.¹¹⁸

Role of Liver Resection in Post-transplant Biliary Stricture

Liver resection is primarily done as a graft saving procedure to treat biliary complications, particularly in isolated sectorial duct involvement and to avoid retransplantation. Early resection has high mortality rate as compared to the resection carried out later than 3 months, 22 and 66% respectively.⁹⁹

Role of Retransplantation

Retransplantation is considered when the graft function is deteriorating in spite of repeated endoscopic maneuver,

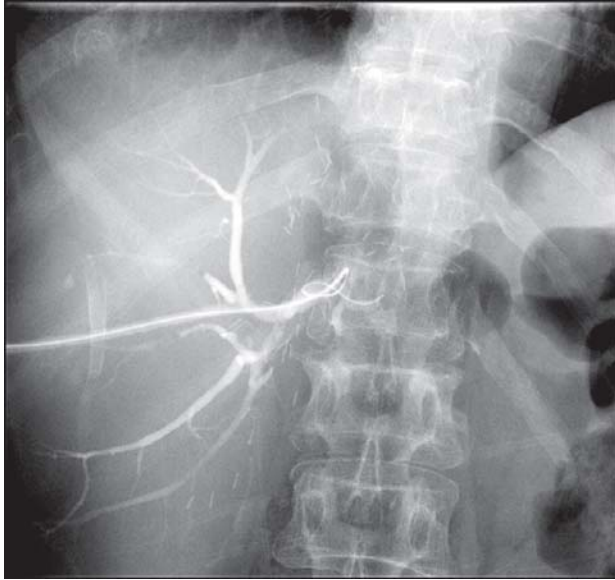


Figure 26.24: PTC catheter passed along the guide wire

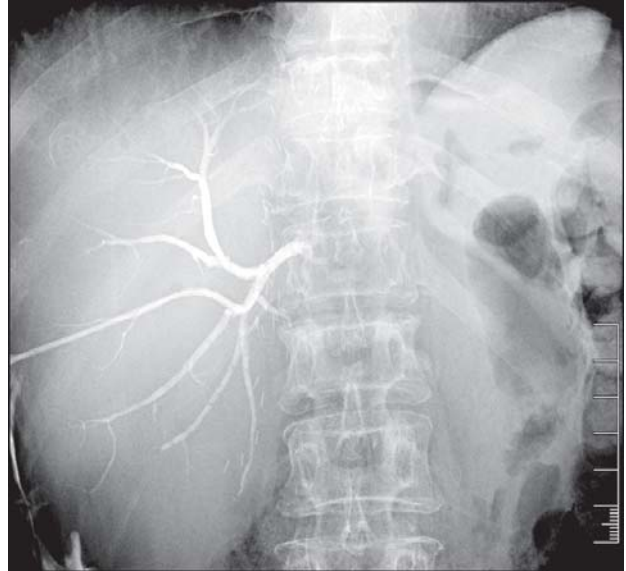


Figure 26.25: Dilatated intrahepatic biliary ducts (right lobe grafts)

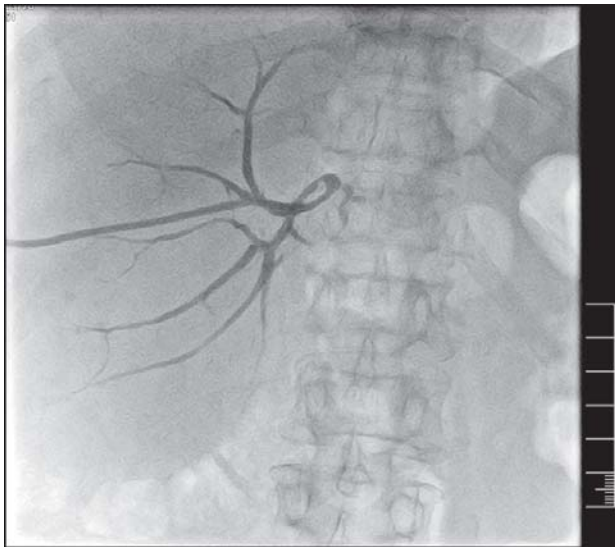


Figure 26.26

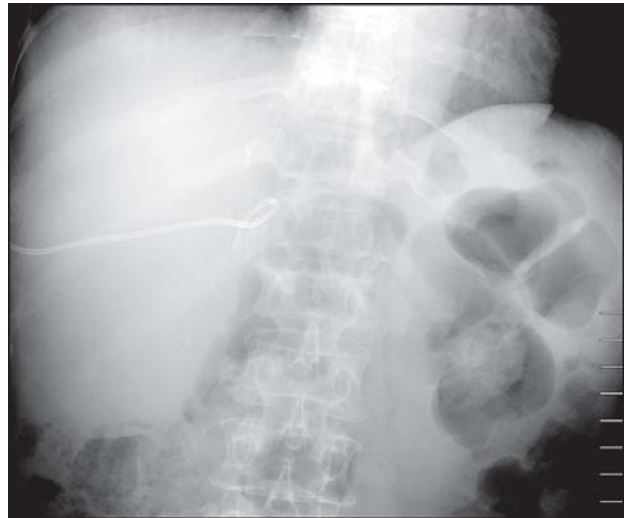


Figure 26.27

Figures 26.26 and 26.27: PTC drainage catheter in the right posterior sectorial duct



Figure 26.28: ERC shows a stricture at the proximally tree after balloon dilatation



Figure 26.30: Guide wire with catheter passed into the left hepatic duct

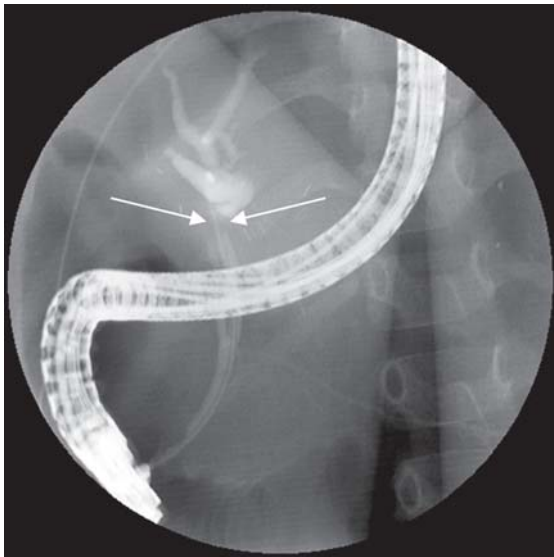


Figure 26.29: Contrast enhancement proximal biliary anastomosis. Contrast not passing



Figure 26.31: Plastic stent being pushed upwards along the stricture



Figure 26.32



Figure 26.33

Figures 26.32 and 26.33: Placement of a plastic stent (8 Fr.) across the stricture with dilated proximal biliary tract in left lateral segment

poor quality of life and recurrent cholangitis. When retransplantation is considered, nutritional status of the patient is improved, low levels of immunosuppression is maintained and temporary palliative stenting procedures are carried out till the graft is available.

Biliary Complication in Posterior Sector Grafts

The first worldwide application of LDLT using a posterior sector graft (PSG) was reported by Sugawara et al.⁴⁵ They concluded that posterior sector grafts are susceptible to more bile leakage as compared with other types of grafts. Tanaka et al. described that exact aetiology is not known, but probably the remaining part of segment 8 of allograft is the source of bile leak in the recipient.¹¹⁹

OTHER BILIARY COMPLICATIONS IN THE RECIPIENT

SLUDGE AND STONE FORMATION

Incidence of stones after liver transplantation is very less but when present causes significant morbidity. Sludge and stone formation is related to ischemia and bile duct necrosis. Bile stasis due to stricture is the predisposing primary cause. Total cholesterol > 200 mg/dL and triglyceride > 150 mg/dL as well as bile duct pathology confer a significant risk of clinically significant BDS post-transplantation.¹²¹ Ursodeoxycholic acid (UDCA), when taken at the standard dose of 300 mg twice daily, may

be an effective therapy in this subgroup of patients and is recommended for up to 1 year post-transplant and possibly further if patients have persisting risk factors such as hyperlipidemia or biliary strictures. Treatment usually by endoscopic procedures like ERC, PTC guided removal and stenting or lithotripsy.¹²¹

SPHINCTER OF ODDI DYSFUNCTION

Diagnosis is difficult. Findings in the disorder are diffuse dilatation of recipient and donor bile ducts in the absence of any mechanical obstruction.⁴² Pathogenesis may be explained in terms of devascularisation and denervation of papilla during donor hepatectomy. Delayed passage of contrast in a cholangiogram gives a clue to the diagnosis. Treatment is transpapillary stenting with or without sphincterotomy for 3-6 months will give better results. Surgical revision of anastomosis is rarely required.

REDUNDANT BILE DUCT AFTER LTX

If long length of bile duct is left during the biliary anastomosis, this will cause kinking and partial obstruction and signs of biliary obstruction and cholangitis. This complication occurs usually in duct-to-duct anastomosis. Every effort is made during the anastomosis that there is no extra length of bile duct left to avoid this complication. Treatment by ERC and stent placement for 2-3 months will resolve this problem by causing fibrosis and scar formation around the bile duct.

EXTRAHEPATIC BILE DUCT NECROSIS

Ischemia is the main cause for this complication. This is a rare but serious complication. When it occurs, there is every possibility of complete disruption of anastomosis leading to bilioma and sepsis. Surgical exploration is often required. If there is no infection, anastomosis is reconstructed by Roux-en-Y Hepaticojejunostomy. If there is severe infection, it is better to do an external drainage of bile for 2-3 months and once the infection is controlled, anastomosis can be reconstructed.

BILIARY COMPLICATIONS IN DONORS

BILE LEAK AND INJURY

Bile leak and injury to the LHD or to the confluence are the common biliary complications in the donor.

Bile Leak

Sources of bile leak:

- Cut surface of remnant liver
- Caudate lobe branches
- Right hepatic duct stump
- Cystic duct stump

Steps to prevent bile leak in the donor:

- Meticulous ligation of smaller branches of the 2nd and 3rd order bile ducts and caudate lobe branches.
- Excessive use of argon plasma coagulation is avoided as it sloughs the necrotic parenchyma and causing bile leak.
- Careful closure of RHD stump with 6-0 prolene/PDS.

Treatment

Majority of minor bile leaks stop spontaneously over few days. If no drain is left, a small pigtail catheter can be inserted under USG guidance. In few cases postoperative recovery is uneventful but donor presents with a bilioma during the first CT scan at the end of one month after surgery. Such cases should be drained by CT/USG guided pigtail drainage.

INJURY TO THE CONFLUENCE OF THE HEPATIC DUCTS

Careful delineating of the biliary anatomy in the donor with preoperative MRCP and intraoperative cholangiography is the key to avoid such injuries. Caution is taken to avoid thermal injury to the confluence of the bile ducts. Line of transaction of the bile duct should be perpendicular and should be away from the confluence. If the injury is detected intraoperatively it should be closed over a T-tube, if it is partial and if it is complete, Roux-en-Y Hepaticojejunostomy is preferred.

REFERENCES

1. Greif F, Bronsther OL, Van Thiel DH, et al. The incidence, timing and management of biliary tract complications after orthotopic liver transplantation. *Ann Surg* 1994;219:40.
2. Stratta RJ, Wood RP, Langnas AN, et al. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. *Surgery* 1989;106:675.
3. Pfau PR, Kochman ML, Lewis JD, et al. Endoscopic management of postoperative complications in orthotopic liver transplantation. *Gastrointest Endosc* 2000;52:55.
4. Jeffrey GP, Brind AM, Ormonde DG, et al. Management of biliary tract complications following liver transplantation. *Aust N Z J Surg* 1999;69:717.
5. Sutcliffe R, Maguire D, Mroz A, et al. Bile duct stricture after adult liver transplantation: A role for biliary reconstructive surgery? *Liver Transplantation* 2004;10:928-34.
6. Trotter JF, Wachs M, Everson GT, et al. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002;346:1074-82.
7. Qian YB, Liu CL, Lo CM, et al. Risk factors for biliary reconstructions after liver transplantation. *Arch Surg* 2004;139:1101-05.
8. Liu CL, Lo CM, Fan ST, et al. Safety of duct-to-duct biliary reconstruction in right-lobe live-donor liver transplantation without biliary drainage. *Transplantation* 2004;77:726-32.
9. Gondolesi GE, Varotti G, Florman SS, et al. Biliary complications in 96 consecutive right lobe living donor transplant recipients. *Transplantation* 2004;77:1842-48.
10. Todo S, Furukawa H, Kamiyama T. How to prevent and manage biliary complications in living donor liver transplantation? *J Hepatol* 2005;43:2-27.
11. Hisatsune H, Yazumi S, Egawa H, et al. Endoscopic management of biliary strictures after duct-to-duct biliary reconstruction in rightlobe living-donor liver transplantation. *Transplantation* 2003;76:810-15.
12. Zoepf T, Maldonado-Lopez EJ, Hilgard P, et al. Endoscopic therapy of posttransplant biliary stenoses after right-sided adult living donor liver transplantation. *Clin Gastroenterol Hepatol* 2005;3:1144-49.
13. Ishiko T, Egawa H, Kasahara M, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Ann Surg* 2002;236:235-40.
14. Kasahara M, Egawa H, Ogawa K, et al. Variations in biliary anatomy associated with trifurcated portal vein in right lobe living donor liver transplantation. *Transplantation* 2005;79:626-27.
15. Ohkubo M, Nagino M, Kajima J, et al. Surgical anatomy of the bile ducts at the hepatic hilum as applied to living donor liver transplantation. *Ann Surg* 2004;239:82-86.
16. Gomez R, Moreno E, Castellon C, et al. Choledochocholedochostomy conversion to hepatico-jejunostomy due to biliary obstruction in liver transplantation. *World J Surg* 2001;25:1308-12.
17. Rerknimitr R, Sherman S, Fogel EL, et al. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: Endoscopic findings and results of therapy. *Gastrointest Endosc* 2002;55:224-31.
18. Moser MA, Wall WJ. Management of biliary problems after liver transplantation. *Liver Transpl* 2001;7:S46-S52.
19. Heffron TG, Smallwood GA, Ramcharan T, et al. Duct-to-duct biliary anastomosis for patients with sclerosing cholangitis

- undergoing liver transplantation. *Transplant Proc* 2003;35:3006-07.
20. Scatton O, Meunier B, Cherqui D, et al. Randomized trial of choledochcholedochostomy with or without a T tube in orthotopic liver transplantation. *Ann Surg* 2001;233:432-37.
 21. Amador A, Charco R, Marti J, et al. Cost/efficacy clinical trial about the use of Ttube in cadaveric donor liver transplant: preliminary results. *Transplant Proc* 2005;37:1129-30.
 22. Alsharabi A, Zieniewicz K, Patkowski W, et al. Assessment of early biliary complications after liver orthotopic liver transplantation as related to the technique of biliary reconstruction. *Transplant Proc* 2006;38:244.
 23. Scatton OM, Meunier B, Cherqui D, et al. Randomized trial of choledochcholedochostomy with or without a T tube in orthotopic liver transplantation. *Ann Surg* 2001;233:432.
 24. Thethy S, Thomson BNJ, Pleass H, et al. Management of biliary tract complications after orthotopic liver transplantation. *Clin Transpl* 2004;18:647.
 25. Chen XP, Peng SY, Peng CH, et al. A ten-year study on non-surgical treatment of postoperative bile leakage. *World J Gastroenterol* 2002;8:937.
 26. Johnston TD, Gates R, Reddy KS, et al. Nonoperative management of bile leaks following liver transplantation. *Clin Transplant* 2000;14:365.
 27. Ge BJ, Xing HL, Cai TN: The surgical treatment of bile peritonitis after removal of T-tubes from the common bile duct. *Shanxi Yike Daxue Xuebao* 2001;32:233.
 28. Johnson MW, Thompson P, Meehan A, et al. Internal biliary stenting in orthotopic liver transplantation. *Liver Transpl* 2000;6:356-61.
 29. Barkun JS, Tzimas GN, Cantarovich M, et al. Do biliary endoprotheses decrease biliary complications after liver transplantation? *Transplant Proc* 2003;35:2435-37.
 30. Buczkowski AK, Schaeffer DF, Kim PT, et al. Spatulated end-to-end bile duct reconstruction in orthotopic liver transplantation. *Clin Transplant* 2007;21:7-12.
 31. Soejima Y, Shimada M, Suehiro T, et al. Feasibility of duct-to-duct biliary reconstruction in left-lobe adult-living-donor liver transplantation. *Transplantation* 2003;75:557-59.
 32. Sugawara Y, Makuuchi M, Sano K, et al. Duct-to-duct biliary reconstruction in living-related liver transplantation. *Transplantation* 2002;73:1348-50.
 33. Ohkubo M, Nagino M, Kamiya J, et al. Surgical anatomy of the bile ducts at the hepatic hilum as applied to living donor liver transplantation. *Ann Surg* 2004;239:82-86.
 34. Shah SA, Grant DR, McGilvray ID, et al. Biliary strictures in 130 consecutive right lobe living donor liver transplant recipients: results of a Western center. *Am J Transplant* 2007;7:161-7.
 35. Kim RD, Sakamoto S, Haider MA, et al. Role of magnetic resonance cholangiography in assessing biliary anatomy in right lobe living donors. *Transplantation* 2005;79:1417-21.
 36. Shah SA, Grant DR, Greig PD, et al. Analysis and outcomes of right lobe hepatectomy in 101 consecutive living donors. *Am J Transplant* 2005;5:2764-69.
 37. Fan ST, Lo CM, Liu CL, et al. Biliary reconstruction and complications of right lobe live donor liver transplantation. *Ann Surg* 2002;236:676-83.
 38. Testa G, Malago M, Broelsch CE, et al. Biliary anastomosis in living related liver transplantation using the right liver lobe: techniques and complications. *Liver Transpl* 2000;6:710-14.
 39. Kasahara M, Egawa H, Takada Y, et al. Biliary reconstruction in right lobe livingdonor liver transplantation: comparison of different techniques in 321 recipients. *Ann Surg* 2006;243:559-66.
 40. Wilson BJ, Marsh JW, Makowka L, et al. Biliary tract complications in orthotopic adult liver transplantation. *Am J Surg* 1989;158:68-70.
 41. Azoulay D, Castaing D, Adam R, et al. Adult to adult living-related liver transplantation. The Paul-Brousse Hospital preliminary experience [in French]. *Gastroenterol Clin Biol* 2001;25:773-80.
 42. 122. Mazariegos Gv, Molmenti EP, et al. Early complications after orthotopic liver transplantation. *Surg clin north America* 1999;79(1):109-29.
 43. Yan L, Li B, Zeng Y, et al. Introduction of microsurgical technique to biliary reconstruction in living donor liver transplantation. *Transplant Proc* 2007;39:1513-16.
 44. Kawachi S, Shimazu M, Wakabayashi G, et al. Biliary complications in adult living donor liver transplantation with duct-to-duct hepaticcholedochostomy or Roux-en-Y hepaticojejunostomy biliary reconstruction. *Surgery* 2002;132:48-56.
 45. Sugawara Y, Makuuchi M, Takayama T, et al. Right lateral sector graft in adult living-related liver transplantation. *Transplantation* 2002;73:111.
 46. Northover JM, Terblanche J. A new look at the arterial supply of the bile duct in man and its surgical implications. *Br J Surg* 1979;66:379-84.
 47. Nakamura T, Tanaka K, Kiuchi T, et al. Anatomical variations and surgical strategies in right lobe living donor liver transplantation: lessons from 120 cases. *Transplantation* 2002;73:1896-03.
 48. Dulundu E, Sugawara Y, Sano K, et al. Duct-to-duct biliary reconstruction in adult LDLT. *Transplant* 2004;78:574-79.
 49. Grewal HP, Shokouh-Amiri MH, Vera S, et al. Surgical technique for right lobe adult living donor liver transplantation without venovenous bypass or portocaval shunting and with duct-to-duct biliary reconstruction. *Ann Surg* 2001;233:502-08.
 50. Ishiko T, Egawa H, Kasahara M, et al. Duct-to-duct biliary reconstruction in living donor liver transplantation utilizing right lobe graft. *Ann Surg.* 2002;236:235-240.
 51. Hisatsune H, Yazumi S, Egawa H, et al. Endoscopic management of biliary strictures after duct-to-duct biliary reconstruction in right-lobe living donor liver transplantation. *Transplantation.* 2003;76:810-15.
 52. Van Thiel DH, Fagiuoli S, Wright HI, et al. Biliary complications of liver transplantation. *Gastrointest Endosc* 1993;39:455-60.
 53. Morelli J, Mulcahy HE, Willner IR, et al. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. *Gastrointest Endosc* 2003;58:374-79.
 54. Schwartz DA, Petersen BT, Poterucha JJ, et al. Endoscopic therapy of anastomotic bile duct strictures occurring after liver transplantation. *Gastrointest Endosc* 2000;51:169-74.
 55. Sebah M, Yilmaz F, Azoulay D, et al. The histologic pattern of "biliary tract pathology" is accurate for the diagnosis of biliary complications. *Am J Surg Pathol* 2005;29:318-23.
 56. Venu M, Brown RD, Lepe R, et al. Laboratory diagnosis and nonoperative management of biliary complications in living donor liver transplant patients. *J Clin Gastroenterol* 2007;41:501-06.
 57. Mosca S, Militerno G, Guardascione MA, et al. Late biliary tract complications after orthotopic liver transplantation:

- Diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography. *J Gastroenterol Hepatol* 2000;15:654-60.
58. Thethy S, Thomson BNJ, Pleass H, et al. Management of biliary tract complications after orthotopic liver transplantation. *Clin Transplant* 2004;18:647-53.
59. Jagannath S, Kalloo AN. Biliary complications after liver transplantation. *Curr Treat Options Gastroenterol* 2002;5:101-12.
60. Guichelaar MM, Benson JT, Malinchoc M, et al. Risk factors for and clinical course of non-anastomotic biliary strictures after liver transplantation. *Am J Transplant* 2003;3:885-90.
61. Sanchez-Urdazpal L, Gores GJ, Ward EM, et al. Ischemic-type biliary complications after orthotopic liver transplantation. *Hepatology* 1992;16:49-53.
62. Zajko AB, Campbell WL, Starzl TE, et al. Cholangiographic findings in hepatic artery occlusion after liver transplantation. *AJR Am J Roentgenol* 1987;149:485-89.
63. Li S, Stratta RJ, Langnas AN, et al. Diffuse biliary tract injury after orthotopic liver transplantation. *Am J Surg* 1992;164:536-40.
64. Ward EM, Kiely MJ, Maus TP, et al. Hilar biliary strictures after liver transplantation: Cholangiography and percutaneous treatment. *Radiology* 1990;177:259-63.
65. Pascher A, Neuhaus P. Bile duct complications after liver transplantation. *Transpl Int* 2005;18:627-42.
66. Baccarani U, Risaliti A, Zoratti L, et al. Role of endoscopic retrograde cholangiopancreatography in the diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. *Dig Liver Dis* 2002;34:582-86.
67. Chahin NJ, De Carlis L, Slim AO, et al. Long-term efficacy of endoscopic stenting in patients with stricture of the biliary anastomosis after orthotopic liver transplantation. *Transplant Proc* 2001;33:2738-40.
68. Mahajani RV, Cotler SJ, Uzer MF. Efficacy of endoscopic management of anastomotic biliary strictures after hepatic transplantation. *Endoscopy* 2000;32:943-49.
69. Morelli J, Mulcahy HE, Willner IR, et al. Endoscopic treatment of post-liver transplantation biliary leaks with stent placement across the leak site. *Gastrointest Endosc* 2001;54:471-75.
70. Rossi AF, Grosso C, Zanasi G, et al. Long-term efficacy of endoscopic stenting in patients with stricture of the biliary anastomosis after orthotopic liver transplantation. *Endoscopy* 1998;30:360-66.
71. Thuluvath PJ, Atassi T, Lee J. An endoscopic approach to biliary complications following orthotopic liver transplantation. *Liver Int* 2003;23:156-62.
72. Moench C, Uhrig A, Lohse AW, et al. CC chemokine receptor 5delta32 polymorphism—a risk factor for ischemic-type biliary lesions following orthotopic liver transplantation. *Liver Transpl* 2004;10:434-39.
73. Rull R, Garcia Valdecasas JC, Grande L, et al. Intrahepatic biliary lesions after orthotopic liver transplantation. *Transpl Int* 2001;14:129-34.
74. Rai RM, Boitnott J, Klein AS, et al. Features of recurrent primary sclerosing cholangitis in two consecutive liver allografts after liver transplantation. *J Clin Gastroenterol* 2001;32:151-54.
75. Foley DP, Fernandez LA, Cooper JT, et al. Donation after cardiac death: The University of Wisconsin experience with liver transplantation. *Ann Surg* 2005;242:724-31.
76. Abt P, Crawford M, Desai N, et al. Liver transplantation from controlled nonheart-beating donors: An increased incidence of biliary complications. *Transplantation* 2003;75:1659-63.
77. Canelo R, Hakim NS, Ringe B. Experience with histidine tryptophan ketoglutarate versus University Wisconsin preservation solutions in transplantation. *Int Surg* 2003;88:145-51.
78. Pirenne J, Van Gelder F, Koshiba T, et al. Type of donor aortic preservation solution and not cold ischemia time is a major determinant of biliary strictures after liver transplantation. *Liver Transpl* 2001;7:540-45.
79. Shah SA, Grant DR, McGilvray ID, et al. Biliary strictures in 130 consecutive right lobe living donor liver transplant recipients: results of a Western center. *Am J Transplant* 2007;7:161-67.
80. Hwang S, Lee SG, Sung KB, et al. Long-term incidence, risk factors, and management of biliary complications after adult living donor liver transplantation. *Liver Transpl* 2006;12:831-38.
81. Yazumi S, Yoshimoto T, Hisatsune, et al. Endoscopic treatment of biliary complications after right-lobe living-donor liver transplantation with duct-to-duct biliary anastomosis. *J Hepatobiliary Pancreat Surg* 2006;13:502-10.
82. Tashiro H, Itamoto T, Sasaki T, et al. Biliary complications after duct-to-duct biliary reconstruction in living-donor liver transplantation: causes and treatment. *World J Surg* 2007;31:2222-29.
83. Salvalaggio PR, Whittington PF, Alonso EM, et al. Presence of multiple bile ducts in the liver graft increases the incidence of biliary complications in pediatric liver transplantation. *Liver Transpl* 2005;11:161-66.
84. Gondolesi GE, Varotti G, Florman SS, et al. Biliary complications in 96 consecutive right lobe living donor transplant recipients. *Transplantation* 2004;77:1842-48.
85. Burke DR, Lewis CA, Cardella JF, et al. Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. *J Vasc Interv Radiol* 2003;14:S243-S246.
86. Davidson BR, Rai R, et al. Prospective randomised trial of end-to-end versus side-to-side biliary reconstruction after orthotopic liver transplantation. *Br J Surg* 1999;86(4):447-452.
87. Rabkin JM, Orliff SL, et al. Biliary tract complications of side to side without T-tube versus end-to-end with or without T-tube choledochocholedochostomy in liver transplant recipients. *Transplantation* 1998;65(2):193-99.
88. Kanazawa A, Kubo S, Tanaka H, et al. Bile leakage after living donor liver transplantation demonstrated with hepatobiliary scan using ^{99m}Tc-PMT. *Ann Nucl Med*. 2003;17:507-09.
89. Jeffrey GP, Brind AM, Ormonde DG, et al. Management of biliary tract complications following liver transplantation. *Aust N Z J Surg* 1999;69:717-22.
90. Kok T, Van der Sluis A, Klein JP, et al. Ultrasound and cholangiography for the diagnosis of biliary complications after orthotopic liver transplantation: a comparative study. *J Clin Ultrasound* 1996;24:103-15.
91. St Peter S, Rodriguez-Davalos MI, Rodriguez-Luna HM, et al. Significance of proximal biliary dilatation in patients with anastomotic strictures after liver transplantation. *Dig Dis Sci* 2004;49:1207-11.
92. Linhares MM, Gonzalez AM, Goldman SM, et al. Magnetic resonance cholangiography in the diagnosis of biliary complications after orthotopic liver transplantation. *Transplant Proc* 2004;36:947-48.
93. Meererschaut V, Mortelet KJ, Troisi R, et al. Value of MR cholangiography in the evaluation of postoperative biliary complications following orthotopic liver transplantation. *Eur Radiol* 2000;10:1576-81.

94. Schwarzenberg SJ, Sharp HL, Payne WD, et al. Biliary stricture in living-related donor liver transplantation: management with balloon dilation. *Pediatr Transplant* 2002;6:132-35.
95. Macfarlane B, Davidson B, Dooley JS, et al. Endoscopic retrograde cholangiography in the diagnosis and endoscopic management of biliary complications after liver transplantation. *Eur J Gastroenterol Hepatol* 1996;8:1003-06.
96. Hussaini SH, Sheridan MB, Davies M. The predictive value of transabdominal ultrasonography in the diagnosis of biliary tract complications after orthotopic liver transplantation. *Gut* 1999;45:900-03.
97. Kim JS, Moon DH, Lee SG, et al. The usefulness of hepatobiliary scintigraphy in the diagnosis of complications after adult-to-adult living donor liver transplantation. *Eur J of Nuc med mol imaging* 2002;29(4):473-79.
98. Thuluvath PJ, Pfau PR, Kimmey MB, et al. Biliary complications after liver transplantation: The role of endoscopy. *Endoscopy* 2005;37:857.
99. Catalano G, Urbani L, et al. Hepatic resection after liver transplantation as a graft saving procedure: Indication criteria, timing and outcome. *Transplantation* 2004;36(3):545-46.
100. Leonardi MI, Ataide EC, Boin IFSF, et al. Role of choledochojunostomy in liver transplantation. *Transplant Proc* 2005;37:1126.
101. JHP Garcia, JBM Vasconcelos, BPA Gonçalves, et al. A new biliodigestive anastomosis technique after hepatic artery thrombosis as bridge to liver retransplantation: A Case Presentation. *Transplant Proceed* 2007;39:3523-26.
102. L Polese, U Cillo, et al. Endoscopic treatment of bile duct complications after orthotopic liver transplantation. *Transplant Proceed* 2007;39:2785-87.
103. Davidson BR, Rai R, Nandy A, et al. Results of choledochojunostomy in the treatment of biliary complications after liver transplantation in the era of nonsurgical therapies. *Liver Transpl* 2000;6:201.
104. Colonna JO II, Shaked A, Gomes AS, et al. Biliary strictures complicating liver transplantation: incidence, pathogenesis, management, and outcome. *Ann Surg* 1992;216:344-50.
105. Greif F, Bronsther OL, Van Thiel DH, et al. The incidence, timing, and management of biliary tract complications after orthotopic liver transplantation. *Ann Surg* 1994;219:40-45.
106. SF Pasha, E Harrison, et al. Endoscopic treatment of anastomotic biliary strictures after deceased donor liver transplantation: Outcomes after maximal stent therapy. *Gastrointest Endosc* 2007;66: 44-51.
107. Morelli J, Mulcahy HE, Willner IR, et al. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. *Gastrointest Endosc* 2003;58:374.
108. Alazmi WM, Fogel EL, Watkins JL, et al. Recurrence rate of anastomotic biliary strictures in patients who have had previous successful endoscopic therapy for anastomotic narrowing after orthotopic liver transplantation. *Endoscopy* 2006;38:571-74.
109. Thuluvath PJ, Pfau R, Kimmey MB, et al. Biliary complications after liver transplantation: the role of endoscopy. *Endoscopy* 2005;37:857.
110. Roumilhac D, Poyet G, Sergent G, et al. Long-term results of percutaneous management for anastomotic biliary stricture after orthotopic liver transplantation. *Liver Transpl* 2003;9:394-400.
111. Civelli EM, Meroni R, Cozzi G, et al. The role of interventional radiology in biliary complications after orthotopic liver transplantation: a single-center experience. *Eur Radiol* 2004;14:579-82.
112. Sung RS, Campbell DA Jr, Rudich SM, et al. Long-term follow-up of percutaneous transhepatic balloon cholangioplasty in the management of biliary strictures after liver transplantation. *Transplantation* 2004;77:110-15.
113. Gomez R, Moreno E, Castellon C, et al. Choledochocholangiostomy conversion to hepaticojunostomy due to biliary obstruction in liver transplantation. *World J Surg* 2001;25:1308-12.
114. Sutcliffe R, Maguire D, Mro'z A, et al. Bile duct strictures after adult liver transplantation: A role for biliary reconstructive surgery? *Liver Transpl* 2004;10:928-34.
115. Lee HW, Suh KS, Shin WY, et al. Classification and prognosis of intrahepatic biliary stricture after liver transplantation. *Liver transpl*. 2007;13:1736-42.
116. T Tsujino, H Isayama, M Makuuchi, et al. Endoscopic management of biliary complications after adult living donor liver transplantation. *Am J Gastroenterol* 2006;101:2230-36.
117. Shah JN, Ahmad NA, Brensinger CM, et al. Endoscopic management of biliary complications after adult living donor liver transplantation. *Am J Gastroenterol* 2004;99:1291-95.
118. Tsujino T, Isayama H, Sugawara Y, et al. Endoscopic management of biliary complications after adult living donor liver transplantation. *Am J Gastroenterol* 2006;101:2230-36.
119. D Morioka, K Tanaka, K, et al. Delayed bile leakage from a remaining part of segment 8 in a posterior section graft after living donor liver transplantation: A common pitfall in harvesting a posterior section graft? A case report. *Transplant Proceed* 2007;39:3515-18.
120. S Sharma, A Gurakar, N Jabbour. Biliary strictures following liver transplantation: Past, present and preventive strategies. *Liver transplant* 2008;14:759-69.
121. Bret J Spier, Patrick R Pfau, Katelin R Lorenze, et al. Risk factors and outcomes in post-liver transplantation bile duct stones and casts: A case-control study. *Liver transplant* 2008;14:1461-65.

(D) VASCULAR COMPLICATIONS

PORTAL VEIN COMPLICATIONS

Under normal conditions portal vein flow (PVF) is higher than hepatic artery flow (HAF). In cirrhosis PVF is reduced. The hepatic artery buffer response (HABR) controls total blood perfusion in normal livers as well as in cirrhosis.¹ HABR is an intrinsic autoregulatory mechanism that maintains hepatic oxygen delivery during splanchnic hypoperfusion [i.e. reduction in portal vein blood flow] through compensatory increases in hepatic artery blood flow.^{2,3} The maintenance of HAF and the preserved HABR must be considered to be protective effects on overall hepatic circulation, counteracting impaired nutritive blood supply via portal vein (PV). This compensatory mechanism has been proposed to be mediated by adenosine washout.⁴ Obstruction of the portal vein and outflow veins may also have deleterious consequences, including ascites, abdominal distention, liver enzyme elevation, and gastrointestinal bleeding.^{5,6}

It was assumed earlier that the existence of gastroesophageal collaterals may be associated with PV thrombosis after OLT.¹ Patent gastroesophageal collaterals with hepatofugal flow decrease portal perfusion pressure and hepatic blood flow to the transplanted graft. Such hemodynamic alterations could have adverse effects on the transplanted liver. This hemodynamic status is similar to the situation when OLT is attempted in a patient with a patent mesocaval or proximal splenorenal shunt. These shunts should be ligated during OLT to maintain adequate portal flow. Distal splenorenal shunts have been reported as well to decrease the total hepatic blood flow. Esquivel, et al.⁷ reviewed their experience with liver transplantation in patients with patent distal splenorenal shunts and concluded that the patent shunt should be divided after OLT. To the contrary, Brems, et al.⁸ did not advocate division of these shunts during transplantation. Lyass et al. reported that in OLT in which significant gastroesophageal collaterals are expected, the portal vein flow should be measured before and after coronary vein compression. When significant increase (30%) of portal vein flow is observed during coronary vein compression, the latter should be ligated.⁹ Diagnosis of PV complications is by of clinical suspicion from abnormal liver biochemistry and confirmation by DUS, 3-Phase CT scan and MR angiography.

PV STENOSIS

Clinically significant portal vein stenosis is more common following pediatric LTX adult LTX, and this has been

presumed to be due to a size discrepancy between recipient and donor portal vein.^{10,11} Reduction in PV diameter of greater than 40% at the site of the anastomosis without adverse clinical effect suggests that adults may have a greater capacity to tolerate the consequences of PV stenosis than pediatric patients.¹²

PV velocity decreases in the first week posttransplantation, despite the unchanging diameter of the portal vein. Portal blood flow has been shown to decline gradually for up to 2 years after LTX.¹³ Increased hepatic arterial flow velocity is noted in the first week may be due in part to the fall in portal flow during the same period, as the reciprocal regulation of portal and hepatic arterial flow is intact in transplanted livers.¹⁴ Preferred treatment option is by interventional radiological procedures and stenting of the stenotic PV.

PV THROMBOSIS

Portal vein thrombosis (PVT) following LTX is an uncommon complication but a serious complication after transplantation. This can occur early or late after the transplantation. In adults, the reported incidence of PVT is 1-2.7%.^{15,16} and in children it is more than 10%.¹⁷ Lerut et al. reported 43% mortality in patients with acute PVT after OLT.¹⁸ Children are at high risk of vessel thrombosis when compared with adults. Advanced hepatic disease increases PV pressure, alters splanchnic circulation, and leads to development of collateral circulation. In children, more often than "true" thrombosis of the PV, it is more likely to find hepatofugal, absent, or poor PVF due to neoformation of spontaneous collaterals. This situation is especially relevant in infants with biliary atresia and hypoplasia of PV.

Causes of poor portal flow in recipient

- Anastomotic stenosis
- Occluded or a partially removed thrombus in the recipient portal system
- Steal phenomena due to native portosystemic communications

Symptoms and Signs

Symptoms and signs vary from minor to life-threatening fulminant liver failure. The most severe presentation may include variceal bleeding, intractable ascities, sepsis, acidosis and hypoglycemia, hepatic encephalopathy, and bowel infarction.

Early PVT presents acutely as severe graft dysfunction, variceal bleeding, encephalopathy, sepsis, and hypoglycemia and, rarely, as bowel infarction requiring immediate intervention. This complication of OLT is associated with a high morbidity and mortality.

Late PVT may be asymptomatic or present as graft dysfunction or with signs of portal hypertension.

Factors predisposing to PVT after OLT¹⁹⁻²²

- Presence of preoperative recipient portal vein thrombosis (incidence in cirrhosis patients: 0.5 to 21% and HCC with cirrhosis: 34.8%)
- Budd-Chiari syndrome (22.2%)
- Post-necrotic cirrhosis (15.7%).
- Chronic active hepatitis
- Hypercoagulable states
- Trauma from previous porta hepatis dissection
- Splenectomy
- Technical problems
 - Vessel size mismatch
 - Misalignment
 - Clot formation from the portal venous bypass catheter
- Rejection,
- Decreased portal flow due to
 - Stenosis
 - Portosystemic shunts, either surgical or spontaneous

Rethrombosis

Incidence of rethrombosis varies from 21-33% in patients with previous preoperative PVT.^{21,22}

Treatment

Treatment depends on the clinical presentation, condition of the patient and availability of technical resources. Presence of PVT makes surgery more difficult (reflected in the increased surgical time, RBC transfusion, and hospital and ICU stay), but that it does not affect post-operative mortality or survival.

Treatment of early PVT^{16,23-30}

- Surgical thrombectomy and reconstruction of the portal anastomosis
- Percutaneous thrombolysis, balloon angioplasty and metallic stent placement
- Spontaneous resolution is possible in instances of the late form, requiring only symptomatic treatment with the occurrence of portal rechanneling
- Intrahepatic PVT: Successful treatment by mesentericocaval or splenorenal shunting or TIPS
- Local thrombolysis
- Retransplantation is the last option.

Percutaneous Fragmentation and Stent Placement

Percutaneous transhepatic angioplasty offers an option for treating PVT^{26,27,29,30} diminishing surgically related morbidity and the need for retransplantation even in cases of complete late PVT. The adoption of the technique of mechanical fragmentation results in rapid removal of the thrombus from the vessel while diminishing the dose of recombinant tissue plasminogen activator (rTPA) needed to lyse the clot and avoiding long-term fibrinolysis (24 hours) with the related bleeding risks. The use of cylinders of collagen assures secure sealing of the percutaneous hepatic access, reducing the risk of peritoneal bleeding. Minimally invasive treatment like percutaneous mechanical fragmentation and thrombolytic therapy represent alternative treatments for late PVT that decrease surgery-related morbidity and the need for emergency retransplantation.

Surgical treatment^{15,16,18,31-33}

- Surgical thrombectomy with anastomosis to PV or SMV and splenic vein confluence.
- Portal vein bypass grafting from the SMV
- Portosystemic shunt or anastomosis to an accessible varix.
- Cavoportal hemitransposition if there is extensive thrombosis of splanchnic circulation
- Retransplantation is always an option if suitable donor is available

Operative mortality of surgical procedures remains high (9.1 to 42%). Gomez, et al. reported the placement of endovascular stent in splenomesentericoportal veins and closure of competitive shunts via endovascular techniques after surgical thrombectomy.

LATE PV ANEURYSM AFTER TRANSPLANTATION

PV Aneurysms are rare lesions that may be associated with congenital vascular anomalies or portal hypertension. Despite the usual benign evolution, aneurysms may develop complications including rupture, portal-systemic shunts, recurrence of portal hypertension, thrombosis, or biliary compression.

The etiology of a portal vein aneurysm is not totally clear. There are two theories: congenital and acquired.³³ Congenital theory cites a weak vein as the main cause of aneurysm development; it is based on the presence of these aneurysms in children and young adults without portal hypertension.^{33,34} Acquired lesions are secondary to hepatic diseases, portal hypertension, trauma, or degenerative modifications.³³ PV aneurysm can be classified as intra- or extra-hepatic. Most intrahepatic PV aneurysms occur at its bifurcations and extrahepatic

aneurysms usually develop at the confluence between the SMV and splenic veins.^{35,37}

The clinical importance of a portal vein aneurysm is related to the size of the dilation. A small aneurysm usually does not show symptoms, while large ones have been described as the cause of duodenal compression, biliary tract obstruction, chronic portal hypertension, portal vein occlusion due to thrombosis, acute portal hypertension, rupture, pain, and abdominal discomfort.³⁸ The natural history of portal vein aneurysms is not totally clear, but the risk of complications seems to be small.^{38,39}

Surgical treatment of a portal vein aneurysm depends on the size, symptoms, complications, and the patient clinical conditions.³⁴ Ozbek, et al.³⁸ supported the conclusion that a portal vein aneurysm usually does not cause any problem over the ensuing years. An expectant role and regular follow-up are usually adopted. Intrahepatic portal vein aneurysms are associated with a probable-recurrence of portal hypertension after liver transplantation. Therapeutic interventional radiological procedures (endovascular stents or coil) may be necessary, if complications develop. Retransplantation might be an alternative.

HEPATIC VEIN COMPLICATIONS

Hepatic venous occlusion is a rare but fatal complication⁴⁰ following segmental liver transplantation. Most of the reported cases were due to hepatic vein stenosis which could be relieved by transhepatic balloon angioplasty.⁴¹ Hepatic vein stenosis, thrombosis, and IVC thrombosis are rare complications, occurring in 1-2% of liver transplant patients and usually resulting from vessel torsion or extrinsic compression.^{42,43} Hepatic vein and IVC stenosis can lead to hepatic congestion and graft dysfunction.⁴³ The incidence of hepatic venous outflow obstruction or thrombosis in caval preserving surgery is reported to be 2-10%.^{44,45,49,50}

The Kyoto group had reported five hepatic vein stenoses, detected by Doppler ultrasonography, after LDLT. They were successfully managed by percutaneous transhepatic balloon angioplasty. The stenosis could be successfully dilated by balloon angioplasty, but it would not work in hepatic vein thrombosis. If streptokinase and angioplasty fail to dissolve the thrombus, we suggest that open thrombectomy is an effective method to manage hepatic vein thrombosis after a piggyback liver transplant.

Causes of hepatic venous outflow obstruction^{46,47,50}

Early hepatic outflow obstruction: Mostly technical complication

- Tight suture line causing anastomotic stenosis
- Twisting of the HV anastomosis by displacement of the graft to right hepatic fossa
- Caval compression from a large graft
- Squeezing the liver in the abdomen despite closure of the skin

Late hepatic outflow obstruction:

- Neointimal fibrous hyperplasia
- Fibrosis around the anastomotic site/suprahepatic anastomosis
- Compression of the anastomosis from the hypertrophic graft

Diagnosis⁴⁸

- Abdominal pain, massive ascites, hypotension and abrupt elevation of AST and ALT.
- DUS-Low velocity and monophasic wave form
- 2-Phase CT Scan

Because of the persistent ascites for a few weeks following transplantation in patients with chronic hepatic disorders, this complication can be missed, causing difficulty in the diagnosis of this venous complication.⁴⁹ Hence, hepatic vein stenosis and/or thrombosis should be taken into consideration in every transplanted patient with ascites and pleural effusion.

Treatment

- Percutaneous transfemoral thrombolytic therapy with urokinase or tissue plasminogen activator.
- Balloon angioplasty and stenting.
- Surgical thrombectomy is the last option.

OCCCLUSION / STENOSIS OF MHV GRAFT IN RIGHT LOBE LDLT (FIGURES 26.34 AND 26.35)

Hepatic venous complications are not common following whole liver transplantation because direct anastomosis of the hepatic vein is usually not involved. In LDLT using right lobe hepatic venous congestion caused by deprivation of middle hepatic vein (MHV) drainage is usually tolerated if the graft volume is adequate. There has been much debate on the natural resolution of hepatic venous congestion and need for MHV reconstruction.⁵¹⁻⁵³ But many studies reported the need for MHV reconstruction in order to prevent hepatic congestion.^{51,54,55}



Figure 26.34: Hepatic venogram show kinking and narrowing of the V5 and V8 interposition vascular graft⁵⁷ (Reprinted with permission of John Wiley and Sons, Inc)⁵⁷

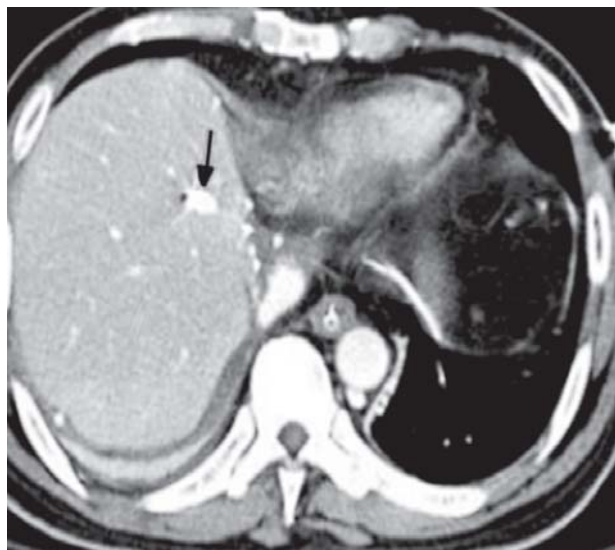


Figure 26.35: Complete resolution of low attenuation areas with good hepatic venous outflow after stent placement in V5 and V8 (Reprinted with permission of John Wiley and Sons, Inc)⁵⁷

Lee, et al.⁵⁵ reported that 1 patient died of HV thrombosis and resultant ischemic necrosis of the right paramedian sector among the 5 patients who underwent right liver grafts without MHV reconstruction. 6-months graft and patient survival rates have markedly increased from around 70% to around 95% after the adoption of MHV reconstruction in the right-lobe graft and liberal use of large volume graft. MHV reconstruction is performed by connecting the segment V (V5) and/or segment VIII (V8) hepatic veins to the recipient's MHV or LHV or IVC with the interposition vein graft. Interposition venous graft stenosis is common during follow up.⁵⁶

Diagnosis

- DUS shows persistent monophasic wave pattern or slow Doppler flow < 10 cm/sec. DUS can reveal reversal of portal flow direction in patients with acute and severe venous congestion and can show the presence of a functional intrahepatic anastomosis between the hepatic vein tributaries during the follow-up period in those with improved congestion.⁶⁰
- 2 phases-CT scan shows non-opacification of the vascular graft and their tributaries, with low-attenuation areas in the right paramedian sector.⁵⁸
- Liver biopsy confirms the centrilobular hepatic congestion without evidence of rejection, compatible with outflow occlusion. Routine liver biopsy is not recommended.

Treatment

Percutaneous balloon angioplasty or stent placement has been safely recommended in the early postoperative period as the initial treatment.⁵⁷⁻⁵⁹ Through right internal jugular vein approach, under US guidance, and a selective hepatic venogram is performed using a 5-Fr Cobra catheter to evaluate the abnormality of the vascular graft and anastomoses. A 0.035-inch angled hydrophilic guide wire is used to traverse the stenosis or occlusion. Balloon angioplasty alone is not effective in early postoperative period as there is possibility of kinking of external compression. Primary stent placement is preferred using self-expandable metallic stents. Wall stents can also be used. Stents were intentionally oversized by approximately 1-2 mm to minimize the risk of migration.⁵⁷

INFERIOR VENA CAVA THROMBOSIS

Vascular complications involving the IVC are less common, but remain a serious problem in liver transplant recipients. IVC thrombosis is a potentially lethal complication.⁶¹⁻⁶³ and occurs in less than 2% of cases post-OLT.⁶¹ They most often are recognized within the first month post-liver transplantation, but can occur later.⁶¹ They are usually related to technical problems associated with the vascular anastomoses.^{61,64}

Factors contributed to the complete IVC obstruction and thrombosis:^{65,66}

- Compression and torsion of this IVC anastomosis secondary to adhesions.
- Diminutive size of the third graft and the presence of a major discrepancy between the size of the IVC of the graft as compared to that of the recipient.

Presentation of IVC Thrombosis

- Reduced urine output
- Abdominal wall edema
- Hepatic congestion
- Bilateral lower extremity edema

Treatment Options

Treatment options are:^{61,63,65-69}

- Thrombolysis with tPA, urokinase and heparin
- Balloon dilatation, angioplasty with or without stent placement
- Early reoperation with thrombectomy
- Retransplantation.

Sotiropoulos, et al. reported a case of complete suprarenal thrombosis of the retrohepatic IVC in a live donor after a right hepatectomy which was managed by surgical thrombectomy and postoperative anticoagulant therapy.⁷⁰

REFERENCES

1. Richter S, Mücke I, Menger MD, et al. Impact of intrinsic blood flow regulation in cirrhosis: maintenance of hepatic arterial buffer response. *Am J Physiol Gastrointest Liver Physiol* 2000;279:G454.
2. Jakob SM, Tenhunen JJ, Heino A, et al. Splanchnic vasoregulation during mesenteric ischemia and reperfusion in pigs. *Shock* 2002;18:142.
3. Jakob SM, Tenhunen JJ, Laitinen S, et al. Effects of systemic arterial hypoperfusion on splanchnic hemodynamics and hepatic arterial buffer response in pigs. *Am J Physiol* 2001;280:G819.
4. Lauth W, Legare D, d'Almeida M. Adenosine as putative regulator of hepatic arterial flow (the buffer response). *Am J Physiol* 1985;248:H331.
5. Zanolini ML, Vieira S, Alencastro R, et al. Management of vascular complications after pediatric liver transplantation. *Transplant Proc* 2004;36:945-46.
6. Totsuka E, Hakamada K, Narumi S, et al. Hepatic vein anastomotic stricture after living donor liver transplantation. *Transplant Proc* 2004;36:2252-54.
7. Esquivel CO, Klintmalm G, Iwatsuki S, et al. Surgery 1987;101:430.
8. Brems JJ, Hiatt JR, Klein AS, et al. *Ann Surg* 1989;209:51.
9. SLYass, A Eid, O Jurim. Coronary vein "steal" and portal vein thrombosis after orthotopic liver transplantation. *Transplant Proceed* 2000;32:702-03.
10. Millis JM, Seaman DS, Piper JB, et al. Portal vein thrombosis and stenosis in pediatric liver transplantation. *Transplantation* 1996;62:748-54.
11. Sieders E, Peeters PM, TenVergert EM, et al. Early vascular complications after pediatric liver transplantation. *Liver Transpl* 2000;6:326-32.
12. David S, Donal D, Paul M, et al. Prospective Evaluation of the Role of Quantitative Doppler Ultrasound Surveillance in Liver Transplantation. *Liver Transpl* 2004;10(9):1183-88.
13. Bolognesi M, Sacerdoti D, Bombonato G, et al. Change in portal flow after liver transplantation: effect on hepatic arterial resistance indices and role of spleen size. *Hepatology* 2002;35:601-08.
14. Henderson JM, Gilmore GT, Mackay GJ, et al. Hemodynamics during liver transplantation: the interactions between cardiac output and portal venous and hepatic arterial flows. *Hepatology* 1992;16:715-18.
15. Gibson M, Dick R, Burroughs A, et al. Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. *Transplantation* 1994;57:1174.
16. Settmacer U, Nussler NC, Neuhaus P, et al. Venous complications after orthotopic liver transplantation. *Clin Transplant* 2000;14:235.
17. Funaki B, Rosenblum JD, Leef JA, et al. *Am J Roentgenol* 1997;169:551.
18. Lerut J, Tzakis AG, Bron K, et al. Complications of venous reconstruction in human orthotopic liver transplantation. *Ann Surg* 1987;205:404.
19. Okuda K, Ohnishi K, Kimura K, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology* 1985;89:279.
20. Nonami T, Yokoyama I, Starzl TE, et al. The incidence of portal vein thrombosis at liver transplantation. *Hepatology* 1992;16:1195.
21. Shaked A, Busuttil RW. Liver transplantation in patients with portal vein thrombosis and central portacaval shunts. *Ann Surg* 1991;214:696.
22. Davidson BR, Gibson M, Dick R, et al. Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. *Transplantation* 1994;57:1174.
23. Sanchez-Bueno F, Hernandez Q, Ramirez R, et al. Vascular complications in a series of 300 orthotopic liver transplants. *Transplant Proc* 1999;31:2409.
24. Cherukuri R, Haskal ZJ, Naji A, et al. *Transplantation* 1998;65:1124.
25. Funaki B, Rosenblum JD, Leef JA, et al. *Am J Roentgenol* 1997;169:551.
26. Baccarani U, Gasparini D, Risaliti A, et al. Percutaneous mechanical fragmentation and stent placement for the treatment of early posttransplantation portal vein thrombosis. *Transplantation* 2001;72:1572.
27. Cherukuri R, Haskal ZJ, Naji A, et al. Percutaneous thrombolysis and stent placement for the treatment of portal vein thrombosis after liver transplantation. *Transplantation* 1998;65:1124.
28. Olcott EW, Ring EJ, Roberts JP, et al. Percutaneous transhepatic portal vein angioplasty and stent placement after liver transplantation: early experience. *J Vasc Interv Radiol* 1990;1:17.
29. Sainz-Barriga M, Baccarani U, Risaliti A, et al. Successful minimally invasive management of late portal vein thrombosis after splenectomy due to splenic artery steal syndrome following liver transplantation: A Case Report. *Transplant Proceed* 2001;36:558-59.

30. Rouch DA, Emond JC, Ferrari M, et al. The successful management of portal vein thrombosis after hepatic transplantation with a splenorenal shunt. *Surg Gynecol Obstet* 1988;166:311.
31. Tzakis AG, Kirkegaard P, Pinna AD et al. Liver transplantation with cavoportal hemitransposition in the presence of diffuse portal vein thrombosis. *Transplantation* 1998;65:619.
32. Cherukuri R, Haskal ZJ, Naji A, et al. Percutaneous thrombolysis and stent placement for the treatment of portal vein thrombosis after American Journal of Transplantation 2001;1:284-87.
33. Gómez GM, Quintela J, et al. Portal Vein Thrombosis in Patients Undergoing Orthotopic Liver Transplantation: Intraoperative Endovascular Radiological Procedures. *Transplant Proceed* 2005;37:3906-08.
34. Arda K, Kizilkanat KT, Tosun O, et al. *Acta Gastroenterologica Belgica* 2002;65:136.
35. Fukui H, Kashiwagi T, Kimura K. *Clin Nucl Med* 1992;17:871.
36. Ohnani Y, Ishida H, Konno K: *Abdom Imaging* 1997;22:281.
37. Blasbalg R, Yamada RM, Tiferes DA. *AJR Am J Roentgenol* 2000;174:877.
38. Ozbek SS, Killi MR, Pourbagher MA. *J Ultrasound Med* 1999;18:417.
39. Lau H, Chew DK, Belkin M. *Cardiovasc Surg* 2002;10:58.
40. Emond J, Heffron T, Broelsch C. *Surg Gynecol Obstet* 1993;176:11.
41. Egawa H, Tanaka K, Uemoto S, et al. *Clin Transplant* 1993;7:306.
42. Mazariegos GV, Molmenti EP, Kramer DJ. Early complications after orthotopic liver transplantation. *Surg Clin North Am* 1999;79:109-29.
43. Friedewald SM, Molmenti EP, DeJong MR, et al. Vascular and nonvascular complications of liver transplants: Sonographic evaluation and correlation with other imaging modalities and findings at surgery and pathology. *Ultrasound Q* 2003;19:71-85.
44. Saing H, Fan ST, Tam PKH, et al. Surgical complications and outcome of pediatric liver transplantation in Hong Kong. *J Pediatr Surg* 2002;37:1673.
45. Ibrahim KM, Ahmed TIF, Hiroto E, et al. Innovative techniques for and results of portal vein reconstruction in living-related liver transplantation. *Surgery* 1999;125:265.
46. Zaiko AB, Claus D, Clapuyt P, et al. *Radiology* 1989;170:763.
47. Sayers RD, Watt PA, Muller S, et al. *Eur J Vasc Surg* 1992;6:354.
48. Cheng YF, Huang TL, Chen CL, et al. Intraoperative Doppler ultrasound in liver transplantation. *Clin Transplant* 1998;12:282.
49. Denys A, Chevallier P, Doenz F, et al. Interventional radiology in the management of complications after liver transplantation. *Eur Radiol* 2004;14:431.
50. Someda H, Moriyasu F, Fujimoto M, et al. Vascular complications in living related liver transplantation detected with intraoperative and post-operative Doppler US. *J Hepatol* 1995;22:623.
51. Sano K, Makuuchi M, Imamura H, et al. Evaluation of hepatic venous congestion: proposed indication criteria for hepatic vein reconstruction. *Ann Surg* 2002;236:241-47.
52. Lee SG, Park KM, Hwang S, et al. Modified right liver graft from a living donor to prevent congestion. *Transplantation* 2002;74:54-59.
53. Hwang S, Lee SG, Park KM, et al. Hepatic venous congestion in living donor liver transplantation: Preoperative quantitative prediction and follow-up using computed tomography. *Liver Transpl* 2004;10:763-70.
54. Lee SG, Park KM, Hwang S, et al. Adult-to-adult living donor liver transplantation at the Asan Medical Center, Korea. *Asian J Surg* 2002;25:277-84.
55. Lee S, Park K, Hwang S, et al. Congestion of right liver graft in living donor liver transplantation. *Transplantation* 2001;71:812-14.
56. Sugawara Y, Makuuchi M, Akamatsu N, et al. Refinement of venous reconstruction using cryopreserved veins in right liver grafts. *Liver Transpl* 2004;10:541-47.
57. Shin JH, Kyu-Bo Sung KB, Yoon HK, et al. Endovascular stent placement for interposed middle hepatic vein graft occlusion after living-donor liver transplantation Using Right-Lobe Graft. *Liver transplant* 2006;12:269-76.
58. Ko GY, Sung KB, Yoon HK, et al. Endovascular treatment of hepatic venous outflow obstruction after living-donor liver transplantation. *J Vasc Interv Radiol* 2002;13:591-99.
59. Yamagiwa K, Yokoi H, Isaji S, et al. Intrahepatic hepatic vein stenosis after living-related liver transplantation treated by insertion of an expandable metallic stent. *Am J Transplant* 2004;4:1006-09.
60. KW Kim, TK Kim, SG Lee, et al. Doppler sonographic abnormalities suggestive of venous congestion in the right lobe graft of living donor liver transplant recipients *AJR* 2007;188:239-45.
61. Kraus TW, Rohren T, Manner M, et al. Successful treatment of complete inferior vena cava thrombosis after liver transplantation by thrombolytic therapy. *Br J Surg* 1992;79:568-69.
62. Raby N, Karani J, Thomas S, et al. Stenoses of vascular anastomoses after hepatic transplantation: Treatment with balloon angioplasty. *AJR Am J Roentgenol* 1991;157:167-71.
63. Cavallari A, Vivarelli M, Bellusci R, et al. Treatment of vascular complications following liver transplantation: Multidisciplinary approach. *Hepatogastroenterology* 2001;48:179-83.
64. Glanemann M, Settmacher U, Stange B, et al. Caval complications after orthotopic liver transplantation. *Transplant Proc* 2000;32:538-40.
65. Brouwers MAM, de Jong KP, Slooff MJH, et al. Inferior vena cava obstruction after orthotopic liver transplantation. *Clin Transplant* 1994;8:19-22.
66. Boillot O, Sarfati PO, Bringier J, et al. Pathology of the inferior vena cava and liver transplantation. *Ann Chir* 1990;44:540-44.
67. Sanchez-Bueno F, Hernandez Q, Rodriguez JM, et al. Vascular complications in a series of 300 orthotopic liver transplants. *Transplant Proc* 1999;31:2409-10.
68. Zulke C, Berger H, Anthuber M, et al. Detection of suprahepatic caval stenosis following liver transplantation and treatment via balloon-expandable intravascular stent. *Transpl Int* 1995;8:330-32.
69. Orons PD, Hari AK, Zajko AB, et al. Thrombolysis and endovascular stent placement for inferior vena cava thrombosis in a liver transplant recipient. *Transplantation* 1997;64:1357-60.
70. GC Sotiropoulos, I Fouzasc, A Paul, et al. Inferior vena cava thrombosis after right hepatectomy for live donor liver transplantation: A major donor complication and a satisfactory treatment modality. *American Journal of Transplantation* 2007;7:2836-37.

ARTERIAL COMPLICATIONS

Arterial complications after orthotopic liver transplantation vary from 2 to 25%.¹ Various complications are hepatic artery thrombosis, stenosis, pseudo aneurysm and rupture. Hepatic artery thrombosis (HAT) is the most frequent vascular complication after OLT. It is associated with a high mortality and morbidity ranging up to 75%.² In the early postoperative period, it has a mortality rate of 50%. The incidence of hepatic artery stenosis (HAS) ranging between 4.8 and 11%.⁴ Other studies reported incidence of HAT is 5% in adults and 9 to 18% in children.^{5,6} Abouljoud, et al. reported that an increased incidence of complications is seen when aberrant anomalies are present in the hepatic allograft⁷ while Ferraz, et al.⁸ found that the correlation is not statistically significant.

HEPATIC ARTERY STENOSIS

The incidence of hepatic artery stenoses (HAS) is as high as 11%.⁹ Initially, the stenosis causes uncomplicated and reversible biliary ischemia; however, it later causes irreversible biliary necrosis, which leads to allograft dysfunction. Therefore, early detection of hepatic artery stenoses and treatment are crucial for good graft survival. HAS is the result of inadequate surgical techniques, vascular trauma by clamps, graft rejection, microvascular lesions associated with preservation solutions,¹³ vasovascular rupture, and recurrent hepatic disease. The clinical presentation usually includes graft dysfunction or biliary complications related to low blood flow. Treatment of HAS is by surgical reanastomosis and more recently interventional vascular procedures such as balloon angioplasty and stent placement are the treatment modalities available. Angiographic method shows lower morbidity than surgery, despite the fact that there are no studies showing long-term arterial patency.¹⁰⁻¹² The angiographic method is useful for treating nonextensive stenoses, and intrahepatic stenosis that are not accessible through surgery.

HEPATIC ARTERY THROMBOSIS

During hepatic artery occlusion, the liver suffers global hypoxia, since almost 50% of oxygen delivery to the organ is maintained through this vessel. A progressive reduction in portal vein blood flow has been shown to occur after hepatic artery ligation in dogs, which can be associated with a further decrease in liver oxygenation.^{13,14}

HAT can be divided into two groups depending upon the time of onset of thrombosis:

- Early HAT is defined as thrombosis occurring within one month of transplantation
- Late HAT is defined as thrombosis occurring after 1 month of transplantation.

Early HAT

It is more common in pediatric liver transplants due to smaller caliber donor/recipient arteries and greater postoperative fluctuations in coagulation factor concentration and hematocrit.⁹

The clinical presentation of a HAT varies from a low grade fever, mild elevation of liver enzyme and bilirubin levels, and right upper quadrant pain to fulminant hepatic necrosis. Acute presentation is usually associated with an early HAT.¹⁵ It is responsible for hepatic ischemia and necrosis, biliary leakage, stricture formation and potential graft loss resulting in need for retransplantation in the early postoperative period. An increased incidence of HAT is reported in the first 30 days after transplantation, by using a CMV seropositive donor allograft in a CMV seronegative recipient.¹⁶

Risk factors for early HAT¹⁷⁻¹⁹

- Technical problems related to:
 - Differences in size and quality of donor and recipient arterial vessels
 - Presence of arterial abnormalities that require complex reconstructions
- ABO incompatibility
- Prolonged cold ischemia time

Late HAT

It is usually rare. Even though it commonly occurs after 1 month of transplantation, is usually diagnosed after 6 months of transplantation.²⁰ Prevalence of late HAT ranges from 2-20%.²¹ Clinical presentation of late HAT is obstructive jaundice with elevated AST and ALT, cholangitis and sepsis. The level of stricture is usually at the level of bifurcation of CHD (in DDLT) where the vascularity is least. It is associated with biliary complications and hepatic bilomas.²²

Onset is more insidious clinical manifestations take long time to develop²³ and showing lower mortality rates than early HAT.²⁴ However, late HAT may lead to graft dysfunction, consequently reducing transplant survival. The pathogenesis of late HAT appearing more frequently after severe rejections may be explained by the damage of the vascular endothelium by immunologic attack and/or to hemodynamic alterations in vascular resistance and flow of the capillary bed.^{21,25,26}

Risk factors for late HAT²⁷⁻³⁰

- Cytomegalovirus infection.
- Chronic HCV infection.
- Accessory hepatic artery anastomosis.
- Preservation injury.
- Recurrent acute cellular rejection.
- Donor and recipient age and atherosclerotic vessels.
- Smoking.

Diagnosis

Protocol **DUS** examination of the recipient is used to detect unsuspected vascular complications in the early postoperative period, particularly HAT.³² Low HA resistive index (< 0.6) and high systolic acceleration time are (> 10 m sec) predictors for vascular complications.³³ Microbubble contrast enhance US is superior to DUS and decreasing the need for angiography in most patients.³¹

Arteriography should be performed to confirm the diagnosis.³⁴ **Spiral CT angiography (CTA)**, especially three-dimensional CTA, is a new noninvasive method to detect HAT with a sensitivity of 100%, a specificity of 89%, and an accuracy of 95%.³³ **Digital subtraction angiography (DSA)** is the gold standard to diagnose hepatic artery complications. Kayahan, et al. suggested that **MDCTA** (multidetector computed tomographic angiography) is noninvasive imaging modality that accurately shows a variety of vascular complications after liver transplantation. If vascular complications are suspected in doppler ultrasound, the patients must undergo MDCT Angiography for diagnosis. If severe/moderate stenosis is detected, the patient must undergo DSA.³⁶

Treatment of Hepatic Arterial Complications

Hepatic artery occlusion is a real emergency requiring endovascular or surgical intervention.

Endovascular thrombolysis:

Endovascular thrombolysis:^{38,39} Different agents used for thrombolysis:

- Low-molecular heparin (50 U/kg SQ)
- Antithrombin III concentrates (500 IU QID IV)
- Prostaglandin E1 (0.01 µg/kg/hour) and a protease inhibitor, i.e. gabexate mesilate: 1 mg/kg per hour for 2-3 weeks
- Urokinase (1,50,000–4,00,000 IU in the first few hours). It is frequently followed by bleeding
- Tissue plasminogen activator (tPA): Dose 1 to 3 mg

Procedure: Continuous transcatheter hepatic arterial thrombolytic treatment is performed with a 4-French

catheter after placement of a 0.014-inch guidewire in the distal hepatic artery. A “Y” connector is attached to the 4 Fr. catheter while the 0.014-inch guidewire is placed. Urokinase 50,000 to 250,000 IU is injected through the catheter during the first 15 minutes. A second dose of urokinase (250,000–750,000 units) may be infused during the next 30 minutes if the thrombolysis is not satisfactory. Catheter is left inside and a continuous perfusion of 50,000 to 100,000 units of urokinase per hour is administered during the next 12 to 24 hours. The catheter may be removed after 24 hours. Zhou, et al. left the intraarterial catheter for 2 to 3 days. During this time, they performed hepatic arteriography once in every 5 to 24 hours to monitor the effect of thrombolysis and to resume thrombolysis, if the thrombus reoccurred.⁴⁰

Surgical thrombectomy and arterial reconstruction is definitive treatment and should be performed immediately.⁴¹ Use of cryopreserved cadaveric iliac arterial or vein graft as interposition graft to the occluded artery is another option when surgical thrombectomy is attempted.⁴²

*Percutaneous transluminal angioplasty (PTA) and stenting of the hepatic arteries:*⁶⁴ Endovascular interventions are performed via right femoral artery access. A 6 Fr. vascular sheath is placed and after selective catheterization of the celiac trunk or the superior mesenteric artery, a microcatheter and a 0.016-inch guidewire are negotiated through the stenosis or the occlusion. Then, a 0.014-inch guidewire is placed in the hepatic artery. Then a 6 Fr. guiding catheter is advanced to the origin of the celiac trunk or the superior mesenteric artery. If the luminal diameter of the hepatic artery is decreased by $>50\%$, a percutaneous transluminal angioplasty (PTA) is performed. Before PTA, heparin (100 units/kg) is injected intravenously. The PTA is performed with a monorail balloon. Balloon size is selected according to the diameter of the hepatic artery, distal to the stenosis. If the hepatic artery remained stenotic after balloon dilatation ($>20\%$ stenosis) or if extravasation of contrast material occurred, then stents are placed. Intra-arterial thrombolysis is performed during the procedure.

Mechanical fragmentation of the thrombus may be performed with a balloon catheter. Owing to the early occlusion of the hepatic arteries, repeat endovascular interventions is another option.

Types of Stents

- Wall stent
- Graft covered stents.

The main indications for using graft-covered stents are rupture of the hepatic artery during endovascular

intervention and early postoperative intervention. Current discussion is regarding the best time for the earliest endovascular intervention after LTX. Kodama, et al. suggested 7 days; Ueno et al. suggested 3 weeks after LTX whereas Boyvat, et al. suggested it should be done within 7 days.⁴³⁻⁴⁵ With the graft-covered stents currently available, there is no time restriction after surgery for performing endovascular interventions as they can be placed safely and effectively in the early postoperative period. Ueno et al. reported 78% patient survival rate after primary stenting of the hepatic arteries, suggesting that stent placement in the hepatic arteries is well tolerated and effective. Ueno, et al.⁴⁵ showed 78% survival of patients treated with stents. Abbasoglu, et al.² described 80% survival with surgical treatment. Da Silva, et al. observed 100% survival with angiographic procedures.⁶³ There are few cases in the literature that show superiority of stents over angioplasty.⁴⁷⁻⁴⁹ The occurrence of restenosis is common (25%) after stent placement.⁴⁵

Follow-up after stent placement: Routinely patients are on anticoagulation with salicylic acid (100 mg QD PO), dipyridamoles (75 mg QD PO) or clopidogrel bisulfate may be used. This was followed by DUS to monitor vessel patency every day until discharge. DUS is performed at 1 week, 1 month, 3 months, and 6 months. Follow-up angiography is scheduled at 1 year after transplant.

- Use of hyperbaric oxygen therapy improves ischemia: 30 applications of HBO in a monoplace chamber

directly pressurized with oxygen. Each daily session lasted 2 hours, with a pressure of 2.5 ATM. Hyperbaric oxygenation may thus provide a means to obviate the effects of interruption of arterial blood flow by increasing portal blood oxygen content and possibly enhancing the development of hepatic artery collaterals.⁵⁰⁻⁵³

- Retransplantation is required in almost 50% of patients with HAT.³

Mycotic Pseudoaneurysm of Hepatic Artery after LTX (Figures 26.36 to 26.39)

The most frequent etiology of visceral artery aneurysms is arteriosclerosis. The prevalence of visceral artery aneurysms in the general population is about 2%. Common cause is pancreatitis, endocarditis and cholecystitis. Aneurysms of the hepatic artery account for 13 to 20% of all aneurysms of visceral arteries: 80% have an extrahepatic location. Of these, 14 to 40% finally rupture, causing hemorrhage, with a mortality rate of 40%.

A non-arteriosclerotic origin and the presence of multiple aneurysms are possible risk factors for rupture.⁵⁴ The incidence of hepatic artery aneurysms after LTX is about 0.7%.⁵⁵ Splenic artery is the other site for pseudoaneurysm. In LTX, clinical picture, etiology, treatment, and prognoses of aneurysms of visceral arteries are characteristically different.



Figure 26.36

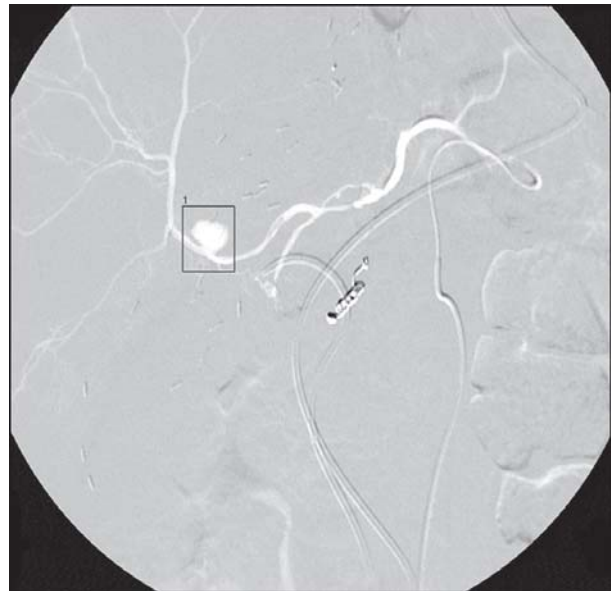


Figure 26.37

Figures 26.36 and 26.37: Pseudoaneurysm of RHA following PTCD for biliary complication presented with hemobilia and massive upper GI bleeding.

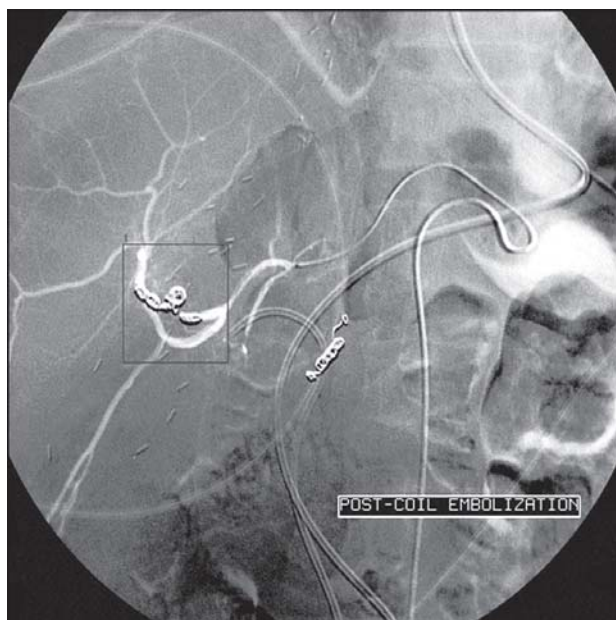


Figure 26.38

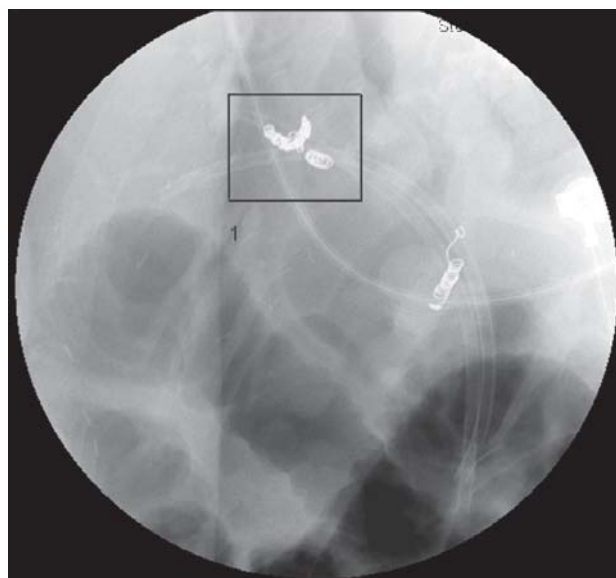


Figure 26.39

Figures 26.38 and 26.39: Angiography showing HA aneurysm occluded with coil embolization; additional coil embolization in GDA (HA: hepatic artery, GDA: gastroduodenal artery)

Etiology is dissection or mycotic origin (*E.coli*, *Pseudomonas* or *Enterobacterium*). Various interventional procedures like vascular manipulation or PTCO or ERCP result in pseudoaneurysm formation. They have a tendency for bacterial contamination. Perforation of the biliary duct with stents has been reported.⁵⁶ Thrombosis of the hepatic artery is the most frequent complication in these patients. Liver graft may be lost because of ischemia secondary to thrombosis of the aneurysm.

Clinical presentation is usually cataclysmic. Patient may present with massive upper GI bleeding, hemoperitoneum, hemobilia or bile duct fistula.^{57,58} They may rupture into the portal vein producing a portal hypertension syndrome, though this is unusual. Mortality rate is usually around 33%.⁵⁹ Diagnosis is by Doppler ultrasonography, Angiography and CT and MR angiography, when this complication is suspected.

Treatment: Stents or percutaneous thrombin injection^{40,60-62} may be the technique of choice if they are diagnosed early. In unstable patients, immediate resuscitation with plasma expanders, vasopressors and massive blood transfusion is life saving. Once the patient is hemodynamically stabilized, then definitive treatment by interventional radiological techniques (preferred choice) and embolisation of the aneurysm with coils or cyanoacrylate is performed.⁴⁶ Surgery is preferred in failure of

interventional procedures. If surgery is required, the best option is aneurysmectomy with reanastomosis or revascularization with arterial/venous grafts. Treatment with endoscopic embucrilate injection into fistulas into the bile duct has been described.⁴³ Splenectomy was required in the patient with a mycotic pseudoaneurysm of the splenic artery.

REFERENCES

1. Settmacher U, Stange B, Haase R, et al. Arterial complications after liver transplantation. *Transpl Int* 2000;13:372.
2. Abbasoglu O, Levy MF, Vodapally MS, et al. Hepatic artery stenosis after liver transplantation-incidence, presentation, treatment, and long term outcome. *Transplantation* 1997;63:250.
3. Stange BJ, Glanemann M, Nuessler NC, et al. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2003;9:612.
4. Orons PD, Zajko AB. *Radiol Clin North Am* 1995;33:541.
5. Starzl TE, Demetris AJ. Liver transplantation: A 31-year perspective, part I and II. *Curr Probl Surg* 1990;27:51.
6. Drazan K, Shaked A, Olthoff KM, et al. Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). *Am Surg* 1996;62:237.
7. Abouljoud MS, Kim DY, Yoshida A, et al. Impact of aberrant arterial anatomy and location of anastomosis on technical outcomes after liver transplantation. *J Gastrointest Surg* 2005;9:672.

8. BH Ferraz-Neto, SR Meira-Filho, R Hidalgo, et al. Correlation between graft arterial anatomy and biliary complications after liver transplantation. *Transplant Proceed* 2007;39:2514-15.
9. Mazzaferro V, Esquivel CO, Makowka L, et al. Transplantation 1985;47:971.
10. Orons PD, Zajko AB, Bron KM, et al. Hepatic artery angioplasty after liver transplantation: Experience in 21 allografts. *J Vasc Interv Radiol* 1995;6:523.
11. Abad J, Hidalgo EG, Cantarero JM, et al. Hepatic artery anastomotic stenosis after transplantation: treatment with percutaneous transluminal angioplasty. *Radiology* 1989;171:661.
12. Mondragon RS, Karani JB, Heaton ND, et al. The use of percutaneous transluminal angioplasty in hepatic artery stenosis after transplantation. *Transplantation* 1994;57:228.
13. Ujita T, Nonami T, Kurokawa T, et al. Hepatic hemodynamics and oxygen metabolism during hepatic artery occlusion and reperfusion: Effects of dobutamine and inhalation of 100% oxygen. *Eur Surg Res* 1994;26:149.
14. Kurokawa T, Nonami T, Ujita T, et al. Dopamine compensates for deterioration of hepatic hemodynamics and metabolism during occlusion and reperfusion of the hepatic artery. *Arch Surg* 1995;130:1085.
15. Silva MA, Jambulingam PS, Gunson BK, et al. Hepatic artery thrombosis following orthotopic liver transplantation: A 10-year experience from a single centre in the United Kingdom. *Liver Transpl* 2006 ;12:146.
16. Madalosso C, de Souza NF, Ilstrup DM, et al. Transplantation 1998;66:294.
17. Merion RM, Burtch GD, Ham JM, et al. The hepatic artery in liver transplantation. *Transplantation* 1989;48:438.
18. Goldstein RM, Secrest CL, Klintmalm GB, et al. Problematic vascular reconstruction in liver transplantation. Part 1. Arterial. *Surgery* 1990;107:540.
19. Sanchez-Bueno F, Robles R, Ramirez P, et al. Hepatic artery complications after liver transplantation. *Clin Transplant* 1994;8:399.
20. Gunsar F, Rolando N, Pastacaldi F, et al. Late hepatic artery thrombosis after orthotopic liver transplantation. *Liver Transpl* 2003;9:605.
21. Hidalgo E, Cantarell C, Charco R, et al. *Transplant Proc* 1999;31:2416.
22. Orons PD, Sheng R, Zajko AB: Hepatic artery stenosis in liver transplant recipients: Prevalence and cholangiographic appearance of associated biliary complications. *AJR Am J Roentgenol* 1995;165:1145.
23. Abbasoglu O, Levy M, Vodapally MS, et al. Transplantation 1997;63:250.
24. Marujo WC, Langnas NA, Wood RP, et al. *Transplant Proc* 23:1991
25. Yanaga K, Makowka L, Starzl TE: *Transplant Proc* 1989;21:3511.
26. Todo S, Makowka L, Tzakis AG, et al. *Transplant Proc* 1987;19:2406
27. Gunsar F, Rolando N, Pastacaldi F, et al. Late hepatic artery thrombosis after orthotopic liver transplantation. *Liver Transpl* 2003;9:605.
28. Leonardi MI, Boin I, Leonardi LS. Late hepatic artery thrombosis after liver transplantation: clinical setting and risk factors. *Transplant Proc* 2004;36:967.
29. Pastacaldi S, Teixeira R, Montalto P, et al. *Liver Transpl* 2001;7:75.
30. Pungpapong S, Manzarbeitia C, Ortiz J, et al. *Liver Transpl* 2002;8:582.
31. Benjamin KH, Ruchi S, Suzanne LP, et al. Prospective evaluation of vascular complications after liver transplantation: Comparison of conventional and microbubble contrast-enhanced US1 *Radiology* 2006;241(1):267-74
32. Kok T, Slooff MJ, Thijn CJ, et al. Routine Doppler ultrasound for the detection of clinically unsuspected vascular complications in the early postoperative phase after orthotopic liver transplantation. *Transpl Int* 1998;11:272.
33. Uzochukwu LN, Bluth EI, Smetherman DH, et al. Early postoperative hepatic sonography as a predictor of vascular and biliary complications in adult orthotopic liver transplant patients. *AJR Am J Roentgenol* 2005;185:1558.
34. Proposito D, Loinaz Seguro C, Garcia Garcia I, et al. Diagnosis and treatment of hepatic artery thrombosis after liver transplantation. *Chir Ital* 2000;52:505.
35. Brancatelli G, Katyal S, Federle MP, et al. Three-dimensional multislice helical computed tomography with the volume rendering technique in the detection of vascular complications after liver transplantation. *Transplantation* 2002;73:237.
36. EM Kayahan Ulu, M Haberal, et al. Accuracy of multidetector computed tomographic angiography for detecting hepatic artery complications after liver transplantation. *Transplant Proceed* 2007;39:3239-44.
37. J Zhou, J Fan, J-H Wang, Z-Q, et al. Continuous transcatheter arterial thrombolysis for early hepatic artery thrombosis after liver transplantation. *Transplant Proceed* 2005;37:4426-29.
38. Y Sugawara, J Kaneko, N Akamatsu, et al. Anticoagulant therapy against hepatic artery thrombosis in living donor liver transplantation. *Transplant Proceed* 2002;34:3325-26.
39. Hashikura Y, Kawasaki S, Okumura N, et al. *Transplantation*. 1995;60:1109.
40. Venturini M, Angeli E: Hemorrhage from a right hepatic artery pseudoaneurysm: Endovascular treatment with a coronary stent-graft. *J Endovasc Ther* 2002;9:221.
41. Sakamoto Y, Harihara Y, Nakatsuka T, et al. Rescue of liver grafts from hepatic artery occlusion in living-related liver transplantation. *Br J Surg* 1999;86:886.
42. Marty TS, Silke VH, Brendan MMG, et al. Use of preserved vascular homografts in liver transplantation: Hepatic artery aneurysms and other complications. *American Journal of Transplantation* 2002;2:471-75.
43. Ferrari AP, Ferreira JP. Hemobilia caused by a mycotic aneurysm of the hepatic artery treated by embucrilate injection during ERCP. *Gastrointest Endosc* 2003;57:260.
44. Kodama Y, Sakuhara Y, Abo D, et al. Percutaneous transluminal angioplasty for hepatic artery stenosis after living donor liver transplantation. *Liver Transpl* 2006;12:465.
45. Ueno T, Jones G, Martin A, et al. Clinical outcomes from hepatic artery stenting in liver transplantation. *Liver Transpl* 2006;12:422.
46. Yamakado K, Nakatsuka A: Transcatheter arterial embolisation of ruptured pseudoaneurysms with coils and n-butyl cyanoacrylate. *J Vasc Interv Radiol* 2000;11:66.
47. Cotroneo AR, Di Stasi C, Cina A, et al. Stent placement in four patients with hepatic artery stenosis or thrombosis after liver transplantation. *J Vasc Interv Radiol* 2002;13:619.
48. Denys AL, Qanadli SD, Durand F, et al. Feasibility and effectiveness of using coronary stents in the treatment of hepatic artery stenoses after orthotopic liver transplantation: Preliminary report. *AJR Am J Roentgenol* 2002;178:1175.

49. Yang CC, Cheng CC, Hsieh TB, et al. Application of coronary stent in treating hepatic artery stenosis in a liver-grafted patient. *Acta Cardiol Sin* 2003;19:259.
50. O Castro e Silva, AK Sankarankutty, ALC Martinelli, et al. Therapeutic effect of hyperbaric oxygen in hepatic artery thrombosis and functional cholestasis after orthotopic liver transplantation. *Transplant Proceed* 2006;38:1913-17.
51. Mazariegos GV, O'Toole K, Miele LA, et al. Hyperbaric oxygen Rx for hepatic artery thrombosis after liver transplant in children. *Liver Transplant Surg* 1999;5:429.
52. Wong J, Zhang Y, Lee SS. Hemodynamic characterization of arterialized and nonarterialized liver transplant in the rat. *Can J Gastroenterol* 2001;15:435.
53. Dubost J, Goubaux B, Dubaldl M, et al. Use of hyperbaric oxygen for hepatic artery thrombosis following adult orthotopic liver transplantation. *Eur J Anesthes* 2002;19:223.
54. Abbas MA, Fowl RJ. Hepatic artery aneurysm: Factors that predict complications. *J Vasc Surg* 2003;38:41.
55. Settmacher U, Stange B. Arterial complications after liver transplantation. *Transpl Int* 2002;13:372.
56. Ozkan OS, Walser EM. Guglielmi detachable coil erosion into the common bile duct after embolization of iatrogenic hepatic artery pseudoaneurysm. *J Vasc Interv Radiol* 2002;13:935.
57. Iannelli A, Karimjee BS. Hemobilia due to pseudoaneurysm of the right hepatic artery following laparoscopic cholecystectomy. *Gastroenterol Clin Biol* 2003;27:341.
58. Leonardi LS, Soares C. Hemobilia after mycotic hepatic artery pseudoaneurysm after liver transplantation. *Transplant Proc* 2001;33:2850.
59. JM Álamo, MA Gómez, MJ Tamayo, et al. Mycotic pseudoaneurysms after liver transplantation. *Transplant Proceed* 2004;37:1512-14.
60. Patel JV, Weston MJ. Hepatic artery pseudoaneurysm after liver transplantation: treatment with percutaneous thrombin injection. *Transplantation* 2003;75:1755.
61. Larson RA, Solomon J. Stent graft repair of visceral artery aneurysms. *J Vasc Surg* 2002;36:1260.
62. Little AF, Lee WK. Percutaneous and endovascular embolisation of ruptured hepatic artery aneurysm. *Cardiovasc Intervent Radiol* 2002;25:208.
63. RF da Silva, R Raphe, HC Felício, et al. Prevalence, treatment, and outcomes of the hepatic artery stenosis after liver transplantation. *Transplant Proceed* 2008;40:805-07.
64. F Boyvat, C Aytekin, A Harman, S, et al. Endovascular stent placement in patients with hepatic artery stenoses or thromboses after liver transplant. *Transplant Proceed* 2008;40:22-26.

ARTERIAL STEAL SYNDROME

Arterial steal syndrome after orthotopic liver transplantation is characterized by arterial hypoperfusion of the graft that is caused by a shift in blood flow into other arteries that originate from the same trunk. Pathogenesis of the steal has not been identified; the development of the disorder after liver transplantation is becoming more common.

Causes of post-transplant hepatic ischemia^{1,2}

- Acute thrombosis of the hepatic artery
- Anastomotic stricture of the hepatic artery
- Arterial steal syndrome.

Splenic arterial steal syndrome (SASS) was first described in 1990, in which hepatic ischemia was caused by reduced perfusion or reduced blood flow through the hepatic artery rather than by obstruction.³ Most cases of liver ischemia are caused by splenic artery steal syndrome, which has been reported in 3.2% to 4% of patients.^{3,4}

Common sites of steal⁵⁻⁷

- Splenic artery (most common): 3.2-4% of the liver transplants
- Gastroduodenal artery steal syndrome
- Left gastric artery

Probable causes for steal syndrome⁶⁻⁹

- Stenosis of the graft artery
- Rejection of the transplanted tissue
- Flow pattern changes involving increased portal blood flow and decreased compensatory hepatic arterial blood flow.

DIFFERENT MECHANISMS OF SASS

- If the hyperdynamic state does not improve immediately after LTX, reduced splenic arterial resistance and increased splenic arterial flow may divert celiac blood flow into the spleen.
- Swelling of the liver due to preservation injury causes increased intrahepatic arterial resistance and further diversion of blood flow away from the hepatic artery into the splenic artery.
- It may be more related to the progressive increase in splenic arterial flow caused by the presurgical hyperdynamic state, with or without the development of clinical hypersplenism.
- Late development of SASS might also be related to presurgical increased splenic arterial flow that is not clinically significant at the time of transplantation but is exacerbated by the rejection of the graft or by viral hepatitis.^{3,10}

Onset of the SASS varies among patients. It may occur either within few hours after liver transplantation or as late as several weeks after transplantation.

Presentation of SASS¹⁻⁶

- Elevated liver enzyme levels
- Impaired graft function
- Cholestasis
- Hepatic arterial thrombosis
- Multiple episodes of rejection.

DIAGNOSIS**Angiography**

- Hepatic artery is patent but characterized by sluggish flow
- Delayed perfusion or filling of the Intrahepatic arterial branches by contrast material in comparison with the filling of other branches of the celiac trunk
- Poor peripheral parenchymal perfusion (enhancement)
- Early and abundant filling of the splenic or left gastric artery and increased size and flow of these vessels.

3-D CT Scan

Splenomegaly, marked enlargement of the splenic artery and narrowing of the CHA.

DIFFERENTIAL DIAGNOSIS

Graft rejection and Ischemia, related to preservation injury.

TREATMENT^{3,8,11-14}

- Splenectomy
- Ligation of splenic artery
- Coil embolization of the involved artery (splenic/GDA/LGA)
- Intraluminal stent placement
- Banding, the use of the splenic artery for the reconstruction of hepatic arterial flow
- Aortic implantation of the graft artery

Intraoperative ligation of the splenic artery may also be performed to prevent SASS. Although a splenic hyperdynamic state cannot be detected prior to transplantation surgery, intraoperative ligation of the splenic artery should be performed in cases of intraoperative portal pressure > 20 mm Hg, a small-for-size graft, or large splenomegaly.¹⁵ In fact, elevated PVP (> 20 mm Hg) in the early postoperative phase is strongly associated with poor survival, attributable, at least in part, to small-for-size syndrome.¹⁶

FOLLOW-UP

Increased flow in the hepatic artery after treatment of arterial steal syndrome can be confirmed by DUS or control angiography. MDCT Angiography can be used to follow the improvement of graft function among liver transplant patients after partial splenic embolization.⁴ Normally, the SA is considered to be enlarged when it is above the normal value of 5.6 ± 13 mm.¹⁴ An enlarged splenic artery (> 4 mm or 150% of hepatic artery) is one of the accepted signs of SASS; it can be reduced following partial SA embolization.^{18,19}

REFERENCES

1. Pinna AD, Smith CV, Furukawa H, et al. Urgent revascularization of liver allografts after early hepatic artery thrombosis. *Transplantation* 1996;62:1584.
2. Langer R, Langer M, Neuhaus P, et al. Angiographic diagnostics in liver transplantation. Part II: Angiography after transplantation. *Digitale Bildgebung* 1990;10:92.
3. Uflacker R, Selby JB, Chavin K, et al. Transcatheter splenic artery occlusion for treatment of splenic artery steal syndrome after orthotopic liver transplantation. *Cardiovasc Intervent Radiol* 2002;25:300.
4. Tan KC, Yandza T, de Hemptinne B, et al. Hepatic artery thrombosis in pediatric liver transplantation. *J Pediatr Surg* 1998;23:927.
5. Nüssler NC, Settmacher U, Haase R, et al. Diagnosis and treatment of arterial steal syndromes in liver transplant recipients. *Liver Transpl* 2003;9:596.
6. Langer R, Langer M, Scholz A, et al. The splenic steal syndrome and the gastroduodenal steal syndrome in patients before and after liver transplantation. *Aktuelle Radiol* 1992;2:55 (in German).
7. Vogl TJ, Pegios W, Balzer JO, et al. Arterial steal syndrome in patients after liver transplantation: Transarterial embolization of the splenic and gastroduodenal arteries. *Rofo* 2001;173:908 (in German).
8. De Carlis L, Sansalone CV, Rondinara GF, et al. Splenic artery steal syndrome after orthotopic liver transplantation: Diagnosis and treatment. *Transplant Proc* 1993;25:2594.
9. Valente JF, Alonso MH, Weber FL, et al. Late hepatic artery thrombosis in liver allograft recipients is associated with intrahepatic biliary necrosis. *Transplantation* 1996;61:61.
10. Sheiner PA, Varma CV, Guarrera JV, et al. Selective revascularization of hepatic artery thromboses after liver transplantation improves patient and graft survival. *Transplantation* 1997;64:1295.
11. Manner M, Otto G, Senninger N, et al. Arterial steal: An unusual cause for hepatic hypoperfusion after liver transplantation. *Transpl Int* 1991;4:122.
12. Rasmussen A, Hjortrup A, Kirkegaard P. Intraoperative measurement of graft blood flow—a necessity in liver transplantation. *Transpl Int* 1997;10:74.
13. Geissler I, Lamesch P, Witzigmann H, et al. Splenohepatic arterial steal syndrome in liver transplantation: clinical features and management. *Transpl Int* 2002;15:139.
14. S Sevmis, F Boyvat, C Aytekin, et al. Arterial steal syndrome after orthotopic liver transplantation. *Transplant Proceed* 2006;38:3651-55.
15. Troisi R, Cammu G, Militerio G, et al. Modulation of portal graft inflow: A necessity in adult living-donor liver transplantation? *Ann Surg* 2003;237:429.
16. Ito T, Kiuch T, Yamamoto H, et al. Changes in portal venous pressure in the early phase after living-donor liver transplantation: Pathogenesis and clinical implications. *Transplantation* 2003;75:1313.
17. Machalek L, Holibkova A, Tuma J, et al. The size of the splenic hilus, diameter of the splenic artery and its branches in the human spleen. *Acta Univ Palacki Olomuc Fac Med* 1998;141:65.
18. Barcena R, Moreno A, Foruny JR, et al. Improved graft function in liver-transplanted patients after partial splenic embolisation: reversal of splenic artery steal syndrome. *Clin Transplant* 2006;20:517.
19. K Shimizu, H Tashiro, Y Fudaba, et al. Splenic artery steal syndrome in living donor liver transplantation: A case report. *Transplant Proceed* 2007;39:3519-22.

(E) POST-TRANSPLANT INFECTIONS

INTRODUCTION

Infections in solid organ transplants contribute to a significant morbidity and mortality. In early transplant period, bacterial, viral and fungal infections are common. Early diagnosis and control of infection is an important to achieve successful outcome after LTX. Improvement in the treatment of post-transplant infections has been associated with decreased mortality rates.¹

CLASSIFICATION

EARLY INFECTIONS

These are the infections in the first 6 months after transplantation. These infections are mostly related to transplant surgery and wound related in the early post-transplant period, followed by bacterial, viral and fungal infections.

LATE INFECTIONS

These are the infections occurring after 6 months of transplantation. Opportunistic infections are less common after 6 months of post-transplant period. Transplant patients are at risk for the same causes of infection as the general population.

ABDOMINAL INFECTIONS

WOUND RELATED INFECTIONS

These are seen in 2% to 8% of cases.² Seroma, peri-graft fluid collections, and deep wound collections can lead to more chronic problems after transplantation.²

BILOMAS

These are infected fluid collection in the intrahepatic or perihepatic area due to biliary complications such as leak, stricture or necrosis. Incidence is approximately 10% and usually occur in the 1st year of transplantation.³ Bilomas present with fever, abdominal pain; bile stained drain fluid and increased TWBC, AST and ALT levels. Usually diagnosed by routine USG examination or contrast enhanced CT scan (seen as low attenuated area).¹²³

Risk factors for biloma⁴

- HAT
- Hepatic artery stenosis
- Roux-en-Y choledochojejunostomy
- T-tube placement.

Treatment

Percutaneous drainage and insertion of a pigtail catheter is recommended. Drained fluid should be sent for culture and sensitivity. In noncommunicating bilomas, simple drainage is necessary. But in bilomas communicating directly with the biliary tract, PTBD should be performed. Antibiotics are continued for 1-2 weeks as per the culture and sensitivity report. Common organism in post-transplant biliomas are usually enterococci, staphylococci, and candida.^{3,4} In case of extrahepatic biliary strictures stent placement is required by ERCP. Patency of drainage catheters should be confirmed in every 2 to 4 weeks under fluoroscopic guidance. Factors that predict failure of medical therapy without retransplantation include HAT and the presence of enterococci or candida infection.³ Predictors of mortality include pre-LT renal disease and infection with either gram-negative bacilli or Candida species.³

PERITONITIS

Peritonitis after liver transplantation is a serious complication and is associated with a risk of graft loss and mortality.⁵ Majority (80%) these cases are due to wound infections or surgical complications such as intra-abdominal bleeding, biliary leak/stricture, or bowel perforation.⁵ Approximately two thirds of all episodes of peritonitis are associated with complications that are potentially amenable to surgical repair.⁵

Risk factors for peritonitis⁵

- MELD score
- Previous abdominal surgery
- Prolonged surgery
- Roux-en-Y biliary anastomosis
- Post-transplant renal replacement therapy

Diagnosis of source of peritonitis is based on clinical findings supported by USG or contrast-enhanced CT scan. Treatment includes early surgical intervention and systemic broad spectrum antimicrobial therapy.

PULMONARY INFECTIONS

Pulmonary infections are common in early post transplant period. Incidence varies from 10-40%. Pleural effusion, atelectasis (RT > LT), pneumonia and ARDS are the various pulmonary complications after transplantation. Most common causes of pneumonia are staphylococcus,

Different types of infection after LTX

	1st Month	2nd–6th Month	> 6 Months
	Nosocomial infection Donor related infections in recipient	Opportunistic infections Reactivation of latent viral infections	Community acquired infections
Bacterial etiology	Gram +ve bacteria Gram –ve bacteria MRSA, VRE Clostridium difficile Legionella infection	Pneumocystis carinii Nocardia Listeria Tuberculosis	Listeria Tuberculosis
Fungal etiology	Candida	Candida Aspergillosis Cryptococcus Endemic fungi	Cryptococcus Endemic fungi
Viral etiology	HSV, HBV, HCV	HBV, HCV, HSV CMV, EBV, VZV Influenza, Adeno virus	CMV, EBV HCV, HBV Papilloma virus
Parasitic infections		Strongyloides, Toxoplasma Leishmania, Trypanosoma	Strongyloides

anerobic gram negative rods, pseudomonas and enterobacter group of organisms. Other causes like streptococcus, h. influenza and viruses should also be considered. Cavitory lung lesions are seen in mycobacterial infections and nodular lesions are seen in cryptococcus infection.

Diagnosis is usually by chest X-ray and culture of sputum/bronchial secretions. Less percentage of cases requires CT scan, bronchoscopy and lung biopsy by video assisted thoracoscopic surgery for diagnosis.¹²³ Pleural effusions should be drained by pigtail catheters under USG guidance and aggressive lung expansion therapy along with proper antibiotic therapy; cough suppressants are useful in controlling lung infections. There is an increased suscep-tibility for pulmonary infections due to legionella pneumonia and fungi.^{6,7} Rapidly progressing lung infiltrations on chest × ray while the patient is on antibiotic therapy, gives a clue to exclude the possibility of fungal pneumonias particularly aspergillus.

CNS INFECTIONS

Early CNS manifestations after LTX are due to vascular origin. Other CNS manifestations are acute or chronic meningitis, encephalitis and brain abscess. Acute meningitis caused by Listeria or viral aetiology and chronic meningitis is caused by mycobacterium or fungus

like cryptococcus.¹²³ Brain abscess in post transplant period are mostly fungal origin and carry high mortality. They present with fever, headache, convulsions, and focal neurological deficits. Bacterial/fungal culture from blood, CSF and CT scan will give clues to the diagnosis. Treatment is according to the etiological organism and sensitivity to the antibiotics.

BACTERIAL INFECTIONS

Bacterial infections are the most common infections after LTX and are associated with significant morbidity and mortality. Most of the infections within the first month of transplant are nosocomial bacterial infections like surgery or catheter-related, blood borne infections, pneumonia, UTI, and colitis due to clostridium difficile. Sepsis is a frequent complication of intra-abdominal infections in liver transplant recipients due to immunosuppression. Early recognition and effective antimicrobial therapy is important. Treatment is greatly limited due to emergence of multidrug-resistant pathogens and immunosuppression.

Preoperative prophylactic antibiotics are started 24 hours before transplant and should target the gastrointestinal flora as well as staphylococcus aureus. In post-transplant period initially broad spectrum group of antibiotics including, ampicillin, cephalosporins and

aminoglycosides are used. Aminoglycosides should be used with caution in case of renal compromise in the recipient. If any evidence of infection is noticed, appropriate antibiotics are started as per the culture and sensitivity reports. Co-trimoxazole, used for prophylaxis of *Pneumocystis carinii* pneumonia may prevent bacterial (and parasitic) pathogens including *Nocardia*, *Streptococcus pneumoniae*, *Legionella*, community-acquired methicillin-resistant *S aureus*, gram-negative infections (eg, susceptible *E coli*, *Klebsiella*, and *Salmonella*), *Listeria*, *Toxoplasma*, *Isospora*, and *Cyclospora*. The emergence of resistant strains like MRSA (methicillin-resistant staphylococcus aureus), VRE (vancomycin-resistant enterococci), extended-spectrum β -lactamase-producing *E. coli* and *Klebsiella pneumoniae* can cause serious complications and mortality. Antibiotics like vancomycin, salbactam, imipenem, cilastin are reserved as 2nd line antibiotics to be used in post-transplant period in case of resistant strains.¹²³

MYCOBACTERIUM TUBERCULOSIS

Tuberculosis (TB) is a severe opportunistic infection with a high risk of mortality in solid organ transplant patients. The reported incidence varies in different areas from 0.35-15%.⁸ The prevalence of TB after solid organ transplantation is significantly greater in developing countries (up to 15%) than in developed countries (1.2-6.4%) but the mortality rate is high, ranging from 25 to 40%.^{9,10} Prevalence of post-transplantation TB varies from 1-15% depending on the endemic area. It is a common problem in developing countries like India. The immunosuppressive status after transplantation makes the patient more prone to opportunistic TB infection or reactivation of mycobacterium tuberculosis.

The reported prevalence of TB in liver transplant recipients is 0.7-2.5% and in renal transplants the rate is 0.5-15%.¹⁰ TB most frequently developed within the first year after solid organ transplantation.¹¹ The diagnosis of TB among immunosuppressed patients is more complicated than in normal people.

Modes of transmission: Reactivation, nosocomial acquisition and from infected donor. Recently, Sabbatani et al. reported severe reactivation of pulmonary tuberculosis in a patient with chronic hepatitis C during treatment with Pegylated interferon and Ribavirin. The risk for TB reactivation due to antiviral treatment of hepatitis C is an important issue, not just in anecdotal cases such as ours, but also considering the large number of patients with recurrent HCV after OLT who undergo antiviral therapy, especially those with latent tubercular infection.^{12,13} Antiviral treatment with Interferon and

Ribavirin seems to be safe in recurrent HCV chronic liver disease and recently treated active TB following OLT.¹⁴

Problems Related to Tuberculosis in Solid Organ Transplants

- Atypical presentation and coexisting infections make the diagnosis of TB difficult.
- Hepatotoxicity of antitubercular drugs and their interactions with immunosuppressive agents render TB treatment a great challenge after transplantation.

Presentation

All post-transplantation patients with pyrexia of unknown origin should be investigated aggressively to exclude TB infection, especially among those with a history of TB infection. Fever, leukocytosis, weight loss, poor appetite and lymphadenopathy are frequent symptoms in the early stage of infection.

Diagnosis

- Chest X-ray
- Microbiologic culture of mycobacterium tuberculosis (100% specificity), but sensitivity is low in pleural fluid (17%).
- Acid-fast bacilli in caseating granuloma on histological material from biopsy sample. Z-N staining is a rapid technique but its specificity and sensitivity are 79% and 6-20%.
- TB PCR for TB-DNA detection is very useful and efficient. PCR assay seems to be the fastest, most sensitive method for identifying mycobacterium infection in pleural fluid. Its sensitivity reportedly ranges from 50 to 81%, while its specificity ranges from 61 to 100%.^{15,16}
- Routine purified protein derivative (PPD) test has low significance in patients on immunosuppression and regular vaccination with *Bacillus Calmette-Guerin* in childhood. A negative PPD test in an immunocompromized patient does not exclude TB infection.
- QuantiFERON-TB Gold (QFT Gold) is an enzyme linked immunosorbent assay that effectively evaluates the interferon gamma response to mycobacterium tuberculosis-specific antigens early secreted antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). The test has recently become commercially available. Test is considered positive if the concentration of interferon gamma in the sample, after stimulation with ESAT-6 and CFP-10, is greater than or equal to 0.35 IU/ml.¹⁷
- T-SPOT TB, interferon gamma—based method, has recently become commercially available. This test

measures interferon gamma produced by tubercular-specific T-lymphocytes using an in vitro enzyme-linked immunospot assay that has been shown to have good sensitivity in patients with active tuberculosis. Even low numbers of interferon gamma-releasing T-cells can be detected after stimulation with MTB antigens ESAT-6 and CFP-10.¹⁸

Treatment

Early diagnosis and treatment is very important. There are still no consensus on how many and which drugs should be used or for how long duration. Standard treatment protocols for post-transplantation TB vary widely in different centers, depending on the patient's general condition, as well as the hepatic and renal function.

Isoniazid (5 to 10 mg/kg/day, maximum of 300 mg), rifampicin (10 mg/kg), ethambutol (15 mg/kg) / pyrazinamide (15 to 30 mg/kg/day, maximum of 2 grams) for 6 to 14 months. Fluoroquinolones (Ofloxacin, 400 mg/day) which are being more and more broadly used, have proven effective and safe to treat posttransplantation TB, especially in liver transplant recipients.^{11,19} Prophylactic pyridoxine administration (10 to 50 mg/day) should probably be given routinely in individuals predisposed to develop peripheral neuropathies secondary to isoniazid therapy. A high degree of hepatotoxicity (41-80%) of anti-TB drugs, mainly isoniazid, has been reported. Anti-TB treatment requires close follow-up to adjust the immunosuppressive drugs to avoid rejection which has been reported among 35% of cases.^{8,20}

Triple drug antituberculosis protocol for at least 1 year is reported by earlier author.²¹ Shorter duration for 6 to 9 months has also proven equally effective as reported by another study.²² One study reported that fluoroquinolones should have first-line status in post-transplantation TB treatment.²³ Zhang, et al. reported the use of isoniazid, rifampicin, ethambutol, and ofloxacin for 3 months followed by isoniazid and rifabutin for 6 months.²⁴ Fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, sparfloxacin) are commonly used against active TB, although they need to be combined with at least 2 other anti-TB agents to be effective.²⁵

Hepatotoxicity is a complication during treatment as a result of direct hepatic cell injury by isoniazid and rifampicin. Thus hepatic function should be closely monitored; the drugs should be withdrawn in severe conditions. Drug interaction: Rifampin interacts with Cs A and tacrolimus and reportedly reduces tacrolimus levels, thereby increasing the risk for rejection.²⁶

Role of INH Prophylaxis

Indications of isoniazid prophylaxis as reported by Singh, et al:²⁷

- Tuberculin skin test > 5 mm before transplantation
- Regardless of tuberculin skin test, radiographic evidence of old active tuberculosis and no prior prophylaxis, history of inadequately treated tuberculosis, close contact with an infected patients, or receipt of an allograft from a donor with a history of untreated tuberculosis of tuberculin reactivity without adequate prophylaxis.
- Newly infected persons (recent conversion of tuberculin skin test to positive)

Nagai et al reported that post-transplant management without isoniazid prophylaxis for liver transplant recipients with a history of tuberculosis can be acceptable, when old tuberculosis is considered to be inactive. However, because of its small number of patients and short follow-up period in this study, they did not clarify the safety of post-transplant management without isoniazid prophylaxis.²⁸

LEGIONELLA PNEUMOPHILA INFECTION

Legionella is one of the opportunistic infection is solid organ transplants. 10-40% of bacterial pneumonias are by legionella species. Serotype 1 causes majority of human infections. Present with pneumonia with lung cavitation and watery diarrhea. Diagnosis is by culture of the organism and legionella urine antigen test.

NOCARDIA

Nocardia is an opportunistic bacterial pathogen and is clinically manifested as pulmonary and CNS disease. Diagnosis is by culture of the organism. Treatment includes surgical drainage followed by long duration of sulfonamides (Usually 6-12 months).

LISTERIA MONOCYTOGENES

Listeria manifests as bacteremia and meningitis. Early diagnosis and treatment with high dose ampicillin is recommended. It is transmitted through contaminated milk, uncooked food and meat.

VIRAL INFECTIONS

Viral infections are common after liver transplantation due to immunosuppression. Common viral infections are HBV and HCV reactivation, CMV, EBV and others. After establishing latent infection, herpes viruses (Herpes simplex, Varicella, CMV, etc.) can reactivate due to immunosuppression.

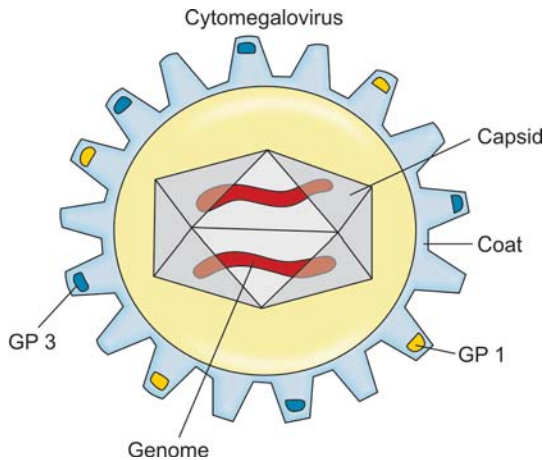


Figure 26.40: Structure of cytomegalovirus (GP 1-glycoprotein 1; GP 2-glycoprotein 2)

CYTOMEGALOVIRUS INFECTION (CMV)

CMV is the most important in solid organ transplants because it can cause both direct and indirect clinical effects, and disease prevention remains a challenge. It belongs to herpes virus family. Time of onset of infection: 3-8 weeks. Most of CMV infection occurs in the first 6 months. CMV is one of the common viral infections in solid organ transplants. If untreated, CMV infection is associated with 4 fold increase in mortality.²⁹ Without prophylaxis, the incidence of CMV infection is around 64% use of CMV prophylaxis has shifted the onset of disease so that it occurs at a later period after transplantation, called delayed onset of CMV.³⁰ Symptomatic CMV disease is seen in 29% of liver transplant recipients. CMV disease was an independent predictor of patient and allograft survival. Directly or indirectly affects graft and patient survival.³¹⁻³³

CMV infection is one of the most common viral infections in post-transplant period. The risk for CMV infection depends largely on the presence or absence of latent CMV in the donor and recipient. Individuals who are latently infected with CMV have detectable CMV IgG antibodies and are defined as being seropositive for CMV. Seropositive recipients (R+ve) are at risk for CMV regardless of the donor serostatus (D+ve/D-ve).

Source of CMV Infection in Recipient

- Donor allograft
- Blood products from a sero positive donor
- Reactivation of endogenous virus

Types of Infection

- Latent infection

- Opportunistic infection in immunocompromised patients
 - Solid organ transplant recipients
 - AIDS

Pathogenesis

- Tumor necrosis factor- α plays a vital role in latency or reactivation of CMV infection.
- Factors like infection, rejection and treatment of rejection with ALG or ATG and OKT3 will stimulate the release of TNF- α , thus reactivating the virus.
- Immunomodulating properties of CMV has been associated with recurrence and increased risk of allograft failure and mortality in chronic hepatitis C recipients.³⁴

The following diagnostic distinctions should be made in the assessment of a patient who has CMV infection or disease.

CMV infection: CMV has been identified by detecting viral proteins (eg, pp65 antigenemia) or nucleic acid (e.g. DNA PCR) in any body fluid or tissue specimen.

CMV disease/CMV syndrome: Patients who have clinical signs or symptoms (fever, Neutrogena and/or thrombocytopenia) but no evidence of end-organ disease can be defined as having "symptomatic CMV infection".

Asymptomatic CMV infection: Patients who do not have clinical signs or symptoms of CMV infection.

Tissue-invasive CMV disease: The patients who have evidence of end organ disease due to CMV. (Based on organ-specific symptoms and histologic evidence of invasive CMV). It invades GI tract, liver, lungs and central nervous system.

CMV disease is an immunomodulatory virus and indirectly it acts as an independent risk factor for³⁷

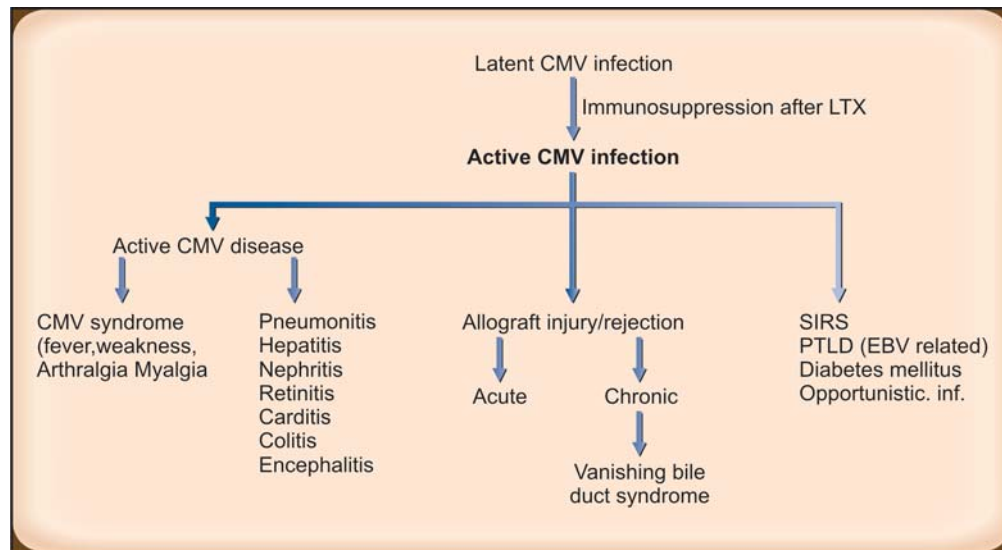
- Bacteremia
- Invasive fungal infections
- EBV-related PTLD
- Acute and chronic allograft injury

CLINICAL COURSE OF CMV INFECTION

See Figure 26.41.

Indications for CMV treatment in LTX

- Donor +ve/Recipient -ve: Universal prophylaxis
- Recipient+ve/(D+/R+, D-/R+) irrespective of donor status: Universal prophylaxis or pre-emptive therapy
- Donor and recipient both -ve (D-/R-): Pre-emptive treatment (Risk of transfusion acquired CMV)



(PTLD: Post-transplant lymphoproliferative disease, SIRS: Systemic inflammatory response syndrome)

Figure 26.41: Schematic presentation of CMV infection^{35,36}

High risk patients for CMV infection

- Donor +ve/Recipient -ve
- Induction or anti rejection therapy with ATG or ALG or OKT3

Transplant recipients who are at risk of CMV infections

- Classical Donor +/Recipient -ve (D+/R-)
- Heavy immunosuppression (Anti-Lymphocyte antibody therapy)
- Use of high doses of corticosteroids
- Recipients with acute rejection
- Lack of CMV specific immunity
- Prolonged antiviral treatment
- Suboptimal antiviral treatment
- High viral multiplication

Diagnosis

Most infections are asymptomatic. Patients infected with CMV develop antibodies to the virus, and these antibodies persist in the body for the lifetime of that individual.

Diagnosis of CMV infection

- Culture of organism: Classic tissue histological finding in CMV disease is the inclusion cells on viral culture.
- ELISA is used for measuring antibodies (IgG and IgM) to CMV.

- Rapid shell viral antigen detection
- Detection of PP65 antigen
- CMV DNA hybrid capture test
- CMV DNA by PCR

Prophylaxis and Treatment of CMV Infection and Disease in Recipient

Drugs

- Ganciclovir
- Valganciclovir
- Foscarnet or Cidofovir
- CMV IG

CMV Prophylaxis

Universal CMV prophylaxis for 3 months to all CMV D+/R-liver transplant recipients.

CMV prophylaxis

On the day of liver transplantation

- IV Ganciclovir, 5 mg/kg twice daily (adjusted on the basis of renal function)

When the patient can tolerate oral medications

- Oral Ganciclovir, 1 gm 3 times/day or oral Valganciclovir, 900 mg QD.
- Continued through 90-100 days after transplant
- Dose is adjusted on the basis of creatinine clearance

Some centers use CMV prophylaxis during episodes of acute rejection during the first year after transplantation during the course of treatment with IV methylprednisolone, Muromonab-CD3 (OKT3), or antithymocyte globulin (rabbit) and for 4 weeks after antirejection therapy.

Pre-emptive Treatment

Antiviral therapy is not administered to all patients following LTX. Instead, weekly surveillance for CMV is performed using markers such as pp65 antigenemia and quantitative polymerase chain reaction (PCR) assays. Antiviral therapy is initiated only when CMV is detected and subsequently discontinued when the assay is negative. It usually takes 2-4 weeks for the disappearance of antigenemia.¹²³ Pre-emptive strategies using pp65 antigenemia or quantitative PCR to direct therapy with intravenous and oral ganciclovir as well as oral valganciclovir in the same doses as mentioned above, have proved effective at limiting both early- and late-onset CMV disease and in reducing the number of patients exposed to antiviral therapy.³⁸⁻⁴¹ A meta-analysis of prospective, randomized trials that was not limited to LT recipients but included all SOT recipients demonstrated that the overall reduction in the risk of CMV disease was approximately 80% with both universal prophylaxis and pre-emptive strategies.⁴⁴ Only universal prophylaxis, however, reduced CMV disease in patients who received antilymphocyte antibody induction therapy or who were D+ve/R-ve. Furthermore, reduction in overall bacterial and fungal infections and mortality was demonstrated only with universal prophylaxis. On the other hand, pre-emptive strategies potentially can minimize the burden of late-onset CMV disease, antiviral drug exposure, ganciclovir resistance, and cost.^{42,43}

Late-onset CMV Disease

Incidence of CMV disease has diminished during the 3 months immediately following LTX.⁴⁴ But late-onset CMV disease has emerged as a major challenge, particularly in patients receiving universal antiviral prophylaxis,^{45,46} and may be associated independently with mortality. Late-onset CMV disease nearly always occurs within 12 months of transplantation; risk factors include D+ve/R-ve status and rejection.^{46,47} CMV seronegativity at 6 months also has been shown to be a predictor of late-onset CMV disease.⁴⁸ Strategies need to be developed to prevent late-onset CMV in patients at risk. Routine surveillance using quantitative PCR in D+ve/R-ve patients unfortunately was able to predict disease in only approximately one third of the patients who developed late-onset CMV disease.⁴⁹ PCR testing in this study was

less frequent between months 4 and 12, however, and it is possible that more rigorous testing might have identified patients who had viremia before the onset of CMV disease. Late-onset CMV disease may be less frequent with pre-emptive strategies.⁴¹ One proposed mechanism for this phenomenon is that antiviral prophylaxis delays the recovery of CMV-specific T-cell responses, whereas low-level CMV exposures before antiviral therapy may lead to appropriate viral-specific immune responses.⁴² Future studies that compare the prophylaxis and pre-emptive strategies should focus on a primary end point of late-onset CMV disease.¹²³

Treatment of CMV Disease

Molecular diagnostic tests may be used to guide the duration of therapy, because the risk for relapse has been shown to be lower in patients who have no detectable CMV DNA.⁵⁰ In transplant patients, valganciclovir has been shown to be safe and effective for pre-emptive therapy.⁴¹ Valganciclovir usually is discontinued when the CMV DNA is undetectable and all clinical signs and symptoms have resolved. In patients who have tissue-invasive CMV disease, a more aggressive approach may be required, and intravenous ganciclovir is continued until all signs and symptoms of disease have resolved. Oral valganciclovir is given until CMV is no longer detected on PCR. The decision to continue with a lower maintenance dose of valganciclovir or to initiate CMV PCR surveillance following treatment of disease needs to be individualized based on ongoing risks.¹²³

Ganciclovir:

- Intravenous: 5mg /kg twice daily for 2-4 weeks.³⁷
- Confirm clearance of viremia prior to stopping the treatment
- Oral: 1gm thrice daily can be given for 2-3 months
- Side effects: Leucopenia, treated with G-CSF (granulocyte colony stimulating factor)

Valganciclovir:

- It is oral valine ester of ganciclovir
- Oral dose had better bioavailability than oral ganciclovir
- Oral dose: 900 mg twice daily
- Dose adjustment of valganciclovir in patients of renal impairment.

Creatinine clearance	Induction dose	Maintenance dose
• > 60	900 mg BID	900 mg QD
• 40-59	450 mg BID	450 mg QD
• 25-39	450 mg QD	450 mg every 2 days
• 10-24	450 mg every 2 days	450 mg twice weekly

CMV IG: It is an anti CMV hyperimmune globulin.

Indications:

- Prophylaxis against CMV infection specially after induction therapy
- Suspected or confirmed gancyclovir resistant cases
- Patients of renal impairment who can't tolerate other virostatic drugs
- Patients with hypogammaglobulinemia
 - Moderate (Ig G-350-500 mg/ dl)
 - Severe (Ig G-<300 mg/dl)

Dose of CMV IG

- 150 mg/kg within 72 hours
- 100 mg/kg at week 2 and 4
- 50 mg/kg at week 6, 8, 12 and 16

Munich protocol¹⁴

- 3 doses of CMV IG -100 mg/kg on day 0, 7 and 14.
- Followed by preemptive therapy using IV Gancyclovir.
- If there is evidence of CMV disease
 - CMV IG is added to the standard treatment
 - Dose of 100-200 mg/kg/day for 5 days

Advantages: Absence of nephrotoxicity and neutropenia as compared to standard virostatic drugs.

EPSTEIN-BARR VIRUS (EBV)

It belongs to herpes virus family. Source of infection is from the infected donor or community acquired. Post-transplant lymphoproliferative disease (PTLD) occurs upto 2.7% of the infected individuals which is due to uncontrolled proliferation of EBV infected B-lymphocytes. T-cell derived PTLD also occurs in 2% of the recipients.

PTLD

Reactivation of EBV can result in PTLD. Use of increasingly potent immunosuppressives has been associated with an increased rate of EBV associated PTLD, especially in pediatric patients.^{51,52} During the early 1980s when cyclosporine was the primary immunosuppressant, the incidence of PTLD in pediatric patients was approximately 4%.⁵³ With the introduction of tacrolimus the incidence of PTLD has increased to 6 to 13%.^{51,52} In patients with resistant rejection requiring conversion from cyclosporine to tacrolimus, incidence of PTLD is as high as 27%.⁵² Calcineurin inhibitors act via suppression of cytotoxic T-cells resulting in inhibition of host's immune surveillance against EBV. The role of EBV in PTLD is well established.⁵⁴ The risk of developing PTLD is much greater in a primary EBV infection. Mortality rate is 69-81%.

Classification of PTLD based on clinical types⁷²

- Mononucleosis-type syndrome
- Lymphoproliferation
- Malignant lymphoma

Histology ranges from well-localized polyclonal lymphocyte proliferation to malignant lymphoma.

Risk factors for PTLD⁵⁵

- Primary EBV infection after OLT
- Young age
- EBV: D +ve and R -ve
- Induction therapy

Presentation^{51,52}

PTLD is usually found in allograft, GI tract and abdominal and peripheral lymph nodes.

- Fever of unknown origin
- Lymphadenopathy
- Unexplained graft dysfunction
- Gastrointestinal bleeding or perforation
- Upper airway obstruction

Treatment of PTLD

- Monitor EBV viral load through EBV-PCR.
- Decrease dose of immunosuppression when there is evidence of increased viral load (200 genome copies/ 10⁵ peripheral blood lymphocytes) before symptoms of PTLD.
- Antiviral therapy is started in patients who fail to respond to decreased immunosuppression.
- Antiviral treatment along with withdrawal of immunosuppression may be insufficient and courses of Rituximab and cyclophosphamide may be added, if necessary.⁵⁵
- Prophylaxis against EBV infection in high risk pediatric recipients.
- Ganciclovir for 2 weeks postoperatively followed by oral Valganciclovir for 90 days.
- Prophylaxis is used in all patients or only in high risk patients, defined as seronegative recipients for EBV receiving grafts from a seropositive donor depending on the center protocol.
- Treatment of PTLD by reduction of immunosuppression led to a high incidence of chronic rejection in patients who survived PTLD. Judicial reintroduction of immunosuppression is necessary in patients who are cleared from PTLD and started to show symptoms of rejection.

- Patients who present with malignant lymphoma need conventional lymphoma chemotherapy^{51,52}
- Decrease in the morbidity and mortality in PTLD is achieved by aggressive prophylactic and therapeutic treatment of EBV.^{51,52}

HIV POSITIVE RECIPIENT

Recent reports have achieved successful LTX in HIV infected individuals. In the modern era of highly active antiretroviral therapy (HAART), the survival of HIV infected patients has improved dramatically.⁵⁷ As a result, patients are now experiencing significant morbidity and mortality related to ESLD, and LTX is being offered at some transplantation centers, including 20 centers involved in an ongoing trial by the National Institutes of Health.

In the USA and Europe, 15-30% of people with HIV are co-infected with HCV. Among these patients, approximately 80% are intravenous drug users (IVDU) and around 20% are homosexual/bisexual men.⁵⁸ A major concern of LT in HIV-infected individuals is that the immunosuppressive therapies associated with transplantation may compromise further an already immunocompromized host. According to UNOS database, the overall transplantation outcomes in HIV-infected patients, however, were similar those in HIV-negative recipients.⁵⁹ The impact on survival of a post-LT CD₄ cell count < 200 or detectable HIV RNA is unclear,^{59,60} but virologic suppression is generally not an issue after LT. Types of opportunistic infections seen in these patients were typical for the post-LT recipient and probably were not related to the underlying HIV.⁶⁰

Drug Interaction

In all cases, calcineurin inhibitor doses need to be decreased dramatically in the presence of protease inhibitors to avoid potentially toxic levels and drug levels should be closely monitored to avoid subtherapeutic levels that may increase the risk for rejection. Though successful control of HIV after LTX is satisfactory, an emerging concern is the impact of HCV recurrence in patients coinfecting with HIV and HCV. Patients coinfecting with HIV and HCV and undergoing LTX have shorter survival and increased rates of cirrhosis and death from HCV-related complications than do HCV-monoinfected LTX recipients.⁶⁰ Mortality was high (5/7 patients) in the series at King's College⁶¹ and in Essen (3/5 patients).⁶²

Risk factors for poor survival in co-infection of HIV and HCV

- African American race
- MELD score > 20
- Intolerance to HAART after LTX
- HCV RNA above 30 million IU/ml after LTX⁶⁰

Coinfection with HCV or HBV

Coinfection with HCV or HBV is common in HIV infected persons, particularly in patients with hemophilia and injection drug use. 30% of HIV-infected persons are coinfecting with HCV; that estimate rises to 50 to 80% of HIV-positive intravenous drug users.⁶³ LTX in HIV positive patients was the only chance for survival from chronic hepatitis and HCC. The survival of HIV/HCV positive patients in ESLD is shorter than that of other HCV-positive patients experiencing ESLD. The HIV-positive cohort of patients was younger than the HIV-negative ESLD patients. The outcome of these recipients was extremely dependent on the status of the patient at the time of transplantation. In persons infected with HIV, the combination of Peg. Interferon and Ribavirin is superior to the combination of interferon and Ribavirin in the treatment of chronic hepatitis C.⁶⁴

LTX in HIV infected recipients with ESLD⁶⁵ Inclusion criteria

- Long-term nonprogression patients with CD₄₊ >200 (350) cells/mm³
- Patients on HAART and CD₄₊ >200 (350) cells/mm³ for 6 months and HIV-RNA undetectable
- Patients with advanced liver disease not tolerating HAART, but CD₄₊ >100 (200) cells/mm³

Exclusion criteria

- AIDS-defining events
- Kaposi's sarcoma with visceral localization, sarcoma, or history of neoplasia
- Fulminant hepatic failure
- CD₄ count <100 cells/mm³
- Detectable HIV-RNA on HAART.
- Antiretroviral intolerance is not an absolute contraindication to OLT (Associated with 100% mortality)

Higher Risk of Post-transplant Complications⁶⁶

- Infections
- HCV recurrence

- Rejection
- High incidence of vascular complications

In Miami and Pittsburgh studies there was a 38% rejection rate. They administered steroids for 12 weeks after OLT and started HAART, 2 weeks after OLT. The HAART must be restarted when hepatic function begins to normalize and when the immunosuppression is stable.⁶⁸ Moreno et al. reported that moderate decrease in CD₄ T-cell count during the first month post-OLT.⁶⁷ Normal liver function tests, total bilirubin < 2 mg/dL is necessary for initiation of HAART in post-transplant period.

HAART Regimen

A nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor (PI) or an NRTI plus a non NRTI (nevirapine was avoided due to severe potential hepatotoxicity posttransplant). CD₄ counts and HIV viral titers are measured every 4-8 weeks.

Immunosuppression

CINs, steroids can be used safely and avoid induction therapy. MMF or Sirolimus were utilized for patients with renal insufficiency or as additional immunosuppression for those who had acute cellular rejection.

The largest reported study of OLT in HIV-infected patients showed good results at 12 and 36 months with survival rates of 87.1 and 72.8%, respectively.^{69,70} Hence HIV infection should no longer be an absolute contraindication to transplantation. The outcome of liver transplantation in HIV patients was influenced by infections (HCV, CMV, and EBV) and Kaposi's Sarcoma.¹²⁴

HERPES SIMPLEX VIRUS

This group of viruses is largely controlled by strategies to prevent CMV. Human herpes virus 6 and 7 are emerging pathogens that may interact with CMV.⁷¹ Finally, human herpes virus 8 may be associated with the development of Kaposi sarcoma in transplant recipients. Prime target of these viruses are CD₄ lymphocytes. Usually they manifest between 2-4 weeks after transplantation. Pulmonary and meningeal infections are common. Diagnosis is by cell culture, antigen assay and PCR test. Treatment is by acyclovir, gancyclovir and foscarnet.

VARICELLA ZOSTER VIRUS

Manifests after 3 months as cutaneous lesions in 3-7% of patients after LTX. Induction therapy precipitates infection. Treated with acyclovir or gancyclovir.

OTHER VIRUSES

Respiratory syncytial viruses, adeno virus, influenza A and B virus may cause severe infections in immunocompromised patients unlike normal individuals and infection persists for long time. Supportive treatment is important in such infections. Amantidine and rimantidine have been used for influenza A. But now a day's zanamavir and oseltamivir are recommended for influenza A and B viruses. Ribavirin is used for treatment in RSV induced respiratory disease. No specific drug recommended for adenovirus.

FUNGAL INFECTIONS

The incidence of invasive fungal infections has been reported in 5 to 42% of liver transplant recipients with an associated mortality of 11 to 81%, mostly greater than 50%.⁷² Currently, most infections of invasive aspergillosis occur later in the liver post-transplant period, as compared with those in the early 1990s.^{73,74} Prevention and treatment of fungal infections in LTX recipients is a major challenge and account for significant morbidity and mortality. Invasive candida and aspergillus infections remain the predominant fungal infections in the early post-transplant period followed by cryptococcus infections and reactivation of endemic mycoses such as histoplasmosis and coccidiomycosis. Pneumocystis carinii pneumonia is prevented effectively with universal cotrimoxazole prophylaxis.¹²³

CANDIDA INFECTION

Risk factors for invasive candidiasis^{75,76}

- Renal failure and post-transplant dialysis
- Fulminant hepatic failure
- Retransplantation
- Prolonged surgery
- Greater intraoperative transfusion
- Antibiotic prophylaxis for spontaneous bacterial peritonitis
- Post-transplantation dialysis

Source of Infection

Catheter related or an intra-abdominal infection (abscess and/or peritonitis).

Diagnosis

Fungal culture showing yeast from sterile specimens such as blood or peritoneal fluid.

Treatment

Precipitating cause should be treated first such as removal of intravascular catheters and drainage of intra-abdominal

abscesses should be drained and infected wounds should be debrided. Patients with candidemia are examined to rule out endophthalmitis.

Antifungal agents:

- Fluconazole is the antifungal agent of choice for treating most cases of invasive candidiasis. *Candida glabrata* is increasing in incidence and is mostly resistant to fluconazole.¹²³
- Other antifungal drugs like amphotericin B, voriconazole and echinocandins such as caspofungin, micafungin and anidulafungin may be preferred in resistant cases. echinocandins are most preferred antifungal in resistant cases keeping in view of the safety and efficacy compared to amphotericin B and azoles.⁷⁸
- Fluconazole is used in *calbicans*, *candida tropicalis*, and *candida parapsilosis*.⁷⁷ *candida glabrata* infections should be treated echinocandins, if it is resistant to fluconazole.

Dose of antifungal agents

- Fluconazole 400 mg/day IV
- Amphotericin B: 30-50 mg/day IV
- Voriconazole: 6 mg/kg IV 12 hrly, followed by 4 mg/kg IV thereafter.
- Caspofungin sodium: 70 mg IV on day 1, followed by 50 mg/day IV thereafter
- Mycofungin: 100-150 mg/day IV

Duration of treatment: At least 2 weeks after blood cultures have been sterilized and all signs and symptoms of infection have resolved.

Role of antifungal prophylaxis: Prophylactic fluconazole prevented invasive candidiasis only in high-risk LT recipients but did not affect overall survival.⁷⁹ A recent meta-analysis suggests that antifungal prophylaxis effectively prevents *C albicans* infections and decreases mortality attributable to *C albicans*.⁸⁰

ASPERGILLUS INFECTION

Incidence of invasive aspergillosis is <10% in LTX recipients⁸¹ but remains the most dreaded fungal infection following transplantation and still is associated with a high mortality rate of 60%.⁸²

Risk factors for aspergillus infection^{83,84}

- CMV infection
- Post-transplantation renal failure
- Patients on dialysis
- Poor graft function
- Retransplantation

Earlier reports suggest that invasive aspergillosis occur in the first 2 to 4 weeks of LTX.⁸⁵ But in recent years almost half of all cases occur after 6 months, with approximately one third occurring after 1 year⁸⁶ and mostly restricted to lungs⁸⁵ In contrary to earlier reports of 50% of lung invasion⁸⁵ Risk factors for this late onset is use of sirolimus in combination with tacrolimus.⁸⁶

Diagnosis⁸⁷

- Clinical findings
- Radiological evidence in the chest X-ray
- Microbiologic confirmation of aspergillus species from respiratory sample (positive predictive value of 41 to 72%)
- Histologic evidence
- Serum aspergillus galactomannan assay (specificity-98.5%) which detects a cell wall component of aspergillus.⁸⁸

Treatment

Delayed in diagnosis and treatment leads to significant mortality.

- Voriconazole is the drug of choice. In a randomized study, voriconazole was found to be superior to conventional amphotericin B.⁸⁹
- Combination of voriconazole and caspofungin is associated with reduced mortality in patients who have renal failure or aspergillus fumigatus infection.⁹⁰
- Duration of treatment: antifungal therapy should be continued until all clinical and radiographic evidence of disease has resolved. Despite improvements in antifungal therapy, overall outcomes remain poor even with voriconazole⁸⁹
- Drug interaction: voriconazole should be used with care in recipients on calcineurin inhibitors. cyclosporine A and tacrolimus dosing should be reduced by 50% and 66% respectively.¹²³
- Antifungal prophylaxis to prevent invasive aspergillosis is a controversial issue. But a recent meta-analysis of antifungal prophylaxis in LTX recipients demonstrated no beneficial effect on invasive aspergillosis.⁸⁰ Prophylaxis with liposomal amphotericin B may be effective in preventing invasive aspergillosis in high risk patients.^{91,92}

CRYPTOCOCCUS

Cryptococcus is the third most common invasive fungal infection in organ transplant recipients after candidiasis and aspergillosis. Most cases occur more than 6 months after transplantation.⁹³ *Cryptococcus neoformans* is a significant opportunistic infection in solid organ transplant recipients, with a reported incidence of 1 to

5% and mortality rate of 20 to 40%.^{93,94} Route of infection is by inhalation of aerosolized particles from the environment.

Presentation

Pulmonary cryptococcosis: Nodular pulmonary infiltrates ranging in size from small nodules to mass-like lesions.

Meningitis: CINs and sirolimus are effective against cryptococcus. A lower incidence of CNS than extraneural manifestations of cryptococcosis in patients receiving tacrolimus may also be due to higher relative cerebrospinal fluid levels of tacrolimus compared with cyclosporine.

Liver failure is a risk factor for poor prognosis.⁹⁵

Diagnosis

- Recovery of organism for clinical samples
- Positive serum cryptococcal antigen test (serum/CSF) may be predictive of meningitis and dissemination, but cannot be used reliably in the diagnosis of pulmonary cryptococcosis.⁹⁴
- Immunoblot assay

Cryptococcus neoformans, in immunocompetent individuals causes a subclinical pulmonary infection which can evolve to a quiescent latent state with the potential for later reactivation in the context of acquired immunosuppression. Symptomatic disease may result from a primary progressive process.

Treatment

Amphotericin B and flucytosine in the first 2 weeks followed by fluconazole next 10 weeks or till all clinical signs and symptoms of the disease have resolved and serum cryptococcal antigen has become negative. Lipid preparations of amphotericin B can also be used.

PNEUMOCYSTIS CARINII / JIROVECI

Pneumocystis is an opportunistic infection associated with increased morbidity and mortality in solid-organ transplant recipients. Earlier it was considered as protozoa. But now it is reclassified as fungus. It causes pneumonia in 3-7% of the recipients, in between 2nd to 6th month after transplantation. Clinically presents as fever, cough, breathlessness and hypoxia. Before instituting PCP prophylaxis, the incidence in this population was reported to be up to 10%.

Diagnosis

Diagnosis is by methenamine silver stain and/or by immunofluorescence test from cellular smears of BAL specimens.

Prophylaxis

Cotrimoxazole (Trimethoprim+sulfamethoxazole - 80/400 mg) 3 times a week is almost 100% effective in preventing PCP in immunosuppressed patients, but its use is limited by the high incidence of adverse reactions (in upto 50% of patients), in particular, bone-marrow suppression and skin manifestations, both major concerns in transplant patients. Inhaled pentamidine every 2 to 4 weeks can also be used. Atovaquone is an alternative for PCP prophylaxis at a dose of 1,500 mg once daily, with a trend for lower efficacy at a dose of 750 mg once daily.

Treatment

High dose of cotrimoxazole. Steroids may be added to fasten the recovery if there is evidence of infection.

Other fungal infections are endemic mycoses and dermatiaceous fungi.

PROTOZOA

TOXOPLASMA GONDII

Toxoplasma is a rare but potentially life-threatening infection in solid organ transplant recipients. They are at risk for developing severe toxoplasmosis by reactivation of a chronic infection or from transmission of toxoplasma cysts with the transplanted organ.⁹⁶ Life-threatening toxoplasmosis with pulmonary and cerebral manifestations has been previously reported⁹⁷ suggesting that despite the low risk, it must always be considered in seropositive patients, especially when the donor is seropositive. The diagnosis of toxoplasmosis high index of suspicion because the clinical manifestations and laboratory findings may not be specific. There is no single serologic test that is accurate enough to be recommended for diagnostic use.⁹⁸⁻¹⁰⁰

Diagnosis is based on

- Direct demonstration of the parasite in tissues or biological fluids
- Detection of Toxoplasma DNA by PCR.
- ELISA for antitoxoplasma antibody (IgG/ Ig M) to T gondii.^{101,102}

Treatment: High dose of cotrimoxazole.

PARASITES

Strongyloides stercoralis, trypanosoma cruzi and giardia lamblia infections can occur in solid organ transplants.

STRONGYLOIDES STERCORALIS

The incidence and prevalence of parasitic infections in transplant recipients is unknown; only a few patients are

symptomatic.¹⁰⁴ Only 5% of known human pathogenic parasitic infections have been reported in transplant recipients. Since the use of CINs has become a cornerstone in prophylactic immunosuppression, this syndrome has become exceedingly rare, owing to the strong parasitocidal effect of the group of drugs against a wide range of organisms, as documented in mice and humans.¹⁰³ Most infections were caused by *strongyloides stercoralis*. The main symptoms are gastrointestinal. This is a helminthic parasite endemic to tropical and subtropical areas. The cycle of autoinfection can perpetuate in healthy hosts, causing chronic or subclinical infections that may persist for decades without an adverse event.^{108,109} Disseminated strongyloidiasis is asymptomatic in the majority of individuals. Examination of a stool sample should be mandatory for all patients on long-term immunosuppressive therapy to prevent the disease's morbidity and mortality.¹⁰⁵⁻¹⁰⁷ Paula, et al. showed the value of an indirect immunofluorescence antibody test and enzyme-linked immunosorbent assay to detect IgG and IgM antibodies to diagnose human strongyloidiasis among immunocompromised hosts.¹¹⁰ Treatment is by albendazole or thiabendazole,

VACCINATION

It should be carried out early in the course of liver disease as the development of immune responses is decreased in ESLD or due to immunosuppression after transplantation. These vaccines include:

- Inactivated vaccines are given either before/after transplantation¹¹⁰
 - Tetanus vaccine
 - Hepatitis A vaccine
 - Hepatitis B
 - Influenza vaccine (annually)
 - Pneumococcal vaccine
 - Meningitis vaccine
- Live attenuated vaccine like varicella vaccine are given to non-immune patients prior to transplantation. They are contraindicated in immunosuppressed recipients.¹¹⁰

If the patient is not vaccinated, administration of all vaccines should be delayed until at least 6 months after transplantation when the patient is receiving immunosuppression.

HELICOBACTER PYLORI AND LTX

Helicobacter pylori (*H.pylori*) infection is associated with post-transplantation MALTomas.¹¹¹ Their distinction

from other forms of EBV negative post-transplantation lymphomas¹¹² is important, since indolent behavior is more common in MALTomas, and eradication of *H. pylori* can lead to tumor regression in some post-transplant patients.¹¹³

These lymphomas need not be a contraindication to transplant, even if present around the time of transplantation. MALTomas (more properly known as marginal zone lymphomas) are a form of B-cell non-Hodgkin's lymphoma that arises most commonly in the stomach in association with *H. pylori* infection. The stomach does not normally possess a significant component of mucosa-associated lymphoid tissue but can acquire it as a result of colonization with this bacterium.¹¹⁴ This fact originally led to the suggestion that the infection might predispose to MALToma at this site¹¹⁴ and also inspired the first successful efforts to treat gastric MALToma by antibiotic eradication of *H. pylori*.¹¹⁵ This therapy is best applied to histologically low-grade MALTomas that are restricted to the gastric mucosa and submucosa.

Foxton et al.¹¹⁶ reported a middle-aged man with HCV-associated cirrhosis, while waiting for a transplant the patient was found to have low-grade gastric MALToma and concurrent *H. pylori* infection. The tumor was unresponsive to anti-*Helicobacter* and chlorambucil therapy. Rituximab was also given, with no apparent response by scan. Liver transplantation was performed, followed 5 months later by subtotal gastrectomy. No residual tumor was seen. Interestingly, several inflammatory polyps in the gastric specimen were found to harbor HCV RNA. This patient remained tumor free 23 months after transplantation.

Studies to date estimate a 60 to 80% remission rate of such lymphomas with anti-*Helicobacter* therapy alone.^{117,118} However, recent data suggest that minimally detectable clones may persist in more than 50% of such responders, indicating a need for long-term follow-up.¹¹⁹ *H. Pylori* is not thought to be directly oncogenic for lymphocytes.¹²⁰ Rather, early lesions may remain dependent upon T-cell help for growth.¹²¹ With progression, tumor cells lose this dependence and become unresponsive to elimination of the bacterium. The translocation t (11;18) (q21;q21) in neoplastic cells corresponds to this form of tumor escape.¹²²

REFERENCES

1. Snyderman DR. Infection in solid organ transplantation. *Transpl Infect Dis* 1999;1(1):21-8.
2. Singh N. Infectious diseases in the liver transplant recipient. *Semin Gastrointest Dis* 1998;9:136-46.
3. Safdar N, Said A, Lucey MR, et al. Infected bilomas in liver transplant recipients: clinical features, optimal management,

- and risk factors for mortality. *Clin Infect Dis* 2004;39(4):517-25.
4. Said A, Safdar N, Lucey MR, et al. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. *Am J Transplant* 2004;4(4):574-82.
 5. Pungpapong S, Alvarez S, Hellinger WC, et al. Peritonitis after liver transplantation: Incidence, risk factors, microbiology profiles, and outcome. *Liver Transpl* 2006;12(8):1244-52.
 6. Singh N, Muder RR, Yu VL, et al. Legionella infection in liver transplant recipients: Implications for management. *Transplantation* 1993;56:1549-51.
 7. Singh N, Gayowski T, Wagener M, et al. Pulmonary infections in liver transplant recipients receiving tacrolimus. Changing pattern of microbial etiologies. *Transplantation* 1996;61:396-401.
 8. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid organ transplant recipients: Impact and implications for management. *Clin Infect Dis* 1998;27:1266.
 9. Ghafari A, Makhdooni K, Ahmadpoor P, et al. Tuberculosis in Iranian kidney transplant recipients: A single-center experience. *Transplant Proc* 2007;39:1008.
 10. Benito N, Sued O, Moreno A, et al. Diagnosis and treatment of latent tuberculosis infection in liver transplant recipients in an endemic area. *Transplantation* 2002;74:1381.
 11. Verma A, Dhawan A, Wade JJ, et al. Mycobacterium tuberculosis infection in pediatric liver transplant recipients. *Pediatr Infect Dis J* 2000;19:625.
 12. Sabbatani S, Manfredi R, Marinacci G, et al. Reactivation of severe, acute pulmonary tuberculosis during treatment with pegylated interferon-alpha and ribavirin for chronic HCV hepatitis. *Scand J Infect Dis* 2006;38:205.
 13. B. Wang, Y. Lü, L. Yú, C. Liu, et al. Diagnosis and Treatment for Tuberculosis Infection in Liver Transplant Recipients: Case Reports. *Transplant Proceed* 2007;39:3509-11.
 14. A. Grasso, P. De Leo, F. Malfatti, et al. Late occurrence of pleural and peritoneal effusion due to mycobacterium tuberculosis Infection (TB) in a patient with posttransplantation recurrent HCV chronic hepatitis: Safety of peginterferon and ribavirin treatment after recovery of TB—A case report. *Transplant Proceed* 2008;40:1783-85.
 15. Nagesh BS, Sehgal S, Jindal SK, et al. Evaluation of polymerase chain reaction for detection of Mycobacterium tuberculosis in pleural fluid. *Chest* 2001;119:1737.
 16. Reechaipichitkul W, Lulitanond V, Sungkeeree S, et al. Rapid diagnosis of tuberculous pleural effusion using polymerase chain reaction. *Southeast Asian J Trop Med Public Health* 2000;31:509.
 17. Mazurek GH, Villarino ME: CDC guidelines for using the QuantiFERON®-TB test for diagnosing latent Mycobacterium tuberculosis infection. *MMWR Recomm Rep* 2003;52(RR02):15.
 18. Meier T, Eulenbruch HP, Wighton-Smith P, et al. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. *Eur J Clin Microbiol Infect Dis* 2005;24:529.
 19. Meyers BR, Papanicolaou GA, Sheiner P, et al. Tuberculosis in orthotopic liver transplant patients: Increased toxicity of recommended agents; cure of disseminated infection with nonconventional regimens. *Transplantation* 2000;69:64.
 20. Aguado JM, Herrero JA, Gavalda J, et al. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation* 1997;63:1278.
 21. Sakhuja V, Varma PP, Kathuria P, et al. Bone tuberculosis: An unusual case of mycobacterial infection in a renal allograft recipient. *Nephrol Dial Transplant* 1993;8:868.
 22. Riska H, Gronhagen-Riska C, Ahonen J. Tuberculosis in renal allograft transplantation. *Transplant Proc* 1987;19:4096.
 23. Munoz P, Rodriguez C, Bouza E: Mycobacterium tuberculosis infection in recipients of solid organ transplants. *Clin Infect Dis* 2005;40:581.
 24. Bryskier A, Lowter J. Fluoroquinolones and tuberculosis. *Expert Opin Invest Drugs* 2002;11:233.
 25. XF Zhang, Y Lv, WJ Xue, et al. Mycobacterium tuberculosis infection in solid organ transplant recipients: Experience from a single center in China. *Transplant Proceed* 2008;40:1382-85.
 26. Hebert MF, Fisher RM, Marsh CL, et al. Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. *J Clin Pharmacol* 1999;39:91.
 27. Singh N, Wagener MM, Gayowski T. Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis. *Transplantation* 2002;74:892.
 28. Shunji N, Yasuhiro F, Kaoru T, et al. Liver transplantation without isoniazid prophylaxis for recipients with a history of tuberculosis. *Clin Transplant* 2007;21:229-34.
 29. Falagas ME, Snyderman DR et al. Effect of CMV infection on 1 st year mortality rates among orthotopic liver transplant recipients: *Ann of int med* 1997;126(4):275-9.
 30. Limaye AP, Bhakthavasthalam R et al. Impact of CMV on organ transplant recipients in the era of antiviral prophylaxis 2006;81:1645-52.
 31. de Otero J, Gavalda J, Murio E, et al. Cytomegalovirus disease as a risk factor for graft loss and death after orthotopic liver transplantation. *Clin Infect Dis* 1998;26:865-70.
 32. Burak KW, Kremers WK, Batts KP, et al. Impact of cytomegalovirus infection, year of transplantation, and donor age on outcomes after liver transplantation for hepatitis C. *Liver Transpl* 2002;8:362-69.
 33. Rosen HR, Chou S, Corless CL, et al. Cytomegalovirus viremia: Risk factor for allograft cirrhosis after liver transplantation for hepatitis C. *Transplantation* 1997;64:721-26.
 34. Burak KW, Kramers WK et al. Impact of cytomegalovirus and donor age on outcomes of liver transplantation for hepatitis C: *Liver transplantation* 2002;8:362-68.
 35. Fisman JA, Rubin RH. *N Engl J Med* 1998;338:1741.
 36. Hjelmestaeth J et al. *Diabetologia* 2004;47:1550.
 37. Cytomegalovirus. *Am J Transplant* 2004;4(Suppl 10):51-8.
 38. Singh N, Yu VL, Miele L, et al. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. A randomized trial. *Ann Intern Med* 1994;120(5):375-81.
 39. Singh N, Paterson DL, Gayowski T, et al. Cytomegalovirus antigenemia directed preemptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: A randomized, controlled trial. *Transplantation* 2000;70(5):717-22.
 40. Daly JS, Kopasz A, Anandakrishnan R, et al. Preemptive strategy for ganciclovir administration against cytomegalovirus in liver transplantation recipients. *Am J Transplant* 2002;2(10):955-58.
 41. Singh N, Wannstedt C, Keyes L, et al. Efficacy of valganciclovir administered as preemptive therapy for cytomegalovirus disease in liver transplant recipients: Impact on viral load and

- late-onset cytomegalovirus disease. *Transplantation* 2005;79(1):85-90.
42. Singh N. Late-onset cytomegalovirus disease as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: A call to heed the mounting evidence. *Clin Infect Dis* 2005;40(5):704-08.
 43. Kusne S, Grossi P, Irish W, et al. Cytomegalovirus PP65 antigenemia monitoring as a guide for preemptive therapy: A cost effective strategy for prevention of cytomegalovirus disease in adult liver transplant recipients. *Transplantation* 1999;68(8):1125-31.
 44. Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med* 2005;143(12):870-80.
 45. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. *Lancet* 1997;350(9093):1729-33.
 46. Limaye AP, Bakthavatsalam R, Kim HW, et al. Late-onset cytomegalovirus disease in liver transplant recipients despite antiviral prophylaxis. *Transplantation* 2004;78(9):1390-96.
 47. Razonable RR, Rivero A, Rodriguez A, et al. Allograft rejection predicts the occurrence of late-onset cytomegalovirus (CMV) disease among CMV-mismatched solid organ transplant patients receiving prophylaxis with oral ganciclovir. *J Infect Dis* 2001;184(11):1461-64.
 48. Humar A, Mazzulli T, Moussa G, et al. Clinical utility of cytomegalovirus (CMV) serology testing in high-risk CMV Dp/R- transplant recipients. *Am J Transplant* 2005;5(5):1065-70.
 49. Humar A, Paya C, Pescovitz MD, et al. Clinical utility of cytomegalovirus viral load testing for predicting CMV disease in Dp/R- solid organ transplant recipients. *Am J Transplant* 2004;4(4):644-49.
 50. Humar A, Kumar D, Boivin G, et al. Cytomegalovirus (CMV) virus load kinetics to predict recurrent disease in solid-organ transplant patients with CMV disease. *J Infect Dis* 2002;186(6):829-33.
 51. Cacciarelli TV, Green M, Jaffe R, et al. Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. *Transplantation* 1998;66:1047.
 52. Newell KA, Alonso EM, Whittington PF, et al. Posttransplant lymphoproliferative disease in pediatric liver transplantation. Interplay between primary Epstein-Barr virus infection and immunosuppression. *Transplantation* 1996;62:370.
 53. Tocci MJ, Matkovich DA, Collier DA, et al. The immunosuppressant FK506 selectively inhibits expression of early T-cell activation genes. *J Immunol* 1989;143:718.
 54. Ho M, Jaffe R, Miller G, et al. The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. *Transplantation* 1998;45:719.
 55. J Roque, G Rios, R Humeres, et al. Early posttransplant lymphoproliferative disease in pediatric liver transplant recipients. *Transplant Proceed* 2006;38:930-31.
 56. McDiarmid SV, Jordan S, Lee GS, et al. Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998;66:1604.
 57. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. *N Engl J Med* 1998;338(13):853-60.
 58. V Barbanti Silva, M Ferrara, F Mazzi, et al. What is the biopsychosocial role of human immunodeficiency virus positivity in patients with end-stage liver disease who undergo orthotopic liver transplantation? *Transplant Proceed* 2008;40:1910-12.
 59. Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003;188(10):1412-20.
 60. de Vera ME, Dvorchik I, Tom K, et al. Survival of liver transplant patients coinfecting with HIV and HCV is adversely impacted by recurrent Hepatitis C. *Am J Transplant* 2006;6(12):2983-93.
 61. Norris S, Taylor C, Muiesan P, et al. Outcomes of liver transplantation in HIV-infected individuals: The impact of HCV and HBV infection. *Liver Transpl* 2004;10:1271-78.
 62. Radeke K, Fruhauf NR, Miller M, et al. Outcome after orthotopic liver transplantation in five HIV-infected patients with virus hepatitis-induced cirrhosis. *Liver Int* 2005;25:101-08.
 63. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infection: The Swiss HIV Cohort Study. *Lancet* 2000;356:1800-05.
 64. RT. Chung, J Andersen, P Volberding, et al. Peginterferon Alfa-2a plus Ribavirin versus Interferon Alfa-2a plus Ribavirin for Chronic Hepatitis C in HIV-Coinfected Persons. *N engl j med* 2004;5 (29):451-59.
 65. G. Vennarecci, G.M. Ettorre, M. Antonini, et al. Liver Transplantation in HIV-positive patients. *Transplantation Proceedings* 2007;39:1936-38.
 66. 107. Lijfering WM, Ten Kate MK, Sprenger HG, et al. Absolute risk of venous and arterial thrombosis in HIV-infected patients and effects of combination antiretroviral therapy. *J Thromb Haemost* 2006;4:1928.
 67. Moreno S, Fortun J, Quereda C, et al. Liver transplantation in HIV-infected recipients. *Liver Transpl* 2005 ;11:76.
 68. F. Di Benedetto, S. Di Sandro, N. De Ruvo, et al. Human Immunodeficiency Virus and Liver Transplantation: Our Point of View. *Transplant Proceed* 2008;40:1965-71.
 69. Fung J, Egtesad B, Patel-Tom K, et al. Liver transplantation in patients with HIV infection. *Liver Transpl* 2004;10(10 suppl 2):S39.
 70. Neff GW, Bonham A, Tzakis AG, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. *Liver Transpl* 2003;9:239.
 71. Kusne S, Blair JE. Viral and fungal infections after liver transplantation—part II. *Liver Transpl* 2006;12(1):2-11
 72. Singh N. Antifungal prophylaxis in solid-organ transplant recipients: considerations for clinical trial design. *Clin Infect Dis* 2004;39(Suppl 4):S200-S206.
 73. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. *Clin Infect Dis* 2003;36:46-52.
 74. Fortún J, Martín-Dávila P, Moreno S, et al. Risk factors for invasive aspergillosis in liver transplant recipients. *Liver Transpl* 2002;8:1065-70.

75. Patel R, Portela D, Badley AD, et al. Risk factors of invasive *Candida* and non-*Candida* fungal infections after liver transplantation. *Transplantation* 1996;62(7):926-34.
76. Husain S, Tollemar J, Dominguez EA, et al. Changes in the spectrum and risk factors for invasive candidiasis in liver transplant recipients: prospective, multicenter, case-controlled study. *Transplantation* 2003;75(12):2023-9.
77. Pfaller MA, Diekema DJ, Jones RN, et al. Trends in antifungal susceptibility of *Candida* spp. isolated from pediatric and adult patients with bloodstream infections: Antimicrobial Surveillance Program, 1997 to 2000. *J Clin Microbiol* 2002;40(3):852-6.
78. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002;347(25):2020-29.
79. Winston DJ, Pakrasi A, Busuttill RW. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999;131(10):729-37.
80. Cruciani M, Mengoli C, Malena M, et al. Antifungal prophylaxis in liver transplant patients: A systematic review and meta-analysis. *Liver Transpl* 2006;12(5):850-58.
81. Singh N, Paterson DL. Aspergillus infections in transplant recipients. *Clin Microbiol Rev* 2005;18(1):44-69.
82. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. *Clin Infect Dis* 2003;36(1):46-52.
83. Fortun J, Martin-Davila P, Moreno S, et al. Risk factors for invasive aspergillosis in liver transplant recipients. *Liver Transpl* 2002;8(11):1065-70.
84. Gavalda J, Len O, San Juan R, et al. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. *Clin Infect Dis* 2005;41(1):52-59.
85. Singh N, Arnow PM, Bonham A, et al. Invasive aspergillosis in liver transplant recipients in the 1990s. *Transplantation* 1997;64(5):716-20.
86. Singh N, Limaye AP, Forrest G, et al. Late-onset invasive aspergillosis in organ transplant recipients in the current era. *Med Mycol* 2006;44(5):445-49.
87. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. *Clin Infect Dis* 2002;34(1):7-14.
88. Kwak EJ, Husain S, Obman A, et al. Efficacy of galactomannan antigen in the *Platelia Aspergillus* enzyme immunoassay for diagnosis of invasive aspergillosis in liver transplant recipients. *J Clin Microbiol* 2004;42(1):435-8.
89. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347(6):408-15.
90. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. *Transplantation* 2006;81(3):320-26.
91. Singh N, Paterson DL, Gayowski T, et al. Preemptive prophylaxis with a lipid preparation of amphotericin B for invasive fungal infections in liver transplant recipients requiring renal replacement therapy. *Transplantation* 2001;71(7):910-13.
92. Fortun J, Martin-Davila P, Moreno S, et al. Prevention of invasive fungal infections in liver transplant recipients: The role of prophylaxis with lipid formulations of amphotericin B in high-risk patients. *J Antimicrob Chemother* 2003;52(5):813-19.
93. Vilcheza RA, Fung J, Kusnea S. Cryptococcosis in organ transplant recipients: an overview. *Am J Transplant* 2002;2:575-80.
94. Vilchez R, Shapiro R, McCurry K, et al. Longitudinal study of cryptococcosis in adult solid-organ transplant recipients. *Transpl Int* 2003;16:336-40.
95. Wu G, Vilchez RA, Eidelman B, Fung J, Kormos R, Kusne S. Cryptococcal meningitis: An analysis among 5521 consecutive organ transplant recipients. *Transpl Infect Dis* 2002;4:183-88.
96. Luft BJ, Remington JS. *Clin Infect Dis* 1992;15:211.
97. Renoult E, Georges E, Biava MF, et al. *Transplant Proc* 1997;29:821.
98. Sukthana Y, Chintana T, Supatanapong W, et al. *Southeast Asian J Trop Med Public Health* 2001;32:314.
99. Sarwat MA, Ahmed AB, Zamzami OM, et al. *J Egypt Soc Parasitol* 1993;23:751.
100. Aubert D, Foudrinier F, Villena I, et al. *J Clin Microbiol* 1996 ;34:1347.
101. J Iqbal, MRN Nampoory, KV Johnv, et al. Determination of antibodies to toxoplasma gondii and CMV in renal transplant recipients. *Transplant Proceed* 2003;35:2703-05.
102. F Botterel, P Ichai, 2C Feray, et al. Disseminated toxoplasmosis, Resulting from Infection of Allograft, after orthotopic liver transplantation: Usefulness of quantitative PCR. *J of clinical microbio* 2002:1648-50.
103. Barsoum RS: Parasitic infections in organ transplantation. *Exp Clin Transplant* 2004;2:258.
104. Thom K, Forrest G: Gastrointestinal infections in immunocompromised hosts. *Curr Opin Gastroenterol* 2006;22:18.
105. Salluh JI, Bozza FA, Pinto TS, et al. Cutaneous periumbilical purpura in disseminated strongyloidiasis in cancer patients: a pathognomonic feature of potentially lethal disease? *Braz J Infect Dis* 2005;9:419.
106. Reddy IS, Swarnalata G: Fatal disseminated strongyloidiasis in patients on immunosuppressive therapy: report of two cases. *Indian J Dermatol Venereol Leprol* 2005;71:38.
107. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev* 2004;17:208.
108. Schaeffer MW, Buell JF, Gupta M, et al. *Strongyloides* hyperinfection syndrome after heart transplantation: Case report and review of the literature. *J Heart Lung Transplant* 2004;23:905.
109. de Paula FM, de Castro E, Goncalves-Pires M, et al. Parasitological and immunological diagnoses of strongyloidiasis in immunocompromised and non-immunocompromised children at Uberlandia, State of Minas Gerais, Brazil. *Rev Inst Med Trop Sao Paulo* 2000;42:51.
110. Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant* 2004;4(suppl 10):160-3.
111. Hsi ED, Singleton TP, Swinnen L, et al. Mucosa-associated lymphoid tissue-type lymphomas occurring in posttransplantation patients. *Am J Surg Pathol* 2000;24:100-06.
112. Nelson BP, Locker J, Nalesnik MA, et al. Clonal and morphological variation in a posttransplant lymphoproliferative disorder: Evolution from clonal T-cell to clonal B-cell predominance. *Hum Pathol* 1998;29:416-21.

113. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.6.1. Cancer risk after renal transplantation. Post-transplant lymphoproliferative disease (PTLD): prevention and treatment. *Nephrol Dial Transplant* 2002;17(Suppl 4):31-36.
114. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, et al. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991;338:1175-76.
115. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet* 1993;342:575-77.
116. Foxton MR, Knight L, Knisely AS, et al. Liver transplantation for HCV-related cirrhosis in a patient with gastric mucosa-associated lymphoma (MALToma) pretreated with rituximab. *Liver Transpl* 2005;11:839-42.
117. Dragosics B. Significance of *Helicobacter pylori* infection for stomach lymphoma and stomach carcinoma. *Wien Med Wochenschr* 2002;152:135-40.
118. Fischbach W, Goebeler-Kolve ME, Dragosics B, et al. Long term outcome of patients with gastric marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT) following exclusive *Helicobacter pylori* eradication therapy: Experience from a large prospective series. *Gut* 2004;53:34-37.
119. Zucca E, Cavalli F. Are antibiotics the treatment of choice for gastric lymphoma? *Curr Hematol Rep* 2004;3:11-16.
120. Pagano JS, Blaser M, Buendia MA, et al. Infectious agents and cancer: criteria for a causal relation. *Semin Cancer Biol* 2004;14:453-471.
121. Isaacson PG, Spencer J. Gastric lymphoma and *Helicobacter pylori*. *Important Adv Oncol* 1996:111-21.
122. Isaacson PG. Update on MALT lymphomas. *Best Pract Res Clin Haematol* 2005;18:57-68.
123. Shirish Huprikar. Update in infectious diseases in liver transplant recipients. *Clin. Liver Dis* 2007;11:337-54.
124. F Di Benedetto, S Di Sandro, N De Ruvo, et al. Human immunodeficiency virus and liver transplantation: Our point of view. *Transplant Proceed* 2008;40:1965-71.

Role of Liver Biopsy in Transplantation

LIVER BIOPSY

There are different methods to obtain a liver biopsy. In patients with abnormal coagulation profile, coagulopathy may be corrected by transfusion of fresh frozen plasma and platelets. Cryoprecipitate requirement is unusual.

DIFFERENT APPROACHES FOR LIVER BIOPSY

- Percutaneous biopsy
- Transjugular liver biopsy
- Open needle liver biopsy
- Laparoscopic liver biopsy

Percutaneous Liver Biopsy

It is the most common method of obtaining the liver biopsy and usually done on the right lobe for diagnosis of rejection. Usually done on bedside with an 18 gauge needle percutaneously under USG guidance which helps to avoid any major vascular injuries and reach the exact site in the liver parenchyma i.e. right lobe or left lobe. Bleeding and pain are the common problems with this method.

Transjugular Biopsy

It is also called as transvenous biopsy, usually required when the patient has a significant coagulopathy or massive ascites where percutaneous biopsy is contraindicated. It is done by seldinger's technique by puncturing the jugular vein and under the fluoroscopic guidance, the guide wire is inserted into the hepatic veins to reach the liver and biopsy is taken. The advantage of this method is that if there is bleeding from the biopsy site, the blood goes directly into the hepatic veins rather than outside of the bloodstream, resulting in minimal risk for blood loss.

Open Needle Biopsy

This is an old technique and rarely performed at present transplant scenario. This requires a small incision and open the abdomen then take a biopsy and control hemorrhage by diathermy. Earlier days few centers used to make a "willows window", a small opening in the incision line for future protocol biopsies or in case of rejection. This method is no longer practiced.

Laparoscopic Liver Biopsy

Biopsy is taken under vision by laparoscopy. This method can be used for donors, but it is more invasive. It is practically difficult in recipients.

Biopsy Sample Processing

Liver tissue is placed in 10% formalin solution and is processed with hemotoxilin and eosin stain. Rapid processing techniques provide permanent fixed slides in 4-6 hours.¹ Other type of stains such as Masson trichrome and PAS (periodic acid-schiff) stain can also be used. For diagnosing the complement deposits, a piece of frozen liver tissue may be sent for immunofluorescence study. For viral study biopsy sample is subjected to gluteraldehyde stain and examined under electron microscopy. Other special stains like immunohistological staining used for T-cell subset analysis and diagnosis of viral infections like HBV, CMV, Herpes virus, etc. *In situ* hybridisation techniques may be used for diagnosis of viral infections.

Complications of Liver Biopsy

Pain, bleeding, hemobilia, infection and AV fistulas.⁴

DONOR LIVER BIOPSY

The issue of whether or not to perform a liver biopsy on all potential right lobe liver donor candidates remains

controversial.^{2,3} Those favoring mandatory biopsy consider it to be the 'gold standard' for evaluation of liver disease. The complication rate associated with liver biopsy has been estimated at 1–2%.⁴ Some reports mention that less incidence of occult liver disease in the general population and argue against including biopsy in all work ups.^{5,6} Currently, there are no specific recommendations regarding the need for preoperative liver biopsy in potential live liver donors. The use of liver biopsy in well-selected potential right lobe live donors results in minimal risk to the affected individuals.⁷ A survey of 42 transplant centers that perform LDLT showed that only 14% performed routine liver biopsies, 60% performed liver biopsies only in selected cases, and 26% did not do biopsy in any donor candidates.⁸ BMI, body topography, serum aminotransferase and lipid levels, waist/hip ratio, USG, CT and MRI are other means of common noninvasive means of estimating hepatic fat content, but their sensitivities for identifying hepatic fat differ from study to study. USG, CT and MRI had an overall accuracy rate of 65%–80% for moderate to severe degree of hepatic steatosis.^{16–19}

BODY MASS INDEX (BMI)

Rinella et al¹⁵ reported BMI as a reliable predictor of hepatic steatosis with a positive correlation between increasing BMI and steatosis grade on biopsy. Liver biopsy can be avoided in subjects with normal BMI but that living donors with high BMI should undergo liver biopsy because biochemical and imaging data are not reliable enough to accurately diagnose the degree of steatosis.¹⁶ Conversely, Ryan et al. suggested that BMI was not a predictive factor for steatosis.¹⁸ BMI may suggest the presence of liver steatosis but not other liver pathologies including fibrosis, hepatitis, and granulomatous reactions.

BMI= Body weight (BW in kg)/ body height (BH in meter square)

Liver biopsy is safe and currently the gold standard for detecting pathological liver abnormalities, but is invasive procedure with acceptable morbidity. In mild to moderate pathological steatosis, liver biopsies are taken to best predict the overall histologic characteristics of donor livers. Current recommendation continues to be for selective biopsy of potential donors, with emphasis on those identified by the algorithm as being at significant risk for hepatic dysfunction.⁷

Indications of liver biopsy in a donor⁷

- Abnormal LFTs, including results one point above the reference range or positive results for hepatitis or antinuclear serology.
- Imaging studies suggestive of steatosis, NASH or other parenchymal abnormalities.
- Body Mass Index (BMI) > 28.
- Genetic relation to a recipient with, or a family history of, immune mediated liver disease.
- Prior history of alcohol or substance abuse.

Morbidity and mortality of the donor and recipient in subsequent stages could be prevented by pretransplant liver biopsy of the donor. Less invasive investigations with a high rate of donor exclusion should precede liver biopsy.²⁰ If it is a steatosis, the donor can be put on exercise, diet control and hypolipidemic agents and once the donor is fit then the donor graft can be harvested. If it is nonalcoholic steatohepatitis (NASH), donor usually is rejected.

LDLT is guided by 2 main principles:

- Donor morbidity and mortality must be kept to a minimum
- Graft and recipient survival should be acceptably high, as in conventional DDLT.⁹

Ideal donor evaluation process should thoroughly assess potential graft function while minimizing risks to the donor candidate. Each percentage of macrovesicular steatosis might reduce the functional mass of the graft by 1% and increased rates of PNF.¹⁰ With moderate to severe steatosis in DDLT showed increased rates of initial PNF, increased graft loss rates, and higher 3-month patient mortality rates in the recipients.¹¹ Severe macrovesicular steatosis in live donor is associated with > 60% risk of PNF after transplantation due to decreased hepatocyte regeneration and higher rates of graft dysfunction, nonfunction, and ischemic injury.¹² Nonsteatotic pathologies like hepatitis, fibrosis, granulomatous reactions and moderate/severe steatosis are absolute contraindication for living donation at most centers regardless of normal liver function tests and radiologic findings. Both deceased donors with > 30% steatosis are considered by some to be a relative risk factor for liver dysfunction and an absolute risk factor when it is greater than 60%.^{13–15}

RECIPIENT LIVER BIOPSY

LIVER BIOPSY FOR ACUTE REJECTION

Liver biopsy is the gold standard for the diagnosis of ACR. It can also be used as a response to treatment with

immunosuppression by identification of mononuclear cells. In biopsy sample, at least two hematoxylin and eosin stained sections from at least two different levels, of a core needle biopsy containing at least five triads should be examined to confirm rejection.

Histologic findings in acute cellular rejection (Snover's triad)^{21,22}

- Portal inflammation
- Non suppurative obstructive cholangitis
- Endothelitis (**Figure 27.1**)

(Endothelitis: Attachment of inflammatory cells to the endothelial surface of portal or terminal hepatic veins)

Immunostaining, including CD₄ and CD₈ using an automatized process, has become widespread, now being done in most pathology laboratories, thereby increasing reproducibility and objectivity. ACR on H and E sections of liver needle biopsies can be diagnosed pathologically on the same day even in formalin-fixed and paraffin-embedded tissues, and CD₈ analysis is possible the next day. ACR pathological diagnosis is based on H and E findings, according to the Banff schema.²⁶

Protocol Liver Biopsy after Transplantation

Some centers perform routine protocol biopsies to see the progress of the recurrent disease or any rejection episodes at day 7, 4 months and 1 year after OLT.³¹

Different Types of Cells in Acute Cellular Rejection (ACR)

Liver allograft is infiltrated by different mixture of mononuclear cells and granulocytes. T-lymphocytes

constitute 50% of the inflammatory infiltrate. T-lymphocyte population has CD₄⁺ (helper/inducer) T-cells and CD₈⁺ (cytotoxic) T-cells. CD₄⁺ T-cells mediate the graft injury by elaborating cytokines which activate other effector cells including monocytes and macrophages. CD₈⁺ T-cells cause graft damage by their direct cytotoxic effect. Monocytes and macrophages play their role in rejection due to their lymphokine stimulation and as antigen presenting cells in generation of T-cell response. Eosinophils constitute < 20% of inflammatory infiltrates but their presence significant and indicates ACR. Neutrophils constitute <20%. B-lymphocytes constitute <10% and may indicate development of PTLT.

Grading of acute cellular rejection is based on different systems of classification such as Banff schema, Birmingham system and European grading system. The most accepted scoring system for rejection is Banff schema of grading suggested by international consensus document.²³⁻²⁵ **Banff international consensus, Canada (1995)** developed the scheme of classification for grading of severity of rejection. The severity of rejection is based on **Global assessment** and **Rejection activity index (RAI)**.²⁶

Banff schema^{25,26} of grading of acute cellular rejection: **Global assessment** that provides a verbal grading of hepatic allograft rejection based on the overall appearance of the biopsy specimen with particular weight provided by the severity of portal tract inflammation. Mild (Grade I) is defined as the presence of rejection infiltrate in a minority of the triads, that is generally mild, and confined within the portal spaces (**Figure 27.2**); Moderate (Grade II) is defined by the presence of rejection infiltrate, expanding most or all of the triads (**Figure 27.3**) and Severe (Grade III) is similar to moderate, with spill over

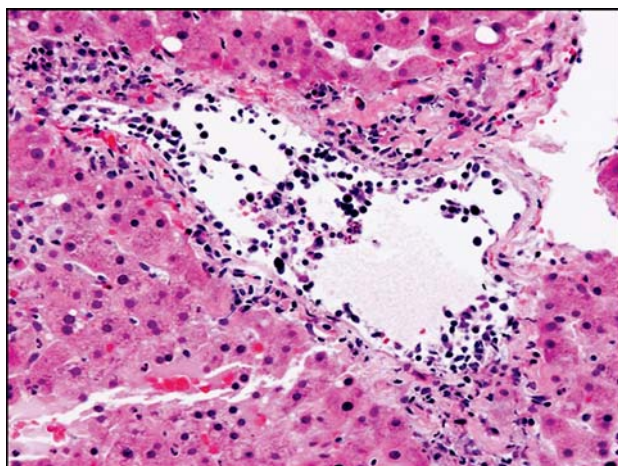


Figure 27.1: Acute rejection showing endothelialitis in the hepatic venule. (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

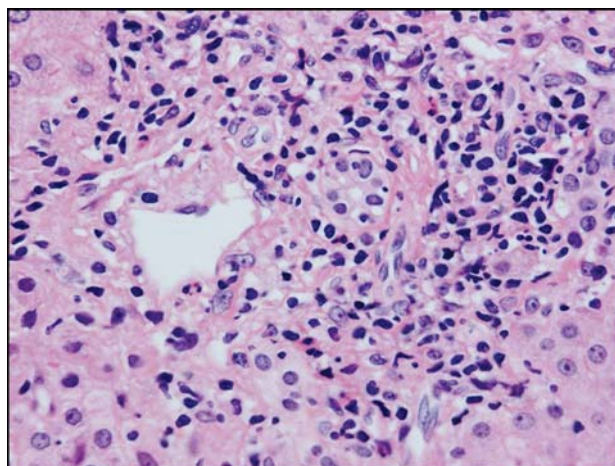


Figure 27.2: Mild acute rejection: Mixed portal inflammation, mainly lymphocytic, is observed. Mild bile duct inflammation is seen (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

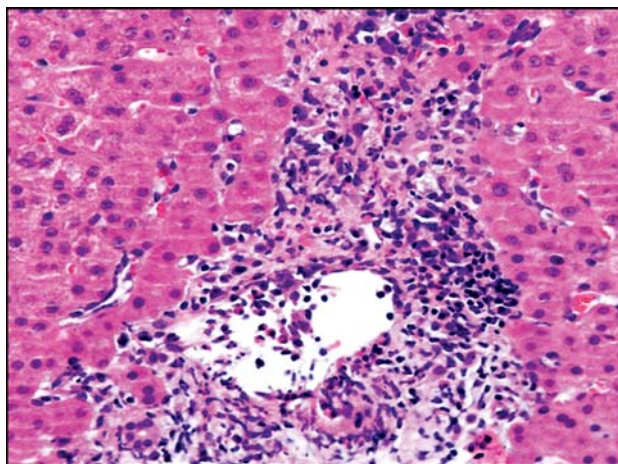


Figure 27.3: Moderate acute rejection. Portal mixed cell infiltration and endothelialitis are evident (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

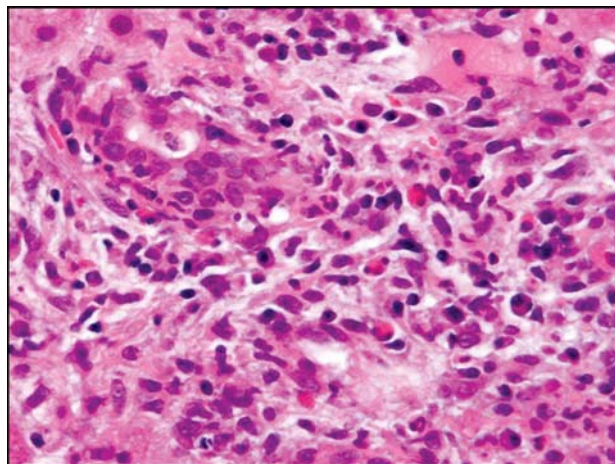


Figure 27.5: Severe acute rejection with bile duct inflammatory damage and eosinophilic infiltration (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University Japan)

into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis (Figures 27.4 and 27.5). Indeterminate is defined as portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection.

Rejection activity index (RAI) is based on the scores given to the histological findings such as severity of portal inflammation, bile duct damage and venous endothelial damage. At least two of these three features are required for a histopathological diagnosis of acute rejection. Each factor has a score of 0-3 and a total score of 0-9. Acute rejection is defined as mild when RAI is < 4 and moderate or severe rejection when RAI is > 6 .

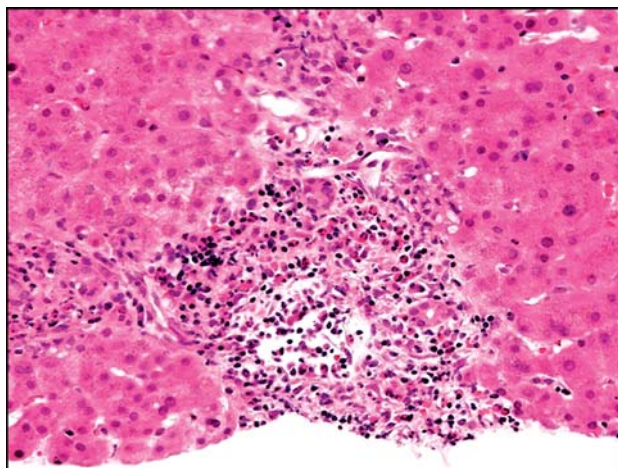


Figure 27.4: Severe acute cellular rejection (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

Birmingham system for rejection score was developed by Hubscher and Dousset²⁵ also includes portal inflammation, bile duct damage and venous endothelial damage. Each factor has a score of 0-3 and a total score of 0-9. The grading system scores for the three main histological features are added to provide a "final rejection score." This is then converted to a histological grade as follows: 0-2, no rejection; 3, borderline; 4-5, mild rejection; 6-7, moderate rejection; 8-9, severe rejection.²⁵

European grading system for acute liver allograft rejection²⁵ estimates the severity of portal inflammation,^{1,2} bile duct damage, and³ venous endothelial inflammation are graded on a scale of 0 = none to 3 = severe and are then collated to provide a final rejection grade.²⁵

LIVER BIOPSY IN HUMORAL/ANTIBODY MEDIATED REJECTION

The incidence of antibody mediated rejection is less in LTx and is seen in ABO incompatible liver transplantations. Important histological markers in humoral rejection are vascular thrombosis, hemorrhage and tissue necrosis (Figures 27.6 and 27.7).

C4d Immunostaining

Vascular deposits of antibodies and complement components are detected by C4d immunostaining. This technique has both diagnostic and prognostic value and could be a hallmark of antibody mediated rejection in liver biopsy.³⁰ A minimum quantitative requirement for the diagnosis of rejection is a biopsy containing at least 5 portal areas.^{28,29} High-postoperative antidonor antibody titer ($> 1:64$) is more frequently seen in C4d-positive

Histological findings in humoral rejection (Figures 27.6 and 27.7)

- Congestion, platelet and fibrin thrombi in the medium and large sized vessels leading to centrilobular damage and hemorrhagic infarcts
- Periportal edema and necrosis indicates early humoral rejection
- Neutrophil margination and tissue infiltration
- Changes in hepatic sinusoids
- Bile duct changes: Cholestasis, bile duct proliferation and cholangitis like changes

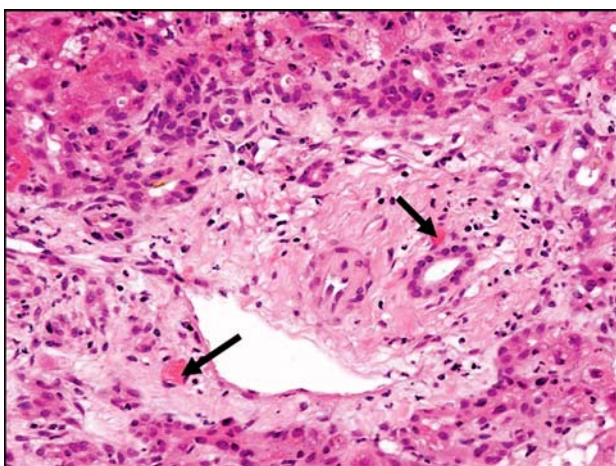


Figure 27.6: ABO-incompatible transplantation. Microthrombus (arrows) ductile reaction (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

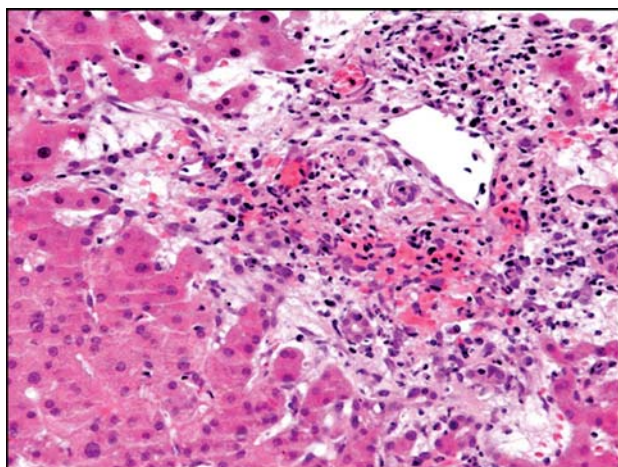


Figure 27.7: ABO-incompatible rejection. Portal edema and hemorrhage (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

patients than in C_{4d}-indeterminate and -negative ones. Immunostaining of IgM or other complements such as C₃ are technically difficult.²⁷

Interpretation of C4d Immunoperoxidase Staining³⁰ (Figure 27.8)

C4d staining is evaluated in terms of the percentage of portal tracts containing distinctly stained stroma and/or endothelium.

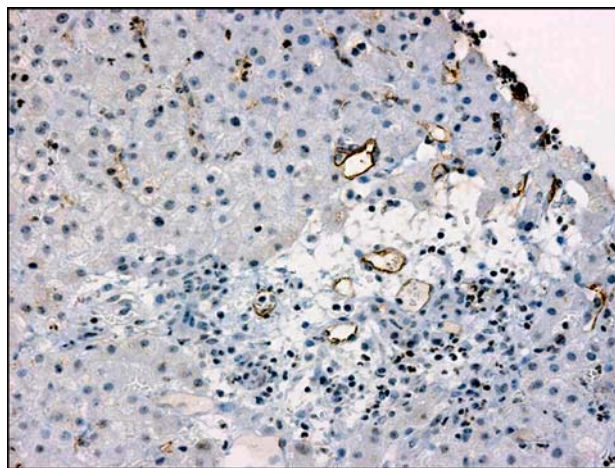


Figure 27.8: ABO-incompatible rejection C4d staining in capillary and sinusoids (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

Interpretation of C4d immunoperoxidase staining³⁰

- Positive: > 50% Stromal-positive portal tracts
- Indeterminate: < 50% Stromal-positive portal tracts or positive staining only in the vascular endothelium or sinusoids.
- Negative: Completely negative staining.

LIVER BIOPSY IN CHRONIC REJECTION

Chronic rejection (CR) is a late complication occurring from 6 weeks to 6 months after transplantation. Histological changes are seen interlobular bile ducts and intimal layers of muscular arteries which are the main target sites.

Histological changes in chronic rejection (Figure 27.9)**Bile ducts:**

- Epithelial atrophy with pyknosis followed by complete disappearance of bile ducts. Loss of bile ducts in 50% of the portal triads is needed to diagnose chronic rejection.
- Canalicular cholestasis in advanced cases
- Mild inflammatory changes

Vascular changes:

- Obliterative arteriopathy and obliterative endarteritis
- Foam cell arteriopathy: Thick intima layer of artery with abundant foamy histiocytes.
- Progressive expansion of intima of large hepatic arteries
- Atrophy and disappearance of small arteries and arterioles
- Balloon degeneration or drop out of centrilobular hepatocytes
- Perivenular sclerosis

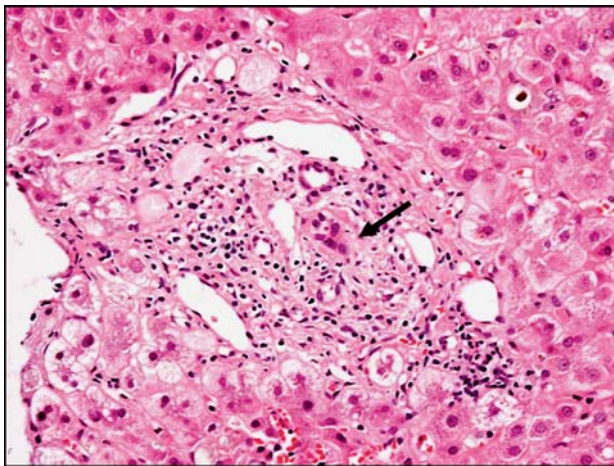


Figure 27.9: Chronic rejection, early phase, showing severe bile duct damage and hepatocanicular cholestasis (Contributed and reproduced with permission of by Hironori Haga, Hokkaido University, Japan)

Banff schema subdivided chronic rejection into 2 groups^{25,26}

Early CR: It is reversible.

Ductal degeneration and bile duct changes in minority (<50%) of portal triads.

Late CR: It is irreversible.

Loss of >50% of bile ducts in portal triads.

Degenerative changes in the remainder of bile ducts
Obliteration of terminal hepatic venules with bridging fibrosis.

Acute on Chronic Rejection

Histological diagnosis of acute on chronic rejection is difficult. But in such scenario the histological features both acute and chronic rejection exists in the biopsy sample.

Treated Rejection

If sequential biopsies are performed, then the biopsies can be compared to know the treatment response. Incomplete response to antirejection therapy is judged by presence of persistence of portal and/or centrilobular inflammation, inflammation of the bile ducts and endothelitis. Complete response to treatment is shown as decrease in the number of inflammatory cells particularly T-cells and eosinophils. When the inflammatory cells die, they are visible as less densely packed spaces.

Perfusion/Preservation Injury**Histological findings in perfusion/preservation injury**

- Balloon degeneration of hepatocytes
- Centrilobular pallor
- Canalicular cholestasis
- Spotty hepatocyte necrosis
- Recurrent disease

Liver Biopsy following OLT to Assess Hepatic Fibrosis due to Recurrent HBV/HCV Disease

Ishak et al³¹ reported the modified staging to mention the severity of architectural changes, fibrosis and cirrhosis. He designed a scoring system. Maximum possible score is 6. The scoring according to severity of fibrosis is as follows- No fibrosis: 0; Fibrous expansion of some portal areas, with or without short fibrous septa: 1; Fibrous expansion of most portal areas, with or without short fibrous septa: 2; Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging: 3; Fibrous expansion of portal areas with marked bridging [portal to portal (P-P) as well as portal to central (P-C)]: 4; Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis): 5; Cirrhosis, probable or definite: 6.³¹ Ludwig-Batt³² designed another scoring system for hepatic fibrosis: F0: Absent fibrosis; F1: Portal fibrosis; F2: Periportal fibrosis; F3: Bridging fibrosis; F4: Cirrhosis. Advanced hepatic fibrosis is defined as the presence of stage F3 or F4

Liver biopsy helps in assessing the degree of damage due to HCV and amount of fibrosis.

Other Indications of Liver Biopsy in Hepatic Allograft

Other recurrent diseases after transplant such as reactivation of viral diseases like autoimmune diseases

like PBC, PSC, autoimmune hepatitis and NASH can be diagnosed by liver biopsy. Opportunistic infections such as viral infections like CMV, EBV, Herpes zooster, and adenovirus, bacterial and fungal infections also leave some histological changes in hepatic allograft which give a clue in liver biopsy sample studies. The detail histological changes of all these pathologies are beyond the scope of this book.

REFERENCES

1. N Kubota, M Sugitani, S Takano, et al. Correlation between acute rejection severity and CD8-positive T-cells in living related liver transplantation. *Transplant Immunology* 2006;16:60-64.
2. Trotter JF, Campsen J, Bak T et al. Outcomes of donor evaluations for adult-to-adult right hepatic lobe living donor liver transplantation. *Am J Transplant* 2006;6:1882-89.
3. Yamashiki N, Sugawara Y, Tamura S, et al. Selection of liver transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. *Liver Transpl* 2006;12:1077-83.
4. Valentin-Gamazo C, Malago M, et al. Experience after the evaluation of 700 potential donors for living donor liver transplantation in a single center. *Liver Transpl* 2004;10:1087-96.
5. Baker A, Dhawan A, Devlin J, et al. Assessment of potential donors for living related liver transplantation. *Br J Surg* 1999;86:200-05.
6. Florman S, Miller CM. Live donor liver transplantation. *Liver Transpl* 2006;12:499-510.
7. Simpson MA, Verbesey JE, et al. Successful Algorithm for Selective Liver Biopsy in the Right Hepatic Lobe Live Donor (RHLD) *American Journal of Transplantation* 2008;8:832-38.
8. Brown RS Jr, Russo MW, Shiffman ML, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:818-25.
9. Nadalin S, Malago M, Valentin-Gamazo C, et al. Preoperative donor liver biopsy for adult living donor liver transplantation: Risks and benefits. *Liver Transpl* 2005;11:980-86.
10. Sanyal AJ, et al. Selection and outcome of living donors for adult to adult right lobe transplantation. *Transplantation* 2000;69:2410-15.
11. Verran D, Kusyk T, Strasser S, et al. Clinical experience gained from the use of 120 steatotic donor livers for orthotopic liver transplantation. *Liver Transpl* 2003;9:500-05.
12. Ploeg RJ, D'Alessandro AM, Hoffmann RM, et al. Risk factors for primary dysfunction after liver transplantation—a multivariate analysis. *Transplantation* 1993;55:807-13.
13. Limanond P, Raman SS, Busuttil RW, et al. Macrovesicular hepatic steatosis in living related liver donors: Correlation between CT and histologic findings. *Radiology* 2004;230:276-80.
14. Strasberg SM, Howard TK, Molmenti EP, et al. Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation [review]. *Hepatology* 1994;20(pt 1):829-38.
15. Iwasaki M, Takada Y, Maetani Y, et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. *Transplantation* 2004;78:1501-05.
16. Rinella ME, Alonso E, Abecassis M, et al. Body mass index as a predictor of hepatic steatosis in living liver donors. *Liver Transpl* 2001;7:409-14.
17. Van Ness MM, Diehl AM. Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? *Ann Intern Med* 1989;111:473-78.
18. Ryan CK, Johnson LA, Germin BI, et al. One hundred consecutive hepatic biopsies in the workup of living donors for right lobe liver transplantation. *Liver Transpl* 2002;8:1114-22.
19. Park SH, Kim PN, Park SW, et al. Macrovesicular hepatic steatosis in living liver donors: use of CT for quantitative and qualitative assessment. *Radiology* 2006;239:105-12.
20. N Savas, M Haberal et al. Value of an individual liver biopsy in the preoperative evaluation of apparently healthy potential liver donors. *Liver transpl* 2008;14:541-46.
21. Demetris AJ, Seaberg EC, Markin RS, et al. Reliability and predictive value of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database nomenclature and grading system for cellular rejection of liver allografts. *Hepatology* 1995;21(2):408-16.
22. Demetris AJ, Batts KP, Hart J, et al. Banff schema for grading liver allograft rejection: An international consensus document. *Hepatology* 1997; 25(3):658-63.
23. Ormonde DG, de Boer WB, House AK, et al. Banff schema for grading liver allograft rejection: utility in clinical practice. *Liver Transpl Surg* 1999; 5:261-67.
24. Blakolmer K, Jain A, Murase N, et al. Chronic liver allograft rejection in a population treated primarily with tacrolimus as baseline immunosuppression: long-term follow-up and evaluation of features for histopathological staging. *Transplantation* 2000; 69:2330-36.
25. DG Ormonde, W Bastiaan de Boer, A Kierath, et al. Banff Schema for Grading Liver Allograft Rejection: Utility in Clinical Practice. *Liver Transplantation and Surgery* 1999;(5):261-68.
26. International Panel. Banff schema for grading liver allograft rejection: an international consensus document. *Hepatology* 1997; 25:658-63.
27. Egawa H, Oike F, Haga H, et al. Impact of recipient age on outcome of ABO incompatible living-donor liver transplantation. *Transplantation* 2004; 77:403-11.
28. Magro CM, Pope Harman A, Waldman J, et al. Use of C4d as a diagnostic adjunct in lung allograft biopsies. *Am J Transplant* 2003; 3:1143-54.
29. Ruiz P, Garcia M, Kato T, et al. Mucosal vascular alterations in isolated small bowel allografts: relationship to humoral sensitization. *Am J Transplant* 2003;3:43-49.
30. H Haga, H Egawa, Y Fujimoto, et al. Acute Humoral Rejection and C4d Immunostaining in ABO Blood Type-Incompatible Liver Transplantation. *Liver transpl* 2006;12:457-64.
31. K Ishak, A Baptista, L Bianchi, et al. Histological grading and staging of chronic hepatitis. *Journal of Hepatology* 1995;22:666-99.
32. Ibrahim AH, Ariel EF, Arthor J M, et al. The significance of metabolic syndrome in the setting of recurrent hepatitis C after Liver transplantation. *Liver transplantation* 2008;14:1287-93.

Renal Dysfunction in Liver Transplantation

INTRODUCTION

Renal failure is a common complication in the postoperative period after orthotopic liver transplantation (OLT), ranging from 12 to 70%,¹ depending on several issues related to transplant center characteristics, preoperative renal function, perioperative factors, and immunosuppressive drugs.^{3,4} High mortality rates are observed when renal replacement therapy (RRT) is required, ranging from 40 to 90%.¹⁻⁴ Pre-OLT renal dysfunction identified by high preoperative serum creatinine levels in cirrhotic patients is an important predictor of postoperative sepsis, RRT, overall cost of transplantation, and patient and graft short-term survival rates.⁵⁻⁸ Data from England suggest a 68% incidence at 1 year, and 78% at 5 years of an elevated serum creatinine (>1.4 mg/dL).⁹ In Pittsburgh reported series, 28% incidence of elevated serum creatinine (>2.0 mg/dL) among recipients who survived at least 6 months after transplantation.¹⁰ A low creatinine clearance preoperatively was the most important risk factor for the development of postoperative renal dysfunction.¹¹

Renal dysfunction is common in patients on waiting list due to hepatorenal syndrome, which carries a 10% risk of chronic renal failure after transplantation.²³ The incidence of severe renal dysfunction post-transplant ranges from 8 to 18% in retrospective series with 10 to 13 years of follow-up.^{24,25} Four to 9% of patients required hemodialysis. In another study, only 14% of patients had a normal glomerular filtration rate (GFR) at 6 months post-transplant, indicating that most patients have at least mild renal insufficiency.²⁶ Pretransplantation renal failure decreases the survival of liver transplant recipients and predicts the risk for post-transplantation renal failure and infection.¹²⁻¹⁴ The duration of pre-transplant renal dysfunction, rather than the cause, is proposed to be an independent predictor of renal function after liver transplantation.¹⁶ Renal dysfunction after liver

transplantation causes increased morbidity and mortality.^{17,18} GFR falls to approximately 60% of the pre-transplantation GFR in 6 weeks after transplantation.¹⁹ Renal function at the time of transplantation in patients with HRS is not a good predictor of subsequent renal function.^{35,36}

Risk factors for renal dysfunction^{20,21,22}

- Calcineurin inhibitors (Cs A/Tacrolimus)
- Pre-transplant renal disease such as hepatorenal syndrome
- Intraoperative change in hemodynamics
- Hypertension
- DM
- Dyslipidemia
- Use of NSAIDs and salicylates

Recently there are many reports about the MELD score as a predictor of postoperative renal dysfunction or hepatorenal syndrome and is a useful predictor of early renal dysfunction and requirement for RRT in postoperative adult LDLT patients.^{27,28} There is a significant relationship between SFS graft (GRWR<0.8%) and early postoperative renal dysfunction.²⁸

CINS AND RENAL TOXICITY

CINs produce a reversible acute form of nephrotoxicity, resulting from renal artery vasoconstriction involving both afferent and efferent arterioles and an irreversible chronic form of injury characterized by renal arteriopathy and interstitial fibrosis.²⁹⁻³⁰ In more severe cases, there is tubular damage and a clinical picture of acute tubular necrosis, perhaps on the basis of ischemia. CINs are common causes of reduced GFR in transplant recipients. High levels of CINs appear to act as direct proximal tubular toxin and contribute to the onset or

progression of post-transplant renal dysfunction.³² The mechanism of renal hemodynamic effects of CINs involves increased production of thromboxane A2 and probably due to endothelins, a potent vasoconstrictor. Risk for chronic renal failure is more in patients treated with cyclosporine than tacrolimus.³¹ CINs can cause acute nephrotoxicity manifested as acute renal failure in early post-transplant period. But this type of nephrotoxicity is uncommon. In such condition, histologically kidney shows endothelial damage, formation of fibrin thrombi in the capillaries, eosinophilic material in the walls of arterioles and small arteries with a patchy necrosis of smooth muscle cells. Most important side effect of CINs is chronic nephrotoxicity, manifested by gradually deteriorating renal functions over months to years with mild proteinuria. Histologically chronic toxicity is visible as interstitial fibrosis and tubular atrophy. Degenerative hyaline changes seen in the arterial walls. But glomeruli are well preserved in the initial stage of chronic nephrotoxicity.

HBV AND HCV RELATED NEPHROTOXICITY

Both HBV and HCV can cause nephrotoxicity in ESLD and due to relapse of viral infection after transplantation. They cause glomerulonephritis in some patients. They cause progressive deterioration of renal function and nephrotic syndrome. Degree of proteinuria is closely correlated with severity of viremia. HBV usually causes membranous glomerulonephritis. But other forms of glomerulonephritis like membranoproliferative, mesangioproliferative and focal segmental glomerulonephritis are possible. HBV antigens are localized in the glomeruli. HBsAg is associated with mesangial deposits, while HBeAg is associated with capillary membrane deposits. With clearance of viral antigen, spontaneous clearance of glomerulonephritis occurs. HCV causes membranoproliferative glomerulonephritis. These patients usually have hypocomplementemia, cryoglobulinemia and Ig M antibodies against HCV-RNA.

MONITORING RENAL FUNCTION

There is no single standard test available which can predict future renal function after transplant. GFR, Blood urea nitrogen (BUN) and serum creatinine have limitations in LTX patients.

GFR

It is difficult to estimate GFR due to abnormalities in fluid status.³⁴ GFR at one year post-transplant, can predict the patients who are likely to develop renal dysfunction and failure.^{33,34} Malnutrition and poor hepatic function can

falsely cause low levels of BUN leading to overestimation of GFR. In contrary GI bleeding, hypovolemia leading to renal hypoperfusion and corticosteroids cause elevation of BUN higher than the expected level for a given GFR. Measurement of GFR is usually done by using EDTA (Ethylene diamine tetra-acetic acid) or DTPA (Diethylene triamine penta acetic acid) or iothalamate which are neither secreted nor absorbed by the kidney. Other methods of measuring GFR are by using radiolabelled GFR markers called Isotope GFR measurement. It is based on the decay of injected radiolabelled GFR marker in few hours. This method is expensive.

SERUM CREATININE

It is mostly produced in muscles and its level is influenced by the patient's muscle mass. Patients of cirrhosis with less muscle mass can have falsely low levels of serum creatinine. Drugs like cefazolin, cimetidine and trimethoprim inhibit secretion of creatinine. Patients on these drugs may show elevated serum creatinine levels without any significant change on GFR.

CREATININE CLEARANCE

It is one of the most common methods of estimating the GFR. It is estimated from a timed urine sample or as measured from:

COCKCROFT-GAULT FORMULA

$$\frac{140 - \text{Age}}{\text{Creatinine}} \times (\text{weight in kg}) \times (0.85 \text{ for females})$$

RENAL USG

It is used to rule out obstructive pathology in collecting system. Doppler ultrasound may show increased renal vascular resistance in case of hepatorenal syndrome.

CARE IN PATIENTS WITH RENAL DISEASE

- Routine screening for albuminuria
- Measurement of GFR and creatinine clearance.
- Avoidance/minimal use of NSAIDs, aminoglycosides and other potentially nephrotoxic drugs in patients receiving CINs.
- Control of blood pressure and blood glucose.
- Control of volume depletion, hypotension and sepsis, if any
- Treatment of HBV/HCV related glomerulonephritis: Treatment aim is clearance of viremia. For HBV patients lamivudine/adefovir dipivoxil and Hepatitis B

immune globulins, and for HCV α -interferon and ribavirin are useful in controlling viremia. Treatment of nephrotic syndrome includes diuretics correction of hypokalemia, use of ACE inhibitors and/or angiotensin receptor blockers.

- In post-transplant period, use of less nephrotoxic immunosuppression may improve existing renal dysfunction. Low dose CINs along with MMF is a better combination^{37,38} sirolimus is another alternative.³⁹⁻⁴³

ACUTE RENAL INJURY AFTER LIVER TRANSPLANTATION

In liver transplantation, the postoperative appearance of acute renal injury requiring renal replacement therapy is a serious event, often complicating the outcome of these patients. The incidences in the literature vary from 3 to 20%.^{47,48} Renal function immediately after and also during the later course exerts an important influence on the quality of life and survival of transplant recipients. ARF after OLT showed good prognosis with a recompensation rate of 97% within 4 weeks after surgery. Mortality is also high, from 45.1 to 67%.^{49,50} Several factors are involved in the pathogenesis of ARF after liver transplantation. They may influence patient outcomes and mortality rates. Etiology is multifactorial. Although a strong correlation exists between diuresis, serum creatinine, blood urea nitrogen and outcome;^{47-49,52} patients may show a progressive increase in renal function tests, with progressively decreasing diuresis.^{47-49,52,53} Predictors of post-transplant renal failure are serum creatinine above 1.5 mg/dl and GFR <50 ml/min.⁵⁶

Risk factors for acute renal injury after LTX^{47,48,50,51,56-59}

- Sepsis
- Nephrotoxicity due to immunosuppression.
- Unstable hemodynamic conditions in the early postoperative periods
- Pre-transplant HRS type II
- GFR <30 ml/min
- Hepatitis C +ve recipient
- Prolonged cold ischemic time (in deceased donor)
- Preexistent diabetes
- Presence of ascites and hepatic encephalopathy as well as impaired renal function
- Massive blood loss and excessive blood transfusion
- Reoperation.

In OLT, piggyback technique reduces the number of postoperative ARF episodes compared with venovenous bypass.^{44,45} Patients with graft failure are at high risk for severe ARF. Graft failure decreases immunosuppressive

drug (particularly CINs) metabolism, injuring renal function. Serum creatinine increases with increase in trough levels of tacrolimus. Between 25 and 50% of liver transplant recipients develop acute renal injury during the first postoperative days due to CIN nephrotoxicity and impaired hemodynamics.^{60,61,88}

TREATMENT

Renal replacement therapy (RRT) is needed to support till the kidney recovers its function. Early RRT is the most important factor to improve outcomes in our ICU after liver transplantation.⁵⁴ ARF after OLT showed good prognosis with a recompensation rate of 97% within 4 weeks after surgery. Since multifactorial genesis is the most frequent cause of ARF, only two major risk factors have been associated with ARF after OLT: Serum creatinine above 1.5 mg/dl GFR <50 ml/min. To be able to identify this is advance and apply optimally adjusted immunosuppressive and drug therapy may have a significant impact on the outcome of this cohort of liver transplant recipients.^{49,51}

The choice of intermittent hemodialysis (HD) versus continuous renal replacement therapy (CRRT) is often based on the hemodynamic stability of the patient. In patients with severe liver disease and significant hypotension, intermittent HD may worsen the hemodynamic status. Slow continuous correction of volume and solutes with CRRT (continuous arteriovenous hemodialysis (CAVHD) or continuous venovenous hemodialysis (CVVHD) among these patients is preferred for better maintenance of cardiovascular and cerebral stability. Peritoneal dialysis (PD) may offer similar hemodynamic advantage as CRRT, but is not preferred as the effective solute clearance among hypotensive patients may be reduced because of the associated reduction in peritoneal capillary blood flow.

Complications of CRRT⁴⁶

- Thermal instability
- Loss of nutritional substrates
- Excessive load of glucose, citrate, lactate, or citrate from the dialysate

Studies from DDLT showed that in ARF, between 8.2 and 18% of patients require dialysis after LT.^{62-70,72,74} Associated mortality in this group of patients is high, namely 39 to 90%.^{62-64,75}

DRUG CLEARANCE BY DIALYSIS

Immunosuppressive drugs: Prednisolone, CINs (Cs A and tacrolimus), MMF are not removed by dialysis while methylprednisolone and azathioprine are cleared

partially during dialysis. Hypertension drugs: β -blockers like atenolol, nadolol, metoprolol and sotalol are dialyzable. ACE inhibitors are usually dialyzable exceptions being benazepril and quinapril. Calcium channel blockers are not dialyzable. Verapamil is avoided in transplant recipients on hemodialysis as its metabolites can accumulate and show antihypertensive effect.

CHRONIC RENAL DISEASE AFTER LIVER TRANSPLANTATION

Fisher, et al.⁷⁷ analyzed the outcomes of 139 OLT patients surviving >5 years, showing an incidence of chronic renal disease of 78% at 5 years. Acute renal dysfunction early after OLT has been recognized as a risk factor for chronic renal disease. In a study by Gonwa, et al. the incidence of end stage renal failure (ESRF) was 9.5%.⁷⁹ Hepatorenal syndrome and early renal failure both were associated with ESRD.^{79,80}

Cauley, et al.⁷⁶ reported that serum creatinine levels among patients with chronic renal disease usually increases during the first 3 years after surgery, remaining stable thereafter during the follow-up. They found that the greatest impairment took place during the first 18 months after OLT. There was a trend to greater nephrotoxicity among patients treated with the microemulsion formulation of cyclosporine compared with tacrolimus.⁷⁸

Risk factors for chronic renal disease after LTX

- Age > 45 years
- Prolonged surgery
- Pre-transplant renal dysfunction,
- Renal dysfunction within the 1st 6 months
- Hyperuricemia at 1 month after OLT
- Use of conventional (microemulsion) cyclosporine

In OLT, chronic renal disease appears early, and after a steady worsening of renal function during the first 3 years, only minorities of these patients develop ESRF. Patient survival is shorter than in patients without this complication.⁸² CINs dose reduction or replacement with MMF or sirolimus shows a beneficial effect on the evolution of chronic renal disease, which rapidly improves renal function, without affecting liver function.⁸³ On the other hand, there are suggestions from other transplantation centers that MMF monotherapy is associated with an increased risk of rejection.⁸⁴ Other drugs such as sirolimus need further evaluation for the prevention of CRF after liver transplantation.⁸⁵

HYPERKALEMIA AND LIVER TRANSPLANTATION

Hyperkalemia poses serious hazards to patients undergoing OLT. Most concerns have been associated with severe hypotension, hypokalemia, and subsequent deaths in the reperfusion period.⁸⁹ The occurrence of hyperkalemia in the period just following recirculation of blood during the liver transplant surgery has been correlated with death. Nakasuji and Bookallil⁸⁶ concluded that the occurrence of hyperkalemia after revascularization is correlated with serum potassium concentrations and metabolic acidosis due to insufficient cardiac output during the anhepatic phase. There have been several accounts of treating impending hyperkalemia with insulin infusion during the anhepatic phase.⁸⁶

Long term nephrotoxicity of cyclosporine and tacrolimus (FK-506) are associated with hypertension, hyperkalemia, hypomagnesemia and metabolic acidosis (Gordon's syndrome). Both of these essential immunosuppressive agents carry the risk of long-term irreversible toxicity.⁸⁷

REFERENCES

1. Chuang FR, Lin CC, Wang PH, et al. Acute renal failure after cadaveric related liver transplantation. *Transplant Proc* 2004;36:2328-30.
2. Faenza S, Santoro A, Mancini E, et al. Acute renal failure requiring renal replacement therapy after orthotopic liver transplantation. *Transplant Proc* 2006;38:1141.
3. Gainza FJ, Valdivieso N, Quintanilla N, et al. Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. *Transplant Proc* 2002;34:250.
4. De Mendonça A, Vincent JL, Suter PM, et al. ARF in ICU: Risk factors and outcome evaluated by SOFA score. *Intensive Care Med* 2000;26:921.
5. Nair S, Verma S, Thuluvath P: Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002;35:1179.
6. Baliga P, Merion RM, Turcotte JG, et al. Preoperative risk factor assessment in liver transplantation. *Surgery* 1992;112:704.
7. Cuervas-Mons V, Millan I, Gavalier JS, et al. Prognostic value of pre-operatively obtained clinical and laboratorial data in predicting survival following orthotopic liver transplantation. *Hepatology* 1986;6:922.
8. Lafayette RA, Pare G, Schmidt CH, et al. Pretransplant renal dysfunction poorer outcome in liver transplantation. *Clin Nephrol* 1997;48:159.
9. Fisher NC, Nightingale PG, Gunson BK, et al. *Transplantation* 1998;66:59.
10. Gayowski T, Singh N, Keyes L, et al. *Transplantation* 2000 ;69:383.
11. SG Kim, HJ Kim, JP Lee, et al. Incidence and risk factors of renal dysfunction after liver transplantation in Korea. *Transplant Proceed* 2004;36:2318-20.

12. Bilbao I, Charco R, Balsells J, et al. Risk factors for acute renal failure requiring dialysis after liver transplantation. *Clin Transplant* 1998;12(2):123-29.
13. Singh N, Gayowski T, Wagener MM. Post-transplant dialysis-associated morbidity and impact on outcome in liver transplant recipients. *Liver Transpl* 2001;7(2):100-05.
14. Fisher NC, Nightingale PG, Gunson BK, et al. Chronic renal failure following liver transplantation. *Transplantation* 1998;66(1):59-66.
15. Lafayette RA, Pare G, Schmid CH, et al. Pre-transplant renal dysfunction predicts poorer outcome in liver transplantation. *Clin Nephrol* 1997;48(3):159-64.
16. Campbell MS, Kotlyar DS, Brensinger CM, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. *Liver Transpl* 2005;11(9):1048-55.
17. Porayko MK, Gonwa TA, Klintmalm GB, et al. Comparing nephrotoxicity of FK506 and cyclosporine regimens after liver transplantation: preliminary results from US Multicenter trial. *Transplant Proc* 1995;27(1):1114-16.
18. Brown RS Jr, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. *Transplantation* 1996;62(12):1788-93.
19. Gonwa TA, Morris CA, Goldstein RM, et al. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome: experience in 300 patients. *Transplantation* 1991;51(2):428-30.
20. Bennett WM. Insights into chronic cyclosporine nephrotoxicity. *Int J Clin Pharmacol Ther* 1996;34(11):515-19.
21. Guitard J, Ribes D, Kamar N, et al. Predictive factors for chronic renal failure one year after orthotopic liver transplantation. *Ren Fail* 2006;28(5):419-25.
22. Weir MR, Fink JC. Risk for posttransplant diabetes mellitus with current immunosuppressive medications. *Am J Kidney Dis* 1999;34(1):1-13.
23. Gonwa TA, Morris CA, Goldstein RM, et al. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome: Experience in 300 patients. *Transplantation* 1991;51:428-30.
24. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLT) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001;72:1934-39.
25. Fisher NC, Nightingale PG, Gunson BK, et al. Chronic renal failure following liver transplantation: A retrospective analysis. *Transplantation* 1998;66:59-66.
26. Kim DY, Lim C, Parasuraman R, et al. Renal disease burden following liver transplantation. *Transplant Proc* 2006;38:3663-65.
27. Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2005;41:1282.
28. SK Lee, JB Park, SJ Kim, et al. Early postoperative renal dysfunction in the adult living donor liver transplantation. *Transplant Proceed* 2007;39:1517-19.
29. Andoh TF, Burdmann EA, Bennett WM. Nephrotoxicity of immunosuppressive drugs: Experimental and clinical observations. *Semin Nephrol* 1997;17:34-45.
30. Kopp JB, Klotman PE. Cellular and molecular mechanisms of cyclosporin nephrotoxicity. *J Am Soc Nephrol* 1990;1:162-79.
31. Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003;349:2326-33.
32. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;349(10):931-40.
33. Morard I, Mentha G, Spahr L, et al. Long-term renal function after liver transplantation is related to calcineurin inhibitors blood levels. *Clin Transplant* 2005;20(1):96-101.
34. Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. *Liver Transpl* 2003;9(7):741-47.
35. Cohen AJ, Stegall MD, Rosen CB, et al. Chronic renal dysfunction late after liver transplantation. *Liver Transpl* 2002;8(10):916-21.
36. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLT) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation* 2001;72(12):1934-39.
37. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002;35(5):1179-85.
38. Raimundo ML, Dagher L, Papatheodoridis GV, et al. Long-term mycophenolate mofetil monotherapy in combination with calcineurin inhibitors for chronic renal dysfunction after liver transplantation. *Transplantation* 2003;75(2):186-90.
39. Reich DJ, Clavien PA, Hodge EE, MMF Renal Dysfunction after Liver Transplantation Working Group. Mycophenolate mofetil for renal dysfunction in liver transplant recipients on cyclosporine or tacrolimus: Randomized, prospective, multicenter pilot study results. *Transplantation* 2005;80(1):18-25.
40. Johnson RW, Kreis H, Oberbauer R, et al. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001;72(5):777-86.
41. Fairbanks KD, Eustace JA, Fine D, et al. Renal function improves in liver transplant recipients when switched from a calcineurin inhibitor to sirolimus. *Liver Transpl* 2003;9(10):1079-85.
42. Nair S, Eason J, Loss G. Sirolimus monotherapy in nephrotoxicity due to calcineurin inhibitors in liver transplant recipients. *Liver Transpl* 2003;9(2):126-29.
43. Kniepeiss D, Iberer F, Schaffellner S, et al. Nonnephrotoxic immunosuppression in patients after liver transplantation. *Int Immunopharmacol* 2005;5(1):133-36.
44. Sanchez EQ, Martin AP, Ikegami T, et al. Sirolimus conversion after liver transplantation: improvement in measured glomerular filtration rate after 2 years. *Transplant Proc* 2005;37(10):4416-23.
45. Jovine E, Mazziotti A, Grazi GL, et al. *Transpl Int* 1997;10:109.
46. J.B. Cabezuolo, P. Ramirez, F. Acosta, et al. Does the Standard vs Piggyback Surgical Technique Affect The Development of Early Acute Renal Failure After Orthotopic Liver Transplantation? *Transplant Proceed* 2003;35:1913-14.
47. Fraley D, Burr R, Bernardini J, et al. Impact of ARF on mortality in end-stage liver disease with or without transplantation. *Kidney Int* 1998;54:518.
48. Chang T-J. Prognostic factors of postoperative ARF. *Dialysis & Transplantation* 1999;28

49. De Mendoça A, Vincent JL, Suter PM, et al. ARF in ICU: risk factors and outcome evaluated by SOFA score. *Intensive Care Med* 2000;26:921.
50. Cabezuolo JB, Ramirez P, Acosta F, et al. Prognostic factors of early ARF in liver transplantation. *Transplant Proc* 2002;34:254.
51. Reddy SS: Critically ill patients receiving CRRT: patients survival, renal function recovery, complications of therapy. *Dialysis & Transplantation* 2002;31
52. Van Buren D, Payne J, Gevarghese S, et al. Renal function in primary liver transplant recipients receiving Neoral vs Prograf. *Transplant Proc* 1998;30:1401.
53. Gowna TA, Mai ML, Helton LB, et al. Renal replacement therapy and OLT: role of CVVH. *Transplantation* 2001;71:1424.
54. Rimola A, Van Thiel DH: Effects or renal impairment on liver transplantation. *Gastroenterology* 1987;93:148.
55. S Faenza, A Santoro, E Mancini, et al. Acute Renal Failure Requiring Renal Replacement Therapy After Orthotopic Liver Transplantation. *Transplant Proceed* 2006;38:1141-42
56. Paramesh AS, Roayaie S, Doan Y, et al. Post liver-transplant acute renal failure: factors predicting development of end-stage renal disease. *Clin Transplant* 2004;18:94.
57. Alvares-da-Silva MR, Waechter FL, Francisconi CF, et al. Risk factors for postoperative acute renal failure at a new orthotopic liver transplantation program. *Transplant Proc* 1999;31:3050.
58. Gainza FJ, Valdivieso A, Quintanilla N, et al. Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. *Transplant Proc* 2002;34:250.
59. Chuang FR, Lee CH, Chien YS, et al. Acute renal failure after living-related liver transplantation. *Transplant Proc* 2003;35:429.
60. Bilbao I, Balsells J, Lazaro JL, et al. *Clin Transplant* 1998;12:123.
61. Haller M, Schonfelder R, Breigler J, et al. *Transplant Proc* 1992;24:2704.
62. Danovitch GM, Wilkinson AH, Colonna JO, et al. *Kidney Int* 1987;31:195.
63. McCauley J, Vanthel DH, Starzl TE, et al. *Nephron* 1990;55:121.
64. Haller M, Schonfelder R, Briegel J, et al. *Transplant Proc* 1992;24:2704.
65. Andres A, Morales JM, Farias J, et al. *Transplant Proc* 1992;24:126.
66. Pascual E, Gomez-Arnau, Pensado A, et al. *Transplant Proc* 1993;25:1837.
67. Cabezuolo JB, Ramirez P, Acosta F, et al. *Transplant Proc* 2002;34:254.
68. Gainza FJ, Valdivieso A, Quintanilla N, et al. *Transplant Proc* 2002 ;35:250.
69. Jindal RM, Popescue I: *Postgrade Med J (Engl)* 1995;71:513.
70. Dibona GF: *Kidney Int* 1984;25:841.
71. Thomas G, Kelly S, Norris O, et al. *Irish J Med Science* 1996;165:271.
72. Bilbao I, Charco R, Balsells J, et al. *Clin Transplantation* 1998;12:123.
73. Gonwa TA, Mai ML, Melton LB, et al. *Transplantation* 2001;71:1424.
74. Lima EQ, Zanetta DMT, Castro I, et al. *Renal Failure* 2003;25:553.
75. Franley DS, Burr R, Bernardini J, et al. *Kidney Int* 1998;54:518.
76. McCauley J, Van Thiel D, Starzl T, et al. *Nephron* 1990;55:121.
77. Fisher NC, Nightingale PG, Gunson BK, et al. *Transplantation* 1998;66:59.
78. Wiesner RW: *Transplantation* 1998 ;66:493.
79. Gonwa TA, Mai ML, Melton LB, et al. *Transplantation* 2001;72:1934.
80. Gonwa TA, Morris CA, Goldstein RM, et al. *Transplantation* 1991;51:428.
81. Nair S, Verma S, Thuluvath PJ: *Hepatology* 2002;35:1179.
82. JM Moreno, V Cuervas-Mons, E Rubio, et al. Chronic renal dysfunction after liver transplantation in adult patients: Prevalence, risk factors, and impact on mortality. *Transplant Proceed* 2007;35:1907-08.
83. J Ziolkowski, L Paczek, G Senatorski, et al. Renal function after liver transplantation: Calcineurin inhibitor nephrotoxicity. *Transplant Proceed* 2003;35, 2307-09.
84. Schlitt JH, Barkmann A, Boker KHW, et al. *Lancet* 2001;357:587.
85. Wyzgal J, Paczek L, Senatorski G, et al. *Transplant Proc* 2002;34:3185.
86. Nakasuji M, Bookallil MJ. Pathophysiological mechanisms of postrevascularization hyperkalemia in orthotopic liver transplantation. *Anesth Analg* 2000;91:1351-55.
87. McDiarmid SV. Renal function in pediatric liver transplant patients. *Kidney Int Suppl.* 1996;53:S77-84.
88. RC Afonso, R Hidalgo, MPVC Zurstrassen, et al. Impact of renal failure on liver transplantation survival. *Transplantation Proceedings* 2008;40:808-10.
89. Perkins JD. Hyperkalemia and liver transplantation. *Liver Transpl.* 2008;14(2):252-53.

Long-term Care of Recipient

INTRODUCTION

Long-term complications are frequently seen in recipients due to the improved graft and patient survival rates with improvement in surgical techniques, quality of post-operative care and better immunosuppression. Long-term survivors are at risk for developing various medical diseases like cardiovascular, metabolic, and neoplastic conditions.¹⁻⁴

Long-term problems¹²⁶

- Medical diseases
 - Obesity
 - Metabolic syndrome
 - Hypertension
 - Renal dysfunction
 - Hyperuricemia
 - Malignancy
 - Diabetes mellitus
 - Dyslipidemia
 - Cardiovascular risk
 - Osteoporosis
 - Cutaneous disorder
 - Pregnancy, reproductive life and family planning
- Recurrent diseases after liver transplantation
 - Viral etiology-HBV and HCV reactivation
 - Autoimmune hepatitis
 - Primary biliary cirrhosis
 - Primary sclerosing cholangitis
 - Alcohol relapse and liver disease
 - Nonalcoholic steatohepatitis
 - Budd chiari syndrome

OBESITY

In western countries 20-30% of cirrhotic patients are obese at the time of their referral for liver transplantation. The incidence of pretransplant obesity is much less in Asian countries. Weight gain is common after LTX. The over all post-transplant obesity is approximately 20%.⁵ The prevalence of obesity post-transplantation is increasing. Post transplant obesity leads to hepatic steatosis; de novo nonalcoholic fatty liver disease may be more common

than previously thought.⁶ It has been implicated in morbidity among live donors for liver transplantation.⁷

ETIOLOGY

Etiology of post-transplant obesity:¹²⁵

- Lack of diet control
- Less physical activity
- Immunosuppressive drugs—steroids and calcineurin inhibitors
- Diabetes mellitus

Classification of obesity

Status	BMI (wt. kg/ht. meter ²)	Obesity risk
Ideal body weight	18.5-24.9	—
Under weight	< 18.5	+
Over weight	25-29.9	+
Class I obesity	30-34.9	++
Class II obesity	35-39.9	+++
Class III / Morbid obesity	> 40	++++

Wt: weight, ht: height

MANAGEMENT

Management of post-transplant obesity should be aggressive.^{8,9}

- Counseling about obesity related problems like HTN, DM and hyperlipidemia
- Early withdrawal of steroids at 3 months
- Diet control
- Regular exercise
- Hypolipidemic agents for a limited 3-6 month period
- Bariatric surgery is last option, rarely required.

Pre-transplant obesity represents an important cause of morbidity in liver transplant recipients. Obese patients undergoing LTX have an increased risk of complications during the operation and in the immediate postoperative

period, such as wound infections.¹⁰ Weight gain is particularly common during the first year post-transplantation, with close to one-half of patients becoming overweight or obese.^{11,12}

DIABETES MELLITUS

Pre-transplant prevalence of DM in ESLD patients ranges from 1 to 25%^{13–16} and prevalence of post-transplantation diabetes mellitus (PTDM) is 5 to 27%.^{17–20} 5 years patient survival rate is lower in patients with type 2 DM compared to nondiabetics, patient and graft survival rates are lower for type 1 patients compared with type 2 or nondiabetic patients.¹⁶ Mortality rates are high in patients with PTDM.¹⁸ PTDM usually resembles as type I in early post-transplant period but later common resemblance with type II DM. The prevalence of PTDM tends to decrease as levels of immunosuppression are tapered after transplantation.²¹

Canadian diabetes association defines the DM when the fasting plasma blood glucose levels > 7 mmol/L and 2 hr post glucose (75 gm) > 11.1 mmol/L.²²

In ESLD, etiology of DM is^{23–30,125}

- Impaired glucose metabolism
- Insulin resistance (related to impaired liver function as a result of corticosteroid treatment of AIH)
- Underlying liver disease
 - HCV infection (10 times increased risk, prevalence: 21–50%). In contrast Kishi et al reported that HCV was not associated with the prevalence of PTDM after LDLT. PTDM did not influence patient survival.¹⁶⁹
 - NASH
 - Hemochromatosis^{5,6}

RISK FACTORS FOR PTDM^{31–41}

- Pre-transplant DM
- Male gender
- HCV
- Corticosteroids
- Obesity
- Type of immunosuppression
- Alcohol

Patients on tacrolimus have higher rates of hyperglycemia than cyclosporine.¹²⁵ It is due to impaired b-cell function and increased insulin resistance.⁴² Corticosteroids cause poor glucose tolerance because of increased peripheral insulin resistance. HCV infection is an independent predictor for development of PTDM.⁴³ There is a higher prevalence of PTDM in recipients transplanted for HCV compared with 10% or less in those transplanted for other causes.⁴⁴ Mortality risk is also higher among HCV positive recipients with PTDM due

to faster onset and progression of hepatic fibrosis.³⁹ Aldosary et al.¹⁹ also found that recipients transplanted for HCV were at risk for developing PTDM, but he reported that recipients developing PTDM were not found to have a higher incidence of increased graft loss or the onset of malignancy. Glycemic control merits meticulous attention because patients who develop PTDM are at an increased risk for cardiac complications and infections.⁴⁵

TREATMENT

Close monitoring of blood glucose levels is necessary in early post-transplant period regardless of diabetic status or risk.⁴⁶ Both insulin and oral hypoglycemic agents (OHA) are used in PTDM. Many patients cannot achieve glycemic control with oral agents and require insulin.¹²⁶

Monitoring of Blood Glucose in Post-transplant Period

- 1st week: 6 hrly monitoring
- 2nd week to 4th week: Weekly once
- Once at 2nd, 6th and 12 months
- HbA1C once in 3 months if the patient develops PTDM. Treatment required if HbA1C > 6.5%.

If the patient develops diabetes the frequency of monitoring differs from the standard protocols depending severity in glucose intolerance and response to treatment. In patients of PTDM, annual screening for microalbuminemia, complications of DM, lipid profiles and HTN is essential.

Classification of OHA

- Sulfonylurea compounds

<i>1st generation sulfonylureas</i>	<i>2nd generation sulfonylureas</i>
Acetohexamide	Glibenclamide
Chlorpropamide	Glyburide
Tolazamide	Glipizide
Tolbutamide	Glicazide
	Glimepiride
- Biguanides
 - Phenformin
 - Metformin
- α -Glucosidase inhibitors
- Meglitinides: Recent addition to the OHA group. ultra short acting drug
- Thiazolidinediones (known as glitazones) extremely potent in reducing peripheral insulin resistance. Weight gain is common side effect.
 - Troglitazone: First glitazone, though widely used, now it has been withdrawn from the market due to hepatocellular toxicity and death secondary to liver failure.
 - Rosiglitazone (Avandia)
 - Pioglitazone (Actos)

Treatment Recommendations

- Early postoperative period, insulin is required. Once patient starts oral diet, shifted to OHAs
- If the blood sugar control is not adequate with OHAs, then insulin may be added
- One study reported that insulin used in thin patients and OHA in obese patients⁴⁷
- Rosiglitazone with/without sulfonylureas is the standard treatment^{48,49}
- Pioglitazone is an alternative choice to Rosiglitazone⁵⁰
- Metformin is avoided in recipients with renal insufficiency as it precipitates lactic acidosis
- Control of HTN is important to reduce the risk for diabetic complications⁵¹
- Weight control is important to decreased insulin resistance
- Serum lipid levels are also monitored to reduce the cardiovascular morbidity.⁴⁷

DYSLIPIDEMIA

Lipid disorders include elevated low-density lipoprotein (LDL) and triglyceride levels and low high-density lipoprotein levels (HDL). Mixed abnormalities are common. The prevalence of dyslipidemia after liver transplantation is approximately 45%.^{52,53} Recipients with ESLD have altered lipid metabolism and typically hypocholesterolemia except in the presence of cholestatic diseases.

RISK FACTORS

- Obesity
- DM
- Immunosuppressive agents: CYNs, prednisolone and sirolimus.⁵⁴⁻⁵⁷ Cs A induce more hyperlipidemia than tacrolimus⁵⁸

Sirolimus causes dose-dependent dyslipidemia^{59,60} in 50% of kidney⁶¹ and 3.6 to 20%⁶⁴⁻⁶⁷ of liver transplant recipients. It can exacerbate cyclosporine and steroid-induced hypercholesterolemia.⁶² It delays the clearance of circulating LDL, IDL and VLDL due to increased activity of apolipoprotein C, an inhibitor of lipoprotein lipase.⁶³

TREATMENT

- Dietary fat control. Dyslipidemia post-transplantation usually persists despite dietary modification⁵²
- Change the immunosuppressive regimen from cyclosporine to tacrolimus, if required.^{52,67-69}
- Sirolimus should be avoided in lipid abnormalities⁴⁷
- Drug combinations are preferable in dyslipidemia⁶⁷

- LDL-Cholesterol is important in monitoring the patient. If LDL-C is >100 mg/dL, life style modification is necessary.
- Pharmacotherapy
 - Indication for medical treatment:⁹
 - No response/minimal response to life style modification with LDL-Cholesterol >100 mg/dL
 - Baseline LDL-C > 130 mg/dL or if the recipient also has diabetes mellitus
 - Statins (such as lovastatin, simvastatin, pravastatin, cerivastatin and atorvastatin) are the preferred choice.^{71,72} They reduce LDL-C by acting as HMG-CoA reductase inhibitors. Side effects are myopathy and dose related hepatotoxicity. They are known to induce immunomodulation in heart and kidney transplants.

Drug Interactions

Statins interact with CYNs as both are metabolized by the cytochrome CYP3A4.⁷³ Atorvastatin given at 10 mg daily causes increased cyclosporine AUC by approximately 10% without any clinical significance.⁷⁴ Pravastatin has less drug interaction with CYNs.

FOLLOW-UP

Annual screening of lipid profile in patients with cardiovascular risk factors.

METABOLIC SYNDROME

It is more prevalent in liver transplant recipients. It is associated with increased risk of developing cardiovascular morbidity and mortality. NCEP ATP III criteria—Presence of 3 or more of the below mentioned risk factors makes the diagnosis of metabolic syndrome. Treatment of metabolic syndrome is control of the risk factors like control of obesity, HTN, DM and hyperlipidemia.^{75,76}

Factors	Blood level
Fasting blood glucose	≥ 6.1 mmol/L
Fasting triglycerides	
HDL Cholesterol	
Male	< 1.0 mmol/L
Female	< 1.3 mmol/L
Arterial blood pressure	≥ 130/85 mm of Hg
Obesity	Waist circumference
Male	> 102 cm
Women	> 88 cm

CARDIAC DISEASE

Common cardiac problems associated in cirrhotic patients with ESLD are:¹³³

- Ischemic heart disease
- Alcohol related cardiomyopathy
- Cirrhotic cardiomyopathy
- Hypertrophic cardiomyopathy
- Portopulmonary hypertension and right ventricular dysfunction

The presence of these cardiac problems need careful evaluation prior to transplantation and has a significant impact on the post-transplant survival. Cardiovascular disease is a leading cause of death in the late post-transplant period.⁷⁷ Common causes are myocardial ischemia or infarction, arrhythmias during donor liver reperfusion, congestive heart failure, and unstable angina. In patients with symptomatic coronary artery disease outcome of transplantation is poor.

Risk factors for cardiovascular disease¹²⁶

- Advanced age
- Male gender
- Smoking
- Hypertension
- Diabetes mellitus
- Obesity and impaired lipid metabolism (↑ LDL-C, ↓ low HDL-C, ↑ Triglycerides)
- Excessive alcohol abuse
- Less physical activity.

Major cardiac events are more common in patients with the metabolic syndrome compared with those without the metabolic syndrome.¹²⁷ Dobutamine stress echocardiography (DSE) and Nuclear perfusion scan⁷⁸⁻⁸⁰ are useful in pre-operative evaluation. DSE can assess intrapulmonary shunting, pulmonary hypertension and valvular heart disease.¹²⁶

HYPERTENSION

Hypertension is common after LTX, prevalence ranging from 40-80%.⁸¹⁻⁸⁴

RISK FACTORS⁸⁵

- Immunosuppressive treatment-corticosteroids and CINs
- Obesity
- Metabolic syndrome

Immunosuppressive drugs: Tacrolimus causes less hypertension and cardiovascular diseases than cyclosporine.⁸⁶⁻⁸⁸

- Act on renal microvasculature causing renal vasoconstriction
- Promote sodium and water retention by the kidney

TREATMENT

- Lifestyle modification required in diastolic BP 80-90 mm of Hg.⁸⁵
 - Weight loss for overweight recipients
 - Smoking cessation
 - Regular aerobic exercise
- Dietary sodium reduction
- Medical treatment: Indicated when diastolic BP > 90 mm of Hg.
 - Calcium channel blockers (CCBs) (e.g. Amlodipine and Beta blockers, with or without the addition of thiazide diuretics. If edema develops during CCBs treatment it can be controlled by adding thiazide diuretics.
 - Dihydropyridine CCBs (Amlodipine and Nifedipine) are considered as 1st choice antihypertensives as they inhibit endothelin, a potent vasoconstrictor implicated in the pathogenesis of post-transplant hypertension.⁸⁹
 - Spironolactone, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can be beneficial in patients with PTDM, but potassium levels should be monitored as these medications can augment CIN-related hyperkalemia.
 - Thiazide diuretics when combined with CINs, may precipitate hyperuricemia and gout.
 - CCB when combined with CINs, may elevate the trough levels of CINs by competing for CYP3A4.

Recently Galioto et al¹³⁴ in his series, reported that monotherapy with anti-hypertensive schedule is efficient in 20.6 and 28.6% of patients with *de novo* arterial hypertension after OLT at 6 months and 12 months, respectively. Carvedilol monotherapy is probably preferable as the first-choice drug because it is far better tolerated than nifedipine. CINs trough blood levels during treatment with carvedilol should be closely monitored in order to promptly adjust the CIN dose. In partial responders to monotherapy, the introduction of an ACE inhibitor as a second drug normalizes blood pressure in less than 20% of cases. In this context, the combined schedule with nifedipine plus ramipril is more effective than that with carvedilol plus ramipril. The normalization of blood pressure is an important factor for preserving renal function after LTX.

OSTEOPOROSIS

Bone mineral density is low in patients with cirrhosis caused by both cholestatic and non-cholestatic liver diseases.⁹⁰⁻⁹⁴ Osteoporosis is more common in cholestatic liver diseases like primary biliary cirrhosis and primary sclerosing cholangitis,⁹⁵ which may be one of the initial clinical manifestations.⁹⁶ Fracture rates up to 25 to 35%,

usually occur in the first 3-6 months⁹⁷ Fracture rate is gradually declining after introduction of CINs and early withdrawal of steroids. Bai et al. reported the presence of high incidence of low bone mineral density (BMD) in the pre-transplant patients with liver diseases. The elevated intact parathyroid hormone (iPTH) level is the predominant risk factor for low BMD and both BMD and iPTH examinations should be considered routine tests to identify the status of bone mass and bone metabolism among recipients prior to LTX.¹²⁸

RISK FACTORS

- Female gender
- Postmenopausal age/hypogonadism
- Advanced age
- Smoking.

MECHANISM OF OSTEOPOROSIS⁹⁸

Hepatic osteodystrophy⁹⁹ due to

- Intestinal malabsorption of calcium
- Ineffective vitamin D regulation
- Hypogonadism
- Cholestasis.

PRESENTATION

- Avascular necrosis
- Fractures mostly in the spine
- Osteoporosis.

EFFECT OF CORTICOSTEROIDS ON BONES¹⁰⁰⁻¹⁰³

- Suppression of bone formation.
- Trabecular bone loss occurs early during treatment followed by cortical bone.
- Bone loss is not dose related and more bone loss in the 1st 6 months of treatment, rate of Fragility fracture increased even in those taking low doses.
- Fracture risk returns to baseline after treatment is discontinued.
- Steroid withdrawal has been shown to hasten the recovery of spinal bone mass.

INVESTIGATIONS

- Serum calcium and phosphate level
- Alkaline phosphatase
- Parathyroid hormone level and serum 25-hydroxyvitamin D levels.
- Spine radiographs show vertebral deformity
- Bone densitometry (DXA scan): It is the gold standard for diagnosing osteoporosis. Usually done at the level

of lumbar spine and femoral neck. Bone mineral density (BMD) score less than - 2.5 indicates osteoporosis and in between - 1 to - 2.5 indicates osteopenia.

Khan, et al. reported that osteopenia determined by lumbar spine BMD underestimates poor BMD in young adults after LTX. Maintaining muscle mass may be helpful in preserving BMD.

TREATMENT

Aim of Treatment

To achieve optimal bone health before transplantation and to prevent bone loss by prophylactic treatment.

- Lifestyle modifications
 - Adequate calcium intake
 - Proper nutrition
 - Reduction of caffeine intake
 - Maintenance of normal body weight
 - Regular physical exercise
 - Discontinuation of smoking and alcohol use.
- Revision of the immunosuppression regimen, particularly duration of corticosteroid use.
- Start antiresorptive agents: Alendronate 70 mg/wk after transplantation.
- Calcium supplementation: 1-1.5 gm/day
- Vitamin D supplementation: 400-800 IU/day
- Intravenous pamidronate effective in preventing post-transplant bone loss in trabecular bone (i.e. lumbar spine) and not long bones¹⁰⁴
- Calcitonin: Available as injection and nasal inhaler. it decreases bone resorption through osteoclast activity inhibition effective in the treatment of corticosteroid-induced osteoporosis⁹⁹ used in patients who cannot tolerate bisphosphonate therapy.¹⁰⁵

HYPERURICEMIA

The incidence of hyperuricemia in post-transplant patients is > 40%. There is no significant difference in the development of gout in CsA and tacrolimus.

ETIOLOGY

Decreased uric acid clearance by the kidneys due to CIN induced decrease in GFR. Hyperuricemia may further decrease the renal function causing more hyperuricemia.

RISK FACTORS

- Immunosuppression: CINs
- Obesity
- Diuretic therapy: thiazide diuretics

TREATMENT

- Colchicine: 1st line treatment for gout.
- NSAIDs have role, but used with caution in patients with compromised renal function. They may further reduce GFR.
- Allopurinol: It is used as maintenance therapy to decrease the blood uric acid levels and to prevent the secondary attack on in patients with history of gout. Its use in liver transplant patients with hyperuricemia with increased serum creatinine is found to improve the renal function. In the absence of gout, allopurinol may be used to improve the renal function in patients with impaired GFR.¹⁰⁶ Allopurinol should not be combined with azathioprine, as it interferes with metabolism of azathioprine.

MALIGNANCY

Liver transplant recipients have a high risk of developing de novo cancers as compared to the general population with a greater tendency to relapse, as a result of the immunosuppressive treatment, which they must endure for life. Various tumors seen in after liver transplantation are originating from skin, lung, urothelium, buccal cavity, brain, thyroid gland, stomach, non-hodgkins lymphoma and some unknown tumors. The most frequent neoplasms are skin cancers. The most common cancer types were lymphoma and skin cancer. Non-Hodgkin lymphoma in the form of PTLD occurs in male patients transplanted at a younger age, and soon after transplantation.¹³² Some studies have reported that the use of an alternative immunosuppressive regimen, such as MMF, is associated with a lower risk for leukemia and lymphoma.^{130,131} Nonmelanoma skin cancer, on the other hand, occurred more often at an older age, and the risk did not vary between genders or with the time after transplantation. Induction therapy with antibodies was associated with a 6-fold risk of skin cancers in comparison with patients that had not received antibodies.

Cutaneous malignancies and lymphomas are the most common after LTX. Incidence of malignancy rate ranges from 2.3 to 26.2%.¹⁰⁷⁻¹¹³ In one study, GI malignancies (e.g. colon adenocarcinoma) constitute 46% of all nonskin and nonlymphoid tumors. Malignancies are one of the important causes of late mortality in long-term survivors of LTX.¹¹⁴⁻¹¹⁶ Incidence of de novo malignancies is on rise in liver transplant patients. Aberg et al.¹³² reported that the cumulative incidence of post-transplant de novo cancer at 1, 5, 10, and 20 years was 3%, 5%, 13%, and 16%, respectively. The respective cumulative de novo cancer related mortality rates were 0%, 1%, 2%, and 2%. Eighty percent of the post-transplant cancers were detected at an age of 45-74 years.¹³² Oropharyngeal

cancers are more commonly seen in those with alcoholic liver disease and particularly in those with a smoking history.¹³⁵ The rate of renal cell cancers was much higher in the series of cases from the Netherlands. Colonic cancers are more common in patients with PSC and IBD. Barrett's esophagitis is a risk for carcinoma esophagus.¹³⁵

RISK FACTORS FOR POST-TRANSPLANT MALIGNANCIES^{110,114,117-120}

- Older age
- Infection with hepatitis C and CMV
- Prolonged exposure to immunosuppression
- Tobacco use
- Alcohol
- Diagnosis at the time of transplantation
- Child score at the time of transplantation
- EBV seronegativity pretransplantation
- Use of OKT3

Alcohol and Tobacco

Patients transplanted for alcoholic liver disease have a higher incidence of oropharyngeal tumors compared to other indications.¹²¹ Long-term alcohol intake can induce genetic alterations that potentiate those of tobacco smoke.¹²²

CINs

Higher incidence of neoplasia in those receiving tacrolimus in comparison to cyclosporine.¹¹⁴ Azathioprine has been found to be an independent risk factor for tumor development.¹²³ But it is less frequently used in present LTX programs.

Cutaneous Diseases

Skin of transplant patient requires special attention. Mucocutaneous and dermatological manifestations of ESLD disappear after transplantation. Maculopapular lesions appear in graft versus host disease. Transplant patients are at increased risk of developing nonmelanotic skin cancer and squamous cell cancer (around 70 times more than general population). Squamous cell carcinoma is more common followed by basal cell carcinoma.¹²⁴ Precautions to prevent skin cancers are to avoid intense exposure to sunlight, use of sunscreen lotions and dark clothes. Lesions like leukoplakia, verrucae should be referred for opinion of dermatologist.

SURVIVAL

Survival rate is better in cutaneous cancers than nonskin cancers.¹⁰⁹ Use of adequate sunscreen is recommended

along with an annual dermatology assessment. Higher mortality rate is in recipients with lung cancers and lymphomas.¹¹³

REFERENCES

1. Stegall MD, Everson G, Schroter G, et al. Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension, and obesity. *Transplantation* 1995;60(9):1057-60.
2. Reuben A. Long-term management of the liver transplant patient: Diabetes, hyperlipidemia, and obesity. *Liver Transp.* 2001;7(11 Suppl 1):S13-21.
3. Rabkin JM, de La Melena V, Orloff SL, et al. Late mortality after orthotopic liver transplantation. *Am J Surg* 2001;181(5):475-79.
4. Asfar S, Metrakos P, Fryer J, et al. An analysis of late deaths after liver transplantation. *Transplantation* 1996;61(9):1377-81.
5. Everheart JE, Lombardero, Lake JR, et al. Weight change and obesity after liver transplantation: Incidence and risk factors. *Liver transp. surg* 1998;4:285-96.
6. Seo S, Maganti K, Khehra M, et al. De novo nonalcoholic fatty liver disease after liver transplantation. *Liver Transp.* 2007;13(6):844-47.
7. Yamamoto K, Takada Y, Fujimoto Y, et al. Nonalcoholic steatohepatitis in donors for living donor liver transplantation. *Transplantation* 2007;83(3):257-62.
8. Cassiman D, Roelants M, Vandenplas G, et al. Orlistat treatment is safe in overweight and obese liver transplant recipients: A prospective, open label trial. *Transp. Int* 2006;19(12):1000-05.
9. Muñoz SJ, ElGenaidi H. Cardiovascular risk factors after liver transplantation. *Liver Transp.* 2005;11(11 Suppl 1):S52-6.
10. Sawyer RG, Pelletier SJ, Pruett TL. Increased early morbidity and mortality with acceptable long-term function in severely obese patients undergoing liver transplantation. *Clin Transplant* 1999;13:126-30.
11. Munoz SJ, Deems RO, Moritz MJ, et al. Hyperlipidemia and obesity after orthotopic liver transplantation. *Transplant Proc* 1991;23:1480-83.
12. Stegall MD, Everson G, Schroter G, et al. Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension, and obesity. *Transplantation* 1995;60:1057-60.
13. Baid S, Cosimi AB, Farrell ML, et al. Post-transplant diabetes mellitus in liver transplant recipients: Risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation* 2001;72(6):1066-72.
14. Blanco JJ, Herrero JL, Quiroga J, et al. Liver transplantation in cirrhotic patients with diabetes mellitus: Midterm results, survival, and adverse events. *Liver Transpl* 2001;7(3):226-33.
15. Zein NN, Abdulkarim AS, Wiesner RH, et al. Prevalence of diabetes mellitus inpatients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol* 2000;32(2):209-17.
16. Yoo HY, Thuluvath PJ. The effect of insulin-dependent diabetes mellitus on outcome of liver transplantation. *Transplantation* 2002;74(7):1007-12.
17. Krentz AJ, Dmitrevski J, Mayer D, et al. Postoperative glucose metabolism in liver transplant recipients: A two-year prospective randomized study of cyclosporine versus FK506. *Transplantation* 1994;57(11):1666-69.
18. Navasa M, Bustamante J, Marroni C, et al. Diabetes mellitus after liver transplantation: Prevalence and predictive factors. *J Hepatol* 1996;25(1):64-71.
19. AlDosary AA, Ramji AS, Elliott TG, et al. Post-liver transplantation diabetes mellitus: An association with hepatitis C. *Liver Transpl* 2002;8(4):356-61.
20. Saab S, Shpaner A, Zhao Y, et al. Prevalence and risk factors for diabetes mellitus in moderate term survivors of liver transplantation. *Am J Transplant* 2006;6(8):1890-95.
21. Navasa M, Bustamante J, Marroni C, et al. Diabetes mellitus after liver transplantation: Prevalence and predictive factors. *J Hepatol* 1996;25:64-71.
22. Canadian diabetic association. Clinical practice guidelines expert committee. Pharmacological management of type II diabetes; website: www.diabetes.ca/cpg2003
23. Nolte W, Hartmann H, Ramadori G. Glucose metabolism and liver cirrhosis. *Exp Clin Endocrinol Diabetes* 1995;103(2):63-74.
24. Letiexhe MR, Scheen AJ, Gerard PL, et al. Insulin secretion, clearance, and action on glucose metabolism in cirrhotic patients. *J Clin Endocrinol Metab* 1993;77(5):1263-8.
25. Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999;30(4):1059-63.
26. Allison ME, Wreghitt T, Palmer CR, et al. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol* 1994;21(6):1135-39.
27. Lecube A, Hernandez C, Genesca J, et al. High prevalence of glucose abnormalities in patients with hepatitis C virus infection: A multivariate analysis considering the liver injury. *Diabetes Care* 2004;27(5):1171-75.
28. Kingston ME, Ashcraft M, Atiyeh M, et al. Diabetes mellitus in chronic active hepatitis and cirrhosis. *Gastroenterology* 1984;87(3):688-94.
29. Collins JR, Lacy WW, Stiel JN, et al. Glucose intolerance and insulin resistance in patients with liver disease. *Arch Intern Med* 1970;126(4):608-14.
30. Mason AL, Lau JY, Hoang N, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999;29(2):328-33.
31. Trail KC, McCashland TM, Larsen JL, et al. Morbidity in patients with post-transplant diabetes mellitus following orthotopic liver transplantation. *Liver Transpl Surg* 1996;2(4):276-83.
32. Steinmuller TH, Stockmann M, Bechstein WO, et al. Liver transplantation and diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2000;108(6):401-05.
33. Wahlstrom HE, Cooper J, Gores G, et al. Survival after liver transplantation in diabetics. *Transplant Proc* 1991;23(1 Pt 2):1565-6.
34. Khalili M, Lim JW, Bass N, et al. New onset diabetes mellitus after liver transplantation: The critical role of hepatitis C infection. *Liver Transpl* 2004;10(3):349-55.
35. Marroni CA, Hoppe L, Diehl JL, et al. Diabetes mellitus and liver transplantation in adults. *Transplant Proc* 1999;31(7):3046.
36. Ericzon B, Groth C, Bismuth H, et al. Glucose metabolism in liver transplant recipients treated with FK 506 or cyclosporine in the European multicentre study. *Transpl Int* 1994;7(Suppl 1):S11-4.
37. Tueche SG. Diabetes mellitus after liver transplant new etiologic clues and cornerstones for understanding. *Transplant Proc* 2003;35(4):1466-68.

38. Mora PF. Post-transplantation diabetes mellitus. *Am J Med Sci* 2005;329(2):86-94.
39. Foxton MR, Quaglia A, Muiesan P, et al. The impact of diabetes mellitus on fibrosis progression in patients transplanted for hepatitis C. *Am J Transplant* 2006;6(8):1922-29.
40. Krentz AJ, Dousset B, Mayer D, et al. Metabolic effects of cyclosporine A and FK506 in liver transplant recipients. *Diabetes* 1993;42(12):1753-59.
41. US Multicentre FK506 Liver Study Group. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994;331(17): 1110-15.
42. Rilo HL, Zeng Y, Alejandro R, et al. Effect of FK506 on human islets of Langerhans. *Transplant Proc* 1991;23(6):3164-65.
43. Soule JL, Olyaei AJ, Boslaugh TA, et al. Hepatitis C infection increases the risk of new-onset diabetes after transplantation in liver allograft recipients. *Am J Surg* 2005;189(5):522-27.
44. Bigam DL, Pennington JJ, Carpentier A, et al. Hepatitis C-related cirrhosis: A predictor of diabetes after liver transplantation. *Hepatology* 2000;32(1):87-90.
45. John PR, Thuluvath PJ. Outcome of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. *Liver Transplant* 2002;8:708-13.
46. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. *Transplantation* 2003;75(10 Suppl):S3-24.
47. Salvadori M, Bertoni E, Rosati A, et al. Post-transplant diabetes mellitus. *J Nephrol* 2003;16(5):626-34.
48. Villanueva G, Baldwin D. Rosiglitazone therapy of post-transplant diabetes mellitus. *Transplantation* 2005;80(10):1402-05.
49. Baldwin D Jr, Duffin KE. Rosiglitazone treatment of diabetes mellitus after solid organ transplantation. *Transplantation* 2004;77(7):1009-14.
50. Luther P, Baldwin D Jr. Pioglitazone in the management of diabetes mellitus after transplantation. *Am J Transplant* 2004;4(12):2135-8.
51. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837-53.
52. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. *Transplantation* 1997;63(3):331-38.
53. Palombo JD, Lopes SM, Zeisel SH, et al. Effectiveness of orthotopic liver transplantation on the restoration of cholesterol metabolism in patients with end-stage liver disease. *Gastroenterology* 1987;93(6):1170-77.
54. Trotter JF, Wachs M, Bak T, et al. Liver transplantation using sirolimus and minimal corticosteroids (3-day taper). *Transplantation* 2001;7(4):343-51.
55. Charco R, Cantarell C, Vargas V, et al. Serum cholesterol changes in long-term survivors of liver transplantation: A comparison between cyclosporine and tacrolimus therapy. *Liver Transplant Surg* 1999;5:204-08.
56. Manzarbeitia C, Reich DJ, Rothstein KD, et al. Tacrolimus conversion improves hyperlipidemic states in stable liver transplant recipients. *Liver Transplant* 2001;7:93-99.
57. Trotter JF, Wachs ME, Trouillot TE, et al. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. *Liver Transplant* 2001;7:401-08.
58. Steinüller TM, Graef KJ, Schleicher J, et al. The effect of FK 506 vs. cyclosporine on glucose and lipid metabolism—a randomized trial. *Transplantation* 1994;58(6):669-74.
59. Kahan BD. Sirolimus: A new agent for clinical renal transplantation. *Transplant Proc* 1997;29(1-2):48-50.
60. Murgia MG, Jordan S, Kahan BD. The side effect profile of sirolimus: A phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients. *Kidney Int* 1996;49(1):209-16.
61. MacDonald AS, RAPAMUNE Global Study Group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001;71(2):271-80.
62. Keane WF. Lipids and progressive renal disease: The cardio-renal link. *Am J Kidney Dis* 1999;34(2):xliii-vi.
63. Morrisett JD, Abdel-Fattah G, Hoogveen R, et al. Effect of sirolimus on plasma lipids and lipoprotein levels in renal transplant patients. *Transplantation* 1999;67(Suppl):S60.
64. Trotter JF, Wachs ME, Trouillot TE, et al. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. *Liver Transpl* 2001;7(5):401-08.
65. Watson CJ, Friend PJ, Jamieson NV, et al. Sirolimus: A potent new immunosuppressant for liver transplantation. *Transplantation* 1999;67(4):505-09.
66. McAlister VC, Peltekian KM, Malatjalian DA, et al. Orthotopic liver transplantation using low-dose tacrolimus and sirolimus. *Liver Transpl* 2001;7(8):701-08.
67. Kniepeiss D, Iberer F, Schaffellner S, et al. Dyslipidemia during sirolimus therapy in patients after liver transplantation. *Clin Transplant* 2004;18(6):642-46.
68. Pratschke J, Neuhaus R, Tullius SG, et al. Treatment of cyclosporine-related adverse effects by conversion to tacrolimus after liver transplantation. *Transplantation* 1997;64(6):938-40.
69. Manzarbeitia C, Reich DJ, Rothstein KD, et al. Tacrolimus conversion improves hyperlipidemic states in stable liver transplant recipients. *Liver Transpl* 2001;7(2):93-99.
70. Roy A, Kneteman N, Lilly L, et al. Tacrolimus as intervention in the treatment of hyperlipidemia after liver transplant. *Transplantation* 2006;82(4):494-500.
71. Grundy S, Cleeman J, Bairey N, et al. Implications of recent clinical trials for the national Cholesterol Education program adult treatment panel III guidelines. *Circulation* 2004;110(2):227-39.
72. Gazi IF, Liberopoulos EN, Athyros VG, et al. Statins and solid organ transplantation. *Curr Pharm Des* 2006;12(36):4771-83.
73. Holdaas H, Fellstrom B, Jardine A. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: Lessons to be learnt from the assessment of Lescol in renal transplantation (ALERT) trial. *Am J Transplant* 2005;5(6):1574-75.
74. Taylor PJ, Kubler PA, Lynch SV, et al. Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. *Ann Pharmacother* 2003;38(2):205-08.
75. National cholesterol education programme (NCEP) expert panel. Expert panel on detection, elevation and treatment of high blood cholesterol in adults. Final report. *Circulation* 2002;106:3143-21.
76. Grundy SM, Brewer B, Cleeman JI, et al. Definition of metabolic syndrome. Report of national heart, lung and blood

- institute/American heart association on scientific issues related to identification. *Circulation* 2004;109:433-38.
77. Abbasoglu O, Levy MF, Brkic BB, et al. Ten years of liver transplantation: An evolving understanding of late graft loss. *Transplantation* 1997;64:1801-07.
78. Plotkin JS, Scott VL, Pinna A, et al. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996;2(6):426-30.
79. Donovan CL, Marcovitz PA, Punch JD, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation* 1996;61(8):1180-88.
80. Williams K, Lewis JF, Davis G, et al. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. *Transplantation* 2000;69(11):2354-56.
81. Neal DA, Tom BD, Luan J, et al. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? *Transplantation* 2004;77(1):93-99.
82. Stegall MD, Everson G, Schorter G, et al. Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension and obesity. *Transplantation* 1995;15:1057-60.
83. Gonwa TA. Hypertension and renal dysfunction in long-term liver transplant recipients. *Liver transpl* 2001;7:22-26.
84. Johnston SD, Norris JK, Cramb R, et al. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation* 2002;73:901-06.
85. Munoz SJ, ElGenaidi H. Cardiovascular risk factors after liver transplantation. *Liver Transpl* 2005;11(11 Suppl 1):S52-6.
86. Rabkin J, Corless C, Rosen H, et al. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. *Am J Surg* 2002;183(5):595-99.
87. Neal DA, Gimson AE, Gibbs P, et al. Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl* 2001;7(6):533-39.
88. Dikow R, Degenhard M, Kraus T, et al. Blood pressure profile and treatment quality in liver allograft recipients: benefit of tacrolimus versus cyclosporine. *Transplant Proc* 2004;36(5):1512-5.
89. Lerman A, Click RL, Narr BJ, et al. Elevation of plasma endothelin associated with systemic hypertension in humans following orthotopic liver transplantation. *Transplantation* 1991;51:646-50.
90. Giannini S, Nobile M, Dalle Carbonare L, et al. Vertebral morphometry by X-ray absorptiometry before and after liver transplant: A cross-sectional study. *Eur J Gastroenterol Hepatol* 2001;13:1201-07.
91. Figueiredo FA, Brandao C, Perez Rde M, et al. Low bone mineral density in noncholestatic liver cirrhosis: Prevalence, severity and prediction. *Arq Gastroenterol* 2003;40:152-58.
92. Guichelaar MM, Malinchoc M, Sibonga J, et al. Bone metabolism in advanced cholestatic liver disease: Analysis by bone histomorphometry. *Hepatology* 2002;36:895-903.
93. Hodgson SF, Dickson ER, Wahner HW, et al. Bone loss and reduced osteoblast function in primary biliary cirrhosis. *Ann Intern Med* 1985;103:855-60.
94. Monegal A, Navasa M, Guanabens N, et al. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. *Calcif Tissue Int* 1997;60:148-54.
95. Collier JD, Ninkovic M. Guidelines on the management of osteoporosis associated with chronic liver disease. *Gut* 2002;50(Suppl 1):1-19.
96. Leslie WD, Bernstein CN, Leboff MS. American gastroenterological association clinical practice committee. AGA technical review on osteoporosis in hepatic disorders. *Gastroenterology* 2003;125(3):941-66.
97. Haagsma EB, Thijn CJ, Post JG, et al. Bone disease after orthotopic liver transplantation. *J Hepatol* 1988;6(1):94-100.
98. McCaughan GW, Feller RB. Osteoporosis in chronic liver disease: Pathogenesis, risk factors, and management. *Dig Dis* 1994;12:223-31.
99. Rouillard S, Lane NE. Hepatic osteodystrophy. *Hepatology* 2001;33(1):301-7.
100. Lichtenstein GR, Sands BE, Pazianas M. Prevention and treatment of osteoporosis in inflammatory bowel disease. *Inflamm Bowel Dis* 2006;12(8):797-813.
101. Sambrook P, Birmingham J, Kempster S, et al. Corticosteroid effects on proximal femur bone loss. *J Bone Miner Res* 1990;5(12):1211-6.
102. Van Staa T, Leufkens HG, Abenhaim L, et al. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15(6):993-1000.
103. Diaz-Guerra GM, Gomez R, Jodar E, et al. Long-term follow-up of bone mass after orthotopic liver transplantation: Effect of steroid withdrawal from the immunosuppressive regimen. *Osteoporos Int* 2002;13:147-50.
104. Pennisi P, Trombetti A, Giostra E, et al. Pamidronate and osteoporosis prevention in liver transplant recipients. *Rheumatol Int* 2006;27(3):251-56.
105. Sanchez AJ, Aranda-Michel J. Liver disease and osteoporosis. *Nutr Clin Pract* 2006;21(3):273-78.
106. Neal DA, Tom BDM, Gimson AES, et al. Hyperuricemia, gout and renal function after liver transplantation. *Transplantation* 2001;72:1689-91.
107. ME Romero-Vargas, M Flores-Cortés, Z Valera, et al. Cancers of new appearance in liver transplant recipients: Incidence and Evolution. *Transplant Proceed* 2006;38:2508-10.
108. Sheil AGR. Malignancy following liver transplantation: A report from the Australian Combined Liver Transplant Registry. *Transplant Proc* 1995;27(1):1247.
109. Jain AB, Yee LD, Nalesnik MA, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end results data. *Transplantation* 1998;66(9):1193-200.
110. Jain A, DiMartini A, Kashyap R, et al. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. *Transplantation* 2000;70(9):1335-42.
111. Levy M, Backman L, Husberg B, et al. De novo malignancy following liver transplantation: a single center study. *Transplant Proc* 1993;25(1 Pt 2):1397-99.
112. Sheiner PA, Magliocca JF, Bodian CA, et al. Long-term medical complications in patients surviving 5 years after liver transplantation. *Transplantation* 2000;69(5):781-89.
113. Sanchez EQ, Marubashi S, Jung G, et al. De novo tumors after liver transplantation: A single-institution experience. *Liver Transpl* 2002;8(3):285-91.
114. Herrero JI, Lorenzo M, Quiroga J, et al. De novo neoplasia after liver transplantation: An analysis of risk factors and influence on survival. *Liver Transpl* 2005;11(1):89-97.

115. Fung JJ, Jain A, Kwak EJ, et al. De novo malignancies after liver transplantation: A major cause of late death. *Liver Transpl* 2001;7(Suppl 1):S109-18.
116. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. *Crit Rev Oncol Hematol* 2005;56(1):87-99.
117. Herrero JI, Lucena JF, Quiroga J, et al. Liver transplantation recipients older than 60 years have lower survival and higher incidence of malignancy. *Am J Transplant* 2003;3(11):1407-12.
118. Saigal S, Norris S, Muiesan P, et al. Evidence of differential risk for post-transplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. *Liver Transpl* 2002;8(5):482-87.
119. Jimenez C, Marques E, Manrique A, et al. Incidence and risk factors of development of lung tumors after liver transplantation. *Transplant Proc* 2005;37(9):3970-72.
120. Duvoux C, Pageaux GP, Vanlemmens C, et al. Risk factors for lymphoproliferative disorders after liver transplantation in adults: An analysis of 480 patients. *Transplantation* 2002;74(8):1103-09.
121. Duvoux C, Delacroix I, Richardet JP, et al. Increased incidence of oropharyngeal squamous cell carcinomas after liver transplantation for alcoholic cirrhosis. *Transplantation* 1999;67(3):418-21.
122. Castelli E, Hrelia P, Maffei F, et al. Indicators of genetic damage in alcoholics: Reversibility after alcohol abstinence. *Hepatogastroenterology* 1999;46(27):1664-68.
123. Su CG, Stein RB, Lewis JD, et al. Azathioprine or 6-mercaptopurine for inflammatory bowel disease: Do risks outweigh benefits? *Dig Liver Dis* 2000;32(6):518-31.
124. Mitboefer AB, Sapran S, Freeman R. Risk factors associated with the development of skin cancer after liver transplantation. *Liver Transpl* 2002;8:939.
125. Y Kishi, Y Sugawara, S Tamura, et al. New-onset diabetes mellitus after living donor liver transplantation: Possible association with hepatitis C. *Transplant Proceed* 2008;38:2989-92.
126. Lawrence U, Liu, Thomas D, Schiano. Long-term care of the liver transplant recipient. *Clin Liver Dis* 2007;11:397-416.
127. Laryea M, Watt KD, Molinari M, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transplant* 2007;13:1109-14.
128. XL Bai, TB Liang, LH Wu, et al. Elevation of intact parathyroid hormone level is a risk factor for low bone mineral density in pretransplant patients with liver diseases. *Transplant Proceed* 2007;39:3182-85.
129. KM Khan, S Mulia, R Kaul, et al. Effect of nutrition and body composition on bone density after liver transplantation. *Transplant Proceed* 2007;39:3292-94.
130. Dharmidharka VR, Ho PL, Stablein DM, et al. Mycophenolate, tacrolimus and post-transplant lymphoproliferative disorder: A report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002;6:396-99.
131. Triemer HL, Pearson TC, Odom KL, et al. Analysis of a single-center experience with mycophenolate mofetil based immunosuppression in renal transplantation. *Clin Transplant* 2000;14(pt 2):413-20.
132. F Åberg, E Pukkala, K Höckerstedt, et al. Risk of malignant neoplasms after liver transplantation: A population-based study. *Liver transplantation* 2008;14:1428-36.
133. G Della Rocca, MG Costa, L Pompei, et al. The Liver Transplant Recipient With Cardiac Disease. *Transplant Proceed* 2008;40:1172-74.
134. A Galioto, A Semplicini, G Zanusi, et al. Nifedipine versus carvedilol in the treatment of De Novo arterial hypertension after liver transplantation: Results of a controlled clinical trial. *Liver transplantation* 2008;14:1020-28.
135. AK Jain, VP Patil, and John Fung. Incidence of De Novo cancer and lymphoproliferative disorders after liver transplantation in relation to age and duration of follow-up. *Liver transplantation* 2008;14:1406-11.

Pregnancy after Liver Transplantation

INTRODUCTION

Pregnancy after liver transplantation is generally associated with good outcome and seem to not affect graft and patient survival.^{1,2} The first liver transplantation was performed in 1963 and the first delivery of liver transplanted woman was reported in 1978. In 1991, The National Transplantation Pregnancy Registry (NTPR) was established in USA with the aim of collecting and analyzing data about pregnancies and deliveries among graft recipients.¹ Women constitute one third of liver recipients and approximately 75% of female recipients are of reproductive age. In 50% of females with ESLD, menstrual problems are seen.³ Amenorrhea and subfertility are common. Restoration of menstrual bleeding can occur in 2-6 months and >80% of patients regain their normal menstrual cycle within 8 months after transplantation.⁴⁻⁶

CONTRACEPTION AFTER TRANSPLANTATION

All female recipients of childbearing age should be on contraceptives after transplantation. Low-dose hormonal contraception is effective, well tolerated, and without any adverse effects on the graft,²⁷ alternatively intrauterine contraceptive devices can be used.

TIME INTERVAL BETWEEN TRANSPLANTATION AND PREGNANCY

Usually 1-2 years in most of the transplant programs and is based on pregnancy in renal transplant recipients.⁷ Intervals shorter than 12 months have been associated with poor outcomes and higher complication rates.^{1,2} This is due to increased incidence of graft rejection, infections and achievement of low immunosuppression levels. Rate

of graft rejection in pregnancy ranges from 4 to 17% and responds to corticosteroid boluses.⁸⁻¹⁰

IMMUNOSUPPRESSIVE DRUGS AND PREGNANCY

Women planning for pregnancy should be referred to their transplant center for evaluation of their immunosuppression regimen prior to conception. All immunosuppressive agents cross placental barrier.¹¹

CORTICOSTEROIDS

Cross the placental barrier, but 90% of the maternal dose is metabolized within the placenta before reaching the fetus.¹²

CINs

They cross the placental barrier and enter the fetal circulation¹³ and the blood levels of these agents in the fetus are half the levels in the mother.^{8,14,15}

In a pregnant patient on cyclosporine treatment, there is increased risk of:

- IUGR (Intrauterine growth retardation)
- Preterm delivery
- Pre-eclampsia^{14,16}
- Hypertension (40%-46%)^{2,17}

But after introduction of tacrolimus, the incidence of Pre-eclampsia and hypertension have decreased as compared to cyclosporine.^{8,18} There is no significance difference in the incidence of malformations in children of recipients of liver transplantation and general population (~ 3%).¹⁹ All the pregnancies after liver transplantation should be considered as high risk pregnancies. Tacrolimus-based immunosuppression is believed to be most beneficial for patient and graft

survival in OLT recipients in comparison to a Cyclosporine A.²⁵

MMF

It should be avoided immediately prior to and during pregnancy.

There have been reports of a greater frequency of pruritus and cholestasis of pregnancy among OLT recipients.²⁰

In USA, rate of maternal hypertension was 35%, the rate of pre-eclampsia was 23%, and the rate of a rejection episode during pregnancy was 8%.²⁴ Rate of complications in newborn in transplant recipients is 29% and no neonatal deaths.²⁴ Rate of birth defects in kidney transplant recipients on CINs is 4%.²⁴ Patients with elevated serum creatinine and hypertension were at more risk for preterm delivery.²⁶

DELIVERY IN LIVER TRANSPLANT RECIPIENT

Pregnancy in these patients is considered high-risk but does not itself indicate the need for cesarean section. Vaginal delivery was observed to be uneventful and safe in women after liver transplantation. However the rate of cesarean section among liver recipients remains high and ranges from 45 to 71%.^{2,17,21,27,28} Increased levels of prophylactic steroids may be necessary at delivery.²¹ One study reported that high rate of cesarean sections in liver recipients is associated with a great incidence of obstetric complications of pregnancy.²² Safe and uneventful vaginal delivery is possible and associated with significantly shorter postpartum length of hospitalization.²⁷

BREASTFEEDING

Prednisone and azathioprine are detected in small quantities in breast milk. CINs in breast milk usually reach the same concentrations close to that in maternal serum.^{8,13} There are no definite guidelines for immunosuppression during lactation. American academy of pediatrics endorses breastfeeding by mothers taking prednisone but advises against breastfeeding by those taking cyclosporine due to possible immunosuppression and its unknown effect on growth or carcinogenesis. Recommendations are not clear for those taking tacrolimus or azathioprine.²³

REFERENCES

- Armenti VT, Radomsky JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. *Clin Transpl* 2000;123.
- Radomsky JS, Moritz MJ, Munoz SJ, et al. National transplantation pregnancy registry: Analysis of pregnancy outcomes in female liver transplant recipients. *Liver Transpl Surg* 1995;1:281.
- Christopher V, Al-Chalabi T, Richardson PD, et al. Pregnancy outcome after liver transplantation: A single-center experience of 71 pregnancies in 45 recipients. *Liver Transpl* 2006;12(7):1138-43.
- Cundy TF, O'Grady JG, Williams R. Recovery of menstruation and pregnancy after liver transplantation. *Gut* 1990;31(3):337-38.
- Riely CA. Contraception and pregnancy after liver transplantation. *Liver Transpl* 2001;7(11):S74-6.
- Brown KA, Lucey MR. Liver transplantation restores female reproductive endocrine function. *Hepatology* 1991;13(6):1255-57.
- Hou S. Pregnancy in chronic renal insufficiency and end stage liver disease. *Am J Kidney Dis* 1999;33(2):235-52.
- Jain AB, Reyes J, Marcos A, et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: A single center's experience update after 13 years. *Transplantation* 2003;76(5):827-32.
- Kainz A, Harabacz I, Cowlrick IS, et al. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000;70(12):1718-21.
- Nagy S, Bush MC, Berkowitz R, et al. Pregnancy outcome in liver transplant recipients. *Obstet Gynecol* 2003;102(1):121-28.
- Ostensen M. Disease specific problems related to drug therapy in pregnancy. *Lupus* 2004;13(9):746-50.
- Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol* 1977;127(3):264-67.
- Flechner SM, Katz AR, Rogers AJ, et al. The presence of cyclosporine in body tissues and fluids during pregnancy. *Am J Kidney Dis* 1985;5(1):60-63.
- Venkataramanan R, Koneru B, Wang CC, et al. Cyclosporine and its metabolites in mother and baby. *Transplantation* 1988;46(3):468-69.
- Shaheen FA, al-Sulaiman MH, al-Khader AA. Long-term nephrotoxicity after exposure to cyclosporine in utero. *Transplantation* 1993;56(1):244-45.
- Scantlebury V, Gordon R, Tzakis A, et al. Childbearing after liver transplantation. *Transplantation* 1990;49(2):317-21.
- Celese HL, Laifer SA. Pregnancy after liver transplantation. *Semin Perinatol* 1998;22:149.
- Patapis P, Irani S, Mirza DF, et al. Outcome of graft function and pregnancy following liver transplantation. *Transplant Proc* 1997;29(1-2):1565-66.
- Dei Malatesta MF, Rossi M, Rocca B, et al. Pregnancy after liver transplantation: Report of 8 new cases and review of the literature. *Transpl Immunol* 2006;15(4):297-302.
- Pruvot FR, Declerck N, Valat-Rigos AS, et al. Pregnancy after liver transplantation: Focusing on risks to the mother. *Transplant Proc* 1997;29:1565.
- Armenti VT, Moritz MJ, Radomsky JS, et al. Pregnancy and transplantation. *Graft* 2000;3:59.
- Nagy S, Bush MC, Berkowitz R, et al. Pregnancy outcome in liver transplant recipients. *Obstet Gynecol* 2003;102:121.
- American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001;108(3):776-89.
- Armenti VT, Radomski JS, Moritz MJ, et al. Report from the National Transplantation Pregnancy Registry (NTPR):

- Outcomes of pregnancy after transplantation. *Clin Transplant* 2005;69-83.
25. ZJ Zieniewicz, P Kamin' ski, B Pietrzak, et al. Outcome of four high-risk pregnancies in female liver transplant recipients on tacrolimus immunosuppression. *Transplantation Proceedings* 2006;38:255-57.
26. Sibanda N, Briggs JD, Davison JM, et al. Pregnancy after organ transplantation: A report from the UK Transplant pregnancy registry. *Transplantation* 2007;83:1301-07.
27. ZJ Zieniewicz, K Bobrowska, B Pietrzak, et al. Mode of delivery in women after liver transplantation. *Transplantation Proceedings* 2007;39:2796-99.
28. Lawrence U Liu, Thomas D Schiano. Long-term care of the liver transplant recipient. *Clin Liver Dis* 2007;11:397-416.

Recurrent Diseases after Liver Transplantation

INTRODUCTION

Liver transplantation is an established treatment option for patients with ESLD and acute liver failure. Despite excellent long-term survival, disease recurrence after LTX is a relatively common problem, leading to progressive liver injury and, in some cases, cirrhosis. Wilson Disease,¹ α -1 antitrypsin deficiency,² Glycogen storage diseases and Galactosemia are completely cured after LTX. In hemochromatosis, hepatic iron stores are corrected by LTX, but the metabolic defect persists.

Diseases which recur after transplantation¹¹⁸

- Hepatitis C
- Hepatitis B
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Non-alcoholic fatty liver disease
- Hereditary hemochromatosis
- Budd chiari syndrome
- Hepatocellular carcinoma

HEPATITIS C VIRUS

HCV recurrence defined by histologic injury is almost universal based on the presence of HCV RNA in the serum³ and a significant proportion (20 to 30%) develops allograft cirrhosis by the fifth year post-transplant.⁴⁻⁷ HCV related cirrhosis is the leading indication for LTX in Western countries, where as HBV is most common cause in the Asian countries. During anhepatic period HCV RNA level will decline to low and sometimes even undetectable.^{8,9} Within 4-8 days after transplantation, viral levels often increase to levels > 20-times the pre-transplant period,¹⁰ peaking between 1 and 3 months post-transplantation. One-third of patient deaths after transplantation are related to recurrent HCV.^{11,12} Nearly

all patients develop some evidence of histologic recurrence; approximately a third will develop only minimal fibrosis after 5 years of follow-up.¹³

Around 5% of transplant recipients develop a fibrosing cholestatic form of HCV, presenting as jaundice and elevated aminotransferases and histologically by fibrosis, hepatocyte apoptosis, and cholestasis by the end of 1 to 3 months. This form rapidly progresses to graft loss in 3-6 months.¹⁴ These patients typically have very high serum HCV RNA levels with serum bilirubin level > 6 mg/dL and alkaline phosphatase levels more than five times the upper limit of normal without any history of hepatic artery thrombosis or biliary complications. USG examination reveals no biliary tree dilatation. Liver biopsy reveals ballooning of hepatocytes predominantly in the perivenular zone, paucity of inflammation, and variable degrees of proliferation of cholangiolar proliferation without bile duct loss. Pathogenesis of this syndrome remains undefined, but preferential Th2 cytokine production by intrahepatic lymphocytes has been implicated^{15,16} Treatment for this condition remains undefined, but is focused on reducing very high HCV RNA levels by reducing immunosuppression and indefinite use of interferon.¹⁷ Acute hepatitis C occurs in 60 to 80% in 4 to 6 months after transplantation and chronic hepatitis C in 80 to 100% by the end of 1 to 4 years^{18,19,20}

Risk factors for HCV recurrence after LTX²¹⁻²⁹

- Female recipient
- Pre-LT viral load
- Early post-LT viral load
- Marginal donors
- CMV infection
- Diabetes mellitus
- Prolonged warm ischemic time

- Lack of CD₄⁺ response
- Treatment of rejection with steroids
- Treatment of rejection with anti-lymphocyte preparations
- Metabolic syndrome.

Differential diagnosis of HCV recurrence

- Acute cellular rejection
- Hepatic artery thrombosis
- Other viral infection (CMV/EBV)
- Autoimmune hepatitis.

Diagnosis of HCV recurrence is important to avoid graft loss. Diagnosis depends on the clinical, laboratory evidence and confirmed by significant elevation of HCV RNA levels along with histological proof by liver biopsy. Histologic features of recurrent HCV and acute cellular rejection (ACR) overlap and can be difficult to distinguish. Distinction is not between recurrent HCV infection and ACR, but rather between ACR with or without underlying features of recurrent HCV infection. It is always important to avoid treatment for equivocal evidence of acute cellular rejection in patients with HCV because bolus corticosteroid doses are associated with rapid progression of fibrosis.¹¹ Once cirrhosis develops in the transplant setting, two-thirds will develop decompensation within 3 years.^{30,31}

Treatment with Pegylated interferon and Ribavirin was associated with virologic response rates of 12 to 26% and discontinuation rates of 30 to 37%.^{32,33} Delaying antiviral therapy theoretically allows most patients time to be in better physical shape and to be maintained on lower doses of immunosuppressants (less bone marrow suppression), thereby allowing full antiviral therapy.

Treatment of recurrent HCV infection after LTX

Standard treatment: Interferon + Ribavirin

Dose

Interferon

- Interferon α -2b: 3 million IU/thrice a week (or)
- Pegylated interferon α -2a: 180 μ g/week (or)
- Pegylated Interferon α -2b: 1-1.5 μ g/kg/week subcutaneously

Ribavirin

- Start ribavirin 600 mg/day, gradually increase upto 1000-1200 mg/day

Duration of treatment

- Routine treatment: 24 weeks (SVR 60-80%)
- For genotype 1 and 2: >24 to 48 weeks (SVR 35-45%) (depending on tolerance)
- Ribavirin is continued for another 6 months after discontinuation of Interferon.

Treatment response depends on

- Genotype (Poor response in genotype 1 and 4)
- Baseline viral load
- Patient adherence
- Early systemic virological response

Monitoring of treatment response

- HCV RNA by PCR
- Baseline viral load at 4 weeks and then every 12 weeks to monitor SVR.
- Genotyping
- Histological confirmation by liver biopsy

HEPATITIS B VIRUS

Outcomes of patients transplanted for hepatitis B related ESKD have improved with the use of hepatitis B immune globulin and nucleoside (e.g., lamivudine and adefovir).³⁴ Prior to the use of HBIG, recurrence of HBV infection after transplantation was very high (>80% in patients alive for more than 2 months after LTX was a major factor in 73% of all post-LTX deaths beyond the first 60 days.³⁵ Once recurrence was established it frequently followed by an aggressive course, progressing from severe chronic hepatitis to cirrhosis and graft failure within 1 to 2 years of reinfection and a 2-year mortality of 50% compared with 20% among patients transplanted for other liver diseases.³⁶

Risk of recurrence at 3 years in recipients according to the indication for LTX

• Fulminant HBV	17%
• HBV cirrhosis, HBV replication -ve	20-35
• HBV cirrhosis, HBV replication +ve	30-80
• Cirrhosis with co-infection HBV- HDV	10-20
• HDV-related cirrhosis	32%

Risk of recurrence of HBsAg at 3 years

- HBV DNA + ve at the time of transplant: 83%
- HBV DNA -ve and HBeAg +ve at the time of transplant: 66%
- Both HBV DNA and HBeAg -ve: 58%

Risk of recurrence is significantly reduced with long-term use of HBIG (>6 months) as compared to no immunoprophylaxis or short-term use (<6 months).

Risk factors for HBV recurrence after LTX³⁷⁻⁴³

- HBV DNA >100,000 copies/mL at time of LTX
- Low anti-HBs titers in patients with high viral load
- Development of immune escape mutants
- Pretransplant lamivudine resistance
- HBV pre core mutants

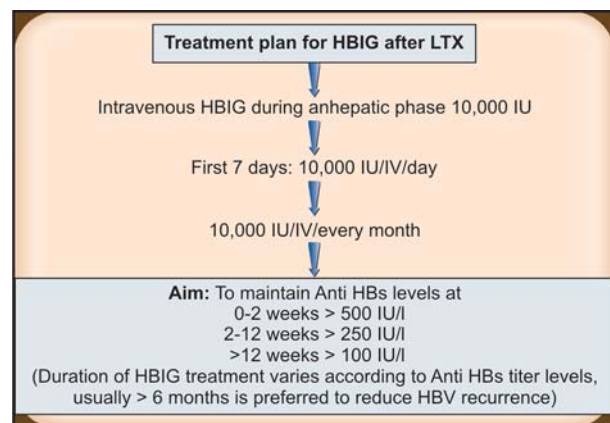
Differential diagnosis of HBV recurrence

- Acute cellular rejection
- Non-HBV viral infection
- Hepatic artery thrombosis
- Autoimmune hepatitis

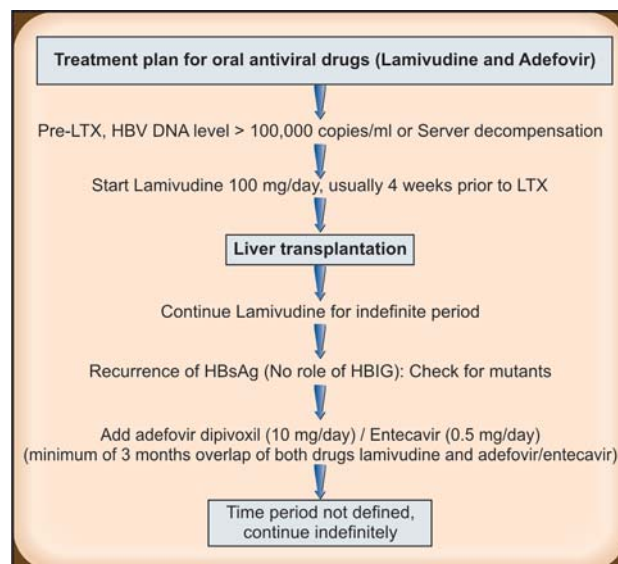
Recurrence of HBV after transplantation is defined by presence of HBsAg. Once recurrence develops, continued use of HBIG is not useful as its role is purely prophylactic one. A study on role of lamivudine in recurrent HBV infection shows that, 60% had undetectable levels of HBV DNA after 52 weeks of therapy; however, 31% developed breakthrough infection secondary to lamivudine resistance.⁴⁴ If recurrence develops in the setting of lamivudine use (i.e., presumed YMDD mutation), adefovir dipivoxil or Entecavir should be added to lamivudine until viral suppression is achieved. Most investigators recommend a minimum of 3 months overlap of the new drug with lamivudine.⁴⁵

The combination of lamivudine and HBIG was shown to reduce post-transplant recurrence of hepatitis B to a rate of less than 10%.⁴⁶ Oral antiviral agents like lamivudine and adefovir dipivoxil (in mutants) are given approximately 4 weeks before transplantation suppress viral replication and reduce the risk of allograft infection around the time of transplantation. Passive immunoprophylaxis with hepatitis B immune globulin (HBIG) generally is given short term post-transplantation, and oral antiviral agents are continued indefinitely. Many transplant centers maintain a trough hepatitis B surface antibody (anti-HBs) titer > 100 IU/l after 6 months of transplantation. Five-year survival for patients with hepatitis B approaches 70%, similar to transplantation for other causes.¹²

TREATMENT OF RECIPIENT: HBIG THERAPY



TREATMENT OF RECIPIENT: ORAL ANTIVIRAL AGENTS



Role of active immunoprophylaxis (HBV vaccination): Studies from Barcelona group showed that 14/22 patients transplanted for HBV-related liver disease, who were receiving HBIG prophylaxis alone or in combination with lamivudine developed anti-HBs titers greater than 10 IU/ml after being immunized with one to two courses of double-dose recombinant HBV vaccine.^{49,50} Another study reported of 9/12 patients developing anti-HBs titers >10 IU/ml after HBV vaccination. In these studies, HBIG or combination of HBIG and lamivudine was stopped and no HBV recurrence occurred over a mean post vaccination follow-up of 40 months.^{51,52} Another group reports similar success with 16/20 patients acquiring anti-HBs after vaccination allowing discontinuation of HBIG.⁵³ It appears that successful vaccination followed by withdrawal of HBIG is possible and is possible with further studies involving larger number of patients will give adequate guidelines for such therapy.

AUTOIMMUNE HEPATITIS

First case of post-transplant recurrence of AIH in 1984 when a 26-year-old woman developed histologic and serologic evidence of AIH after withdrawal of corticosteroids.⁵⁴ The exact frequency of recurrence is unknown, and in early studies, was further confounded by lack of testing for HCV. Published reports have ranged from 2 to 42%⁵⁵⁻⁶⁰ with 20 to 30% noted in most studies. The recurrence rate appears to increase over time, possibly due to reduction in immunosuppression over time. (8% at 1 year increasing to 67% at 5 years).⁵⁵

Recurrence can be indolent and only picked up by either routine laboratory testing or liver biopsy. Histologic findings of recurrent AIH may be less well developed than AIH in the pretransplant setting because of immunosuppressive therapy. Auto antibodies are often present, but they are usually present at lower titers than pre-transplant period, possibly due to impaired autoantibody formation in presence of immunosuppression. It is important to recognize these auto antibodies which are also seen in de novo after liver transplant in the setting of rejection.⁶¹ Differentiating recurrent AIH from rejection on biopsy, namely chronic rejection can be difficult, especially because chronic rejection may be a complication of recurrent AIH.⁶²

Risk factors for recurrent AIH^{55,56,58,63,64}

- HLA DR3 - positive recipients
- Type 1 disease type
- Suboptimal immunosuppression

Differential diagnosis

- Acute cellular rejection
- Viral hepatitis (HCV)
- Drug induced hepatitis
- Hepatic artery thrombosis
- Biliary obstruction

But the course of the disease is mild and responds to modification in immunosuppression.⁶⁵ De novo immune mediated hepatitis has also been reported.⁶⁶ An association exists between recurrence of AIH with reduction in immunosuppression,⁵⁸ suggesting that patients with AIH may require higher doses of immunosuppressive medication and prompting recommendations to wean steroids with caution. Prognosis in children may be worse than in adults and rapid rates of recurrence.⁶⁶ Five-year patient survival after transplantation ranges from 80 to 92%.^{67,68} There does not appear to be a difference between patient and graft survival in patients with and without recurrent disease.

PRIMARY BILIARY CIRRHOSIS

Recurrent primary biliary cirrhosis (PBC) after LTX was first described in 1982.⁶⁹ PBC recurs in 15 to 30% of grafts, with a median time to recurrence of approximately 4 years.⁷⁰⁻⁷⁴ The gold standard for diagnosing recurrent PBC is liver biopsy. The key definitive diagnostic criterion is demonstration of a florid duct lesion (granulomatous cholangitis) or destructive lymphocytic cholangitis within a dense portal infiltrate.⁷⁶ Recurrent PBC is considered definite if three of the four portal tract lesions are present in a patient transplanted for PBC with persistently

positive antimitochondrial antibody (AMA).⁷⁵ Although the AMA is the serologic hallmark of the disease in the pre-transplant setting, these antibodies can persist post-transplant, although there is typically a small and transient fall from pretransplant levels.⁷⁷ Their presence does not correlate with clinical or histologic disease.

Risk factors for recurrence^{78,80}

- Younger donors
- Older recipients
- Prolonged warm ischemic time
- Tacrolimus

Differential diagnosis

- Acute and chronic rejection
- Graft versus host disease (GVHD)
- Biliary obstruction
- CMV and HCV
- Fungal infections

Ursodeoxycholic acid (UDCA) was shown to lower alkaline phosphatase levels in PBC patients after transplantation, although the long-term effect on preserving graft function is not known.⁷² Immunosuppression with azathioprine may have a protective effect on the rate of recurrence.⁷⁹

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) recurs after transplantation, but can be difficult to distinguish from other causes of biliary strictures. Moreover, patients with PSC typically undergo choledochojejunostomy, making them susceptible to episodes of cholangitis.⁸¹ Recurrence rates of PSC ranged from 8.6 to 20% with no associated reduction in patient or graft survival.⁸²⁻⁸⁴ Recurrent PSC recipients present with alkaline phosphatase > 250 U/l after 1 year, recurrence should be suspected and cholangiogram and/or liver biopsy is considered. The diagnosis of recurrent PSC is based largely on cholangiographic findings in combination with biochemical and histologic features of PSC.

Differential diagnosis of PSC

- Chronic rejection
- Anastomotic and nonanastomotic strictures
- Hepatic artery thrombosis
- ABO incompatibility
- CMV infection
- Prolonged ischemia

Steroid resistant rejection was a primary risk factor for recurrence, so it is important to ensure that patients

transplanted for PSC receive adequate levels of immunosuppression.⁸⁵ There is no definite therapy to prevent or modify the rate of PSC recurrence. A trend toward lower rates of recurrent PSC in early withdrawal of corticosteroids has been suggested.⁸⁶ Whether corticosteroids avoidance only delays recurrence is not known. Use of OKT3 has been associated with higher risk of PSC recurrence.⁸⁷ Use of high-dose UDCA (20 to 30 mg/kg) may have clinical benefits in the pretransplant setting,⁸⁷ however, the potential benefits in patients transplanted for PSC is unknown.

ALCOHOLIC LIVER DISEASE

Recurrence of alcohol use after transplantation (recidivism) is a major concern to the transplant centers across the world. Patients transplanted for alcohol-related cirrhosis have an excellent 5-year graft survival. Determining the frequency of alcohol use after LTX is difficult and is usually obtained by patient/family interviews, blood/urine testing or histologic findings. Recurrent alcohol use was reported in 20% of patients within the first year and 40% by the fifth year post-transplant.^{88,89} Only 10% of recipients resume to a pathologic pattern of drinking.⁸⁸⁻⁹⁰

Risk factors for ALD⁹¹⁻⁹⁶

- Abstinence <6 months
- Absence of a life insurance policy
- Family history of alcoholism
- Prior alcohol rehabilitation
- History of drug abuse
- Daily alcohol consumption

In recipients of ALD who resume moderate to heavy drinking, alcohol will damage the allograft either by developing recurrent ALD or by development of ACR or chronic rejection, due to noncompliance.⁹⁷ Cuadrado et al. reported that 10-year survival rates in patients with recidivism to be significantly lower than those without recidivism i.e. 45.1 vs. 85.5%, respectively.⁹⁸ The high mortality rate in this study was explained by more frequent cancer and cardiovascular events. Recidivism does not appear to directly lead to recurrent ALD. Heavy alcohol use after transplantation can contribute significantly to other health problems. Patients transplanted for ALD are at a much greater risk of developing head and neck malignancies, especially if there is a history of heavy tobacco use. In addition, alcohol use in patients infected with HCV has potential to result in rapid recurrence of HCV in the allograft.⁹⁹ Patients transplanted for alcohol-related cirrhosis should be regularly asked about any alcohol consumption, and

continued participation in a substance abuse program is encouraged.

HEREDITARY HEMOCHROMATOSIS

5-year survival of patients transplanted for hemochromatosis was only 34%.¹⁰² In patients of hereditary hemochromatosis is associated with an increased risk of¹⁰⁰⁻¹⁰²

- Infection
- Hepatocellular carcinoma
- Cardiac arrhythmias.

These patients should be phlebotomized before and after transplantation, to maximize outcomes and to prevent the recurrence.¹⁰³

NONALCOHOLIC STEATOHEPATITIS (NASH)

NASH is an important indication for liver transplantation. NASH recurs in 11 to 38% of cases, related in part to weight gain and the metabolic side effects of immunosuppressive treatment.^{104,105} Approximately 12.5% of patients transplanted for NASH develop cirrhosis in the graft.¹⁰⁵

RECURRENT BUDD-CHIARI SYNDROME

Hepatic venous outflow obstruction at any level ranging from small hepatic veins to the junction of the inferior vena cava and the right atrium is termed Budd-Chiari Syndrome (BCS). Cause is due to hypercoagulable states related to underlying myeloproliferative disease (MPD) or inherited thrombogenic diseases. Treatment includes anticoagulation, diuretics, treating underlying hematologic disorder, TIPS and LTX depending upon the severity and level of obstruction. The risk of recurrence after transplantation for BCS around 8.5% (0 to 27%).¹⁰⁶⁻¹⁰⁹ Most cases of recurrence are due to suboptimal levels of anticoagulation. Recurrence usually develops months to years after transplantation but can also recur in early post-transplant period.¹⁰⁹ Anticoagulation is not required for patients transplanted for protein C, protein S and antithrombin III deficiencies, as transplantation cures the underlying thrombogenic disorder. All other patients transplanted for BCS require long-term anticoagulation. Hydroxyurea and aspirin are used as an alternative to anticoagulation in patients with underlying myeloproliferative disease.¹⁰⁸

HEPATOCELLULAR CARCINOMA

Recurrence of hepatocellular carcinoma can be decreased following liver transplantation by appropriate patient

selection. Tumor staging was reported as one of the most important predictive factors for patient outcome,¹¹¹ which supports the usage of the Milan criteria to select OLT candidates. Despite of all precautions 10–60% of HCC patients have recurrences after liver transplantation.^{112,113,117} AFP mRNA in the bone marrow and systemic circulation during the perioperative period predict patient survival and recurrence after living donor liver transplantation for HCC.¹¹⁴ in transplant recipients, HBV and HCC recurrences are closely correlated. The recurrences of HBV and HCC have reduced the recurrence free survival of HCC and HBV, respectively.¹¹⁸

Risk factors for HCC recurrence^{110,115,116}

- Tumor size >5 cm
- Presence of cirrhosis
- More than 5 nodules
- Micro/macro vascular invasion
- High preoperative α -fetoprotein level
- Male gender
- High immunosuppression level

Diseases transmitted by donor organs:

Diseases transmitted from the donor organ

- Hepatitis B and C
- HIV infection
- Factor XI deficiency
- Idiopathic thrombocytopenic purpura
- Gilbert syndrome
- Malignant tumors

REFERENCES

1. Groth CG, Dubois RS, Corman J, et al. Metabolic effects of hepatic replacement in Wilson's disease. *Transplant Proc* 1973;5:829-33.
2. Filipponi F, Soubrane O, Labrousse F, et al. Liver transplantation for end-stage liver disease associated with alpha-1-antitrypsin deficiency in children: Pretransplant natural history, timing and results of transplantation. *J Hepatol* 1994;20:72-78.
3. Ferrell LD, Wright TL, Roberts J, et al. Hepatitis C viral infection in liver transplant recipients. *Hepatology* 1992;16:865-76.
4. Feray C, Caccamo L, Alexander GJ, et al. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C. European Concerted Action on Viral Hepatitis (EUROHEP) Group. *Gastroenterology* 1999;117:619-25.
5. Ghobrial RM, Farmer DG, Baquerizo A, et al. Orthotopic liver transplantation for hepatitis C: Outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Ann Surg* 1999;229:824-31.
6. Prieto M, Berenguer M, Rayon JM, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: Relationship with rejection episodes. *Hepatology* 1999;29:250-56.
7. Testa G, Crippin JS, Netto GJ, et al. Liver transplantation for hepatitis C: Recurrence and disease progression in 300 patients. *Liver Transplant* 2000;6:553-61.
8. Garcia-Tetortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. *Hepatology* 2002;35:680-87.
9. Fukumoto T, Berg T, Ku Y, et al. Viral dynamics of hepatitis C early after orthotopic liver transplantation: Evidence for rapid turnover of serum virions. *Hepatology* 1996;24:1351-54.
10. Chazouilleres O, Kim M, Combs C, et al. Quantitation of hepatitis C virus RNA in liver transplant recipients. *Gastroenterology* 1994;106:994-99.
11. Neumann UP, Berg T, Bahra M, et al. Long-term outcome of liver transplants for chronic hepatitis C: A 10-year follow-up. *Transplantation* 2004;77:226-31.
12. Forman LM, Lewis JD, Berlin JA, et al. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889-96.
13. Charlton M, Wiesner RH. Natural history and management of hepatitis C infection after liver transplantation. *Semin Liver Dis* 2004;24:79-88.
14. Dixon LR, Crawford JM. Early histologic changes in fibrosing cholestatic hepatitis C. *Liver Transplant* 2007;13:219-26.
15. Miner C, Koziel MJ, He Q, et al. Intrahepatic and circulating CD4+ T cells after liver transplantation for hepatitis C: Evidence of compartmentalization [Abstract 761]. *Hepatology* 2001;34:362A.
16. Zekry A, Bishop GA, Bowen DG, et al. Intrahepatic cytokine profiles associated with post-transplantation hepatitis C virus-related liver injury. *Liver Transpl* 2002;8(3):829-301.
17. Gopal DV, Rosen HR. Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite. *Liver Transpl* 2003;9:348-53.
18. Guerrero RB, Batts KP, Burgart LJ, et al. Early detection of hepatitis C allograft reinfection after orthotopic liver transplantation: a molecular and histologic study. *Mod Pathol* 2000;13:229-37.
19. Gane EJ, Naoumov NV, Qian KP, et al. A longitudinal analysis of hepatitis C virus replication following liver transplantation. *Gastroenterology* 1996;110:167-77.
20. Testa G, Crippin JN, Netto GJ, et al. Liver transplantation for hepatitis C: Recurrence and disease progression in 300 patients. *Liver Transpl* 2000;6:553-61.
21. Forman LM, Lewis JD, Berlin JA, et al. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889-96.
22. Charlton M, Seaberg G, Wiesner R, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998;28:823-30.
23. Velidedeoglu E, Mange KC, Frank A, et al. Factors differentially correlated with the outcome of liver transplantation in HCV+ and HCV- recipients. *Transplantation* 2004;77(12):1834-42.
24. Berenguer M, Crippin J, Gish R, et al. A model to predict severe HCV-related disease following liver transplantation. *Hepatology* 2003;38:34.
25. Sreekumar R, Gonzalez-Koch A, Moar-Kendler Y, et al. Early identification of recipients with progressive histologic recurrence of hepatitis C after liver transplantation. *Hepatology* 2000;32:1125-30.
26. Rosen HR, Hinrichs DJ, Gretch DR, et al. Association of multispecific CD4(+) response to hepatitis C and severity of recurrence after liver transplantation. *Gastroenterology* 1999;117:926-32.

27. Baron PW, Sindram D, Higdon D, et al. Prolonged rewarming time during allograft implantation predisposes to recurrent hepatitis C infection after liver transplantation. *Liver Transpl* 2000;6:407-12.
28. Rosen HR, Chou S, Corless CL, et al. Cytomegalovirus viremia: Risk factor for allograft cirrhosis after liver transplantation for hepatitis C. *Transplantation* 1997;64:721-26.
29. Rosen HR, Shackleton CR, Higa L, et al. Use of OKT3 is associated with early and severe recurrence of hepatitis C after liver transplantation. *Am J Gastroenterol* 1997;92:1453-57.
30. Berenguer M, Prieto M, Rayon JM, et al. Natural history of clinically compensated HCV-related graft cirrhosis following liver transplantation. *Hepatology* 2000;32:852-58.
31. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: A retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-72.
32. Rodriguez-Luna H, Khatib A, Sharma P, et al. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: An open-label series. *Transplantation* 2004;77:190-94.
33. Chalasani N, Manzarbeitia C, Ferenci P, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: Two randomized, controlled trials. *Hepatology* 2005;41:289-98.
34. Eisenbach C, Sauer P, Mehrabi A, et al. Prevention of hepatitis B virus recurrence after liver transplantation. *Clin Transplant* 2006;20(suppl 17):111-16.
35. Todo S, Demetris A, Van Thiel D, et al. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology* 1991;13:619-26.
36. Benner K, Lee R, Keeffe E, et al. Fibrosing cytolytic liver failure secondary to recurrent hepatitis B after liver transplantation. *Gastroenterology* 1992;103:1307-12.
37. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transpl* 2005;11:402-09.
38. McGory RW, Ishitani MB, Oliveira WM, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996;61:1358-64.
39. Terrault NA, Zhou S, McCorry RW, et al. Incidence and clinical consequences of surface and polymerase gene mutations in liver transplant recipients on hepatitis B immunoglobulin. *Hepatology* 1998;28:555-61.
40. Rosenau J, Bahr MJ, Tillmann HL, et al. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B reinfection after liver transplantation—possible role of mutations in the YMDD motif prior to transplantation as a risk factor for reinfection. *J Hepatol* 2001;34:895-902.
41. Seehofer D, Rayes N, Naumann U, et al. Preoperative antiviral treatment and postoperative prophylaxis in HBV-DNA positive patients undergoing liver transplantation. *Transplantation* 2001;72:1381-85.
42. Angus PW, Locarnini S, McCaughan GW, et al. Hepatitis B virus precore mutant infection is associated with severe recurrent disease after liver transplantation. *Hepatology* 1995;21:14-18.
43. Fang JWS, Tung FYT, Davis GL, et al. Fibrosing cholestatic hepatitis in a transplant recipient with hepatitis B virus precore mutant. *Gastroenterology* 1993;105:901-04.
44. Perrillo R, Rakela J, Dienstag J, et al. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 1999;29:1581-86.
45. Lok ASF. Liver transplantation for patients with lamivudine-resistant HBV: What is the optimal prophylactic strategy? *Liver Transpl* 2005;11:490-93.
46. Markowitz JS, Martin P, Conrad AJ, et al. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. *Hepatology* 1998;28:585-89.
47. Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: A concise review. *Hepatol* 2000;32:1189-95.
48. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med* 1993;329:1842-47.
49. Sanchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: A new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000;31:496-501.
50. Sanchez-Fueyo A, Martinez-Bauer E, Rimola A. Hepatitis B vaccination after liver transplantation. *Hepatology* 2002;36:257-58.
51. Barcena R, Fernandez-Braso M, Urman J, et al. Response to hepatitis B virus vaccine in patients transplanted for HBV-related liver disease under specific gamma globulin prophylaxis. *Transplant Proc* 1999;31:2459-60.
52. Albeniz-Arbizu E, Barcena-Marugan R, Oton-Nieto E, et al. Prophylaxis of recurrent hepatitis B virus by vaccination after liver transplant: preliminary results. *Transplant Proc* 2003;35:1848-49.
53. Bienzle U, Gunther M, Neuhaus R, et al. Immunization with an adjuvant hepatitis B vaccine after liver transplantation for hepatitis B-related disease. *Hepatology* 2003;38:811-19.
54. Neuberger J, Portmann B, Calne R, et al. Recurrence of autoimmune chronic active hepatitis following orthotopic liver grafting. *Transplantation* 1984;37:363-65.
55. Prados E, Cuervas-Mons V, de la Mata M, et al. Outcome of autoimmune hepatitis after liver transplantation. *Transplantation* 1998;66:1645-50.
56. Molmenti EP, Netto GJ, Murray NG, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. *Liver Transpl* 2002;8:519-26.
57. Vogel A, Heinrich E, Bahr MJ, et al. Long-term outcome of liver transplantation for autoimmune hepatitis. *Clin Transplant* 2004;18:62-69.
58. Ratzu V, Samuel D, Sebach M, et al. Long-term follow-up after liver transplantation for autoimmune hepatitis: Evidence of recurrence of primary disease. *J Hepatol* 1999;30:131-41.
59. Reich DJ, Fiel I, Guarrera JV, et al. Liver transplantation for autoimmune hepatitis. *Hepatology* 2000;32:693-700.
60. Renz JF, Ascher NL. Liver transplantation for nonviral, nonmalignant diseases: Problem of recurrence. *World J Surg* 2002;26:247-56.
61. Lohse AW, Obermayer-Straub P, Gerken G, et al. Development of cytochrome P450 2D6-specific LKM-autoantibodies following liver transplantation for Wilson disease—possible association with a steroid resistant transplant rejection episode. *J Hepatol* 1999;31:1495-55.
62. Milkiewicz P, Hubscher SG, Skiba G, et al. Recurrence of autoimmune hepatitis after liver transplantation. *Transplantation* 1999;68:253-56.
63. Wright HL, Bou-Abboud CF, Hassanein T, et al. Disease recurrence and rejection following liver transplantation for

- autoimmune chronic active liver disease. *Transplantation* 1992;53:136-39.
64. Manns MP, Bahr JM. Recurrent autoimmune hepatitis after liver transplantation—when non-self becomes self. *Hepatology* 2000;32:868-70.
65. Khalaf H, Mourad W, El-Sheikh Y, et al. Liver transplantation for autoimmune hepatitis: A single-center experience. *Transplant Proc* 2007;39:1166-70.
66. Lohse AW, Weiler-Norman C, Burdelski M. De novo autoimmune hepatitis after liver transplantation. *Hepatol Res* 2007;37(suppl 3):S462.
67. Birnbaum AH, Benkov KJ, Pittman NS, et al. Recurrence of autoimmune hepatitis in children after liver transplantation. *J Pediatr Gastroenterol Nutr* 1997;25:20-25.
68. Czaja AJ. The immunoreactive propensity of autoimmune hepatitis: Is it corticosteroid-depend after liver transplantation? *Liver Transpl* 1999;5:460-63.
69. Neuberger J, Portmann B, Macdougall BR, et al. Recurrence of primary biliary cirrhosis after liver transplantation. *N Engl J Med* 1982;306:1-4.
70. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: A systematic review. *Liver Transplant* 2006;12:1813-24.
71. Liermann Garcia RF, Evangelista Garcia C, McMaster P, et al. Transplantation for primary biliary cirrhosis: Retrospective analysis of 400 patients in a single center. *Hepatology* 2001;33:22-27.
72. Guy JE, Qian P, Lowell JA, et al. Recurrent primary biliary cirrhosis: Peritransplant factors and ursodeoxycholic acid treatment post-liver transplant. *Liver Transplant* 2005;11:1252-57.
73. Sylvestre PB, Batts KP, Burgart LJ, et al. Recurrence of primary biliary cirrhosis after liver transplantation: Histologic estimate of incidence and natural history. *Liver Transplant* 2003;9:1086-93.
74. Khettry U, Anand N, Faul PN, et al. Liver transplantation for primary biliary cirrhosis: A long-term pathologic study. *Liver Transplant* 2003;9:87-96.
75. Hubscher S, Elias E, Buckels J, et al. Primary biliary cirrhosis. Histological evidence of disease recurrence after liver transplantation. *J Hepatol* 1993;18:173-84.
76. Sylvestre PB, Batts KP, Burgart LJ, et al. Recurrence of primary biliary cirrhosis after liver transplantation: Histologic estimate of incidence and natural history. *Liver Transpl* 2003;9:1086-93.
77. Dubel L, Gorges O, Bismuth H, et al. Kinetics of anti-M2 antibodies after liver transplantation for PBC. *J Hepatol* 1995;23:674-681.
78. Liermann Garcia RF, Evangelista Garcia C, McMaster P, et al. Transplantation for primary biliary cirrhosis: Retrospective analysis of 400 patients in a single center. *Hepatology* 2001;33:22-27.
79. Khettry U, Anand N, Faul PN, et al. Liver transplantation for primary biliary cirrhosis: A long-term pathologic study. *Liver Transpl* 2003;9:87-96.
80. Neuberger J, Bunson B, Hubscher S, et al. Immunosuppression affects the rate of recurrent primary biliary cirrhosis after liver transplantation. *Liver Transpl* 2004;10:488-91.
81. Schmitz V, Neumann UP, Puhl G, et al. Surgical complications and long-term outcome of different biliary reconstructions in liver transplantation for primary sclerosing cholangitis-choledochoduodenostomy versus choledochojejunostomy. *Am J Transplant* 2006;6:379-85.
82. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis: A 12-year single center experience. *Ann Surg* 1997;225:472-83.
83. Narumi S, Roberts JP, Emond JC, et al. Liver transplantation for sclerosing cholangitis. *Hepatology* 1995;22:451-457.
84. Graziadei IW, Wiesner RH, Batts KP, et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology* 1999;29:1050-56.
85. Brandsaeter B, Schruppf E, Bentsdal O, et al. Recurrent primary sclerosing cholangitis after liver transplantation: a magnetic resonance cholangiography study with analyses of predictive factors. *Liver Transplant* 2005;11:1361-69.
86. Kugelmas M, Spiegelman P, Osgood MJ, et al. Different immunosuppressive regimens and recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 2003;9:727-32.
87. Harnois DM, Angulo P, Jorgensen RA, et al. High-dose ursodeoxycholic acid as therapy for patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2001;96:1558-62.
88. Everson G, Bharadhwaj G, House R, et al. Long-term follow-up of patients with alcoholic liver disease who underwent hepatic transplantation. *Liver Transplant Surg* 1997;3:263-74.
89. DiMartini A, Day N, Dew MA, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transplant* 2006;12:813-20.
90. Tome S, Lucey MR. Timing of liver transplantation in alcoholic cirrhosis. *J Hepatol* 2003;39:302-07.
91. Osorio RW, Ascher NL, Avery M, et al. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. *Hepatology* 1994;20:105-10.
92. Miguet M, Monnet E, Vanlemmens C, et al. Predictive factors of alcohol relapse after orthotopic liver transplantation for alcoholic liver disease. *Gastroenterol Clin Biol* 2004;28:845-51.
93. Foster PF, Fabrega F, Karademir S, et al. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. *Hepatology* 1997;25:1469-77.
94. DiMartini A, Weinreb R, Fireman M. Liver transplantation in patients with alcohol and other substance use disorders. *Psychiatr Clin North Am* 2002;25:195-209.
95. Jauhar S, Talwalkar JA, Schneekloth T, et al. Analysis of factors that predict alcohol relapse following liver transplantation. *Liver Transpl* 2004;10:408-11.
96. Bellamy CO, DiMartini AM, Ruppert K, et al. Liver transplantation for alcoholic cirrhosis: Long-term follow-up and impact of disease recurrence. *Transplantation* 2001;72:619-26.
97. Pageaux GP, Bismuth M, Perney P, et al. Alcohol relapse after liver transplantation for alcoholic liver disease: Does it matter? *J Hepatol* 2003;38:629-34.
98. Cuadrado A, Fabrega E, Casafont F, et al. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2005;11:420-26.
99. Wiley TE, McCarthy M, Breidi L, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998;28:805-09.
100. Kowdley KV, Hassanein T, Kaur S, et al. Primary liver cancer and survival in patients undergoing liver transplantation for hemochromatosis. *Liver Transplant Surg* 1995;1:237-41.
101. Tung BY, Farrell FJ, McCashland TM, et al. Long-term follow-up after liver transplantation in patients with hepatic iron overload. *Liver Transplant Surg* 1999;5:369-74.

102. Kowdley KV, Brandhagen DJ, Gish RG, et al. Survival after liver transplantation in patients with hepatic iron overload: the national hemochromatosis transplant registry. *Gastroenterology* 2005;129:494-503.
103. Powell LW. Hemochromatosis: The impact of early diagnosis and therapy. *Gastroenterology* 1996;110:1304-07.
104. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. *Am J Gastroenterol* 2006;101:1370-78.
105. Charlton M, Kasparova P, Weston S, et al. Frequency of nonalcoholic steatohepatitis as a cause of advanced liver disease. *Liver Transplant* 2001;7:608-14.
106. Hemming AW, Langer B, Greig P, et al. Treatment of Budd-Chiari syndrome with portosystemic shunt or liver transplantation. *Am J Surg* 1996;171-76.
107. Srinivasan P, Rela M, Prachalias A, et al. Liver transplantation for Budd-Chiari syndrome. *Transplantation* 2002;73:973.
108. Melear JM, Goldstein RM, Levy MF, et al. Hematologic aspects of liver transplantation for Budd-Chiari syndrome with special reference to myeloproliferative disorders. *Transplantation* 2002;74:1090.
109. Cruz E, Ascher NL, Robers JP, et al. High incidence of recurrence and hematologic events following liver transplantation for Budd-Chiari syndrome. *Clin Transplant* 2005;19:501-06.
110. Schlitt HJ, Neipp M, Weimann A, et al. Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. *J Clin Oncol* 1999;17:324.
111. Merli M, Nicolini G, Gentili F, et al. Predictive factors of outcome after liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Transplant Proc* 2005;37:2535.
112. Roayaie S, Schwartz JD, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: Patterns and prognosis. *Liver Transpl* 2004;10:534.
113. Wong DK, Yuen MF, Poon RT, et al. Quantification of hepatitis B virus covalently closed circular DNA in patients with hepatocellular carcinoma. *J Hepatol* 2006;45:553.
114. Marubashi S, Dono K, Sugita Y, et al. Alpha-fetoprotein Mrna detection in peripheral blood for prediction of hepatocellular carcinoma recurrence after liver transplantation. *Transplant Proc* 2006;38:3640.
115. Vivarelli M, Cucchetti A, Piscaglia F, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: Key role of immunosuppression. *Liver Transpl* 2005;11:497.
116. JW Park, KW Lee, SJ Kim, et al. Outcome of patients with recurrent hepatocellular carcinoma in liver transplantation. *Transplant Proceed* 2008;38:2121-22.
117. Eric RKM Scott JC. Care of the liver transplant patient. *Dis Mon* 2008;54:494-507.
118. M Kiyici, M Yilmaz, M Akyildiz, et al. Association between hepatitis B and hepatocellular carcinoma recurrence in patients undergoing liver transplantation. *Transplant Proceed* 2008;40:1511-17.

Retransplantation

INTRODUCTION

Retransplantation (Re-TX) is the only life saving and therapeutic option for irreversible liver graft failure and constitutes 8 to 17% of procedures in several studies.¹⁻⁵ Earlier reports suggest that the survival after liver retransplantation (Re-TX) is inferior to that for primary liver transplantation.⁹ The reported 1-year patient or graft survival rates after Re-TX ranges from 50 to 60%.¹⁰ Careful analysis of the potential benefits is essential to justify its role in an era of organ shortage and rising costs. However, medical, ethical, and financial aspects concerning this procedure are complex and somewhat controversial.^{2,5} Patients undergoing early Re-TX for acute HAT thrombosis or PNF fare better than late retransplantation.¹¹ The need for emergent early Re-TX is progressively declining due to improvements in immunosuppressive therapy, surgical technique, organ preservation, and a better understanding of primary nonfunction.¹²

PREDICTIVE FACTORS OF OUTCOME AFTER RE-TX^{2,5-8,14}

- Recipient age
- Bilirubin
- Creatinine
- Coagulation factors (Prothrombin time)
- Graft quality
- Cold ischemic time
- Indication for re-OLT
- Interval following primary transplantation
- Need for prolonged intensive care/mechanical ventilation.

An expected 1-year survival rate of less than 40% is considered a contraindication for Re-TX⁶ and urgent Re-TX should be considered with caution and on a case-by-case basis.^{5,6} Living-related TX may be an option.⁵ In the future, the need for late liver re-OLT may represent a

growing problem. Recurrence of viral disease (HCV) and chronic biliary graft failure may increase further.¹³ Re-TX for HCV recurrence carries worse prognosis.

SURVIVAL AFTER RE-TX

Potsma et al. reported overall good results after Re-TX of the liver in adults with 1- and 5-year patient survival of 73 and 63%, respectively.¹⁴ Yao et al suggested that severity of graft failure based on CTP and MELD scores may be associated with worse outcomes after re-OLT, namely 1- and 5-year survival rates of 69 and 62%.¹⁵ Recent reports suggest that better survival can be obtained after Re-TX. Adani et al. report a limited single-center experience in late liver re-OLT achieving 1-year patient survival of 84%.¹⁶ Gustafsson et al. reported that an 84% overall survival in the elective Re-TX group and 57% survival in urgent Re-TX group.

Maggi et al.¹⁸ recently reported that the 1-, 3-, 5-, and 10-year Re-TX actuarial graft survivals were 59%, 50%, 50%, and 50%. 1-, 3-, 5-, and 10-year actuarial patient survivals for the 32 patients from the first transplantation, were 78%, 65%, 62%, and 56%, respectively. He reported that donor age, recipient sex and MELD score can represent significant prognostic scores for liver Re-TX. Survival rate after late Re-TX is improving and is presently quite high; consequently it should be considered an efficient way to save lives, especially by defining the optimal timing for retransplantation.¹⁶ Careful clinical assessment and timing, when possible, are essential in order to avoid urgent Re-TX.¹⁷ Re-TX is a life saving procedure. Re-TX can be considered the only alternative to death. However, graft survival after Re-TX is, in the largest series, 20% lower than that after primary TX, which means that there is a waste of grafts and resources. Efforts to identify the best graft for a given recipients are needed.¹⁸

REFERENCES

1. Markmann JF, Markowitz JS, Yersiz H, et al. Long-term survival after retransplantation of the liver. *Ann Surg* 1997;226:408.
2. Yoong KF, Gunson BK, Buckels JAC, et al. Repeat orthotopic liver transplantation in the 1990s: is it justified? *Transpl Int* 1998;11(Suppl 1):S221.
3. Kashyap R, Jain A, Reyes J, et al. Causes of retransplantation after primary liver transplantation in 4000 consecutive patients: 2 to 19 years follow-up. *Transplant Proc* 2001;33:1486.
4. De Carlis L, Slim AO, Giacomoni A, et al. Liver Retransplantation: Indications and results over a 15-year experience. *Transplant Proc* 2001;33:1411.
5. Azoulay D, Linhares MM, Huguet E, et al. Decision for retransplantation of the liver. *Ann Surg* 2002;236:713.
6. Rosen HR, Prieto M, Casanovas-Taltavull T, et al. Validation and refinement of survival models for liver retransplantation. *Hepatology* 2003;38:460.
7. Wong T, Devlin J, Rolando N, et al. Clinical characteristics affecting the outcome of liver retransplantation. *Transplantation* 1997;64:878.
8. Markmann J, Gornbein J, Markowitz JS, et al. A simple model to estimate survival after retransplantation of the liver. *Transplantation* 1999;67:422.
9. Markmann JF, Markowitz JS, Yersiz H, et al. Long-term survival after retransplantation of the liver. *Ann Surg* 1997;226:408.
10. Wong T, Devlin J, Rolando N, et al. Clinical characteristics affecting the outcome of liver retransplantation. *Transplantation* 1997;64:878.
11. Rosen HR, Madden JP, Martin P. A model to predict survival following liver retransplantation. *Hepatology* 1999;29:365.
12. Burton JR Jr, Sonnenberg A, Rosen HR. Retransplantation for recurrent hepatitis C in the MELD era: Maximizing utility. *Liver Transpl* 2004;10(10 Suppl 2):S59.
13. Roayaie S, Schiano TD, Thung SN, et al. Results of retransplantation for recurrent hepatitis C. *Hepatology* 2003;38:1428.
14. Postma R, Haagsma EB, Peeters PM, et al. Retransplantation of the liver in adults: outcome and predictive factors for survival. *Transpl Int* 2004;17:234.
15. Yao FY, Saab S, Bass NM, et al. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. *Hepatology* 2004;39:230.
16. GL Adani, U Baccarani, A Risaliti, M, et al. A Single-Center Experience of Late Retransplantation of the Liver. *Transplant Proceed* 2005;37:2599-600.
17. BI Gustafsson, L Backman, S Friman, et al. Retransplantation of the Liver. *Transplantation Proceedings*, 2006;38:1438-39.
18. U Maggi, D Consonni, P Bertoli, et al. A Risk Score and a Flow chart for Liver Retransplantation. *Transplant Proceed* 2008;40:1956-60.

Pediatric Liver Transplantation

INTRODUCTION

Pediatric patients had unacceptably high morbidity and mortality rates while awaiting LTX due to shortage of liver allografts. This donor-recipient disparity in children reportedly caused pretransplant mortality rates as high as 25-50%.

ISSUES RELATED TO PEDIATRIC PRETRANSPLANT CARE

Children with ESLD may manifest with several serious complications such as malnutrition, recurrent infections particularly related to biliary tract, signs of portal hypertension, renal problems, vascular complications and osteopenia.

MALNUTRITION

It is defined as body weight below third percentile. 50-60% of children have malnutrition in cholestatic liver diseases due to fatty malabsorption and catabolic state. Nutritional supplementation with medium chain triglycerides, lipid infusions, fat soluble vitamins Protein supplementation with branched chain amino acids are used to correct malnutrition and to build the patient for surgery.

INFECTIONS

Bacterial infections are most common and are often related to central lines (Strep faecalis, Strep viridans, Pseudomonas Aeroginosa and Staph Aureus). Pulmonary infections also occur frequently. Subacute bacterial peritonitis accounts for 30-40% of infection in patients with ascites. Clinical suspicion and early treatment by proper antibiotics is important. Fungal infections (candida and aspergillus) are more common in ALF with acute hepatic necrosis pretransplant. Young, small patients with

long PICU stays and prolonged ventilation are most at risk of infection.

VASCULAR COMPLICATIONS

In cases of EHBA various congenital anomalies are seen such as:

- Hypoplasia or aplasia of portal vein
- Aplasia of suprarenal IVC
- Preduodenal portal vein
- Polysplenia or Asplenia
- Abdominal situs inversus.

These conditions should be recognized pretransplant evaluation and proper modification in the techniques is planned to achieve good outcome.

ACUTE ON CHRONIC LIVER FAILURE

This condition is usually manifested due to infection or GI bleeding. Metabolic imbalance leads to hypoglycemia, acidosis, cerebral edema, shock and multiorgan failure. Development of cerebral edema and multiorgan failure carries a grave prognosis. Artificial liver supporting systems such as MARS are useful till the suitable donor is available.

Other complications of portal hypertension, HRS, pulmonary hypertension are discussed in respective chapters.

DONOR POOL FOR PEDIATRIC TRANSPLANTATION

Both cadaver donor and liver related donors provide allografts for children. Commonly left lateral segment (segment 2 and 3) graft is harvested from the live related donor and in grown up children, a left lobe graft can be used. But when deceased donor is available for a child on waiting list either reduced size transplantation or split

liver transplantation techniques are used. Auxiliary partial orthotopic liver transplantation (APOLT) has a role in acute liver failure and metabolic liver diseases like Crigler-Najjar syndrome where APOLT will provide the missing enzyme, uridine diphosphate (UDP) glucuronyl transferase and the preserved native liver could act as a safety net in case of graft dysfunction. Domino LTX are also a possibility if recipients have familial amyloid polyneuropathy. Split LTX is a technically difficult, but a good option in children.

ADVANTAGES OF LDLT¹

- Elective surgery carried out when the recipient is relatively stable.
- Ischemic liver injury due to prolonged CIT and subsequent poor function of the graft are avoided.

REDUCED-SIZE LIVER TRANSPLANTATION (RSLT)

In children, more than 75% of ESLD occurs in children < 2 years. A child's small size is an inherent disadvantage in the competition for a donor liver as most of the donor organs are from brain dead adult patients. This donor-recipient size mismatch prompted the development of RSLT. First transplantation of part of a liver was performed in a heterotopic fashion and was reported by Fortner in 1979. Orthotopic transplantation of a reduced-size allograft was first reported by Bismuth in 1984. In RSLT, the liver allograft can be tailored on the back table to a variety of functional lobes or segments. Segment 2 and 3 (left lateral segment) or segment 2, 3, and 4 (left lobe) are commonly used in children. Right lobe grafts are rarely used in pediatric population due to size discrepancy. Previously when a left lateral segment or left lobe allograft was used in RSLT, the remaining right-sided liver parenchyma used to be discarded. But the emergence of split liver transplantation to increase the donor pool has given an opportunity to use the right lobe graft for an adult patient on waiting list. Due to emergence of split liver transplantation, reduced size transplantation is rarely practiced in present days.

SPLIT LIVER TRANSPLANTATION

Split liver transplantation is becoming used more widely with increasing experience in surgical techniques of transplantation. In a normal individual, liver constitutes 2% of the body weight; the right lobe constitutes 60%, left lobe 40%, and the left lateral segment 25% of standard liver volume. A graft-to-recipient weight ratio (GRWR,

expressed as % of body weight) between 0.8 to 1.0 is considered as adequate.

SMALL FOR SIZE SYNDROME

Small for size syndrome, due to inadequate graft size is almost never encountered in pediatric patients as the graft size is often larger than required, causing problems with abdominal wall closure. Now the option of transplanting nonsegment grafts for neonates is evolving. Large for size is rarely seen, leading to graft necrosis, if the GRWR is more than 4-5%.

SELECTION OF GRAFT

Selection of graft according to age:

- Infants: Left lateral segment graft
- Small children <12 years: Left lobe graft
- Adolescents: Right lobe grafts.

INDICATIONS

EXTRAHEPATIC BILIARY ATRESIA (EHBA)

This is the most common indication for liver transplantation in children and accounts for >50% cases of pediatric transplants. But majority of children (>80%) are asymptomatic at birth. Infection or infection induced immunological theory is the cause for cholestatic cirrhosis in these patients. Infants become symptomatic in first few weeks after birth with a rapidly progressing cholestatic liver disease and signs of decompensated liver disease in the first 6 months. Survival beyond 2 years without transplantation is difficult.

The primary surgical procedure in EHBA is the Kasai procedure, i.e. hepato-portoenterostomy. It should be carried as early as possible once the diagnosis of EHBA is made. Delayed surgical intervention after 2 months is associated with more unfavorable outcomes. It is usually effective in 50-60% of children if carried out early after the diagnosis of EHBA. Rest 30-40% children need early LTX. Longterm survival with Kasai procedure and without LTX is <10%. Even with successful drainage and normalization of bilirubin, frequent problems of recurrent cholangitis and eventually development of cirrhosis and portal hypertension, necessitating transplant at a later period of life. If the biliary drainage cannot be established effectively by Kasai procedure, early transplantation is necessary to avoid complications like progressive cholestasis, infection, failure to thrive and signs of portal hypertension. OLT appears to be a very effective treatment modality for biliary atresia, with 1-, 5-, and 10-year actuarial survival for patients undergoing primary OLT for biliary atresia of 92.1%, 87.2%, and 85.8%

respectively.²³ The most common causes of death after primary OLT for biliary atresia are graft failure and infection. Early deaths (<90 days post-OLT) were more often caused by graft failure, whereas late deaths (>90 days post-OLT) were more likely to be caused by malignancy, especially post-transplant lymphoproliferative disease (PTLD).²³

DRUG TOXICITY

Acetaminophen over dose is one of the important causes in this group. In children it is usually controlled by conservative treatment and rarely requires transplantation.

ACUTE LIVER FAILURE

Presentation, definition and etiology of ALF in children is different from adults. In infants and young children, early hepatic encephalopathy (HE) is difficult to assess and is not evident until the late stage of HE.²

Definition of ALF in Children³

- Biochemical evidence of liver injury
- No history of chronic liver disease
- Coagulopathy not corrected by vitamin K
- INR > 1.5 in presence of HE and > 2 in absence of HE.

Common Cause of ALF in Children⁴

- Sero-negative hepatitis (non A-E). (49%),
- Acute acetaminophen toxicity (14%)
- Metabolic disease (10%)
- Autoimmune liver disease (6%)
- Non acetaminophen drug-related toxicity (5%)
- Infections (6%)
- Other causes (10%).

Common Causes of ALF in Infants

- Metabolic disorders
 - Galactosemia
 - Tyrosinemia
 - Hereditary fructose intolerance
- Perinatal acquired infection
- Others (less common)
 - Fatty acid oxidation defects
 - Mitochondrial respiratory chain defects
 - Hemophagocytic lymphohistiocytosis also can cause ALF.⁵

WILSON'S DISEASE

Wilson's disease can cause ESLD or present with acute liver failure. But the incidence of acute liver failure is less below 10 years of age.

VIRAL HEPATITIS

Hepatitis due to HBV and HCV is rare in pediatric patients unlike adults and accounts for 5-10% of cases. Herpes simplex virus is the most common cause of ALF in neonates.

NEONATAL HEMOCHROMATOSIS

This presents during the newborn period. Etiology is unknown and it is thought to be due to gestational alloimmune disease process.⁶ During pregnancy these patients have oligohydramnios, reduced fetal movements, edematous placenta, IUGR.

Diagnosis in Newborn Babies is by the Presence of ^{7,8}

- ALF with high ferritin levels
- Iron deposition is seen in minor salivary glands on biopsy
- MRI: Iron deposits in the extrahepatic reticuloendothelial system.

Treatment⁷

- N-acetyl cysteine
- Vitamin E
- Desferrioxamine
- Selenium
- Prostaglandin E1
- Liver transplantation is the last treatment.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis can cause ESLD or acute liver failure requiring transplantation.

TYROSINEMIA

It is usually diagnosed when succinyl acetone is detected in the urine. Cirrhosis and HCC are usually associated at the time of diagnosis. α -Fetoprotein levels gives clue to the diagnosis of early HCC. It is treated medically with nitro-trifluoromethyl benzoyl cyclohexanedione, which reduces the formation of toxic metabolites.⁹ Presence of ALF or HCC usually requires early transplantation.

Indications for liver transplantation in pediatric age group²⁴

Cholestatic conditions

Extrahepatic biliary atresia (Most common: >50% cases)

Progressive familial intrahepatic cholestasis type 1,2 and 3

Alagille syndrome

Sclerosing cholangitis
 Idiopathic cholestasis
 Total parenteral nutrition associated cholestasis

Acute liver failure**Metabolic liver disease**

Wilson's disease
 α 1-Antitrypsin deficiency
 Tyrosinemia
 Glycogen storage disease
 Crigler-Najjar syndrome
 Branched chain amino acid catabolism disorders
 Protoporphyrria

Autoimmune hepatitis type 1 and 2

Hepatic tumors: Hepatoblastoma, Hepatocellular carcinoma

Drug toxicity: Acetaminophen

Secondary liver diseases

Post-traumatic or post liver resection for hepatic tumors

Veno-occlusive disease

Post-chemotherapy
 Budd-chiari syndrome

Viral hepatitis (less common): HBV, HCV

Miscellaneous

Cryptogenic cirrhosis
 Primary hyperoxaluria
 Urea cycle defects
 Cystic fibrosis
 Neonatal hemochromatosis
 Congenital hepatic fibrosis
 Respiratory chain disorder

Retransplantation**MALIGNANCY**

Hepatoblastoma, more commonly is an indications for transplantation followed by vascular tumors, like heman-gioendothelioma. Hepatocellular carcinoma is less common in pediatric population unlike adults.

ROLE OF MULTI-VISCERAL TRANSPLANTATION IN CHILDREN**INDICATION FOR COMBINED LIVER-KIDNEY TRANSPLANTATION**

- Primary hyperoxaluria
- Congenital hepatic fibrosis with polycystic kidney disease
- In recipients with ESRD (HRS is not an indication for renal transplantation).

PRIMARY HYPEROXALURIA

In this condition there is systemic oxalate deposition and renal failure due to deficiency of a hepatic enzyme called alanine glyoxyl transferase. Renal transplantation is required to treat renal failure and LTX for replacement of the enzyme deficiency.¹⁰

CONGENITAL HEPATIC FIBROSIS AND POLYCYSTIC KIDNEY DISEASE

In this condition, Indication of combined transplantation is presence of:

- Recurrent cholangitis
- Portal hypertension complications not responding to conservative treatment
- Renal failure.

TPN-RELATED CHOLESTASIS

In children who are on longterm total parental nutrition due to extensive or multiple bowel resections develop short bowel syndrome and cholestasis requiring combined liver and small bowel transplantation.

IMMUNODEFICIENCY WITH ESLD

In children with immunodeficiency with liver diseases like sclerosing cholangitis, combined liver and bone marrow transplantation are indicated.

Contraindications for liver transplantation in children**Contraindications**

Coma with irreversible brain injury
 Uncontrolled systemic infection
 Extrahepatic metastatic liver tumor
 Terminal progressive systemic disease
 Advanced liver disease with more than one organ failure

RECIPIENT EVALUATION AND ASSESSMENT

Aim of this evaluation and assessment is recognize the suitable recipient and to establishing a relationship and trust between patient, relatives and the transplant team, including understanding the complexity of transplant operations, realities, expectations from the procedure, and the outcome. The transplant surgeon, pediatric hepatologist, and transplant coordinator can play a vital role. Post-transplant complications, immunosuppression, nutrition, growth and developmental issues should be explained in detail to the family.

Pretransplant Preparation

Immunization status should be checked, if not children should be immunized well in advance. In diseases causing chronic cholestasis, malnourished is common. Nutritional replacement is started via oral/nasogastric tube/parenteral nutrition. Addition of fat-soluble vitamins is necessary. Antibiotics are used in cholangitis or any clinical suspected of infection. Neurologic consultation is necessary as it is very difficult to diagnose neurological deficits in small, critically ill children.

Pediatric recipient evaluation and assessment²⁴ complete hemogram and coagulation profile and blood type

Disease specific:

Autoimmune diseases:	Antinuclear antibody, IgG Anti smooth muscle antibody Liver kidney microsomal antibody Anti neutrophil cytoplasmic antibody
Wilson's disease:	Serum ceruloplasmin level 24-hour urine copper
α 1-Antitrypsin deficiency:	Phenotyping
Neonatal hemochromatosis:	Serum ferritin, transferrin levels Iron studies Salivary gland biopsy (in selected cases) MRI of pancreas
HBV:	HBsAg, HBeAg, Anti HBs Ab, Anti HBc Ab, Anti HBe
HBV	DNA, Mutations in HBV
HCV:	HCV RNA, Genotyping
HAV:	Anti HAV Ig M
CMV screening:	Age > 1 year: IgG and IgM titers Age < 1 year: Urine CMV shell viral culture
EBV screening:	IgG and IgM titers
Varicella zoster:	IgG and IgM
Rubella:	IgG and IgM
Toxoplasma:	IgG
Syphilis:	Rapid plasma reagin (RPR) test (VDRL)
Screening for HIV 1 and 2 (HTLV III)	
HCC screening:	AFP, CEA, CA-19-9 (not routinely done)
Metabolic:	Bone density study Blood glucose level Arterial blood gas analysis Blood lactate, ammonia and pyruvate levels
Radiology:	Chest X-ray, Ultrasound of abdomen, Echocardiogram and Doppler US, CT and MRI scan of abdomen

PELD Scoring System

UNOS has used the pediatric end-stage liver disease (PELD) scoring system as a means for prioritizing children for LTX since February 2002.

PELD Score

$[0.436 (\text{Age} < 1 \text{ year})] - [0.687 \times \text{Loge} (\text{albumin g/dL})] + [0.480 \times \text{Loge} (\text{total bilirubin mg/dL})] + [1.857 \times \text{Loge} (\text{INR})] + [0.667 (\text{Growth failure}) (< 2 \text{ Standard Deviations present})]$.

Immunosuppression

Drugs which are used in adults such as corticosteroids, CINs (cyclosporine and tacrolimus), MMF and sirolimus can also be used in pediatric patients for maintenance of immunosuppression. For induction therapy, IL-2 receptor antibodies such as Basiliximab or Daclizumab, anti-CD3 monoclonal antibody (OKT3) and polyclonal antilymphocyte preparations, such as antilymphocyte globulin (ALG) and antithymocyte globulin (ATG) can be used.

Most transplant programs use triple immunosuppression therapy with CINs, corticosteroids and induction therapy with interleukin-2 receptor antibodies (Basiliximab). Immediately after transplantation induction therapy with steroids and IL-2 receptor antibodies (Daclizumab: 1 mg/kg IV, every 2 weeks, 1 to 3 doses or Basiliximab: 20 mg within 6 hours of reperfusion and on day 4 of post-transplantation) is started. CINs (preferably tacrolimus 0.15 mg/kg/day in 2 doses) are started on postoperative day 1 to day 5 days depending on the center's protocols. MMF (15 mg/kg BID) is also used in combination with CINs in some centers. It is important to wean off steroids as early as possible (usually 3 months) to prevent growth impairment and bone related complications. In patients transplanted for autoimmune hepatitis or chronic rejection, or those who develop recurrent or de novo autoimmune hepatitis,¹¹ immunosuppression is tailored and generally includes triple therapy at least for the first year (i.e. tacrolimus or prednisone with MMF, azathioprine or sirolimus).¹² Higher dose of immunosuppression exposes the children to PTLT which is seen in 20% of the pediatric transplants, more in children on tacrolimus. This is due to high prevalence of EBV in donors in comparison to zero prevalence in pediatric patients. Long-term complications of CINs are nephrotoxicity, hypertension, and cardiovascular complications needs trough level monitoring and dose adjustment of CINs. Diarrhea and gastroenteritis will reduce the immunosuppression levels exposing the patients to more risk of rejection. So drug levels should be closely monitored during such episodes of defective drug absorption.

POSTOPERATIVE COMPLICATIONS

The prevalence of medical complications is as high as 60-80% in pediatric patients.

Various complications²⁴ seen in pediatric liver transplant recipients are:

- Bleeding
- Primary nonfunction
- Hepatic artery thrombosis
- Portal vein thrombosis
- Rejection (seen in 50-60% children in 1st week)
- Biliary complications: Bile leak/biloma/stricture
- Intestinal perforation
- Infections: Bacterial/Viral/Fungal
- Renal complications
- Growth failure
- Post-transplant lymphoproliferative disease (PTLD)

BLEEDING

Immediate postoperative bleeding requires re-exploration and control bleeding. Similarly **intestinal perforation** presents as early peritonitis in 1-4 days after transplantation, requires re-exploration.

HA THROMBOSIS

In pediatric transplants incidence of hepatic artery thrombosis (HAT) is much more than adults (9-18% vs. 5%). Prophylactic continuous heparin infusion in early post-transplant period, close monitoring with regular DUS and early intervention in case of HAT are the essential steps towards successful management of HAT and to avoid early retransplantation or mortality. HA complications lead to biliary complications secondary to ischemic injury. Biliary, arterial, portal, intestinal and bleeding complications have reached a prevalence of <10% due to the improvement in surgical techniques and better postoperative care.

IL-2 RECEPTOR ANTIBODIES AND REJECTION

In pediatric transplant who receive IL-2 receptor antibodies as induction therapy, the incidence of early acute rejection is reduced. Rejection episodes are postponed till 3rd or 4th week in post-transplant period and these episodes have atypical presentation. The incidence of steroid resistant rejection has not been changed in recipients where IL-2 receptor antibodies are used.

INFECTIOUS

Infectious (bacterial, viral, and fungal) complications are a significant cause of morbidity and mortality after transplantation.

BACTERIAL INFECTIONS

Bacterial infections such as staphylococcus and E. coli are common. Pneumonitis, peritonitis, septicemia, abscesses in kidney and brain can occur in pediatric transplant recipients. Prophylactic antibiotics are continued routinely in all pediatric patients in order to avoid such infections. Daily cultures of sputum, blood, urine and abdominal drain fluid and central line tip are also sent for culture to detect early infections.

VIRAL INFECTIONS

Post-transplant EBV and CMV infection is more in pediatric transplants as the recipients are usually negative for both the viruses where in adults donors are often positive. Liberal prophylactic protocols with ganciclovir or acyclovir or hyper immune anti-CMV IgG have been used against these infections in various transplant programs. High immunosuppression exposes the pediatric patients to risk of PTLD. However the infection of EBV ranges from mild seroconversion asymptomatic seroconversion, to symptoms of fever or diarrhea, to PTLD. EBV infection can be diagnosed by estimation of viral load by PCR technique. Immunosuppression is reduced or can be omitted temporarily till the clinical improvement and decrease in viral load. Treatment includes use of ganciclovir, CMV-IgG and selectively rituximab (in cases of CD 20 positive cells on immunostaining) monoclonal antibody, can be undertaken.

Other complications are discussed in detail in the respective chapters.

Analgesia

Regardless of the timing of extubation, children require effective analgesia in the postoperative period. The most popular form of analgesia remains morphine, either as a simple infusion (0-40 µg/kg/hour), patient controlled analgesia, or nurse controlled analgesia. Some authors suggest that there may be less need for opiate analgesia after liver transplantation.^{20,21} There are no published reports of use of epidural analgesia in children undergoing LTX. There is, however, one case report of the use of caudal morphine, which suggested that it facilitated immediate extubation and reduced requirement for systemic analgesia.²²

Post-transplant Vaccination

It is usually recommended to use Hepatitis B vaccine in post-transplant period and to delay other vaccines until

the end of 6 months as the fluctuation in immunosuppression trough levels are high during this period and higher dose of immunosuppression is maintain in the early post-transplant period to prevent rejection.

POST-TRANSPLANT LIFE IN CHILDREN

The long-term life after transplantation depends on immunosuppression, compliance, viral infections, vascular complications and impairment of hepatic, renal, biliary and cerebral functions. CINs are associated with attention deficit syndrome and convulsions in children with pre-existing brain damage and it affects the post-transplant life quality. Renal dysfunction is also influenced by CINs. Hypertension is seen in 20-40% of pediatric transplants. Viral infections particularly CMV and EBV and related PTLTD affect the quality of life on longterm. Close monitoring of EBV serology and EBV PCR is essential in children. Early vascular interventions to deal vascular complications, biliary complications also influence the quality of life. The long-term results of pediatric transplants are good with 1 year survival 90-95% and 10 year survival around 80%.

COMPLIANCE

Compliance is very important in any solid organ transplantation. Lack of compliance to immunosuppressive medications is the leading cause of late morbidity in children and adolescents after solid organ transplantation. The estimated rate of noncompliance varies from 5 to 29%. Noncompliant (Nonadherent) behavior has been linked to negative outcomes in transplantation, primarily rejection, which leads to graft loss. Reports have also linked noncompliant behavior to chronic rejection.¹³⁻¹⁵ The transition of responsibility for medication taking occurred approximately at the age of 12 years. The most common reason cited for not taking medications is forgetfulness, but not side effects due to immunosuppressive medication.

Risk factors for noncompliance in solid organ transplants:¹⁶

Major Risk Factors

Major risk factors in noncompliance:¹⁶

- Childhood or adolescence: a major risk factor
- Pre-transplant noncompliance
- Disturbing side effects of the medication
- Use of alcohol or drugs
- Lack of knowledge about the post-transplant regimen

- Psychiatric disorders such as depression, anxiety, personality disorder
- Dementia or cognitive impairment.

Minor Risk Factors

Minor risk factors in noncompliance:¹⁶

- Longer time of post-transplant follow-up
- Poor perceived health status
- Lack of formal health education
- Dissatisfaction with care
- Severity of illness/postoperative complications.

CAUSES OF NONCOMPLIANCE IN CHILDREN^{17,18}

- Child abuse (physical or sexual)
- Not having two parents at home
- Having received public assistance
- Substance abuse
- Having been diagnosed with a psychiatric disorder
- History of being a school dropout
- Pre-transplant diagnosis of autoimmune hepatitis
- Post-traumatic stress disorder

Methods to Monitor

There are 2 methods to monitor compliance:¹⁹

Subjective method: Direct questioning or questionnaires method. It is not a reliable method of assessing compliance.

Objective method: Monitoring of trough levels of immunosuppressant drugs.

REFERENCES

1. Emre S. Living-donor liver transplantation in children. *Pediatr Transplant* 2002;6(1):43-46.
2. Rivera-Penera T, Moreno J, Skaff C, et al. Delayed encephalopathy in fulminant hepatic failure in the pediatric population and the role of liver transplantation. *J Pediatr Gastroenterol Nutr* 1997;24(2):128-34.
3. Bucuvalas J, Yazigi N, Squires RH Jr. Acute liver failure in children. *Clin Liver Dis* 2006;10(1):149-68, vii.
4. Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006;148(5):652-58.
5. Dhawan A, Mieli-Vergani G. Acute liver failure in neonates. *Early Hum Dev* 2005;81(12): 1005-10.
6. Whittington PF, Malladi P. Neonatal hemochromatosis: Is it an alloimmune disease? *J Pediatr Gastroenterol Nutr* 2005;40(5):544-49.

7. Rodrigues F, Kallas M, Nash R, et al. Neonatal hemochromatosis: medical treatment vs. transplantation: The king's experience. *Liver Transpl* 2005;11(11):1417-24.
8. Smith SR, Shneider BL, Magid M, et al. Minor salivary gland biopsy in neonatal hemochromatosis. *Arch Otolaryngol Head Neck Surg* 2004;130(6):760-63.
9. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. *Clin Liver Dis* 2000;4(4):805-14.
10. Cochat P, Gaulier JM, Koch Nogueira PC, et al. Combined liver-kidney transplantation in primary hyperoxaluria type 1. *Eur J Pediatr* 1999;158(Suppl 2):S75-80.
11. Kerkar N, Hadzic N, Davies ET, et al. De-novo autoimmune hepatitis after liver transplantation. *Lancet* 1998;351(9100):409-13.
12. Kerkar N, Dugan C, Rumbo C, et al. Rapamycin successfully treats post-transplant autoimmune hepatitis. *Am J Transplant* 2005;5(5):1085-9.
13. Hilbrands LB, Hoitsma AJ, Koene RA. Medication compliance after renal transplantation. *Transplantation* 1995;60(9):914-20.
14. Dew MA, Roth LH, Thompson ME, et al. Medical compliance and its predictors in the first year after heart transplantation. *J Heart Lung Transplant* 1996;15(6):631-45.
15. Troppmann C, Benedetti E, Gruessner RWG, et al. Retransplantation after renal allograft loss due to noncompliance. Indications, outcome, and ethical concerns. *Transplantation* 1995;59(4):467-71.
16. DK Hathaway, C Combs, S De Geest, et al. Patient compliance in transplantation: A report on the perceptions of transplant clinicians. *Transplant Proceed* 31 1999;(Suppl 4A):10S-13S.
17. Lurie S, Shemesh E, Sheiner PA, et al. Non-adherence in pediatric liver transplant recipients. An assessment of risk factors and natural history. *Pediatr Transplant* 2000;4(3):200-06.
18. Shemesh E, Lurie S, Stuber ML, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. *Pediatrics* 2000;105(2):E29.
19. Shemesh E. Non-adherence to medications following pediatric liver transplantation. *Pediatr Transplant* 2004;8(6):600-05.
20. Donovan KL, Janicki Pk, Striepe VI, et al. Decreased patient analgesic requirements after liver transplantation and associated neuropeptide levels. *Transplantation* 1997;63(10):1423-29.
21. Moretti EW, Robertson KM, Tuttle-Newhall JE, et al. Orthotopic liver transplant patients require less post operative morphine than do patients undergoing hepatic resection. *J Clin Anesth* 2002;14(6):416-20.
22. Kim TW, Harbott M. The use of caudal morphine for pediatric liver transplantation. *Anesth Analg* 2005;100(2):602-03.
23. NR Barshes, TC Lee, R Balkrishnan, et al. Orthotopic liver transplantation for biliary atresia: The US experience liver transplantation 2005;11(10):1193-200.
24. N Kerkar, S Emre. Issues unique to pediatric liver transplantation. *Clin Liver Dis* 2007;11:323-35.

Anesthesia in Liver Transplantation

INTRODUCTION

Liver transplantation has become the treatment of choice for end stage chronic liver disease and some cases of acute hepatic failure, provided patients are selected without limiting comorbidity.¹

PREOPERATIVE ASSESSMENT

Preoperative assessment is by hepatologist, surgeon and anesthetist prior to listing for transplantation. Assessment is aimed at evaluating both hepatic dysfunction and presence of complications of ESLD and comorbid conditions. Patients often have poor exercise tolerance, ascites and pleural effusions and stigmata of chronic liver disease suggest poor hepatic synthetic function.

CARDIAC FUNCTIONS

Cardiac function monitoring, diagnosis of ischemic heart disease and cardiomyopathy can be done by combination of the following investigations depending on the indications:²

- Exercise ECG
- Echocardiogram
- Gated gamma scintigraphy (MUGA scan)
- Dobutamine stress-testing
- Dipyridamole-thallium scanning
- Coronary angiography

LUNG FUNCTIONS

Upto 10% of cirrhotics suffer some form of pulmonary hypertension. Lung diseases like pleural effusion, restrictive lung diseases, hepatopulmonary syndrome can be diagnosed by:

- Chest radiograph
- Lung function tests
- Pulse oximetry
- Arterial blood gas analysis

- Contrast echocardiography
- Radionuclide lung perfusion scanning
- Pulmonary angiography

HEPATIC DYSFUNCTION

Hepatic dysfunction is roughly evaluated by:

PROTHROMBIN TIME

It indicates the extrinsic coagulation pathway requiring prothrombin, fibrinogen and clotting factors V, VII and IX. 20-30% normal activity of these factors is required for coagulation. Mild changes may reflect severe dysfunction.

INTERNATIONAL NORMALIZED RATIO

INR more than 1.5 not corrected by vitamin K injection indicates severe liver dysfunction.

ALBUMIN

It is decreased in severe hepatic synthetic dysfunction. Its decrease requires at least 3 to 4 weeks of liver dysfunction. Albumin < 2.5 gm/dl indicates a risk for increased third space fluid shift and changes in protein drug binding.

BILIRUBIN

Elevated bilirubin level >1.5 mg/dl is abnormal. Conjugated hyperbilirubinemia indicates hepatocellular damage and dysfunction or obstruction.

AMMONIA

Its elevation indicates hepatic dysfunction in the setting of cirrhosis. Elevation of ammonia level depends on the imbalance between ammoniogenesis in the kidney and gut and synthesis of urea in the liver.

ASCITES

Ascites is often associated with water retention and consequent low serum sodium in ESLD patients. If below 125 mmol/l this should be carefully corrected preoperatively (days or weeks) to reduce the risk of pulmonary edema and central pontine myelinolysis associated with acute peri-operative sodium shifts.

HEPATIC SYNTHETIC FUNCTIONS (HYPOALBUMINEMIA OR COAGULOPATHY)

Preoperative correction is unnecessary unless there is a specific indication like active bleeding. There is little if any relationship between these factors and intraoperative blood loss.³

PREMEDICATION

Sedatives are avoided in with hepatic encephalopathy. Benzodiazepine premedication seems safe in other elective cases.

INTRAOPERATIVE MANAGEMENT

Liver transplantation surgery can be divided into 3 phases:

PHASE I (DISSECTION PHASE)

It involves dissection of the structures around the liver and porta hepatis, achieving complete mobilization of liver.

PHASE II (ANHEPATIC PHASE)

It involves division of bile duct, hepatic artery, portal vein and hepatic veins and taking out the recipient liver. The new liver from deceased/live donor is implanted. Previous technique of removing liver along with IVC with use of venovenous bypass is no longer practiced. Piggyback technique is routinely used in most transplant programs.

PHASE III (REPERFUSION PHASE)

It begins after the vascular reconstruction and blood is allowed to re-enter the portal vein, and vascular inflow and outflow clamps are removed. Hepatic artery and bile ducts are anastomosed after reperfusion.

MONITORING OF PATIENT PRIOR TO INDUCTION**PATIENT'S POSITION**

One or both the arms are abducted to a maximum of 80° (to protect from brachial plexus injury by avoiding

hyperextension). Lower chest and abdomen are exposed for surgery.

IV ACCESS

Venous line, radial arterial line, triple lumen central venous line and Swan Ganz catheter (To monitor pulmonary artery pressure) are inserted for access to IV fluids, blood components and hemodynamic monitoring. IV access and rapid infusion system large bore cannulae are required for rapid transfusion of blood and fluids. This may be achieved by the use of 1 or 2 separate 8.5 Fr. catheters sited either in the antecubital fossa or internal jugular vein. The rapid infusion systems allow transfusion of warmed fluids (37-38°C) at rates of up to 1500 ml/min.⁴ Intravenous infusion is started before induction of anesthesia. Appropriate crystalloid is infused to maintain hydration.

Fresh frozen plasma (FFP), colloid and electrolyte solutions can all be used with packed cells to achieve a hematocrit in the region of 0.28 to 0.32. FFP infusion is started early either as a separate infusion or mixed in the rapid infusion reservoir. The rate of FFP infusion depends on TEG recording.

PREOPERATIVE IMMUNOSUPPRESSION DOSE

Preoperative immunosuppression drugs like tacrolimus/ Cs A are usually given 4-6 hours before surgery to avoid risk of regurgitation and aspiration during anesthesia.

ROLE OF DOPAMINE

In many centers low-dose dopamine is routinely used intraoperatively even though there is less evidence to suggest any significant benefit on renal function.

TEMPERATURE

Temperature is monitored either from the PA catheter or from a central temperature probe. A hot air warming over blanket maintains normothermia.⁵

An 18 FG nasogastric tube and urinary catheter are also required.

CVS MONITORING

ECG and arterial pressure monitoring is started. Invasive cardiovascular monitoring like SVR, EDV, CCO, SV02 may be started either before or after induction of anesthesia. Transesophageal echocardiography provides continuous information on ventricular wall motion and embolic phenomena, but is not available in all centers.

INTRACRANIAL PRESSURE (ICP)

Intraoperative monitoring of ICP is important in patients with acute liver failure who are at risk of raised ICP.

LABORATORY MONITORING

Intraoperative monitoring of complete blood count, coagulation profile, electrolytes and arterial blood gases are monitored hourly or as clinically indicated. These guide subsequent ventilation, $\text{Ca}^{2+}/\text{K}^{+}$ supplementation, glucose and bicarbonate infusions and blood replacement therapy. Thromboelastography (TEG) is commonly used for rapid and sensitive means to monitor clotting factor requirements.^{6,7}

INDUCTION

Aim is to maintain cardiovascular stability and rapid tracheal intubation. Traditional “rapid sequence” technique is usually used. Increasing interest in early extubation has lead to the use of shorter-acting drug combinations, including midazolam, propofol and remifentanyl.

VOLATILE ANESTHETIC AGENT

IPPV is established after intubation with isoflurane 0.5-1.5% end tidal concentration in oxygen-enriched air. Some centers use sevoflurane or desflurane.

TOTAL INTRAVENOUS ANESTHESIA (TIVA)

TIVA using propofol has also been practiced, but may be associated with cardiac depression following reperfusion.⁸

Fentanyl, alfentanil and remifentanyl infusion can be used with good effect. Fentanyl has a tendency to cumulation and need for prolonged postoperative ventilation.

Nitrous oxide is usually avoided to reduce cardiovascular depression, gut distension and bubble formation if on venovenous bypass.

Muscle relaxant: Choice depends on clearance, volume of distribution and clinical preference. Atracurium is preferred and provides reliable relaxation and reversal after prolonged use. Pancuronium has an increased volume of distribution in liver disease, while both pancuronium and vecuronium show reduced clearance.⁹ Their use requires caution.

Hypoglycemia is commonly encountered in ALF patients but uncommon in elective cases. Dextrose 10-50% is used to control hypoglycemia.

Hyperdynamic circulation is not a problem before reperfusion. But patients with ALF usually require vasopressors like noradrenaline or angiotensin II when the cardiac reserve is poor.

SPECIFIC CONSIDERATIONS

PHASE I

Massive Ascites

Rapid decompression of massive ascitic fluid needs monitoring of cardiovascular function.

Role of Cell Saver (Figure 34.1)

Continuous slow oozing or sometimes rapid hemorrhage may occur. A cell saver is used to scavenge lost RBCs and prepare them for re-infusion.¹⁰ Scavenged blood is heparinised as it enters a reservoir, washed with normal saline, centrifuged and returned via the rapid infusion system.

Contraindications for use of cell saver:

- Malignant etiology for transplantation
- Infected ascitic fluid/history of subacute bacterial peritonitis.

Electrolyte Imbalance

Hypokalemia and hypocalcaemia are common, but hypomagnesaemia¹¹ can also occur. K^{+} imbalance is treated by potassium chloride infusion. Calcium



Figure 34.1: Intraoperative cell saver

imbalance develops due citrate accumulation, and is treated by slow IV infusion and ionized calcium is maintained between 0.84-1.4 mmol/l to prevent coagulopathy and cardiac depression.

Hypotension

In centers where venovenous bypass (VVB) is used, cross clamping of IVC, portal vein and hepatic artery is associated with reduced venous return (up to 50%), necessitating large volume infusion prior to and during IVC cross-clamping and often need for vasopressors. Relative volume overload occurs during declamping of IVC. In VVB, blood is taken from the femoral vein and returned to the axillary or internal jugular vein. A flow 20% of cardiac output is readily achieved through the bypass circuit. Adding portal bypass increases flow to about 40% of cardiac output (3-4 liters/min). Hemodynamic stability is improved, and the need for acute volume loading reduced. Complications of bypass are air embolism, clot formation, fragmentation of red cells, and failure of the system.

PHASE II

Fibrinolysis

During phase II, there is no production of clotting factors leading to worsening of coagulopathy, fibrinogen deficiency, decreased anti-thrombin III levels and derangement of the t-PA/ α -2 antiplasmin ratio with the onset of fibrinolysis.^{12,13} Platelet consumption occurs in patients who have already low platelet count. Fibrinolysis can be prevented or attenuated by antifibrinolytic agents, such as aprotinin¹⁴ or tranexamic acid¹⁵ and serine esterase inhibitors such as α -2 antiplasmin.¹⁶

Acidosis

Absence of citrate or lactate metabolism, reduced gluconeogenesis and glucose uptake, leads to acidosis.

Role of Steroids

Methyl prednisolone 10 mg/kg is given as a slow intravenous infusion prior to reperfusion, and protects against graft dysfunction and renal injury.¹⁷

PHASE III

End-stage liver disease (ESLD) is associated with a hyperdynamic state characterized by high cardiac output and low systemic vascular resistance due to peripheral vasodilatation. Peripheral vasodilatation is aggravated by general anesthesia and profound vasodilatation is

often observed during reperfusion phase especially in patients with high MELD scores, resulting in severe drop in blood pressure. To maintain hemodynamic stability, single strategy of volume replacement is not appropriate because the excessive blood volume replacement can lead to pulmonary complications. In addition to the volume replacement, vasopressors are recommended to maintain adequate systemic vascular resistance and blood pressure.

Post-reperfusion Syndrome (PRS)

PRS is defined as a reduction in mean arterial pressure of 30% within 5 minutes of graft reperfusion and persisting for at least one minute.¹⁸ This is due to cytokine mediated and is associated with changes in arachidonic acid metabolism.¹⁹ Activation of complement also plays a major role.²⁰ Hypotension associated with a low systemic vascular resistance (SVR) may persist an hour or more. Most patients tolerate this well, but those with pre-existing cardiac disease cope less effectively and may require vasopressor or inotropic support. If arterial pressure falls excessively, epinephrine (dose of 25-50 μ g) is used.

CVP Monitoring

An increase in CVP may lead to venous congestion in allograft.

Hyperkalemia

Reperfusion of allograft releases cold, hyperkalemia, acidotic fluid which goes directly to the heart. To prevent cardiac arrhythmias from the potassium surge, immediately prior to reperfusion 10 mmols calcium chloride is given.

After the initial plasma potassium rise, the functioning graft avidly takes up potassium. Once the graft starts functioning, it is often necessary to provide 60-120 mmol KCl in the hours following reperfusion. Lactate metabolism and production of bicarbonate are restored. Metabolic acidosis begins to correct.

Other causes of intraoperative hyperkalemia. Causes of hyperkalemia during transplantation surgery

- Administration of blood products to patients with impaired renal function
- Patients on diuretics preoperatively which block aldosterone receptors.
- Factors that promote an extracellular shift of potassium
 - Metabolic acidosis
 - Insulin resistance
 - Irradiation of red blood cells²¹

Pre-emptive methods to reduce hyperkalemia intraoperatively is by

- Removing potassium from transfusion products
 - Use of packed RBC stored for less than 14 days to minimize the natural extracellular flux of potassium into the surrounding plasma
 - Use of blood scavenging devices by washing all red blood cells prior to transfusion
- Reduce serum potassium level by medication/RRT (Renal replacement therapy)

Emergency treatment of hyperkalemia: In cases where hyperkalemia is unanticipated and arises in the operating room, emergency treatment is necessary to prevent cardiac arrest.

- **Insulin and glucose:** Use intraoperatively is a standard approach to decrease serum potassium. Insulin regulates transmembrane flux of potassium and thus is capable of shifting extracellular potassium into the intracellular space.^{22,23}
- **Calcium salts:** Survival benefit using calcium infusions as opposed to intermittent boluses.²⁴ If calcium salts are used to treat hyperkalemia during liver transplantation, the chloride preparation offers significantly better bioavailability as the gluconate preparation needs to be activated by hepatic metabolism.²⁵
- **Sodium bicarbonate:** Use should decrease serum potassium by decreasing proton concentration in the extracellular fluid. This would activate a sodium dependent exchange to move hydrogen ions out and sodium into the cell. Subsequently sodium is actively exchanged for potassium. Complications of sodium bicarbonate use are hypernatremia, volume expansion and fall in ionized serum calcium.

ROLE OF REGIONAL ANESTHESIA

Presence of portal hypertension and presence of large venous collaterals is a relative contraindication for putting a spinal/ epidural catheter due to increased risk of bleeding and hematoma formation. Peripheral nerve block may be selectively.

POST-TRANSPLANT PERIOD

Most transplant recipients require 6-12 hours ventilatory support, in liver transplant ICU. Few patients are suitable for early extubation.²⁶ Postoperatively sedation is continued usually with propofol and alfentanil infusions. Muscle relaxants are not usually required. K⁺ supplementation is required for 24-36 hours. Coagulation tests and full blood count guide further transfusion of blood and blood products. Hematocrit is maintained between 0.26 and 0.32. Higher levels are associated with an increased incidence of hepatic artery thrombosis and

graft failure.²⁷ In hypercoagulable states such as Budd-Chiari syndrome, Protein C and S deficiency, anticoagulation with heparin is required and hematocrit is kept at the lower range.

Weaning from the ventilator after LTX can take longer because of unsatisfactory gas exchange during various attempts of T-piece trials. Rapid extubation followed by an immediate NIV application should be considered in this setting to shorten and accelerate the weaning process in those recipients who do not completely fulfill the criteria for safe extubation.⁴⁶ By adding the pressure support (PS) mode with a continuous positive end expiratory pressure (PEEP), NIV could prevent the loss of vital capacity and impede severe lung derecruitment following extubation. Clinical experience has shown that properly delivered noninvasive ventilation mostly benefits moderately dyspneic recipients in acute respiratory failure, while it appears less promising and efficient in patients ventilated for extended periods of time. It has proven safe and efficient mainly as⁴⁶

- A tool to promote an early ventilatory discontinuation and extubation
- A prophylactic strategy for preventing postoperative pulmonary complications
- A simple method to start with in cases of acute hypoxic and/or hypercapnic respiratory failure.

LIVER TRANSPLANTATION AND COAGULOPATHY

There is a direct correlation between transfusion requirements and patient outcome in LTX.²⁸ Increased transfusions significantly increase postoperative morbidity and mortality in liver graft recipients.²⁹ Coagulopathy is a significant contributing factor towards the total amount of blood lost and components transfused. Multiple mechanisms underlie the coagulation abnormalities encountered in OLT. Pre-existing disorders of coagulation: Both the etiology of the liver disease and its severity are important factors in determining the extent and nature of pre-existing coagulation disorders. The liver is the major site of synthesis of most blood coagulation factors and inhibitory proteins and also plays a central role in the clearance of activated coagulation factors.

CAUSES OF COAGULOPATHY IN ESLD

- Abnormal fibrinogen synthesis
- Thrombocytopenia due to
 - Hypersplenism
 - Impaired platelet function
- Enhanced fibrinolysis
- Low grade DIC with markers of increased activation of the coagulation and fibrinolytic system.

INTRAOPERATIVE COAGULOPATHY

Phase I

It is associated with heavy blood loss from the transection of large collaterals in portal hypertension or vascularised adhesions. Hemodilution will worsen intrinsic hemostatic deficiencies. Intraoperative cell saver is used to decrease the replacement of blood components.

Phase II

During this phase there is a marked increase in tissue plasminogen activity due to the lack of hepatic clearance.

Phase III

Reperfusion is associated with changes in coagulation, much of which is transient and corrects spontaneously with the onset of graft function. 10-20% of patients present with severe fibrinolysis after reperfusion. This may be due to release of endogenous heparin (heparan) from the damaged endothelium of the ischemic graft; this activity is more prolonged in marginally functional grafts.

HIGH BLOOD LOSS (>12 UNITS) DURING LIVER TRANSPLANTATION SURGERY

Risk Factors³⁰

- Low hemoglobin (<10 g/dl)
- High FDP level (>24 mmol/l)
- Previous abdominal surgery
- High INR.

Coagulation Monitoring

Routine coagulation tests such as PT, aPTT, TT, fibrinogen, platelet counts are not very useful as:

- They are static tests, performed on citrated plasma leading to long delay in the result.
- They give no information about the stability of the clot or its strength, both of which are highly relevant to the assessment of perioperative hemostasis.

THROMBOELASTOGRAPHY (TEG) (FIGURE 34.2)

Its value in OLT was first described by Kang et al. in Pittsburgh. It is a whole blood viscoelastic test of clot tensile strength. It enables a global analysis of the whole coagulation process from fibrin formation, through to eventual clot retraction and/or lysis, enabling a visual assessment and quantification of overall clot strength and stability.

It gives information about coagulation factors, platelet number and function, platelet and fibrinogen cross linkage and any fibrinolytic activity.³¹ It has the ability



Figure 34.2: Thromboelastography

to assess the efficacy of pharmacological intervention *in vitro* prior to administering drugs to the patient (e.g. antifibrinolytics). The native TEG is extremely sensitive to the presence of heparin and a straight line TEG at reperfusion is not uncommon. Running simultaneous heparinase and native TEGs will differentiate any heparin effect from other concurrent coagulation defects. The addition of activators such as Kaolin or tissue factor (TF) accelerates the rate at which the TEG trace is generated.

ROTEM

It is also based on similar principles of TEG and gives broadly comparable information. It also estimates functional fibrinogen level similar to TEG.

MANAGEMENT OF COAGULOPATHY IN OLT

Indications for Blood Component Therapy

Platelets: Minimal platelet count for transfusion varies from 30 to 100,000.

FFP: Indication of FFP is based on clinical grounds, maintaining a fixed ratio to the number of RBC transfused, PT time and TEG parameters.

Fibrinogen is generally administered when the value is less than 1.0 g/dl.

Antifibrinolytics: They are used during liver transplant surgery to control hyperfibrinolytic state resulting coagulopathy that can occur at the time of graft reperfusion.

- Synthetic Antifibrinolytic agents:
 - Epsilon Amino Caproic Acid (EACA)
 - Tranexamic Acid (TA)
- Serine—Protease Inhibitors: Aprotinin

EACA: The use of EACA to treat fibrinolysis identified on the TEG was first described by Kang's group in 1983. However they did not recommend routine prophylactic administration because of the possibility of prothrombotic complications.

Tranexamic acid: It inhibits the binding between plasmin and fibrin. Kaspar et al, reported that continuous low dose tranexamic acid (2 mg/Kg/hour), whilst reducing the incidence of fibrinolysis, did not result in a significant reduction in transfusion requirements, whereas high dose (10 mg/Kg/hour) TA was found to reduce blood loss by 50%.

Aprotinin: The effect of Aprotinin in reducing blood loss in OLT was first reported by Neuhaus et al. in 1989. It is a natural proteolytic enzyme derived from bovine lung. One of the primary effects of aprotinin is prevention of plasmin degradation of platelet function. Anti-fibrinolytic effect is dose related. At high doses (200 KIU) aprotinin reduces tPA synthesis through its inhibition of kallikrein, but at low dose (50 KIU) its anti-fibrinolytic effect is almost entirely due to plasmin inhibition. Adverse effects are anaphylaxis and increased risk thromboembolic events. Although many centers do use aprotinin routinely, there still is a need for further studies to determine which subpopulations of patients would truly benefit from its use.

Other drugs which reduce blood loss:

- DDAVP
- Conjugated estrogens
- Anti-Thrombin III.

Activated Recombinant Factor VII (rFVIIa)⁴⁵

It accelerates thrombin generation through TF pathway activation, leading to an enhancement of coagulation at the site of vessel injury, without systemic activation of the coagulation cascades. This occurs after complexing with TF or in interaction with activated platelets. The PT time can be shortened considerably by administration of rFVIIa (90 y/Kg) and this is attributed to the direct activation of factor X by VIIa. TEG analysis following administration of rFVIIa shows that the velocity of clot formation normalises (R and K times shorten) but also that there is a significant increase in α angle, indicating that it not only affects the speed of clot formation but also the tensile properties of the clot. rFVIIa provides a marked decrease in blood loss and platelets transfusion.

ANESTHESIA FOR ACUTE LIVER FAILURE

ALF patients constitute 7 to 10% of liver transplantation recipients in western countries. Current outcome of

patients with ALF who make it to transplantation is excellent.³²

Use of artificial liver support and bridging therapies improve, even the sickest patients will be supported to transplantation, which may lead to more severe perioperative problems. High prevalence of preoperative multiorgan failure creates specific practical and physiological challenges for the transplant anesthetist.

PREOPERATIVE PREPARATION

Preoperative preparation of ALF patient in the ICU is particularly relevant to the transplant anesthetist. Transfer to operation theatre is a potentially destabilizing period and must be performed safely. RRT should be discontinued in ICU and later started in the operation theatre. All infusions should be continued to ensure stability. Sedatives particularly benzodiazepines should be avoided. Ventilation is continued by a portable ventilation system. Positioning regarding ICP must be adhered to including 15% head raised with neutral position. Many centers prefer not to paralyse ALF patients in ICU but paralysis prior to shifting to operation theatre is necessary.

Checklist before shifting to operation theatre includes:

- *Invasive monitoring:* Vascular access and position related to operation theatre requirements, ICP measurement, and access for RRT.
- *Ventilation parameters:* Required to maintain adequate oxygenation and PCO₂ levels, relation to theatre ventilation modes, presence/absence of pulmonary edema
- *Stability issues:* Cardiovascular and ICP stability, response to treatment.
- *Renal support:* Use of RRT, overall fluid balance
- *Sedation and paralysis*
- *Coagulation issues:* Adequate preoperative correction, pre-ordered blood products

ROLE OF HEPATECTOMY AS A BRIDGE TO TRANSPLANTATION

In case of cardiovascular or neurological collapse secondary to liver failure seems imminent and where a donor organ is available and harvest is imminent, the possibility of elective total hepatectomy with portocaval shunting followed by liver transplantation is practiced in west. But this approach is rare in Asian countries as the availability of deceased donors is very limited. "Toxic liver syndrome" could be treated by means of this approach.^{33,34} It has a stabilising effect on the neurological status in patients with ALF^{35,36} but the cardiovascular stability is variable.^{37,38} Ethical aspects need to be questioned.

The primary concerns for the anesthetist involved in emergency transplantation for patients with ALF are those of:

- Cerebrovascular stability
- Fluid imbalance
- Delayed recovery and prolonged ICU stay.

Cerebrovascular Stability

In ALF and encephalopathy, patients have impaired cerebral blood pressure and metabolic autoregulation and variations in mean arterial pressure will be reflected by changes to cerebral blood flow. It follows that cardiovascular stability during transplantation, is of paramount importance to the maintenance of cerebral perfusion pressure (CPP). IOP monitoring is essential during surgery.

Intraoperatively, changes in ICP seem to occur in the reperfusion and dissection phase with either stabilization or more often a reduction in IOP during the anhepatic phase. The temporal changes during the transplantation procedure have been attributed to various mechanisms including inflammatory substances released from the failing liver,³⁹ de novo cytokine production from the new liver, cerebral hyperperfusion secondary to an increase in venous return and cerebral ischemia due to systemic hypotension.

It has been demonstrated that ICP surges in ALF are likely to be due to an increase in CBF.⁴⁰ Intraoperative measurements of the ICP, CMRO₂ and CBF during transplantation in patients with ALF have also demonstrated that ICP is more usually related to rises in CBF than ischemia induced by reduction in CPP, secondary to systemic hypotension.⁴¹ Therefore, although a threshold CPP must be maintained, relative hypertension during and after reperfusion, may be detrimental in terms of increasing the risk of increased microvascular pressure, cerebral hyperperfusion and ultimately cerebral edema.

Hypothermia: Use of moderate hypothermia to control changes in ICP has been used in patients with ALF.⁴² One study reported that moderate hypothermia abolished ICP variability throughout the transplantation procedure in patients with the most difficult preoperative control.⁴³ Hypothermia may reinstate cerebral autoregulation and reduce cerebral hyperperfusion.

Hepatic artery/portal vein clamping: Changes in ICP during the early dissection phase can be reduced by HA/PV clamping. The development of an anhepatic state also promotes a reduction in the requirement for vasoconstrictors and inotropes.⁴⁴

RRT: Fluid removal by continuous veno-venous haemofiltration (CVVH) and mild hyperventilation in anticipation of increased CO₂ production may attenuate increases in IOP at reperfusion.

Fluid Balance

RRT should be continued intraoperatively and immediately after the transplantation, when the recipient reaches the transplant ICU to allow fluid management, ICP control and coagulation control. In addition to rapid fluid removal enabling the transfusion of significant blood products, RRT may also be useful in controlling anhepatic acidosis and prerenal hyperkalemia.

Delay in Recovery of Graft Function

Preoperative severe organ dysfunction and associated other organ failure like kidney and lungs, delays the allograft function which makes the recipient dependent on prolonged supportive care in transplant ICU.

REFERENCES

1. Rudich S, Busuttill: Transplant Proc 1999;31:523.
2. Edwards ND, Reilly CS. Detection of perioperative myocardial ischaemia. Br J Anaesth 1994;72(1):104-15.
3. Calne RY, Williams R, Rolles K. World J Surg 1986;10:422.
4. Sassano JJ. The rapid infusion system. In: Winter PM, Kang YG (eds). Hepatic transplantation: Anesthetic and perioperative management. New York, Praeger, 1986;120-34.
5. Russel SH, Freeman JW. Prevention of hypothermia during orthotopic liver transplantation: Comparison of three different intra-operative warming methods In: Slooff MJH and Wierda JMKH, eds. Proceedings of the 7th. Meeting of the Liver Intensive Care Group of Europe. The Hague: CIP Data Koninklijke Bibliotheek;1994:23.
6. Mallett SV, Cox DJA. Thrombelastography. Brit J Anaesthesia 1992;69:307-13.
7. Kang YG, Martin DJ, Marquez JM, et al. Intra-operative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. Anesthesia and Analgesia 1985;64:888-96.
8. Webster NR, Bellamy MC, Sadek SA, Lodge JPA. Right ventricular function in orthotopic liver transplantation: A comparison of two anaesthetic techniques. British Journal of Anaesthesia 1994;72(4):418-21.
9. Miller RD. Pharmacokinetics of atracurium and other non-depolarizing neuromuscular blocking agents in normal patients and those with renal or hepatic dysfunction. Br J Anaesth 1986;58 (Suppl 1):11S-13S.
10. Lindop MJ, Farman JV, Smith MF. The Cambridge-King's College Hospital Series. In: Calne RY (ed) Liver Transplantation. Grune and Stratton, New York 1983;128-29.
11. Bennett MW, Webster NR, Sadek SA. Alterations in plasma magnesium concentrations during liver transplantation. Transplantation 1993;56(4):859-61.

12. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: Role of tissue-type plasminogen activator. *Blood* 1988;71:1090-95.
13. Cheema SP, Webster NR, Dunn F, Bellamy MC. Mediators of fibrinolysis in orthotopic liver transplantation. *Clin Transplant* 1996;10(1 Pt 1):24-27.
14. Mallett SV, Cox D, Burroughs AK, Rolles R. Aprotinin and reduction of blood loss and transfusion requirements in orthotopic liver transplantation. *Lancet* 1990;ii:886-87.
15. Yassen KA, Bellamy MC, Sadek SA, Webster NR. Tranexamic acid reduces blood loss during orthotopic liver transplantation. *Clinical Transplantation* 1993;7:453-458.
16. Bellamy MC, Mullane D, O'Beirne HA. Is tranexamic acid as effective as alpha 2 antiplasmin at correcting coagulopathy in liver transplantation? *British Journal of Anaesthesia* 1998;81:282P.
17. Bellamy MC, Turner S, Dhamarajah S, Bosomworth M. Effect of perioperative steroids on renal function during liver transplantation. *British Journal of Anaesthesia* 2004;93(1): 169P.
18. Aggarwal S, Kang Y, Freeman JA, et al. Postreperfusion syndrome: Cardiovascular collapse following hepatic reperfusion during liver transplantation. *Transplant Proc* 1987;19(Suppl. 3):54-55.
19. Bellamy MC, Galley HF, Webster NR. Changes in inflammatory mediators during orthotopic liver transplantation. *British Journal of Anaesthesia* 1997;79: 338-41.
20. Bellamy MC, Gedney JA, Buglass H, Gooi JH. Complement membrane attack complex and hemodynamic changes during human orthotopic liver transplantation. *Liver Transpl.* 2004;10(2):273-78.
21. Thorp J, Plapp F, Cohen G, et al. Hyperkalemia after irradiation of packed red blood cells: possible effects with intravascular fetal transfusion. *Am J Obstet Gynecol* 1990;163:607-09.
22. Li Q, Zhou M, Wang Y, et al. Effect of insulin on hyperkalemia during anhepatic stage of liver transplantation. *World J Gastroenterol* 2004;15:2427-29.
23. Takats D. Using calcium salts for hyperkalemia. *Nephrol Dial Transplant* 2004;19:1333-34.
24. Davey M, Caldicott D. Calcium salts in management of hyperkalaemia. *Emerg Med J.* 2002;19:92-93.
25. Blumberg A, Weidmann P, Ferrari P, et al. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int* 1992;41:369-74.
26. Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: Patient attributes that determine early transfer to surgical wards. *Liver Transpl.* 2002 Aug;8(8):682-87.
27. Buckels JA, Tisone G, Gunson BK, McMaster P. Low haematocrit reduces hepatic artery thrombosis after liver transplantation. *Transplant Proc* 1989;21(1 Pt 2):2460-61.
28. Massicotte L, Sassine MP, Lenis S, et al. Survival rate changes with transfusion of blood products during liver transplantation. *Can J Anesth* 2005;52:148-55.
29. Cacciarelli TV, Keefe EB, Moore DH, et al. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. *Arch Surg* 1999;134:25-29.
30. Steib A, Freys G, Lehmann C, Meyer C, Mahoudeau G. Intraoperative blood losses and transfusion requirements during adult liver transplantation remain difficult to predict. *Can J Anaesth* 2001;48:1075-79.
31. Kang Y. Transfusion based on clinical coagulation monitoring does reduce haemorrhage during liver transplantation. *Liver Transpl Surg* 1997;3:655-59.
32. Farmer DG, et al. Liver transplantation for fulminant hepatic failure: Experience with more than 200 patients over a 17-year period. *Ann Surg* 2003;237:666-75.
33. Husberg BS, et al. A totally failing liver may be more harmful than no liver at all: Three cases of total hepatic devascularization in preparation for emergency liver transplantation. *Transplant Proc* 1991;23:1533-35.
34. Ringe B, Lubbe N, Kuse E, Frei U, Pichlmayr R. Total hepatectomy and liver transplantation as two stage procedure. *Ann Surg* 1993;218:3-9.
35. Ejlersen E, et al. Hepatectomy corrects cerebral hyperperfusion in fulminant hepatic failure. *Transplant Proc* 1994;26:1794-95.
36. Rozga J, et al. Control of cerebral edema by total hepatectomy and extracorporeal liver support in fulminant hepatic failure. *Lancet* 1993;342:898-99.
37. Bustamante M, et al. Intensive care during prolonged anhepatic state after total hepatectomy and portocaval shunt (two-stage procedure) in surgical complications of liver transplantation. *Hepatogastroenterology* 2000;47:1343-46.
38. Dominguez FE, Lange K, Lange R, Eigler FW. Relevance of two-stage total hepatectomy and liver transplantation in acute liver failure and severe liver trauma. *Transpl Int* 2001;14:184-90.
39. Jalan R, Pollok A, Shah SH, Madhavan K, Simpson KJ. Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure. *J Hepatol* 2002;37:536-38.
40. Jalan R, Olde Damink SW, Hayes PC, Deutz NE, Lee A. Pathogenesis of intracranial hypertension in acute liver failure: Inflammation, ammonia and cerebral blood flow. *J Hepatol* 2004;41:613-20.
41. Ardizzone G, et al. Cerebral hemodynamic and metabolic changes in patients with fulminant hepatic failure during liver transplantation. *Transplant Proc* 2004;36:3060-64.
42. Roberts DR, Manas D. Induced hypothermia in the management of cerebral edema secondary to fulminant liver failure. *Clin Transplant* 1999;13:545-47.
43. Jalan R, et al. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. *Transplantation* 2003;75:2034-39.
44. Noun R, et al. Liver devascularisation improves the hyperkinetic syndrome in patients with fulminant and subfulminant hepatic failure. *Transplant Proc* 1995;27:1256-57.
45. S Busani, G Semeraro, C Cantaroni, et al. Recombinant Activated Factor VII in Critical Bleeding After Orthotopic Liver Transplantation. *Transplant Proceed* 2008;40:1989-90.
46. P Feltracco, E Serra, S Barbieri, et al. Noninvasive Ventilation in Adult Liver Transplantation. *Transplant Proceed* 2008;40:1979-82.

Extracorporeal Liver Supporting Systems

INTRODUCTION

Liver supporting system is a system of therapies, which aim to improve outcome, provide an environment for regeneration and possible spontaneous recovery or failing that support the patient and bridge until the liver transplantation is an option.

IDEAL LIVER SUPPORTING SYSTEM

- Easy availability
- Optimize or prevent deterioration of patient's condition
- Cost effective
- Minimal adverse effects

INDICATIONS

Liver supporting systems are used in different types of Acute Liver Failure (ALF) such as:

- Fulminant hepatic failure
 - No previous liver disease
 - Encephalopathy within 8 weeks of onset
- Acute alcoholic hepatitis
- Acute decompensation of chronic liver disease
- Primary graft non-function
 - Graft failure immediately after transplantation
- Initial poor graft function after transplantation.

TYPES OF LIVER SUPPORT

- **Transplantation:** Deceased donor, live related donor, split liver, auxiliary and hepatocyte transplantation are the different options for transplantation.
- Plasmapheresis/Exchange transfusion
- Cross perfusion with *ex vivo* liver

- Human
- Porcine
- Extracorporeal liver support systems
 - Bioartificial liver support systems (BAL)
 - Artificial/Non-biological liver support systems
- Molecular Adsorbent Recirculation System (MARS)
 - Detoxification system based on albumin dialysis
 - Most widely studied; inconclusive survival benefit
- Single Pass Albumin Dialysis (SPAD)
- Prometheus system (a dialysis and plasma separation-based system)
- Hemocleanse
- Hemolife.

MOLECULAR ADSORBENT RECIRCULATION SYSTEM (MARS)

MARS, clinically introduced in 1993,¹⁻³ is a modified dialysis system, which uses an albumin-enriched (20%) dialysate, able to remove both albumin-bound and water-soluble toxins from the blood. Albumin dialysis is currently the most widely used non-biological liver support system.⁴ It improves not only the general condition, but also both cardiovascular and renal function. Daniluk, et al. confirmed the safety and tolerability of the non-biological hepatic support of MARS.⁵

PRINCIPLE

Albumin is used as a molecular adsorbent to remove albumin bound liver toxins from the patients' blood compartment: namely, bilirubin, ammonia, free fatty acids, cytokines, and aromatic amino acids. The rationale of albumin dialysis was based on the fact that the majority of potential toxins are protein-bound, usually to albumin and cannot be removed by simple hemodialysis or

hemofiltration (in contrast to renal failure). They are potentially removable by albumin dialysis, since the blood is dialyzed against an albumin-containing solution across a suitable membrane. The albumin-bound toxins should be filtered by the binding sites of the albumin in the dialysate and thus removed from the blood.

MARS is a device in which the patient's blood is dialyzed through an albumin-impregnated membrane against a recirculated albumin containing solution. The technique seems to be effective at removing albumin-bound toxins and soluble substances such as fatty acids, bile acids, and bilirubin. Substances with a molecular weight < 50 kDa, such as essential hormones bound to carrier proteins, growth factors, and albumin, are not removed from the perfused plasma because of the membrane pore size.⁶⁻⁹

INDICATIONS

- Acute decompensation of chronic liver disease
- Acute liver failure
- Primary graft dysfunction
- Liver failure after hepatic surgery
- Intractable pruritus in chronic cholestatic syndromes
- Detoxification
- Serum bilirubin level >15 mg/dl
- Renal dysfunction/Hepatorenal syndrome
- Hepatic encephalopathy (> grade II)
- Increased intracranial pressure
- Ischemic hepatitis with serum bilirubin > 8 mg/dl
- Fulminant Wilson's disease
- ALF due to paracetamol overdose

PROCEDURE

A double-lumen catheter type veno-venous access was used for the blood supply and intravenous heparin for blood anticoagulation to maintain the extracorporeal circuit. Blood flow rate was 150 to 250 ml/min, depending on the patient's hemodynamic parameters. A closed-loop dialysate circuit containing 600 ml of 20% stored human serum albumin was driven by the roller pump of the MARS monitor at 150 ml/min. The dialysate—stored human serum albumin—was passed through the dialysate compartment of the blood dialyzer and subsequently regenerated on line by dialysis against a bicarbonate-buffered dialysate (processed by a dialysis machine) followed by passage through a column with uncoated charcoal and a second column with an anion-exchanger resin. The dialysis bath was adjusted on the basis of the patient's needs (Figures 35.1 and 35.2).

ANTICOAGULATION

- Only 40% liver failure patients need anticoagulation
- Necessary if activated clotting times (ACTs) < 160 sec
- Priming heparin 10000u
- Keep ACTs 160~180 sec

COMPLICATIONS¹⁰

- Hemodynamic instability and hypotension
- Hypoglycemia
- Catheter related infections
- Hemorrhage from the catheter site

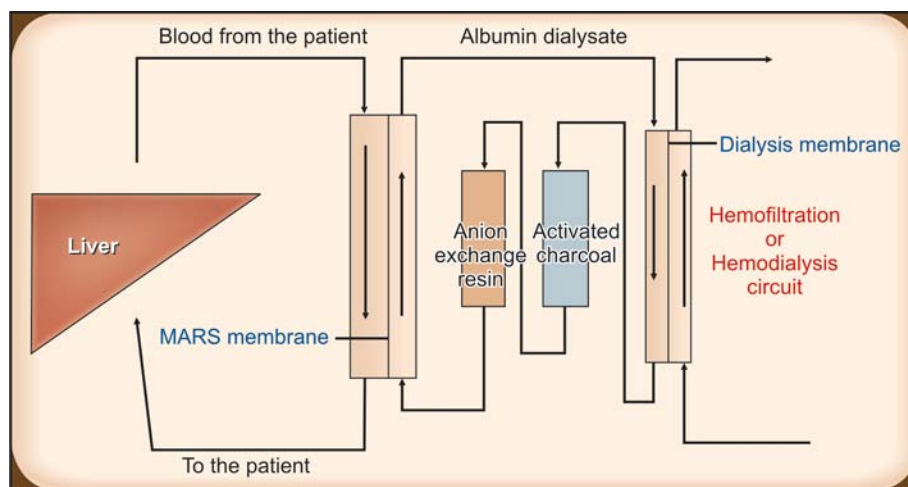


Figure 35.1: Schematic presentation of MARS



Figure 35.2: MARS

CONTRAINDICATIONS

- MAP (using vasopressors) < 55 mm Hg
- Active bleeding
- Uncontrolled systemic infection
- Severe coagulopathy/thrombocytopenia
 - (Hyperfibrinolysis/DIC could be aggravated by extracorporeal circulation)

PROMETHEUS SYSTEM [FRACTIONATED PLASMA SEPARATION, ADSORPTION, AND DIALYSIS (FPSA)]

The Prometheus system removes albumin bound toxins in the patient's blood by combining fractionated plasma separation and adsorption (FPSA) with conventional dialysis. The patient's blood first passes through a plasma separator with a pore size of 250 kDa. The blood flow rate was 150–200 ml/minute.

The filtered plasma fraction then passes over two adsorption columns, a neutral resin and an anion exchange resin adsorber, before it is filtered back to the systemic circulation. The blood then passes through a high-flux dialyzer (F60S, Fresenius, Denmark). The flow rate in the plasma circuit was set to 300 mL/min according to the manufacturer's recommendations. Hemodialysis is performed using a high-flux dialyzer (Figure 35.3).

Comparisons between the MARS and Prometheus systems have shown a significant reduction in total bilirubin, conjugated bilirubin, bile acids, serum urea nitrogen, and serum creatinine with both devices.¹¹ Protein bound toxins were slightly better removed with Prometheus.

SINGLE PASS ALBUMIN DIALYSIS (SPAD)

It is a method of albumin dialysis that uses a standard renal replacement therapy system without an additional

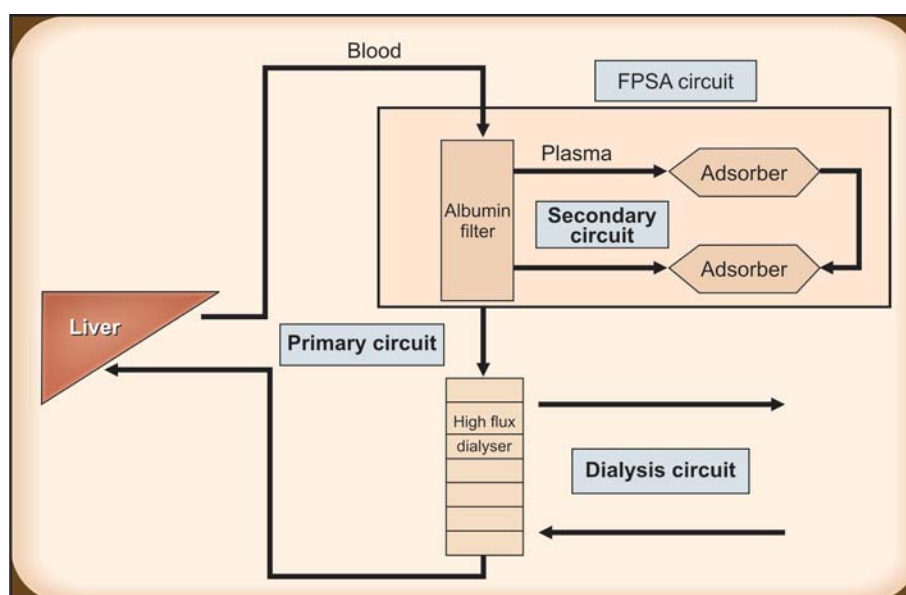


Figure 35.3: Prometheus system: Schematic presentation

pump system. It is easier to establish, as it can simply be performed with continuous venovenous hemodialysis machines. Single-pass albumin dialysis is a quite expensive procedure, due to the costs of large amounts of albumin solutions.

BIOARTIFICIAL LIVER SUPPORT

HISTORY OF BAL DEVICES³³

Xenoperfusion with bioartificial liver devices has been used as a bridge to liver transplantation.^{20,21} After developing, in 1957, the first model of a biological artificial liver (BAL), Motokazu Hori (Tokyo, Japan) treated, in October 1958, for the first time, a human patient in hepatic coma due to liver cirrhosis with a BAL using four live dog's livers.²² In 1963, Yukihiko Nose (Sapporo, Hokkaido, Japan) treated four patients with a BAL using fresh liver slices and freeze-dried canine liver granules; all patients improved but two of them died shortly after treatment.^{23,24} In 1994, the American company, Circe Biomedical (Lexington, MA, USA), developed the Hepat-Assist 2000 System, a BAL device using primary porcine hepatocytes. The first clinical trials were realized shortly after.^{25,26} In 2004, in the first prospective randomized multicenter controlled trial of an extracorporeal liver support system, including 171 patients with fulminant/subfulminant hepatic failure, Achilles Demetriou, et al.²⁷ showed that Hepat-Assist was safe and improved survival.

Since 1999, two other extracorporeal hemofiltration devices using primary porcine hepatocytes have been developed by American companies: LIVER × 2000 System developed by Algenix (Shoreview, MN, USA) and BLSS developed by Excorp Medical (Oakdale near Minneapolis, MN, USA). Excorp Medical and John Patzer from the Thomas Starzl Transplantation Institute (Pittsburgh, PA, USA) collaborated to develop the Bioartificial Liver Support System (BLSS).^{28,29} In 2001 George Mazariegos and John Patzer described the first clinical use of BLSS for the support of a 41-year-old woman with fulminant hepatic failure.³⁰

In Europe, the Academic Medical Center of Amsterdam developed the AMC-BAL system using primary porcine hepatocytes. A phase I clinical trial was carried out in Italy. In 2002, Maarten-Paul van de Kerkhove and Robert Chamuleau (Amsterdam, the Netherlands) reported the first clinical cases. The first patient was a 35-year-old woman with acute liver failure due to hepatitis B infection who received a liver transplantation after two AMC-BAL treatments of 21 and 14 h.³¹ Among the first seven patients treated, six received successful orthotopic liver transplantation and one patient improved after two treatments and did not need

transplantation.³² Because it is not allowed by law to use animal tissues or cells to treat patients in the Netherlands or in Western Europe, the research group at the Academic Medical Center is developing a human-derived hepatocyte cell line BAL.

DIFFERENT BIOARTIFICIAL SYSTEMS

- HepatAssist
- Extracorporeal Liver Assist Device (ELAD)
- Modular Extracorporeal Liver Support system (MELS)
- Amsterdam Medical Center Bioartificial Liver (AMCBAL)

Hepat-Assist System (Circe Biomedical, Inc., Lexington, MA)

- An extracorporeal primary porcine-based system
- Porcine hepatocytes are cryopreserved in liquid nitrogen and stored on site
- Available to treat patients on an emergency basis within three hours
- Patients undergo standard plasmapheresis with the plasma directed toward the HepatAssist® system where it circulates through a charcoal column, an oxygenator, and the hollow fiber cartridge containing freshly thawed, viable, porcine hepatocytes.
- Phase II/III study completed.

Extracorporeal Liver Assist Device (ELAD) (Vital Therapies, San Diego, CA)

ELAD uses about 200 g of cells of the human hepatoblastoma cell line C3A (derived from HepG2) in modified dialysis cartridges. The cells are located in the extracapillary space separated from plasma by the capillary membranes. Prior to entering the bioreactor, the plasma passes a charcoal adsorber and a membrane oxygenator. First clinical applications were performed, to demonstrate the safety of the system.^{12,13}

Modular Extracorporeal Liver Support System (MELS)

MELS is based on the Cell Module,¹⁴ a unit consisting of 3 interwoven capillary bundles in a polyurethane housing. One of the bundles serves as decentralized oxygenation; 2 bundles are used for perfusion with patient plasma. It is operated with primary porcine hepatocytes as well as human hepatocytes isolated from discarded donor organs.¹⁵ For MELS, the CellModule is combined with SPAD and continuous veno-venous hemodiafiltration (CVVHDF). A phase 1 clinical study was performed with the Cell Module charged with porcine hepatocytes¹⁶ and 12 patients were treated with human hepatocytes.¹⁷

Amsterdam Medical Center Bioartificial Liver (AMC-BAL)

In contrast to all other mentioned BAL systems, the capillary membranes exclusively serve oxygenation. The cell compartment of the device, which has a polyester matrix, is loaded with about 200 g of primary porcine hepatocytes. During therapy, the matrix is directly perfused by patient plasma.¹⁸ A phase 1 study showed the safety of the treatment.¹⁹

EVIDENCE-BASED MEDICINE

- A systematic review that pooled 12 randomized controlled trials (with a total of 483 patients) using various bioartificial support systems concluded that overall they had no significant effect on mortality compared with standard medical therapy.
- Meta-regression suggested that their effect depended upon the type of liver failure.
- A 33 percent reduction in mortality was observed in patients with acute-on-chronic liver failure (RR 0.67, 95 percent CI: 0.51 to 0.90) while no significant benefit was detected in those with acute liver failure.

CONCLUSIONS

- Artificial support systems may reduce mortality in acute-on-chronic liver failure.
- Artificial and bioartificial support systems did not appear to affect mortality in acute liver failure.
- Additional randomized clinical trials are needed before any support system can be recommended for routine use.

REFERENCES

1. Stange J, Ramlow W, Mitzner S, et al. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. *Artif Organs* 1993;17:809.
2. Stange J, Mitzner S. A carrier-mediated transport of toxins in a hybrid membrane. Safety barrier between a patients blood and a bioartificial liver. *Int J Artif Organs* 1966;19:677.
3. Stange J, Mitzner SR, Risler T, et al. Molecular adsorbents recycling system (MARS): Clinical result of a new membranebased blood purification system for bioartificial liver support. *Artif Organs* 1999;23:319.
4. Kjaergard LL, Liu J, Als-Nielsen B, et al. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: A systematic review. *JAMA* 2003;289:17.
5. Daniluk J, Szuster-Ciesielska A, Drabko J, et al. Serum cytokine levels in alcohol-related liver cirrhosis. *Alcohol* 2001;23:29.
6. Liu JP, Gluud LL, Als-Nielsen B, et al. Artificial and bioartificial support systems for liver failure. *Cochrane Database Syst Rev* 1:CD003628 2004
7. Mitzner SR, Klammt S, Peszynski P, et al. Improvement of multiple organ functions in hepatorenal syndrome during albumin dialysis with the molecular adsorbent recirculating system. *Ther Apher* 2001;5:417.
8. Daniluk J, Szuster-Ciesielska A, Drabko J, et al. Serum cytokine levels in alcohol-related liver cirrhosis. *Alcohol* 2001;23:29.
9. Nagaki M, Iwai H, Naiki T, et al. High levels of serum interleukin-10 and tumor necrosis factor- α are associated with fatality in fulminant hepatitis. *J Infect Dis* 2000;182:1103.
10. F Pugliese, G Novelli, L Poli, et al. Hemodynamic improvement as an additional parameter to evaluate the safety and tolerability of the molecular adsorbent recirculating system in liver failure patients. *Transplant Proceed* 2008;40:1925-28.
11. Evenepoel P, Laleman W, Wilmer A, et al. Prometheus versus molecular adsorbents recirculating system: Comparison of efficiency in two different liver detoxification devices. *Artif Organs* 2006;30:276.
12. Sussman NL, Gislason GT, Conlin CA, et al. The Hepatix extracorporeal liver assist device: initial clinical experience. *Artif Organs* 1994;18:390.
13. Millis JM, Cronin DC, Johnson R, et al. Initial experience with the modified extracorporeal liver-assist device for patients with fulminant hepatic failure: System modifications and clinical impact. *Transplantation* 2002;74:1735.
14. Gerlach JC, Encke J, Hole O, et al. Bioreactor for a larger scale hepatocyte in vitro perfusion. *Transplantation* 1994;58:984.
15. Sauer IM, Zeilinger K, Obermayer N, et al. Primary human liver cells as source for modular extracorporeal liver support—a preliminary report. *Int J Artif Org* 2002;25:1001.
16. Sauer IM, Kardassis D, Zeilinger K, et al. Clinical extracorporeal hybrid liver support—phase I study with primary porcine liver cells. *Xenotransplantation* 2003;10:460.
17. Sauer IM, Zeilinger K, Pless G, et al. Extracorporeal liver support based on primary human liver cells and albumin dialysis-treatment of a patient with primary graft non-function. *J Hepatol* 2003;39:649.
18. Flendrig LM, la Soe JW, Jorning GG, et al. In vitro evaluation of a novel bioreactor based on an integral oxygenator and a spirally wound nonwoven polyester matrix for hepatocyte culture as small aggregates *J Hepatol* 1997;26:1379.
19. van de Kerkhove MP, Di Florio E, Scuderi V, et al. Phase I clinical trial with the AMC-bioartificial liver. *Int J Artif Organs* 2002;25:950.
20. Court FG, Wemyss-Holden SA, Dennison AR, et al. Bioartificial liver support devices: Historical perspectives. *ANZ J Surg* 2003;73:739.
21. van de Kerkhove MP, Hoekstra R, Chamuleau RA, et al. Clinical application of bioartificial liver support systems. *Ann Surg* 2004;240:216.
22. Hori M. Artificial liver: present and future. *Artif Organs* 1986;10:211.
23. Nose Y, Mikami J, Kasai Y, et al. An experimental artificial liver utilizing extracorporeal metabolism with sliced or granulated canine liver. *Trans Am Soc Artif Intern Organs* 1963;9:358.
24. Nose Y, Mikami J, Kasai Y, et al. An experimental artificial liver utilizing extracorporeal metabolism with sliced or granulated canine liver. 1963. *Ther Apher* 2000;4:10.
25. Watanabe FD, Mullon CJ, Hewitt WR, et al. Clinical experience with a bioartificial liver in the treatment of severe liver failure. A phase I clinical trial. *Ann Surg* 1997;225:484.
26. Custer L, Mullon CJ. Oxygen delivery to and use by primary porcine hepatocytes in the Hepat Assist 2000 system for

- extracorporeal treatment of patients in end-stage liver failure. *Adv Exp Med Biol* 1998;454:261.
27. Demetriou AA, Brown RS Jr, Busuttil RW, et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg* 2004;239: 660.
 28. Patzer JF II, Mazariegos GV, Lopez R, et al. Novel bioartificial liver support system: preclinical evaluation. *Ann N Y Acad Sci* 1999;875:340.
 29. Patzer JF II, Mazariegos GV, Lopez R. Preclinical evaluation of the Excorp Medical, Inc, Bioartificial Liver Support System. *J Am Coll Surg* 2002;195:299.
 30. Mazariegos GV, Patzer JF II, Lopez RC, et al. First clinical use of a novel bioartificial liver support system (BLSS). *Am J Transplant* 2002;2:260.
 31. van de Kerkhove MP, Di Florio E, Scuderi V, et al. Bridging a patient with acute liver failure to liver transplantation by the AMC-bioartificial liver. *Cell Transplant* 2003;12:563.
 32. van de Kerkhove MP, Di Florio E, Scuderi V, et al. Phase I clinical trial with the AMC-bioartificial liver. *Int J Artif Organs* 2002;25:950.
 33. Deschamps J-Y, Roux FA, Say'' P, Gouin E. History of xenotransplantation. *Xenotransplantation* 2005;12:91-109.

Health-related Quality of Life

INTRODUCTION

Health-related quality of life (HRQL) assessment includes the physical, emotional, and social domains.¹ HRQL refers to how illness or its treatment affects a subject's ability to function, and its symptom burden. The impact of OLT on the HRQL is a matter of growing interest especially for long-term survivors. HRQL assessment includes

- Health status
- Disability
- Psychological wellness
- Social performance.

HRQL domains improve after OLT, reaching values close to that of the general population.³ Some authors have reported that the variation in post-transplantation HRQL scores is associated with a number of pre-transplantation factors:²

- Disease severity proxied by Child-Pugh disease class
- Disease duration at the time of transplantation
- Liver transplant history
- Presence of ascites and/or encephalopathy (significantly associated with a poor HRQL)

Barriga et al used a combination of a generic overall HRQL evaluation test (LEIPAD) and a psychological distress perceived by the patient test (BSI), an earlier indicator of psychological discomfort than the overall HRQL test.⁴ Cirrhotic patients listed for OLT evidenced a low level of perceived HRQL in both tests and their complaints are:

- Physical disorders related to ESLD.
- Psychopathological distress arising from the fear of deadly complications associated with the liver disease
- Knowledge of the existing gap between numbers of candidates on waiting list and donors
- Implied risk of exclusion from the waiting list because of clinical deterioration or death.

In this study best results in terms of HRQL were achieved in the group 1 to 2 years after OLT with a worsening in the group at 3 to 4 years after OLT improving in the long-term follow-up group. This decline may express patient difficulty in adapting to the post-transplant situation when they may have to face medical complications of OLT or recurrent liver disease as well as psychological complications related to dependence on chronic immunosuppressive drugs and medical staff and acceptance of their new body identity.⁵

But karam et al reported that in long-term OLT recipients, the well-being and affect scales were better than in the general population expressing a good HRQL in spite of OLT medical or psychological complications.⁶ Another study reported that OLT patients show eventual limitations in daily life, improving progressively in the physical conditions and the expectations for the future.⁷ Time after OLT was a protective factor for perceived physical conditions that improve progressively after OLT. A higher degree of education was protective for managing stressful events as well as married and cohabitant patients. OLT patients who return to work show a better HRQL.⁸

Blanch et al reported that special attention should be paid to women recipients, who seem to have more difficulty than men in adjusting to the psychosocial consequences of the operation. Female patients may be in particular need of psychological intervention after OLT. Support, perhaps in the form of patient groups, could be offered to recently transplanted patients.⁹

FATIGUE AFTER LTX¹⁰

Fatigue is a major problem in patients after liver transplantation. Almost half of the liver transplant recipients were severely fatigued and no indications were

found that complaints of fatigue improve over time. The severity of fatigue was associated with gender, age, self-experienced disabilities, and HRQL. There is was no correlation found between the severity of fatigue and indication for liver transplantation or immunosuppressive medication. Liver transplant recipients experience physical fatigue and reduced activity rather than mental fatigue and reduced motivation. Rehabilitation programs, focusing on improving activity patterns and physical fitness, may reduce complaints of fatigue after liver transplantation.

EMPLOYMENT AFTER TRANSPLANTATION

Post-transplantation employment is a relative term that depends on the type of work (full-time, part time, students), change in work description, and retirement. Unemployment is common after LTX. Post-transplantation employment rates are approximately 30 to 40%.^{12,15,16} Higher rates have been published, but these studies involved much smaller cohorts.^{13,14} Poor physical health is a factor in unemployment post-transplantation.^{15,19} Presence of diabetes further decreases the employment rate.^{17,18} Approximately half of liver transplant recipients return to work after surgery.¹²⁻¹⁶ Most important factors affecting employment include:^{11,12,14-16}

- Gender
- Education level
- Alcohol liver disease etiology
- Pretransplantation employment
- Concerns about losing health insurance
- Age at time of transplantation
- Duration of disability prior to transplantation
- Physical/general health performance status

PSYCHOLOGICAL COMPLICATIONS

Liver transplantation is an alternative therapy that offers patients a greater life expectancy and a better quality of life, in some cases a variety of psychological complications may occur, such as²⁰

- Anxiety
- Depression
- Sexual disorders
- Fantasies about the donor
- Dissatisfaction with body image

Symptoms of anxiety can increase poor adherence to therapy, that is, their own psychological state causes them to pay little attention to healthy habits, which partly accounts for the occurrence of a poor quality of life 1 year after being discharged from hospital after transplantation.^{21,22}

HCV AND HRQL

HCV recurrence was almost universal; chronic hepatitis C is present in 50 to 90% of OLT patients after 12 months with a 5-year actuarial rate of cirrhosis ranging from 10 to 28%. Recurrent HCV hepatitis in liver transplant recipients was associated with impairment in HRQL, functional status, and greater depression as compared to patients who did not have HCV or those without HCV recurrence and the need for psychological interventions to detect and treat depression in this setting.²³

IMMUNOSUPPRESSION AND HRQL

GI complications affect half of liver transplant recipients and they range from mild to moderate disease, such as diarrhea or nausea, to more severe, life-threatening ones, such as colon perforation, digestive bleeding, or others. Diarrhea was the most frequent GI complication. Most immunosuppressive treatments are associated with some type of GI complication, which can be classified into one of several general categories:²⁴

- Infections
- Mucosal injury and ulceration
- Biliary tract diseases
- Diverticular disease
- Pancreatitis
- Malignancy

These problems frequently affect patients HRQL.²⁵ GI complications lead to changes in immunosuppression (MMF and steroids) in 25% of patients. Of these, the drug most frequently modified was MMF (reported to occur in up to 45% of patients).²⁶

MELD SCORE AND HRQL

Rodrigue and colleagues showed that increasing MELD score was negatively associated with HRQL after liver transplantation, especially as it relates to physical functioning.⁶¹ Castaldo et al, have shown that recipients with higher pretransplant MELD have better post-transplant physical HRQL.⁶²

REJECTION AND HRQL

Patients experiencing rejection episodes required either an increase/change in their immunosuppression, pulse-dose steroids, or both. The additional procedures, inpatient admissions, more frequent outpatient visits secondary to these episodes had a negative effect on these patients HRQL.

SEXUAL LIFE AFTER LIVER TRANSPLANTATION

In the last 20 years, OLT has emerged as the treatment of choice for ESLD due to various causes. Most transplant centers reported 5-year survival rates for adult transplant recipients of about 80-90% and 9-year survival rates of 74%.²⁷ Recovery of active sexual life takes few months. Sexual health encompasses not only sexual function, but also involves the full range of human experience. Sexuality allows communication of emotional feelings, provides a means of physical pleasure and gratification, enhances feelings of self-worth, and strengthens relationships.²⁸ Sexual dysfunction can occur in both sexes before and after liver transplantation.²⁹⁻³¹ Discussion of this aspect of health care should take place with patients.

Most common complaints by men

- Inability to reach orgasm
- Erectile dysfunction

Most common complaints by women

- Dyspareunia

Evaluation of sexual health after transplantation is important for several reasons.

- Sexual health is a common concern of many transplant recipients.^{32,33,6,7} Many liver transplant recipients from the transplant clinic have expressed their concerns about the effect of liver transplantation on their sexual health.
- It can provide a more complete estimate of their overall health status after transplantation.
- It can assist health care professionals in educating prospective transplant recipients, and it may help them provide post-transplantation counseling and intervention programs that focus on this specific area of the recipients' lives.

A Spanish study from Barcelona, reported that women and older patients were more likely to experience sexual dysfunction.^{34,8} Riaz et al reported that 24% of the patients perceived that they suffered from sexual problems before transplantation, and this perception persisted in 15% after transplantation.^{35,9} It is unclear whether sexual problems that persist after transplantation result from organic pathology, side effects of therapy, psychological reactions, or anxiety about sexual performance.

Jin, et al. reported that 20% of the male and 26% of the female reported that their libido had decreased since transplantation. 33% of male and 26% of females have difficulty in reaching orgasm with intercourse after transplantation.^{36,10} Another interesting aspect of this survey was the fact that a minority (19%) reported taking sildenafil to improve their sexual function.

PSYCHOLOGICAL PROBLEMS IN PATIENTS ON WAITING LIST

Patients on waiting list for a transplant present anxiety symptoms, fear of surgery, emotional problems, and alterations in mental health.^{37,38} Liver transplant candidates have a considerable need for psychosocial counseling during the evaluation procedure, and professional psychosocial support should therefore be available in this critical period of the transplantation process. The relatively stable psychosocial well-being of patients on the waiting list, however, should not obscure the fact that stress continues after listing.³⁹

HRQL IN PEDIATRIC TRANSPLANTATION

With improved immunosuppressive regimens and operative techniques, survival at 1, 5 and 10 years are 95%, 85% and 80% respectively.⁴⁰ The expectation is that these survivors will lead healthy lives, performing everyday activities, free from the burden of chronic illness pediatric juvenile arthritis, asthma, and epilepsy. HRQL in children includes 5 aspects of health such as physical health, mental health, social functioning, role functioning and general health perceptions.^{41,42} Demographic variables including race and parental education level have a known impact on HRQL in healthy children, with children of non-Caucasian race and those with parents of lower educational status having lower reported HRQL.^{43,44}

Few studies reported that HRQL after transplantation appears to be equal to or better than that of children and adolescents with other chronic illnesses.^{45,46} Alonso et al,⁴⁷ reported the first multicenter study to evaluate HRQL in pediatric liver transplant recipients. The physical function in this older age group is significantly lower than that of healthy children, and their parents experienced more emotional stress and disruption of family activities. In both short-term and long-term follow-up, transplant families frequently struggle with the burden of ongoing medical care, which can disrupt their routines and generate anxiety about their child's future health. Provision of both pre and postoperative psychological support, not only for the child receiving the transplant, but also for his whole family, including the siblings and the partners of the living donors is essential.⁴⁸

PSYCHOLOGICAL COMPLAINTS IN DONORS

Donor procedure in Adult LDLT has an estimated mortality of 0.5%.⁴⁹ Devastating complications of donors themselves undergoing salvage liver transplantation have

also been reported⁵⁰ Apart from these incidences, about 20%⁵¹ and up to 67% of donors in one series⁵² developed complications. Another series says 71% of donors reported abdominal symptoms several months after surgery, which they attributed to the surgery.⁶⁰ 96% of donors were able to return to work 10 weeks (mean) after surgery.

Living liver donors represent a healthy sample who is subjected to emotional and physical stress. Actual donors have better psychosocial resources at their disposal than potential donors and are therefore able to cope with the stress of the operation.

DIFFERENT PSYCHOLOGICAL COMPLAINTS IN THE DONOR

- Diffuse abdominal symptoms^{53,54}
- Sexual dysfunction⁵⁵
- Abdominal pain⁵⁶
- Anxious depression⁵⁷

Erim et al reported that female donors and donors with a more complicated postoperative course more often develop psychiatric symptoms and should receive adequate care.⁵⁸ The benefits of live liver donation outweigh the risks, and that Adult LDLT is justifiable until the supply of deceased donor liver grafts improves significantly. The donor should be provided with more accurate and the most up-to-date information on the success of the recipient operation in practice and the risk to be incurred in the donor operation. Recovery of the donor is most prompt for mental domains. Physical recovery takes 6 to 12 months to complete. This long time interval to return to normalcy is required even in adult-to-pediatric LDLT.⁵⁹

REFERENCES

1. Bruner DW. In search of the "quality" in quality-of-life research. *Int J Radiat Oncol Biol Phys* 1995;31:191-92.
2. Bryan S, Rotcliffe J, Neuberger JM, et al. Health-related quality of life following liver transplantation. *Qual Life Res* 1998;7:115.
3. Younossi AM, Mc Cormick M, Price LL, et al. Impact of liver transplantation on health related quality of life. *Liver Transpl* 2000; 6:779.
4. Barriga MS, Baccarani U, Scudeller L, et al. Quality-of-life assessment before and after liver transplantation. *Transplantation Proceedings* 2005;37:2601-04.
5. Leyendeker B, Bartholomew U, Neuhaus R, et al. Quality of life of liver transplant recipients. *Transplantation* 1993;56:561.
6. Karam VH, Gasquet I, Delvart V, et al. Quality of life in adult survivors beyond 10 years after liver, kidney and heart transplantation. *Transplantation* 2003;76:1699.
7. Kober B, Kuchler T, Broelsch C, et al. A psychological support concept and quality of life research in a liver transplantation program: An interdisciplinary multicenter study. *Psychother Psychosom* 1990;54:117.
8. Hellgren A, Berglund B, Gunnarsson U, et al. Healthrelated quality of life after liver transplantation. *Liver Transplant Surg* 1998;4:215.
9. Blanch J, Sureda B, Flavia M, et al. Psychosocial adjustment to orthotopic liver transplantation in 266 recipients. *Liver Transplantation* 2004;10(2):228-34.
10. R van den Berg-Emons, BV Ginneken, et al. Fatigue is a major problem after liver transplantation. *Liver transplantation* 2006;12:928-33.
11. Bravata DM, Olkin I, Barnato AE, et al. Employment and alcohol use after liver transplantation for alcoholic and nonalcoholic liver disease: A systematic review. *Liver Transpl* 2001;7:191-203.
12. Hunt CM, Tart JS, Dowdy E, et al. Effect of orthotopic liver transplantation on employment and health status. *Liver Transpl Surg* 1996;2:148-53.
13. Eid A, Steffen R, Porayko MK, et al. Beyond 1 year after liver transplantation. *Mayo Clin Proc* 1989;64:446-50.
14. Rongey C, Bambha K, Vanness D, et al. Employment and health insurance in long-term liver transplant recipients. *Am J Transplant* 2005;5:1901-08.
15. Adams PC, Ghent CN, Grant DR, et al. Employment after liver transplantation. *Hepatology* 1995;21:140-44.
16. Sahota A, Zaghla H, Adkins R, et al. Predictors of employment after liver transplantation. *Clin Transplant* 2006;20:490-95.
17. Valdmans V, Smith DW, Page MR. Productivity and economic burden associated with diabetes. *Am J Public Health* 2001;91:129-30.
18. Tunceli K, Bradley CJ, Nerenz D, et al. The impact of diabetes on employment and work productivity. *Diabetes Care* 2005;28:2662-67.
19. S Saab, C Wiese, AB Ibrahim, et al. Employment and quality of life in liver transplant recipients. *Liver transplantation* 2007;13:1330-38.
20. Pérez MA, Martín A, Galan A: Problemas psicológicos asociados al trasplante de órganos. *Inter J Clin Health Psychol* 2005;5:99.
21. Dew MA, Kormos RL, DiMartini AF, et al. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. *Psychosomatics* 2001;42:300.
22. Dew MA, Switzer GE, DiMartini AF, et al. Psychological assessment and outcomes in organ transplantation. *Prog Transplant* 2000;10:239.
23. T Gayowski, MM Wagener, IR Marino, et al. Quality of life and functional status of liver transplant recipients with recurrent viral hepatitis C. *Transplantation Proceedings* 1993;31:1386-87.
24. Helderma JH, Goral S. Gastrointestinal complications of transplant immunosuppression. *Review J Am Nephrol* 2002;13:277.
25. JI Herrero, S Benlloch, A Bernardos, et al. Gastrointestinal complications in liver transplant recipients: MITOS Study. *Transplant Proceed* 2007;39:2311-13.
26. Tierce JC, Porterfield-Baxa J, Petrilla AA, et al. Impact of MMF related gastrointestinal complications and MMF dose alterations on transplant outcomes and health care costs in renal transplant recipients. *Clin Transplant* 2005;19:779.
27. Seaberg EC, Belle SH, Berginger KC, et al. Long-term patient and retransplantation-free survival by selected recipient and donor characteristics: An update from the Pitt-UNOS liver transplant registry. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants*. Los Angeles: UCLA Tissue Typing Laboratory 1997:15-28.

28. Hart LK, Milde FK, Zehr PS, et al. Survey of sexual concerns among organ transplant recipients. *J Transpl Coord* 1997;7:82-87.
29. Ho JK, Ko HH, Schaeffer DF, et al. Sexual health after orthotopic liver transplantation. *Liver Transpl* 2006;12(10):1478-84.
30. Gomez-Lobo V, Burgansky A, Kim-Schluger L, et al. Gynecologic symptoms and sexual function before and after liver transplantation. *J Reprod Med* 2006;51(6):457-62.
31. Sorrell JH, Brown JR. Sexual functioning in patients with end-stage liver disease before and after transplantation. *Liver Transpl* 2006;12(10):1473-77.
32. Bravata DM, Olkin I, Barnato AE, Keefe EB, Owens DK. Health-related quality of life after liver transplantation: A meta-analysis. *Liver Transpl Surg* 1999;5:318-31.
33. Gralnek IM, Hays RD, Kilbourne A, et al. Development and evaluation of the liver disease quality of life instrument in persons with advanced, chronic liver disease—The LDQOL 1.0. *Am J Gastroenterol* 2000;95:3552-65.
34. Blanch J, Sureda B, Flavia M, et al. Psychosocial adjustment to orthotopic liver transplantation in 266 recipients. *Liver Transpl* 2004;10:228-34.
35. Raiz L, Daview EA, Mergusion RM. Sexual functioning following renal transplantation. *Health Social Work* 2003;28:264-73.
36. Jin K, Ho, I Hin Ko, et al. Sexual health after orthotopic liver transplantation. *Liver transpl* 2006;12:1478-84.
37. Shih FJ, Hu RH, Ho MC, et al. Changes in health-related quality of life and working competence before and after liver transplantation. *Transplant Proc* 2000;32:2144.
38. Moore KA, Burrows GD, Hardy KJ. Anxiety in chronic liver disease: changes post transplantation. *Stress Med* 1997;13:49.
39. L Goetzmann, R Wagner-Huber, R Klaghofer, et al. Waiting for a liver transplant: Psychosocial well-being, spirituality and need for counselling. *Transplant Proceed* 2006;38:2931-36.
40. Smith C, Davies D, McBride M. Liver Transplantation in the United States: A report from the Organ Procurement and Transplantation Network. *Clin Transplant* 2000;14:19-30.
41. Eiser C. Children's quality of life measures. *Arch Dis Child* 1997;77:350-54.
42. Levi R, Drotar D. Critical issues and needs in health-related quality of life assessment of children and adolescents with chronic health conditions. In: Drotar D, ed. *Measuring Health-Related Quality of Life in Children and Adolescents*. Mahwah, NJ: Lawrence Erlbaum Associates;1998:3-2.
43. Landgraf J, Abetz L, Ware J. *The CHQ User's Manual*. Boston, MA: HealthAct 1999.
44. Varni J, Burwinkle T, Seid M. The PedsQLTM 4.0 as a school population health measure: feasibility, reliability and validity. *Qual Life Res* 2006;15:203-15.
45. Alonso EM, Neighbors K, Mattson C, Sweet E, Ruch-Ross H, Berry C, et al. Functional outcomes of pediatric liver transplantation. *J Pediatr Gastroenterol Nutr* 2003;37:155-60.
46. Bucuvalas JC, Britto M, Krug S, Ryckman FC, Atherton H, Alonso MP, et al. Health-related quality of life in pediatric liver transplant recipients: A single-center study. *Liver Transpl* 2003;9:62-71.
47. E M Alonso, K Neighbors, FB Barton, et al. Health-related quality of life and family function following pediatric liver transplantation. *Liver transplantation* 2008;14:460-68.
48. KH Schulz, C Hofmann, K Sander, et al. Comparison of quality of life and family stress in families of children with living-related liver transplants versus families of children who received a cadaveric liver. *Transplantation Proceedings* 2001;33:1496-97.
49. Boillot O, Dawahra M, Mechet I, et al. Liver transplantation using a right liver lobe from a living donor. *Transplant Proc* 2002;34:773-76.
50. Brown RS Jr, Russo MW, Lai M, et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003;348:818-25.
51. Umeshita K, Fujiwara K, Kiyosawa K, et al. Operative morbidity of living liver donors in Japan. *Lancet* 2003;362:687-90.
52. Pomfret EA, Pomposelli JJ, Lewis WD, et al. Live donor adult liver transplantation using right lobe grafts: Donor evaluation and surgical outcome. *Arch Surg* 2001;136:425-33.
53. Trotter JF, Talamantes M, McClure M, et al. Right hepatic lobe donation for LDLT: impact on donor quality of life. *Liver Transpl* 2001;7:485-93.
54. Beavers KL, Sandler RS, Fair JH, et al. The living donor experience: Donor health assessment and outcomes after LDLT. *Liver Transpl* 2001;7:943-47.
55. Kim-Schlüger L, Sander SF, Schiano TH, et al. Quality of life after lobectomy for adult liver transplantation. *Transplantation* 2002;73:1593-97.
56. Fukunishi I, Sugawara Y, Makuuchi M, et al. Pain in liver Donors. *Psychosomatics* 2003;44:172-73.
57. Walter M, Pascher A, Jonas S, et al. Living donor liver transplantation from the perspective of the donor: results of a psychosomatic investigation. *Z Psychosom Med Psychother* 2005;51:331-45.
58. Y Erim, M Beckmann, CV Gamazo, et al. Quality of life and psychiatric complications after adult living donor liver transplantation. *Liver transpl* 2006;12:1782-90.
59. Crowley-Matoka M, Siegler M, Cronin DC 2nd. Long-term quality of life issues among adult-to-pediatric living liver donors: a qualitative exploration. *Am J Transplant* 2004;4:744-50.
60. Pascher A, Sauer IM, Walter M, et al. Donor evaluation, donor risks, donor outcome, and donor quality of life in adult-to-adult living donor liver transplantation. *Liver Transpl* 2002;8:829-37.
61. Rodrigue J. Does MELD predict quality of life after liver transplantation? *Transplantation* 2006;82:1016.
62. Castaldo ET, Feurer ID, Russell RT, et al. Does health related quality of life after liver transplantation correlate with the model for end stage liver disease score? Unpublished observation 2007.

Liver Transplantation in Asia and Western Countries

INTRODUCTION

Liver transplantation is well established in Western countries in the 1980s, after the introduction of cyclosporine A in 1979.^{1,2} The number of liver transplants rapidly increased, leading to a serious shortage of grafts in many transplant centers in Europe and the USA. In Asian countries, cadaveric organ transplantation was introduced in 1990s, but due to religious and ethical opposition, debate over the definition of brain death and lack of public understanding about transplantation, the number of DDLTs performed was far less as compared to West. Laws defining brain death were introduced in Taiwan (1987), Singapore (1987), the Philippines (1992) and Japan (1997). Still the rise in the number of DDLTs was not significant. To overcome these obstacles and to meet the donor organ shortage living donor liver transplantation (LDLT) was introduced in Japan, and spread to Korea, Taiwan, Hong Kong and other Asian countries.

Milestones of LDLT ⁵⁻¹²			
Adult to child LDLT			
Year	Surgeon	Country	Type of graft
1988	Raia	Brazil	Left lateral segment graft
1989	Nagasue	Japan	"
1991	Broesch	Europe	"
1993	Yeung	Hong Kong	"
1994	Lee	Korea	"
1993	Chen	Taiwan	"
1997	Dou	China	"
Adult to adult LDLT			
1993	Makuuchi	Japan	Left lobe graft
1994	Fan	Hong Kong	"
1996	Fan	Hong Kong	Right lobe graft
1997	Lee	Korea	"
1998	Broesch	Europe	"
1998	Wachs	USA	"
2000	Chen	Taiwan	"

Asian Society of Transplantation founded in 1989 includes 16 countries involved in this survey were Bangladesh, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Oman, Pakistan, China, Philippines, Saudi Arabia, Singapore, Taiwan, Thailand, and the United Arab Emirates (UAE).⁴ Asian countries such as China, Japan, Korea, India, Hong Kong, Saudi Arabia, Singapore, and Taiwan are performing both living and cadaveric liver transplants.⁴ Liver transplantation was performed in all the countries except Bangladesh, Indonesia, Oman, and the UAE in 2000.⁴

LDLT was originally used initially in small children, but the indications have gradually been extended to larger and older children, small adults, and finally to all adults. Concomitant with this expansion, liver graft has shifted from the left to the right side. Compared to rapid growth of liver transplantation in West, liver transplantation in Asia did not become well accepted until the early 1990s. First LDLT in Asia was performed by Nagasue et al. in 1989 in Japan.³

The initial reports of LDLT grafts comprised left lateral segment graft, extended left lateral segment graft and left lobe graft with middle hepatic vein (MHV), all of which entail similarly small surgical risks to donors. Extension of indications from small children to larger and older children was therefore rather smooth. The next major step was application of the procedure to large adolescents and adults. At this stage, the problem of small-for-size graft was encountered, with associated poor early graft function, hepatocyte injury and, most importantly, reduced patient survival. Overcoming this difficulty required the use of larger hepatic grafts, necessitating right lobe graft. Right lobe graft was introduced by the Kyoto team in 1994.⁵

LIVER TRANSPLANTATION IN ASIAN COUNTRIES**JAPAN**

Law permitting organ retrieval from brain-dead donors was implemented on 16 October 1997. Till 2004 only less than 40 liver grafts from brain-dead donors have been used. First cadaveric liver transplant was performed in February 1999. The number of LDLT cases has exceeded 3000 in Japan by 2004. However, it is still difficult to perform retransplantation because of the shortage of transplantable organs from brain-dead donors.

- First DDLT was performed in 1968
- First LDLT (adult to child) was performed in 1989
- First LDLT (adult to adult) was performed in 1993

According to the Japanese liver transplant registry, 3246 liver transplantations were performed by the end of 2004.

- Total DDLT were 28 (17 Adult + 11 Pediatric patients)
- Total LDLT were 3218 (1790 Adult + 1428 Pediatric)

Cumulative survival rates after liver transplantation in Japan (%)

Type of LTX	1 year	5 years	10 years	15 years
Primary (3129 cases)	82.4	77.0	72.6	72.6
Re-transplantation (85 cases)	45.8	44.3	-	-
Type of graft				
Right lobe graft (1106)	79.5	71.6	69.5	-
Left lobe graft (619)	77.5	71.5	67.5	67.5
Lateral segment (1040)	87.4	85.3	80.1	80.1
Whole liver (10)	80.0	-	-	-
Blood type				
Identical (2290)	83.0	77.5	72.6	72.6
Compatible (661)	81.1	76.4	73.0	-
Incompatible (268)	69.1	64.1	59.9	-
Age (years)				
30-39 (1105)	84.1	80.5	75.6	75.6
40-49 (706)	81.8	75.6	67.6	-
50-59 (423)	73.8	63.1	59.7	-
>60 (103)	66.9	57.1	57.1	-

(Source: Japan liver transplantation registry, 2004 data)

TAIWAN

- First DDLT was performed in March 1984 (Chen CL)
- Transplant legislation act was introduced in 1987
- Brain death declaration legislation act was introduced in 1987
- 1st pediatric liver transplantation was performed in 1992
- 1st LDLT was performed in 1994 (adult-pediatric) (Chen CL)
- 1st Adult to Adult LDLT was performed in 2000
- 1st split liver transplant: May 21, 1997 (First Split LTX was performed in Asia, by Chen CL)

- Taiwan organ registry and sharing center was started in 2002 as per the UNOS policy
- Revision of transplant registration-2003
- No. of transplant centers: 12 for LDLT and 20 for DDLT
- No. of patients on waiting list for liver till Apr, 2008-835 patients
- Longest survival
 - LDLT-23 years (Wilson disease, DDLT-longest survival in Asia)
 - DDLT-14 years

Etiology of liver transplantation in Taiwan: HBV is the most common cause of LTX. Mostly transmitted through vertical transmission rather than other methods.

Etiology	LDLT	DDLT
HBV	34.4%	23.0%
HCV	21.0%	7.8%
HBV+HCV	1.7%	1.1%
HCC	1.1%	0.7%
HBV+HCC	20.0%	13.3%
HCV+HCC	7.8%	6.2%
Others	23.3%	47.9%

(Source: Lee PH, Data from National Taiwan University Hospital Apr 2008)

Country ¹⁷⁻²⁰	Survival	
	1 year	5 years
Taiwan	95%	91%
(CGMH, Kaohsiung)		
USA	88%	77%
Europe		
Pediatric	81%	78%
Adult	74%	58%
Japan		
Pediatric	86%	83%
Adult	76%	69%

KOREA

Korean National Organ Sharing system (KNOS) was established in February 2000. First LTX (DDLT) in Korea was done in 1988 at Seoul National University Hospital (SNUH) in a 26 years old female with Wilson disease.^{13,14}

- First pediatric LDLT-1994
- First adult LDLT-1997
- First dual grafts TX was performed in Korea in 2000
- Brain death account for 1% of all deaths and 9.4% of ICU deaths
- 600 LTXs have been performed in the last 3 years (60% LDLT)

- HBV is the most common etiology and includes 80% of all liver transplants.
- 5 year survival more than 80%
- Donor exchange program was introduced to avoid ABO incompatibility
- 5 centers have a case load of more than 20 cases/year.
- No. of liver transplantation centers 1988–1, 1992–3, 2002–22 and 2006–19.

INDIA

- Human organ transplantation act was introduced by Government of India in 1994
- Approximately 450 liver transplants till end 2007
- Approximately 325 LDLT and 125 DDLT
- 23 liver transplantation centers; only 3 centers have a volume of >20 cases/year. Only two high volume centres from north India with >50 cases per year and so far has more than 200 liver transplantations.
- Donor deaths–3 reported (1 from North and 2 from South)
- First DDLT was attempted in 1995 in AIIMS, New Delhi.
- First successful DDLT was performed in 1998
- First successful LDLT was performed in 2000 (Soin AS)
- Combined Kidney and liver transplant for Hyperoxaluria from two live donors–was performed in May 2007

Major Hurdles for Development of Liver Transplantation in India

- Lack of adequate infrastructure and number of centers as per the population.
- Lack of adequate number of expertise compared to the population.
- Unregulated proliferation of centers.
- Fly by night centers—surgical team fly over night to do transplant in a centre where no expertise available for post-transplant management.
- Lack of interest/attitude for multidisciplinary approach.
- Neurologists/neurosurgeons reluctant to motivate donation as they fear they may be labeled as “organ suppliers”
- Lack of uniform health insurance policy for the population.
- People in low socioeconomic class can’t afford transplantation cost.

- Funds–Self/Govt./NGO/Collection by appeal or loan/Insurance
- Lack of public awareness
- Superstition and misplaced religious beliefs.
- Reluctance to spend money and resources on pediatric transplantation
- All ICUs are not accredited for organ retrieval when cadaver is available.
- Lack of certification of brain death and deferring the announcement of brain death
- Minimal sharing between the states. Lack of centralized organ sharing policy
- Brain death law requires that centers who certify brain death, must be licenced to harvest organs—an unrealistic law
- Medicolegal problems
- Less number of OPOs (Organ procurement organization) compared to the area and population
- Regional OPOs operating in India: 2 govt. and 4 NGO
 - ORBO (organ retrieval and banking organization) by Govt. of India
 - AORTA (Armed Forces Organ Retrieval and Transplantation Authority), from Armed forces
 - Apollo liver transplantation registry
 - MOHAN (Multiorgan harvesting aid network)
 - COPA (City based organ procurement agency)
 - HOPE (Human organ procurement and education)
- Different OPOs operating in different cities
 - ORBO, HOPE, AORTA–New Delhi
 - NKF, NARMADA, MOHAN–Mumbai and Maharashtra
 - MOHAN AND TANKER–Chennai and Tamil Nadu
 - MOHAN–Hyderabad
 - FORTE and ZCCK–Bangalore
 - SORT–Cochin

Alcohol and hepatitis are the common cause of cirrhosis in India. Many patients not able to afford liver transplantation due to poverty and the transplantation mostly restricted to expensive corporate sector hospitals. Public sector hospitals lacking the facility for transplantation.

HONG KONG

Results of adult right lobe transplantation (Source: LDLT by Fan ST).

Years	Graft survival (%)	Patient survival (%)
1 year	92.5	93.2
3 years	85.2	85.9
5 years	80.1	82.6

	LDLT (Rt. lobe) (n=252 cases)	DDLT (n=146 cases)
Actuarial graft survival (%)	83.7	82.2
Actuarial patient survival (%)	84.9	84.2

SINGAPORE

The first liver transplantation in Singapore was performed in National University Hospital (NUH), Singapore in 1990.

LIVER TRANSPLANTATION IN WESTERN COUNTRIES

Liver transplantation results according to data from UNOS¹⁵ as of 22nd August 2008 are shown below (Figures 37.1 to 37.7, Data reproduced with permission).

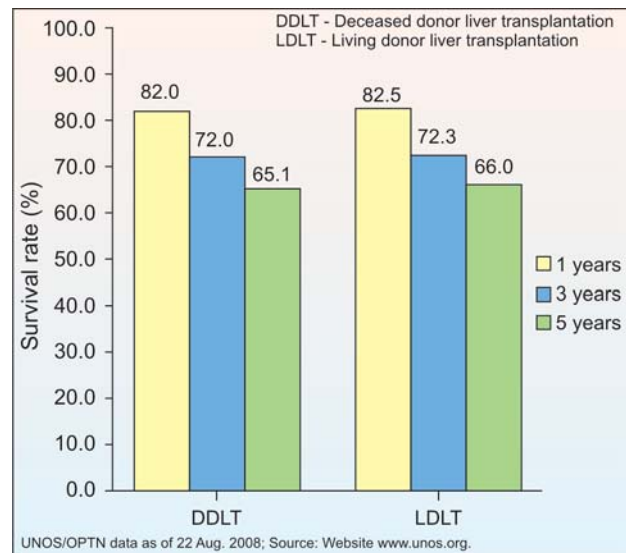


Figure 37.1: 1, 3 and 5 years survival rate in DDLT vs. LDLT (UNOS Data)

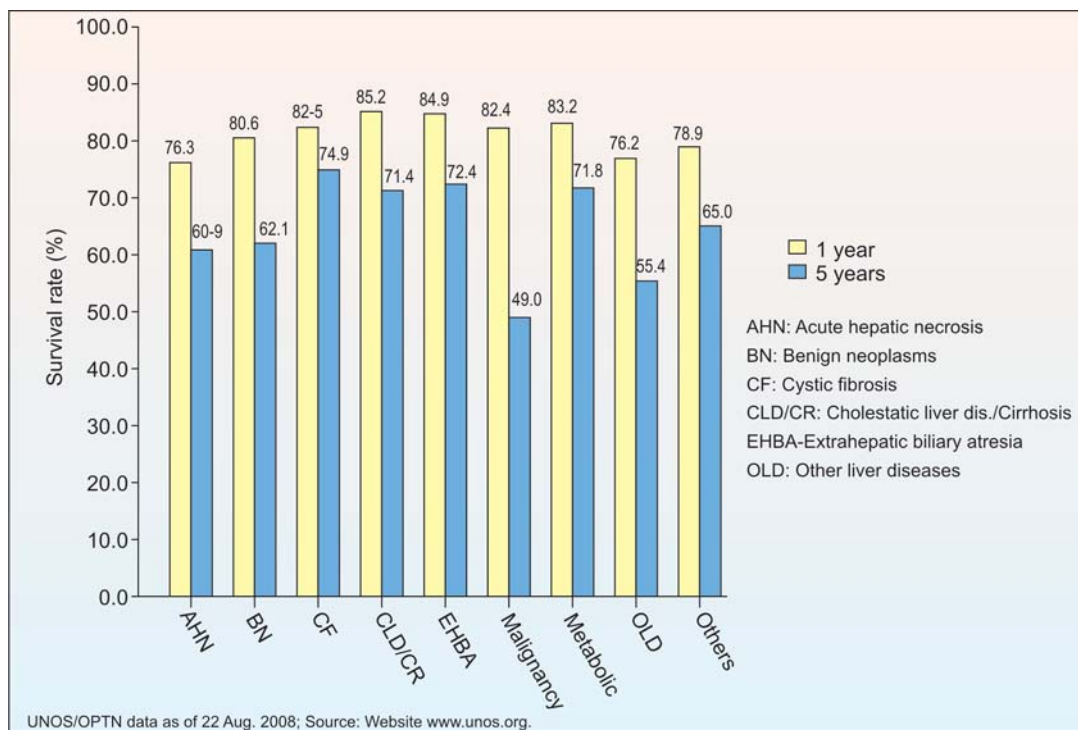


Figure 37.2: 1 and 5 years survival rate according to the indication for LTX (UNOS Data)

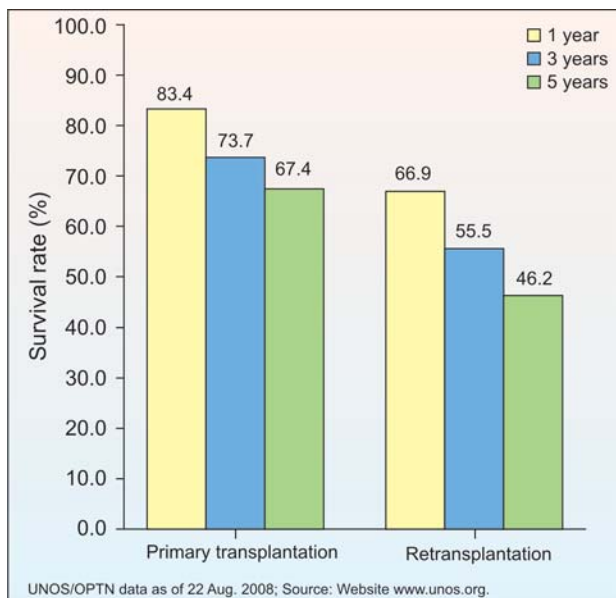


Figure 37.3: 1, 3 and 5 years survival rate in Primary LTX vs. Retransplantation (UNOS Data)

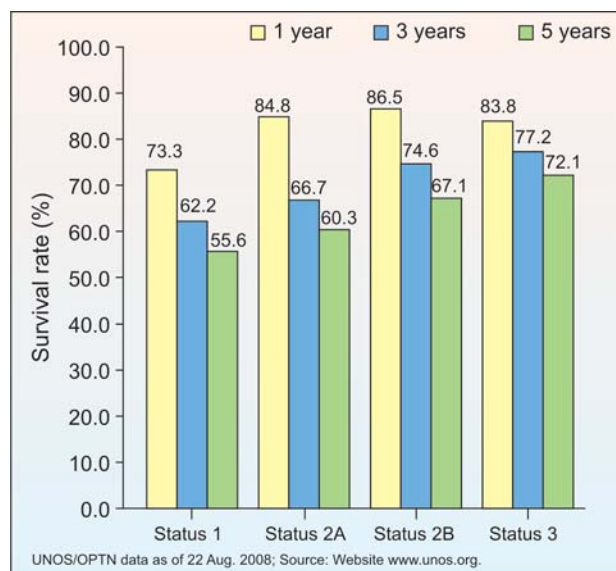


Figure 37.5: 1, 3 and 5 years survival rate according to the status of the recipient at the time of transplantation (UNOS Data)

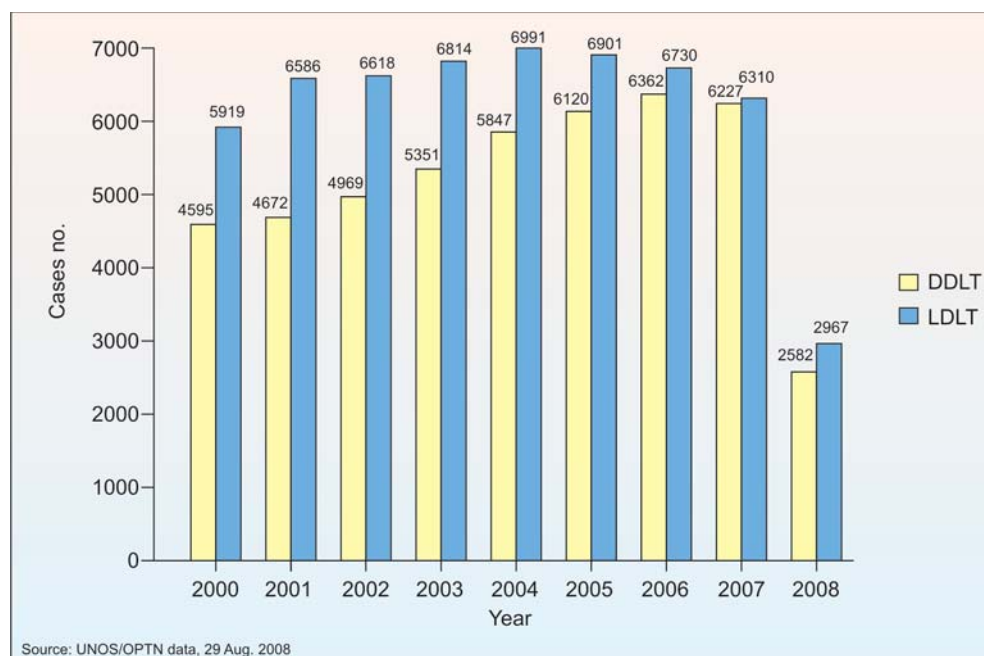


Figure 37.4: No. of liver transplants according to the year in USA (UNOS Data)

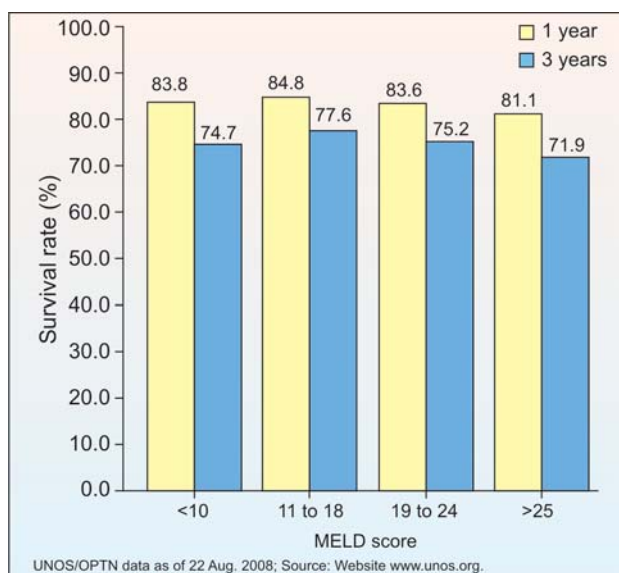


Figure 37.6: 1 and 3 years survival rate according to the MELD score (UNOS Data)

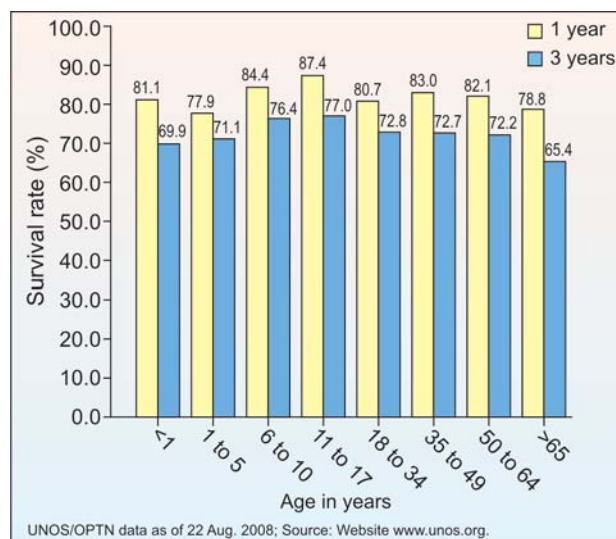


Figure 37.7: 1 and 3 years survival rate according to the age at the time of transplantation (UNOS Data)

LIVER TRANSPLANTATION IN EUROPE

Number of LTX centers in Europe (**Figure 37.8**). 137 centers in 23 Countries. From 1968 and June 2006, 70862 liver transplantations have been performed in Europe.¹⁶

European liver transplant registry statistics upto 10 September 2007

Survival rates	Patient survival (%)		Graft survival (%)	
	1968-1988 (n=2006)	after 1988 (n=65612)	1968-1988 (n=2208)	after 1988 (n=73117)
1 year	53	82	48	75
3 years	45	75	40	68
5 years	41	71	36	63
10 years	36	61	31	53

(Source: www.eltr.org; Last updated-10 Sept 2007)(n= number of patients)

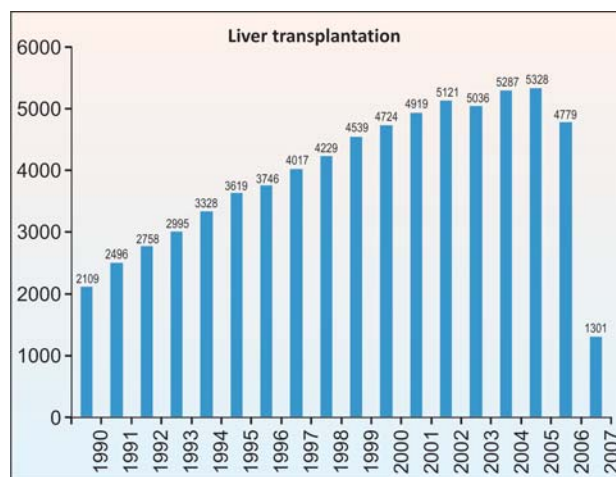


Figure 37.8: Progressive increase in the number of liver transplants in Europe (1990=2007) (Source-www.eltr.org)

REFERENCES

- White DJ, et al. Cyclosporine A initially as the only immunosuppressant in 34 recipients of cada veric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet*. 1979;2:1033-36.
- Starzl TE, Klintmalm GB, Porter KA, Iwatsuki S, Schroter GP. Liver transplantation with use of cyclosporin A and prednisone. *N Engl J Med* 1981;305:266-69.
- Nagasue N, Kohno H, Matsuo S, et al. Segmental (partial) liver transplantation from a living donor. *Transplant Proc*. 1992;24:1958-59.
- K Ota. Current Status of Organ Transplants in Asian Countries. *Transplant Proceed* 2004;36:2535-38.
- Yamaoka Y, Washida M, Honda K, et al. Liver transplantation using a right lobe graft from a living related donor. *Transplantation*. 1994;57:1127-30.
- S Raia, JR Nery, S Mies. Liver transplantation from live donors, *Lancet* 1989;2:497
- Mori K , Nagata K, Yamagata S, et al. The introduction of microvascular surgery to hepatic artery reconstruction in living donor liver transplantation-its surgical disadvantages compared with conventional procedures. *Transplantation* 1992;54:263-68.

8. Testa G, Malagó M, Broelsch CE, et al. Biliary anastomosis in living related liver transplantation using the right liver lobe: techniques and complications. *Liver Transpl* 2000;6(6):710-14.
9. S Todo, H Furukawa, MB Jin, et al. Living Donor Liver Transplantation in Adults: Outcome in Japan. *Liver Transpl* 2000;6:S66-S72.
10. Chen CL, Concejero A, Wang CC, et al. Living donor liver transplantation for biliary atresia: a single-center experience with first 100 cases. *Am J Transplant* 2006;6(11):2672-79.
11. Y Hashikura, M Makuuchi, S Kawasaki. Successful living-related partial liver transplantation to an adult patients, *Lancet* 1994;343:1233-34.
12. Lo CM, Gertsch P, Fan ST. Living unrelated liver transplantation between spouses for fulminant hepatic failure. *Br J Surg*. 1995;82(8):1037.
13. Kim ST, Park YH, Lee KU, et al. *Korean J Transplant* 1998;2:27.
14. KU Lee, SB Kim, SH Kim, et al. Liver Transplantation in Seoul National University Hospital. *Transplant Proceed* 2002;34: 2799-800.
15. United Network per Organ Sharing www.unos.org.
16. European Liver Transplant Registry www.eltr.org
17. Concejero A, Chen CL, Wang CC, et al. Living donor liver transplantation for hepatocellular carcinoma: a single-center experience in Taiwan. *Transplantation* 2008;85(3):398-406.
18. Shiffman ML, Saab S, Feng S, et al. Liver and intestine transplantation in the United States, 1995-2004. *Am J Transplant*. 2006;6(5 Pt 2):1170-87.
19. Sugawara Y, et al. *British medical bull*. 2005;75-76;15
20. Adam R, McMaster P, O'Grady JG, et al. European Liver Transplant Association. Evolution of liver transplantation in Europe: Report of the European Liver Transplant Registry. *Liver Transpl* 2003;9(12):1231-43.

Hepatocellular Carcinoma and Liver Transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and ninth most common cancer in women worldwide with 1 million new cases a year. Its incidence is increasing due to improved diagnostic techniques and due to long-term consequences of HBV and HCV infection. HBV infection is the single most important cause of HCC worldwide, the incidence of HCC is higher in countries like China, Taiwan, South Asia and South Africa where the incidence of HBV infection is high than in Western populations. In Taiwan HCC is the most common malignancy among men. In the West, alcohol use and hepatitis C are the major risk factors for HCC; hepatitis B virus (HBV) infection plays a secondary role.¹ In USA, the incidence of HCC also has been rising during the last decades, from 1.4 per 100,000 populations from 1976 to 1980 to 2.4 per 100,000 populations from 1991 to 1995. This increasing tendency will continue over the next 20 years.^{1,3} 2 to 8% annual incidence of HCC is seen in cirrhotic patients. HCC is a growing indication for LTX as the cirrhotic patients with HCC are given a higher priority for LTX.

STAGING OF HCC

When trying to stratify patients who have HCC, both the tumor characteristics and the underlying liver function should be assessed. Different staging systems of HCC are shown in the tables below:

A. The American Joint Committee on Cancer Tumor-Node-Metastasis (AJCC TNM) classification is used widely but depends on data after resection and is not applicable in patients who do not undergo treatment involving resection.

American joint committee on cancer staging: TNM staging of HCC

Primary tumor (T)

- Tx - Primary tumor can not be assessed
- T0 - No evidence of primary tumor
- T1 - Solitary tumor without vascular invasion
- T2 - Solitary tumor with vascular invasion (or)
Multiple tumors none > 5 cm
- T3 - Multiple tumors more than 5 cm (or)
Tumor involving a major branch of the portal vein or hepatic vein
- T4 - Tumor with direct invasion of adjacent

Regional lymph node (N)

- Nx - Regional nodes cannot be assessed
- N0 - No regional lymph node involvement
- N1 - Regional lymph node involvement

Metastasis

- Mx - Distant metastasis can't be assessed
- M0 - No distant metastasis
- M1 - Distant metastasis

Staging

Stage I - T1 N0 M0	Stage II - T2 N0 M0
Stage IIIA - T3 N0 M0	Stage IIIB - T4 N0 M0
Stage IIIC - TX N1 M0	Stage IV - TX NX M1

B. Okuda system developed in 1985, characterized patients by tumor size, presence of ascites, and biochemical markers such as albumin and bilirubin levels.

Okuda staging

Stage I : 0 points	Stage II : 1 or 2 point
Stage III : 3 or 4 points	

Points	0	1
Tumor size	< 50% of Liver	> 50% of Liver
Ascities	No	Yes
Albumin (gm/dl)	> 3	< 3
Bilirubin (mg/dl)	< 3	> 3

C. CLIP Scoring system

Cancer of the Liver Italian Program (CLIP) scoring system (1988)

Score of 0-2 is assigned for each of the 4 parameters: Range of score is 0-6

Child-Pugh stage

- Stage A = 0
- Stage B = 1
- Stage C = 2

Tumor morphology

- Uninodular and extension < 50% = 0
- Multinodular and extension < 50% = 1
- Massive and extension > 50% = 2

Alpha-fetoprotein

- < 400 = 0
- > 400 = 1

Portal vein thrombosis

- Absent = 0
- Present = 1

D. The Japan Integrated Staging Score from the Cancer Study Group of Japan combines Child-Pugh staging with a **modified TNM classification**

TNM staging by Liver Cancer Study Group of Japan

Factors

- Number of tumors: single
- Tumor size: < 2 cm
- No vascular invasion (portal vein, hepatic vein, bile duct)

Staging definitions

- T1: Fulfilling all three factors
- T2: Fulfilling two factors
- T3: Fulfilling one factor
- T4: Fulfilling none of the factors

N: Regional

- Stage I: T1N0M0
- Stage II: T2N0M0
- Stage III: T3N0M0
- Stage IV-A: T4N0M0 or T1-4, N1M0
- Stage IV-B: T1-4, N0 or 1, M1

DIAGNOSIS

HCC is usually diagnosed during screening/follow up of HBV patients or investigations for symptomatic HCC. Symptomatic HCC has a very poor prognosis, with a median survival of 1 to 8 months and a 5-year survival rate of only 3%.⁴⁻⁶ Screening of HCC includes routine assessment for viral markers, tumor marker (alpha-fetoprotein) and abdominal imaging by USG. α -fetoprotein is neither sensitive nor specific. Alpha-fetoprotein level > 200 ng/dL is highly suspicious for HCC.^{1,5,7} Contrast enhanced CT Scan and MRI imaging are usually done in case of positive findings on initial screening. Maciel et al. showed CT sensitivity of 70.3 and 72% for US⁸ Boin et al. reported that the CT sensitivity was 83.3% and specificity 80.1%, whereas USG sensitivity was 75% and specificity 80.1%.⁹

Burrel et al reported that MRI angiography is significantly better than triphasic helical CT in detection of HCC nodules (76% versus 61%), particularly in additional nodules between 10 to 20 mm in diameter (84% versus 47%).¹⁰ Biopsy and histological proof is not required for diagnosis of HCC. HCC is a highly vascular tumor that demonstrates contrast uptake on dynamic imaging techniques early arterial phase and contrast washout in the delay venous phase. HCC is diagnosed on the basis of typical findings on contrast enhanced CT scan and biopsy is not required in majority of the patients. Torzilli et al. reported that the accuracy of FNA-biopsy to diagnose HCC as 90-95%, a sensitivity of 85-90%, and a specificity of 100%. Similar results have been achieved employing only radiological (ultrasound, abdominal lipiodol-CT, MRI) and biological studies (tumor markers): 99.6% accuracy, 100% sensitivity, and 98.8% specificity. Hence preoperative FNA-biopsy is not necessary and should be avoided before transplantation.^{11,12} Biopsy is recommended in HCC > 2 cm without the typical vascular pattern and normal alpha-fetoprotein level. Nodules of 1 to 2 cm can be diagnosed as HCC when there is concordance between two different imaging techniques. Regular follow-up of tumors < 1 cm.^{2,4}

BCLC STAGING CLASSIFICATION AND TREATMENT (BARCELONA CLINIC LIVER CANCER)⁹⁴

Most widely accepted. This is based on tumor factors (size, nodularity), liver functions and treatment modalities.⁹⁴

EARLY STAGE HCC (STAGE A)

Stage A1: Single tumors and absence of relevant portal hypertension and normal bilirubin.

Stage A2: Single tumors associated with relevant portal hypertension and normal bilirubin.

Stage A3: Single tumors with both relevant portal hypertension and abnormal bilirubin.

Stage A4: Three tumors smaller than 3 cm regardless of liver function.

INTERMEDIATE STAGE

Stage B: Asymptomatic patients with multinodular tumors without vascular invasion or extra hepatic spread.

ADVANCED STAGE (AT LEAST ONE CRITERIA)

Stage C: Symptomatic patients (PS 1-2) and/or those with invasive tumor pattern reflected by vascular invasion or extrahepatic spread.

END STAGE (AT LEAST ONE CRITERION)

Stage D: Patients with severe cancer related symptoms (PS 3-4) or with tumors arising in heavily decompensated cirrhosis (Okuda stage III or Child-Pugh).

End stage disease (D) has an extremely grim prognosis and should receive only symptomatic treatment.^{4,8}

TREATMENT STRATEGY ACCORDING TO BCLC STAGING (FLOW CHART 38.1)

Stage 0: Patients who have very early HCC are optimal candidates for resection.

Stage A: Patients who have early HCC are candidates for radical therapies (Resection, ablation, percutaneous ethanol injection, or liver transplantation).

Stage B: Patients who have intermediate HCC may benefit from chemoembolization.

Stage C: Patients who have advanced HCC may receive new agents in the setting of a randomized, controlled trial.

Stage D: Patients who have end stage disease receive symptomatic treatment.

HCC-ROLE OF LTX

In 1980s, high recurrence rate (32-54%) and poor outcomes (5 year survival < 40%) were obtained after LTX due to the acceptance of exceedingly advanced tumors with adverse prognostic factors such as macroscopic vascular invasion, lymph node involvement, and extrahepatic spread at the time of the procedure.¹³⁻¹⁶ Later reports suggest that more strict selection of patients like patients with solitary HCC < 5 cm or up to three nodules < 3 cm resulted in better survival rates (70% 5-year survival) and with a recurrence rate below 15%.¹⁷⁻²⁰ Reyes et al. evaluated 19 children with HCC who underwent deceased-donor OLT and reported overall 1-, 3-, and 5-year disease-free survival rates of 79%, 68%, and 63%, respectively.²¹

Outcome of HCC after LTX: Survival at 1, 3 and 5 years and recurrence rates in different series^{8,14,15,18,19,95}

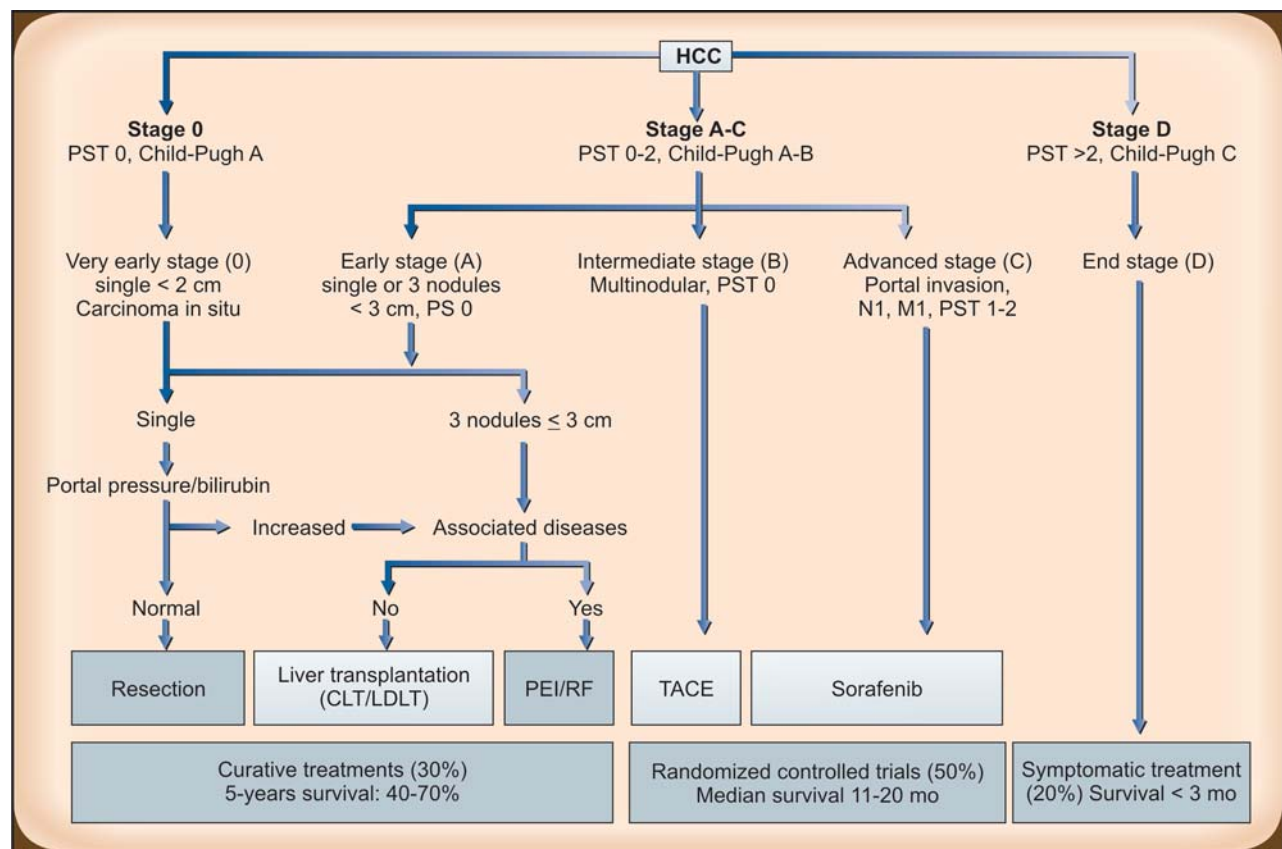


Figure 38.1: Treatment surgery PEI: Percutaneous ethanol injection, LDLT: Living-related donor liver transplantation (Reproduced with permission of J Bruix)⁹⁴

Earlier studies					
Author	1 year	3 years	5 years	Recurrence	year
Iwatsuki	—	39%	36%	43%	1991
Bismuth	—	49%	—	54%	1993
Moreno	—	67%	48%	32%	1995
Studies based on more strict selection criteria					
Mazzaferro	84%	—	74%	8%	1996
Bismuth	82%	—	74%	11%	1999
Llovet	86%	—	75%	4%	1999
Jonas	90%	—	71%	16%	2001

Earlier treatment of HCC was mostly by resection and ablation, but neither therapies minimized the risk of local recurrence nor prevented the complications of cirrhosis. Liver transplantation has emerged as the main treatment for early-stage HCC as it can be curative, minimize the risk of recurrence, and avoid the complications of cirrhosis.²⁶ In cirrhotic patients with HCC, orthotopic liver transplantation offers improved survival.^{23,97}

Milan Criteria

Solitary lesion < 5 cm (stage 1) or < 3 lesions none > 3 cm (stage 2).

Patients who meet the Milan criteria and have no evidence of vascular invasion or metastasis are considered candidates for LTX. Within this criteria, the 1 year survival is 90% and 5-year survival is 75% and recurrence rate < 25%.^{22,25,26}

In early 1990s Bismuth et al.¹⁷ and Iwatsuki et al.¹⁸ identified the clinicopathologic risk factors associated with recurrence that led to the development of the Milan criteria by Mazzaferro et al.²⁵ The Milan criteria now are used worldwide to identify patients who have HCC and who have a potentially good prognosis after LTX. At present transplant scenario, LTX has become a first-line treatment for patients who have early disease.^{24,25} UNOS currently follows the Milan criteria. Patients who have HCC have a priority for organ allocation because of the importance of waiting time for this particular group of recipients.^{22,24} Drop out rates due to tumor progression is >20% at 1 year. Yao et al. (2001) reported that waiting-list dropouts at 1 year are less in patients with solitary tumor < 3 cm and who meet the Milan criteria, but in patients with multiple tumors or a single tumor between 3 and 5 cm had a 50% 1-year dropout rate.^{23,26-28}

Reports using extended indications for HCC in DDLT ²⁹⁻³⁴					
Author	Selection criteria	Total cases	Beyond Milan	5-year survival	Year
Yao	one tumor < 6.5 cm or 3 tumors < 4.5 cm and total tumor diameter < 8.0 cm	70	—	75%	2001
Roayaie	any HCC, no extra-hepatic spread no main portal invasion.	80	80	25%	2002
Cillo	—	33	13	75%	2004
Yao	Milan-UCSF	32	93%	2006	
Marrero	Milan-UCSF	346	38%	2007	
Onaca	Tumor 5-6 cm	24	55%	2007	
Duffy	Milan-UCSF	185	64%	2007	

UCSF Criteria (University of California at San Francisco)

Solitary lesion < 6.5 cm or < 3 lesions none > 4.5 cm and total tumor diameter < 8 cm. Yao et al. showed that the patients who meet the UCSF criteria, achieved excellent results that were not different from those of patients within Milan criteria. The survival at 1 and 5-years are 90 and 75% respectively.²⁹

University of Pittsburgh Criteria

University of Pittsburgh criteria are based on pathologic features (nodal invasion, grade, vascular invasion, pathology size) that usually are not available before transplantation. By contrast, the Milan and UCSF criteria rely on factors (tumor size and number) that can be determined by preoperative imaging.

To meet the donor-recipient disparity and to increase the number of liver transplantations in patients with HCC, techniques such as domino/split-liver transplantation, living-related donor liver transplantation, and use of extended-criteria donor livers are becoming popular. LDLT in patients, who exceed the Milan criteria, offers the possibility of early transplantation and eliminating the need for adjuvant therapies to prevent dropout.^{35,36}

Marsh et al (2000) modified pathologic TNM staging ²¹	
Stage I	Unilobar (Any size/No vascular invasion) Biobar (Size < 2 cm + microvascular invasion)
Stage II	Unilobar (> 2 cm + microvascular invasion)
Stage III A	Bilobar (> 2 cm)
Stage III B	Bilobar (> 2 cm + microvascular invasion)
Stage IV A	Any lobe, any size, macrovascular invasion
Stage IV B	Lymph nodes + metastasis

UNOS SCORING SYSTEM FOR HCC PATIENTS ON WAITING LIST

UNOS adopted the MELD scoring system and a variable score between 24 to 29 points for HCC patients.³⁷ Patients who have HCC are assigned a higher MELD score based on tumor staging. Patients who had a T1 lesion initially were registered at a MELD score equivalent to a 15% 3-month mortality risk before transplantation (i.e. a score of 24), which was revised in April 2003 to an 8% mortality risk, a score of 20. Patients who had a T2 lesion initially were listed at a MELD score of 29, which was equivalent to 30%, 3 month mortality, later revised to a score of 24 or 15% mortality risk. Patients with HCC receive a 10% mortality bonus every 3 months while continuing on the waiting list until they are transplanted, die, or become no longer suitable for transplantation. Later, in November 2003, priority for patients who have a T1 lesion was eliminated.

Volk et al. reported the comparison of mortality risk according to the rise in MELD score in HCC patients:⁹¹ Harm caused to individual patients on the waiting list when the patient with Milan-UCSF+ HCC receives an organ

Patient MELD score	Increase in mortality risk
HCC within Milan criteria	0.4%
MELD 11–20	0.1%
MELD 21–30	1.1%
MELD >30	4.2%

DROP OUT FROM THE WAITING LIST

Drop out from the waiting list is due to tumor progression and while the tumors were listed at a more advanced stage, dropout rates are high. Yao et al. reported cumulative drop-out rates at 6 and 12 months for patients with single HCC >3 cm or with 2–3 nodules to be 12% and 56%, versus 0 and 10% with solitary HCC < 3 cm.³⁸ Poon et al. reported in a series of 80 patients with HCC who were enlisted for LTX with exceeding Milan criteria but without main portal vein invasion and extrahepatic spread.³⁹ Patients were treated with preoperative chemoembolization and adjuvant treatment with systemic doxorubicin. Mean waiting time was 142 days and drop out rate was 46%. Overall 5-year intention-to-treat survival was of 25%. 5-year survival rates above 50% in patients transplanted for tumors of 5–7 cm without vascular invasion. This demonstrates that the group of patients with expanded criteria is obviously heterogeneous, and selection refinements are required.

At present average waiting period in USA and Europe is over 12 months. UNOS data base reveals that the number of patients excluded while waiting almost equals

the number of patients transplanted. The drop out rate may account for 20 to 30% of cases.²³ Roayaie et al. reported that a baseline α -fetoprotein levels > 200 ng/ml, tumors > 3 cm in diameter, tumor doubling time < 6 months, and treatment failure as independent predictors of dropout.²⁴

HCC RECURRENCE

HCC recurrence is difficult to treat in a curative way and can only be prevented by employing restricted criteria for OLT.

Different authors had reported different predictive factors for HCC recurrence such as:^{19,25,24,83,85}

- Tumor size
- Preop AFP level > 200 ng/mL
- Bilobar lesions
- Vascular invasion
- Histological differentiation

Author	Predictive factors of HCC recurrence ^{19,25,24,83,85}
Roayaie	Vascular invasion, tumor size
Jonas	Vascular invasion, histological grade
Hemming	Vascular invasion
Llovet	Vascular invasion
Todo	Tumor size, AFP, bilobar disease, vascular invasion

In patients who met the Milan criteria, the recurrence incidence was < 10%. Larger incidence of extrahepatic recurrence among patients with an AFP level above 200 ng/mL (37.5% vs. 13.3%), however, no relation was observed to hepatic recurrence.⁸¹

OTHER PROGNOSTIC MARKERS

Tanaka et al. reported that the HCC patients with preoperative results of serum **7S collagen level** (<8.0 ng/ml) the average of yearly recurrence rates was 16% in the lower 7S collagen level group versus 27% in the higher level group and suggested that the patients with lower 7S collagen levels are more eligible for initial liver resection than salvage liver transplantation rather than primary LTX.⁴⁰ Yao et al. reported that **serum tissue polypeptide specific antigen (TPS)** levels >150 U/l have been reported to have a 50% recurrence rate at 12 months after resection or transplantation.⁴¹ Low-dose immunosuppressive therapy and expanded criteria for liver transplantation in patients with HCC, especially when donation from a living related donor is possible, appear to inhibit disease recurrence and improve outcomes.⁴²

Marubashi et al. reported that the presence of **AFP mRNA**-expressing cells in the peripheral blood could be a useful predictor of HCC recurrence in liver transplant patients,^{44,47} whereas Oya et al. reported that **Human telomerase reverse transcriptase (h-TERT) mRNA** seemed to prove more valuable than AFP mRNA not only to assess preoperative treatment modalities and postoperative patient surveillance, but also to evaluate prospective LDLT patients with HCC.⁴³ Saborido et al. reported that preoperative **liver biopsy** is associated with a larger incidence of tumor recurrence after LTX and it is not necessary prior to an OLT for HCC.¹¹

CORRELATION OF HBV AND HCC RECURRENCE

HBV infection is a leading cause of HCC worldwide, i.e. approximately 53% of HCC cases are related to HBV.^{45,46} Kiyici et al. demonstrated the relationship between HBV and HCC recurrences in patients with OLT. It is suggested that reappearance of HBsAg can be used as a surrogate marker for the development of HCC recurrence in OLT patients with HBV and HCC.⁸⁸

In patients with HBV related cirrhosis with HCC, antiviral prophylaxis is associated with improved survival and reduction in HCC recurrence after transplantation. Whether the combination of HBIG and lamivudine has a direct antineoplastic effect, distinct from suppression of viral replication, is not known. A multicenter study with a larger cohort of patients will be necessary to validate these findings.⁸⁷

LIVER RESECTION FOR HCC

Liver resection for Child A patients with a single nodule of HCC is now associated with a very low postoperative mortality^{48,81} and a 1-year overall survival rate of up to 70%; 3-year disease-free survival is 50% in most series, and the 5-year disease-free survival is up to 25 to 30%.^{49,50,82} Gaudio et al. reported that keeping in view of the shortage of organs, liver resection is an acceptable treatment with similar overall survival at 5 years³⁰ without an increase in perioperative complications to primary OLT but with an increased risk of recurrence in patients with small HCC and well-compensated cirrhosis, with salvage LTX offered at the time of HCC recurrence or liver decompensation, as a safe and effective approach.⁹³

In contrary, Baccarani et al. reported that OLT is superior to hepatic resection for small HCC in cirrhotic patients assuming that OLT can be performed within 6 to 10 months after listing to reduce dropouts due to tumor progression.⁸⁹ Similarly Rayya et al. reported that liver resection for HCC in cirrhosis should be performed with

caution. OLT showed good long-term survivors in early HCC in cirrhotic patients than liver resection. For HCC in noncirrhotic livers, liver resection remains the treatment of choice, justifying an extensive surgical approach due to favorable long-term survival.^{51,93}

BRIDGING THERAPY

It is the treatment option for HCC patients on waiting list. Purpose of bridging therapy is to prevent the tumor progression during the waiting period and to decrease the drop out rates.

- Transarterial chemoembolisation (TACE)
- Percutaneous ablation therapy:
 - Radiofrequency ablation (RFA)
 - Percutaneous ethanol injection (PEI)
 - Other less commonly used methods
 - Cryotherapy
 - Microwave therapy
 - Laser therapy
 - Hot saline injection

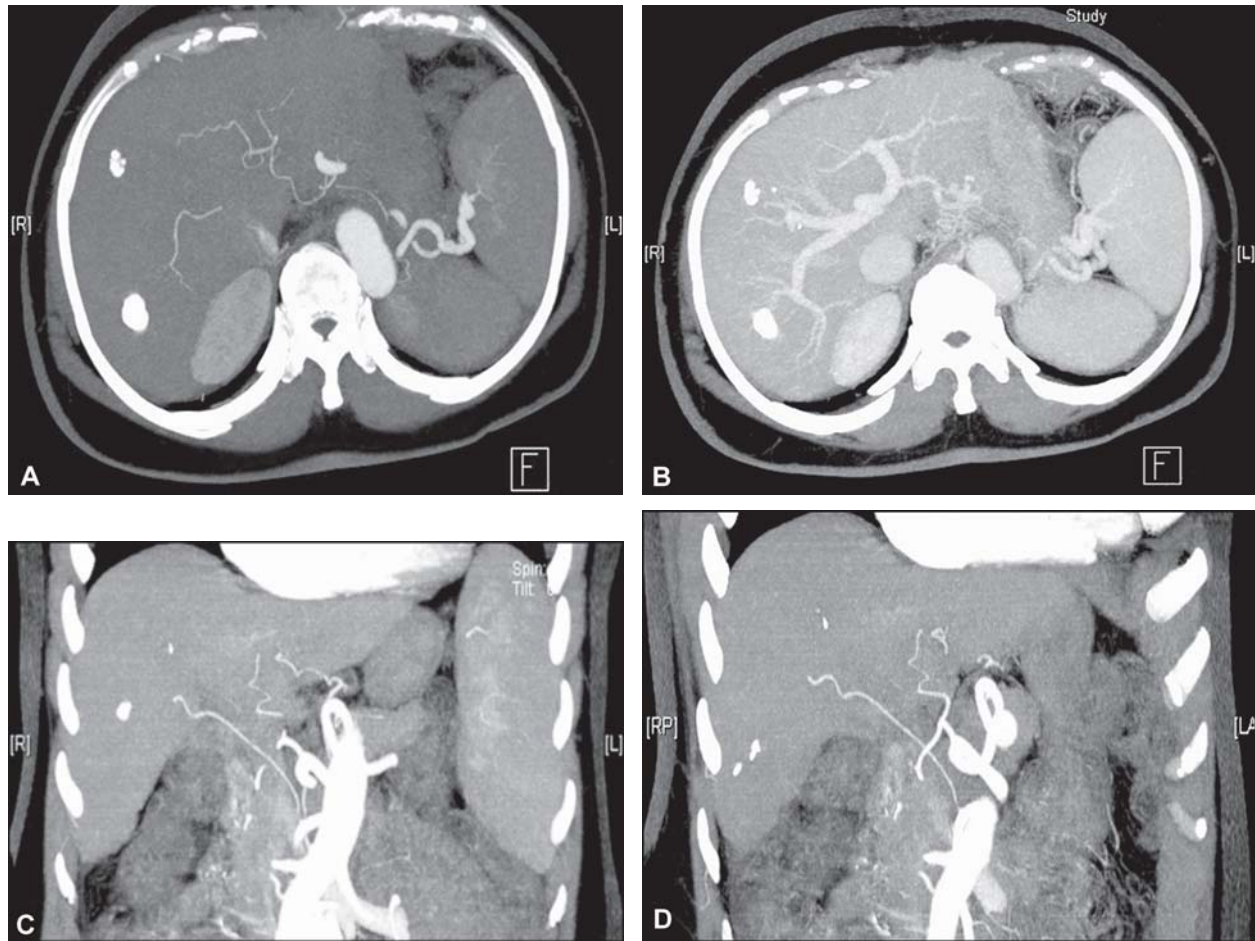
TACE

It is used before transplantation to maintain curability while awaiting a graft, in conjunction with other ablative therapies, or alone as a palliative treatment. TACE is the most common modality used to treat HCC in patients awaiting LTX (**Figures 38.1A to D**). TACE consists of the injection of one or more chemotherapy drugs, with or without lipiodol, into the hepatic artery followed by the administration of embolizing agents (coil/gel foam).³⁹ Most commonly used chemotherapeutic agents are Doxorubicin, Adriamycin, Cisplatin, Mitoxantrone and Mitomycin C. These agents are suspended in a carrier substance, typically lipiodol that is selectively retained within the tumor.^{52,84} Chemotherapeutic agents are delivered with concomitant embolization to increase the local chemotherapeutic dwell time and induce tumor ischemia.

Contraindications for TACE

Portal vein thrombosis
Presence of portosystemic shunt
Renal failure
Extrahepatic metastasis
Advanced liver dysfunction

Child-Pugh class A and B patients can tolerate the procedure, in child patients; mortality rate is as high as 60%.⁵³ Risk is increased in the absence of portal perfusion of the liver due to thrombosis or transjugular portosystemic shunt.



Figures 38.1A to D: HCC, two tumors in the right lobe of a recipient on waiting list. Post TACE necrotic tumors shown as hyper dense lesions due to lipiodol accumulation in the tumor area

Complications of TACE^{54-58,59,60}

- Post embolisation syndrome:
 - Transitory abdominal pain
 - Paralytic ileus
 - Fever (<10-27%)
- Ischemic cholecystitis
- Hepatic abscess/infarction
- Biliary strictures
- Spontaneous bacterial peritonitis
- Tumor rupture
- Biloma
- Sepsis
- Mortality (4%)

RADIOFREQUENCY ABLATION (RFA)

It has emerged as bridging therapy to LTX when the patient is on waiting list.^{22,27} RFA has been used increasingly as the preferred percutaneous therapy,

because it produces more consistent local tumor control.⁶² Using the radiofrequency range of 400 to 500 kHz, it causes thermal damage in the liver tissue. It can be applied percutaneously using ultrasound, CT, or MRI guidance, laparoscopically or by laparotomy.^{63,64} RFA produces better result in tumors smaller than 3 cm. It creates a zone of thermal necrosis encompassing the tumor and a surrounding zone of normal tissue. The disadvantages are the higher cost and the higher rates of complications (8.9%) and mortality (0.5%).^{61,65,66}

Previous reports have demonstrated complete coagulated necrosis in up to 75% of lesions treated with PAI and in 90% of those treated with RFA. 3-year survival rates for patients treated with PAI or RF have been reported to range between 68 and 80%, depending on the size and number of tumors.⁶⁷⁻⁶⁹ Choi et al. reported that the effectiveness rate for RFA in treatment of HCC is 96.7%. The cumulative rates of local tumor progression

at 1, 2, and 3 years were 8.1%, 10.9%, and 11.8%, respectively. The cumulative survival rates at 1, 2, 3, 4, and 5 years were 95.2%, 82.9%, 69.5%, 60.8%, and 58.0%, respectively.⁶³ Patients who had Child-Pugh class A cirrhosis, younger age (< 58 years), and an alpha-fetoprotein level of 100 mg/l or lower demonstrated better survival tumor control rate.

Complications of RFA⁷⁰

Tumor recurrence
Hemothorax
Intraperitoneal bleeding
Bowel perforation
Mortality (<1%)

Shiina et al. reported post-RFA tumor implantation is 2.5%⁷¹ whereas Llovet et al.⁷² reported 12.5%, which related to subcapsular tumor location; no other subsequent series has found a similarly high incidence.

PEI ABLATION

It consists of the injection of absolute ethanol directly into a lesion through a fine needle under USG guidance. This procedure can be performed safely even in lesions protruding from the liver surface and those adjacent to the gallbladder, GI tract or diaphragm, for which it may be difficult to perform RFA safely. PEI is a well-tolerated procedure that is inexpensive and has few side effects with a complete response in 80% of tumors < 3 cm.⁷³ A poorer response is obtained with tumors between 3 and 5 cm: complete necrosis is obtained in less of 50% of these cases, probably because the presence of intratumoral septa limits the spread of injected ethanol in bigger tumors. Response is considered to have occurred when a CT evaluation shows an extensive non-staining low-density area, indicating complete necrosis of the lesion.

Contraindications of PEI^{74,75}

Gross ascites
Severe coagulopathy
Tumor seeding along the needle track (1.7%)

5-year survival rate after PEI is 50% in Child A HCC patients. These results are comparable to those achieved with surgical resection. Ebara et al. reported that cumulative recurrence rates of HCC at the treated site after PEI ablation are 3.4%, 7.1%, and 10% at 1, 2, and 3 years, respectively.⁶⁸ The survival rates at 1, 3, 5, and 10 years after PEI ablation are 99.2%, 81.6%, 60.3%, and 20.7%, respectively. Recurrence at the treated site was observed in 9.3% of patients.⁷³

ROLE OF LDLT IN HCC PATIENTS

LDLT in HCC patients has several benefits, namely, a reduction of pretransplantation waiting time (and therefore less pretransplantation morbidity/mortality as well as reduced overall costs to treat complications of HCC), an elective nature, and a decreased incidence of graft dysfunction, so it is currently being performed at many centers worldwide.^{76,77} The estimated donor death risk is 0.5%. Any transplant center should balance the benefit of the recipient and risk in the donor before going for a LDLT in HCC patients.⁷⁸ The outcome in LDLT is not different from those receiving deceased donor livers. If the patients fulfill the Milan criteria, 3 year survival rate is 78.7% and HCC recurrence rate is 1.4%.⁷⁶ One of the major concerns in LDLT is HCV recurrence in the graft after transplantation leading to more aggressive impact of graft function.

The Milan criteria are derived from cadaveric organ allocation, but the situation is quite different in LDLT, in which the donor has a strong will for giving and dedication, and the liver graft is considered a private gift instead of a public resource. Jiang et al. reported that LDLT offered an acceptable survival for HCC patients who otherwise would die soon because of the particular risk of tumor progression. When the UCSF criteria are applied to HCC patients, the overall 1-year and 3-year actuarial survival rates were 84.01 and 71.40%, respectively, similar to those of patients undergoing LDLT for various nonmalignant diseases during this period.⁹² In another study from Japan,² by the end of 2003, 316 adult patients (246 men and 70 women; median age of 55 years) underwent LDLT in Japan. The median follow-up period was 16 months. Patient survival rate at 1 and 3 years was 78 and 69%, respectively. MELD score and preoperative serum α -fetoprotein level were independent risk factors for patient survival. Recurrence-free survival at 1 and 3 years was 73 and 65%, respectively.

In Tokyo University, between 1996 and 2004, 235 patients underwent LDLT; of these, 61 had HCC and satisfied our criteria (51 men and 10 women; median age of 54 years). Patients were selected based on a tumor number of five or fewer and a maximum diameter of < 5 cm. MELD scores ranged from 2 to 34. In explanted specimens, median tumor number was 2.8 and median size was 2.6 cm. During the median observation period of 25 months, two patients died with HCC recurrence and another six died without recurrence. Patient survival rate at 1 and 3 years was 91 and 82%, respectively, which was comparable to that of patients without HCC ($n = 168$, 90% in both, $P = 0.73$).⁹⁶

Reasons for increased LDLT in Asian countries for HCC patients:

- Shortage of deceased donors in asian countries
- Increased prevalence of chronic HBV related cirrhosis and HCC
- Long waiting list and increased dropout rates.

Barcelona expanded criteria for HCC patients undergoing LDLT⁷⁹

Solitary tumor	< 7 cm
Multiple tumors:	3 tumors < 5 cm
	5 nodules < 3 cm
Down staging:	Partial response to any treatment lasting > 6 months achieving conventional criteria of DDLT

HCC patients beyond Milan criteria are benefited by LDLT and thus achieve longterm survival that otherwise would be unlikely. Our center policy is to follow UCSF criteria for LDLT and Milan criteria for DDLT.

OTHER HEPATIC TUMORS

Fibrolamellar HCC is less aggressive and predominantly affects younger patients. It is not associated with pre-existing liver disease or elevated AFP levels. Recurrence rate is comparable to that of standard HCC, but the 5-year survival rate after liver transplantation is significantly more.⁸⁰ Uncommon primary hepatic malignancies, such as epithelioid hemangioendothelioma and hepatoblastoma demonstrate good survival rate after liver transplantation. But patients with hemangiosarcoma and metastatic liver tumors, with the exception of neuroendocrine tumors, have poor outcome after transplantation.

REFERENCES

- Cormier JN, Thomas KT, Chari RS, et al. Management of hepatocellular carcinoma. *J Gastrointest Surg* 2006;10:761.
- Todo S, Furukawa H. Japanese Study Group on Organ Transplantation. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. *Ann Surg* 2004;240:451-59.
- Lopez PM, Villanueva A, Llovet JM. Systematic review: Evidence-based management of hepatocellular carcinoma—an updated analysis of randomized controlled trials [review]. *Aliment Pharmacol Ther* 2006;23(11):1535-47.
- Forner A, Hessheimer AJ, Isabel Real M, et al. Treatment of hepatocellular carcinoma. *Crit Rev Oncol Hematol* 2006;60(2):89-98.
- Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. *Liver Transpl* 2004;10(2 Suppl 1):S46-52.
- Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. *Hepatology* 1999;30:1434-40.
- Spangenberg HC, Thimme R, Blum HE. Serum markers of hepatocellular carcinoma. *Semin Liver Dis* 2006;26(4):385-90.
- Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-99.
- IFSF Boin, EM Pracucho, MC Rique, et al. Expanded milan criteria on pathological examination after liver transplantation: Analysis of Preoperative Data. *Transplant Proceed* 2008;40:777-79.
- Burrell M, Llovet JM, Ayuso C, et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: An explant correlation. *Hepatology* 2003;38:1034-42.
- BP Saborido, JC Menéu Dý'az, S Jiménez de los Galanes, et al. Does preoperative fine needle aspiration-biopsy produce tumor recurrence in patients following liver transplantation for hepatocellular carcinoma? *Transplant Proceed* 2005;37:3874-77.
- Torzilli G, Minagawa M, Takayama T, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. *Hepatology* 1999;30:889.
- Ringe B, Pichlmayr R, Wittekind C, et al. Surgical treatment of hepatocellular carcinoma: Experience with liver resection and transplantation in 198 patients. *World J Surg* 1991;15:270-85.
- Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221-29.
- Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993;218:145-51.
- Tralhaõ JG, Dagher I, Lino T, et al. Treatment of tumor recurrence after resection of hepatocellular carcinoma. Analysis of 97 consecutive patients. *Eur J Surg Oncol* 2007;33(6):746-51.
- Bismuth H, Chiche L, Adam R, et al. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993;218:145-51.
- Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg* 1991;214:221-28.
- Ringe B, Pichlmayr R, Wittekind C, et al. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991;15:270-85.
- Moreno P, Jaurrieta E, Figueras J, et al. Orthotopic liver transplantation: Treatment of choice in cirrhotic patients with hepatocellular carcinoma? *Transplant Proc* 1995;27:2296-98.
- Reyes JD, Carr B, Dvorchik I, et al. Liver transplantation and chemotherapy for hepatoblastoma and hepatocellular cancer in childhood and adolescence. *J Pediatr* 2000;136:795.
- Sauer P, Kraus TW, Schemmer P, et al. Liver transplantation for hepatocellular carcinoma: is there evidence for expanding the selection criteria. *Transplantation* 2005;80:S105-8.
- Yao F, Bass N, Nikolai B, et al. Liver transplantation for hepatocellular carcinoma: Analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 2002;8:873-83.
- Roayaie S, Schwartz J, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: Patterns and prognosis. *Liver Transpl* 2004;10:534-40.
- Mazzaferro V, Rondinara GF, Rossi G, et al. Milan multicenter experience in liver transplantation for hepatocellular carcinoma. *Transplant Proc* 1994;26:3557-60.

26. Durand F, Belghiti J. Liver transplantation for hepatocellular carcinoma: Should we push the limits? *Liver Transpl* 2003;9:697-99.
27. Ringe B. Can the prognosis of liver transplantation for hepatocellular carcinoma be predicted? *Hepatology* 1997;26:507-50.
28. Cillo U, Vitale A, Bassanello M, et al. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. *Ann Surg* 2004;239:150-59.
29. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-403.
30. Roayaie S, Frischer J, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 cm. *Ann Surg* 2002;235:533-39.
31. Onaca N, Davis GL, Klintmalm GB, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: A report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transpl* 2007;13:391-99.
32. Mashoi J, Puhl S, Thyagarajan V et al. Liver transplantation for hepatocellular carcinoma: Validation of the Milan criteria using the UNOS database. *Hepatology* 2006;44(4 Suppl 1):407A.
33. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: A 22-year experience with 467 patients at UCLA. *Ann Surg* 2007;246:502-09.
34. Yao FY. Liver transplantation for hepatocellular carcinoma: A 5-year prospective study validating expanded criteria applied to preoperative imaging. *Hepatology* 2006;44(4 Suppl 1):191A.
35. Gondolesi G, Roayaie S, Munoz L, et al. Adult living donor liver transplantation for patients with hepatocellular carcinoma: extending UNOS priority criteria. *Ann Surg* 2004;239:142-49.
36. Gondolesi G, Munoz L, Matsumoto C, et al. Hepatocellular carcinoma: a prime indication for living donor liver transplantation. *J Gastrointest Surg* 2002;6:102-07.
37. Roayaie S, Frischer JS, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002;235:533-39.
38. Yao FY, Bass NM, Nikolai B, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: Implications for the current organ allocation policy. *Liver Transpl* 2003;9:684-92.
39. Poon RT, Ngan H, Lo CM, et al. Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. *J Surg Oncol* 2000;73:109-14.
40. H Tanaka, S Kubo, T Tsukamoto, et al. Recurrence rate and transplantability after liver resection in patients with hepatocellular carcinoma who initially met transplantation criteria. *Transplant Proceed* 2005;37:1254-56.
41. Yao WJ, Wang ST, Chow NH, et al. Serum tissue polypeptide specific antigen as a noninvasive prognostic indicator for early recurrence of hepatocellular carcinoma after curative resection. *Cancer* 2002;19:112.
42. H Karakayali, G Moray, H Sozen, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. *Transplant Proceed* 2006;38:575-78.
43. H Oya, Y Sato, S Yamamoto, et al. Comparison between human-telomerase reverse transcriptase mRNA and a-Fetoprotein mRNA as a predictive value for recurrence of hepatocellular carcinoma in living donor liver transplantation. *Transplant Proceed* 2006;38:3636-39.
44. S Marubashi, K Dono, Y Sugita, et al. Alpha-fetoprotein mRNA Detection in Peripheral Blood for Prediction of Hepatocellular Carcinoma Recurrence After Liver Transplantation. *Transplant Proceed* 2006;38:3640-42.
45. Montalto G, Cervello M, Giannitrapani L, et al. Epidemiology, risk factors, and natural history of hepatocellular carcinoma. *Ann NY Acad Sci* 2002;963:13.
46. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001;37(suppl 8):S4.
47. YL Wang, GLD Wu, YW Liu, et al. Analysis of alpha-fetoprotein mRNA level on the tumor cell hematogenous spread of patients with hepatocellular carcinoma undergoing orthotopic liver transplantation. *Transplantat Proceed* 2007;39:166-68.
48. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: Is there a way? A prospective analysis of our approach. *Arch Surg* 1999;134:984-92.
49. Grazi GL, Ercolani G, Pierangeli F, et al. Improved results of liver resections for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg* 2001;234:71-78.
50. Poon RT, Fan ST, Lo CM, et al. Improving survival results after resection of hepatocellular carcinoma: A prospective study of 377 patients over 10 years. *Ann Surg* 2001;234:63-70.
51. Llovet JM, Bruix J, Gores GJ. Surgical resection versus transplantation for early hepatocellular carcinoma: Clues for the best strategy. *Hepatology* 2000;31:1019-21.
52. Jaeger HJ, Mehring UM, Castaneda F, et al. Sequential transarterial chemoembolization for unresectable advanced hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 1996;19:388-96.
53. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepato-cellulaire. *N Engl J Med* 1995;332:1256-61.
54. Makuuchi M, Sukigara M, Mori T, et al. Bile duct necrosis: Complication of transcatheter hepatic arterial embolization. *Radiology* 1985;156:331-34.
55. Rand T, Loewe C, Schoder M, et al. Arterial embolization of unresectable hepatocellular carcinoma with use of microspheres, lipiodol, and cyanoacrylate. *Cardiovasc Intervent Radiol* 2005;28:313-18.
56. Georgiades CS, Hong K, D'Angelo M, et al. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 2005;16:1653-59.
57. Morante A, Romano M, Cuomo A, et al. Massive gastric ulceration after transarterial chemoembolization for hepatocellular carcinoma. *Gastrointest Endosc* 2006;63:718-20.
58. Huo TI, Wu JC, Lee PC, et al. Incidence and risk factors for acute renal failure in patients with hepatocellular carcinoma undergoing transarterial chemoembolization: A prospective study. *Liver Int* 2004;24:210-15.
59. Llovet JM, Real MI, Montana, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. *Lancet* 2002;359:1734-39.

60. Poon RT, Ngan H, Lo CM, Liu CL, Fan ST, Wong J. Transarterial chemoembolization for inoperable hepatocellular carcinoma and post resection intrahepatic recurrence. *J Surg Oncol* 2000;73:109-14.
61. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999;210:655-61.
62. Ikai I, Itai Y, Okita K, et al. Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res* 2004;28:21-29.
63. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: Long-term results and prognostic factors in a large single-institution series. *Eur Radiol* 2007;17(3):684-92.
64. Lencioni R, Della P C, Bartolozzi C. Percutaneous image-guided radiofrequency ablation in the therapeutic management of hepatocellular carcinoma. *Abdom Imaging* 2005;30(4):401-08.
65. Lencioni R, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003;228:235-40.
66. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129(1):122-30.
67. Pearson AS, Izzo F, Fleming RY, et al. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg* 1999;178:592.
68. Ebara M, Ohto M, Sugiyura N, et al. Percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Study of 95 patients. *J Gastroenterol Hepatol* 1990;5:616.
69. Vilana R, Bruix J, Bru C, et al. Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. *Hepatology* 1992;16:353.
70. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of RFA with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129:122-30.
71. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous RFA for single hepatocellular carcinoma. *Hepatology* 2001;33:1124-29.
72. Curley SA, Izzo F, Ellis LM, Nicolas Vauthey J, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann Surg* 2000;232:381-91.
73. Ebara M, Okabe S, Kita K, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005;43(3):458-64.
74. Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. *Radiology* 1995;197:101-08.
75. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129:122-30.
76. Todo S, Furukawa H. Living donor liver transplantation for adult patients with hepatocellular carcinoma: Experience in Japan. *Ann Surg* 2004;240(3):451-59.
77. Hwang S, Lee SG, Joh JW, et al. Liver transplantation for adult patients with hepatocellular carcinoma in Korea: Comparison between cadaveric donor and living donor liver transplantations. *Liver Transpl* 2005;11:1265.
78. Brown RS, Russo MW, Kai M, et al. A survey on liver transplantation from living adult donors in the United states. *N. Engl J Med* 2003;75(3):S6-S11.
79. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in HCC. *Hepatology* 2002;35(3):519-24.
80. Schwartz M. Liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2004;10(2 Suppl 1):S81-5.
81. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: Toward zero hospital deaths. *Ann Surg* 1999;229:322-30.
82. Bruix J, Castells A, Bosch J, et al. Surgical resections of hepatocellular carcinoma in cirrhotic patients: Prognostic value of preoperative portal pressure. *Gastroenterology* 1996;111:1018-22.
83. A Escartin, G Sapisochin, I. Bilbao, et al. Recurrence of hepatocellular carcinoma after liver transplantation. *Transplant Proceed* 2007;39:2308-10.
84. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: Which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;30(1):6-25.
85. Grasso A, Stigliano R, Morisco F, et al. Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and explant study. *Transplantation* 2006;81:1532.
86. B Pérez-Saborido, S Jiménez de los Galanes, JC Menéu-Dí'az, et al. Tumor recurrence after liver transplantation for hepatocellular carcinoma: Recurrence pathway and prognostic factors. *Transplant Proceed* 2007;39:2304-07.
87. MA Zimmerman, RM Ghobrial, MJ Tong, et al. Antiviral Prophylaxis and Recurrence of Hepatocellular Carcinoma Following Liver Transplantation in Patients With Hepatitis B. *Transplant Proceed* 2007;39:3276-80.
88. M Kiyici, M Yilmaz, M Akyildiz, et al. Association between hepatitis B and hepatocellular carcinoma recurrence in patients undergoing liver transplantation. *Transplant Proceed* 2008;40:1511-17.
89. U Baccarani, E Benzoni, GL Adani, et al. Superiority of transplantation versus resection for the treatment of small hepatocellular carcinoma. *Transplant Proceed* 2007;39:1898-900.
90. MD Gaudio, G Ercolani, M Ravaioli, et al. Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of bologna experience. *American Journal of Transplantation* 2008;8:1177-85.
91. ML Volk, S Vijan and JA Marrero. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding milan criteria. *American Journal of Transplantation* 2008;8: 839-46.
92. XZ Jiang, LN Yan, TF. Wen, et al. University of California at San Francisco criteria can be applied to living donor liver transplantation for hepatocellular carcinoma: Single-center preliminary results in 27 patients. *Transplant Proceed* 2008;40:1476-80.
93. F Rayya, J Harms, M Bartels, et al. Results of resection and transplantation for hepatocellular carcinoma in cirrhosis and noncirrhosis. *Transplant Proceed* 2008;40:933-35.
94. JM Llovet, AM Di Bisceglie, J Bruix, et al. For the panel of experts in HCC-design clinical trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100: 698-711.
95. Ana Carolina del Pozo, Patricia Lo'pez. Management of hepatocellular carcinoma. *Clin Liver Dis* 2007;11:305-21.
96. Y Sugawara, M Makuuchi, et al. Living donor liver transplantation: present status and recent advances. *British Medical Bulletin* 2005;75 and 76:15-28.
97. H Karakayali, S Sevmis, GM Haberal, et al. Liver transplantation in patients with hepatocellular carcinoma: One center's experience. *Transplant Proceed* 2008;40:213-18.

Hepatitis B Virus and Liver Transplantation

HEPATITIS B VIRUS

Hepatitis B virus is a DNA virus belonging to hepadnaviridae family of viruses. It replicates within infected hepatocytes with an incubation period of 6-25 weeks.

STRUCTURE

Virus is a spherical particle of diameter of 42 nm. The infectious (Dane) particle consists of an outer shell or envelope, composed of several proteins known collectively as HBs or surface proteins, called surface coat and an inner protein shell, composed of HBc protein, called as core particle or capsid. The core particle surrounds the viral DNA and the enzyme DNA polymerase (Figure 39.1).

VIRAL REPLICATION (FIGURE 39.1)

When the virus enters a new host and passes the immune system, then it can infect the hepatocytes

- First the virus attaches to a liver cells membrane
- Transport of virus into hepatocyte. Core particle releases its contents of DNA and DNA polymerase into the hepatocyte nucleus.
- Within the cell nucleus, hepatitis B DNA causes the liver cell to produce (via messenger RNA) surface (HBs) proteins, core (HBc) protein, DNA polymerase, HBe protein, HBx protein and many other proteins and enzymes. DNA polymerase causes the liver cell to make copies of hepatitis B DNA from messenger RNA.
- Live copies of the hepatitis B virus are constructed in hepatocyte by the above process.
- Many surface proteins produced, stick together to form small spheres and chains, giving a characteristic "ground glass" appearance in blood under a microscope.

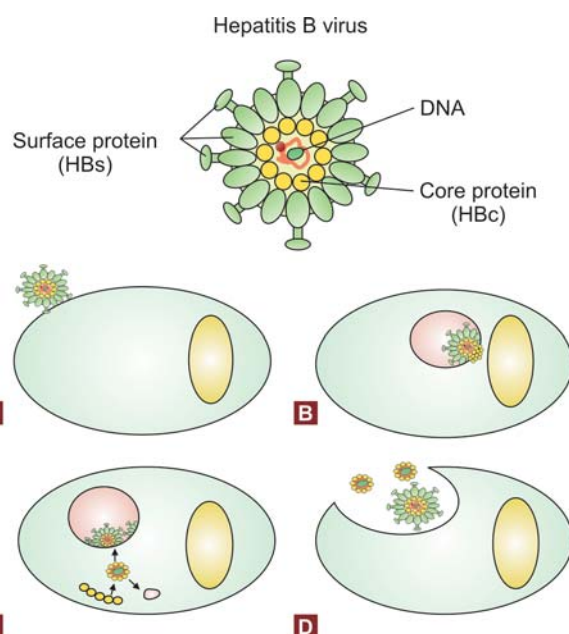


Figure 39.1: Structure of HBV and virus multiplication

- Virus and excess surface antigen are released from hepatocytes into the blood stream to infect other hepatocytes and replicate effectively.

During replication, mistakes may be made in copying viral DNA resulting in different strains and mutant strains of hepatitis B.

DIFFERENT HBV MUTANTS

- YMDD (Tyrosine-methionine-aspartate-aspartate)
- YVDD (Tyrosine-valine-aspartate-aspartate)
- YIDD (Tyrosine-isoleucine-aspartate-aspartate)

These mutants emerge spontaneously or during the course of treatment with antiviral drugs, detected by PCR (polymerase chain reaction).

HBV GENOTYPES: GENOTYPING IS MOSTLY USED FOR RESEARCH PURPOSE

A United States—based study by Gaglio et al.⁸³ reported that 4 major HBV genotypes were observed in liver transplant patients. The genotype C patients were more likely to have HCC at the time of listing and to die after transplant compared to patients with non-C genotypes. Patients with genotype D had the best post-OLT survival, but this was offset by higher waitlist mortality. They suggested that HBV genotypes but not precore or core promoter variants may have an impact on pre-and post-OLT outcomes of hepatitis B patients.

Hepatitis B virus genotypes and geographical location⁷⁹

Genotype	Geographical distribution
A	North Europe, North America, Central Africa
B	East and Far East Asia
C	East and Far East Asia
D	Mediterranean, Middle East, South Asia
E	Western Africa
F	South and Central America
G	France, United States

Methods for Genotyping of HBV

- Direct sequencing
- Enzyme-linked immunosorbent assay
- Restriction fragment length polymorphisms (RFLP)
- Line probe assay (LiPA)

RFLP and LiPA are commonly used methods for genotyping

HEPATITIS B ANTIGENS (HBsAg)

- Hepatitis B surface proteins are produced in larger quantities than required for the virus to reproduce. Incubation of the HBV (Hepatitis B) is between 6 to 25 weeks. After infection and 1 to 6 weeks before symptoms occur HBsAg appears.
- Present infection of HBV is indicated by a positive HBsAg.
- Chronic infection: HBsAg persists for more than 6 months.

HEPATITIS B CORE PROTEIN (HBcAg)

- The core protein (HBc) is not detectable in the bloodstream and be detected in the sample of hepatocytes taken from liver biopsy.
- HBc proteins link together to form the hepatitis B core that encapsulate HBV DNA and DNA polymerase.

HBe PROTEIN/HEPATITIS 'E' ANTIGEN (HBeAg OR 'E' ANTIGEN)

- It is a peptide, detectable in the bloodstream when the hepatitis B virus is actively multiplying.
- Person with HBeAg +ve is more infectious and at a greater risk of progression to liver disease.
- It is thought that HBe may be influential in suppressing the immune systems response to HBV infection.
- HBeAg and HBsAg are detectable at the same time but HBeAg disappears before HBsAg
- The presence of HBeAg in chronic infection is generally taken to indicate that HBV is actively reproducing and there is a higher probability of liver damage.
- In acute infection HBeAg is generally only transiently present.
- Mutant strains of HBV exist that replicate without producing HBeAg and these are more aggressive than HBe producing strains.

HBx PROTEIN

- The function of this protein is not yet known.
- Though it can be detected presently available tests, but is unreliable as other proteins interfere with the results.

HBV DNA

One of the first parameter that can be detected in the bloodstream by PCR in the first week of infection of HBV. It indicates how fast the virus is replicating. It is used to confirm the presence of HBV, measure viral load and to find out the mutants variety that do not produce the "e" and/or normal surface antigens. Tests for HBV DNA are not routine but generally performed during HBV related liver transplantation and for research purposes as it is expensive.

HEPATITIS B DNA POLYMERASE (HBV DNA POLYMERASE, DNAP)

It is an enzyme that can be detected in the bloodstream in the 1st week of infection by HBV at about the same time as HBV DNA. Tests for HBV DNA polymerase are used as indicators of disease progression, suitability for therapy and research purposes.

RESPONSE OF HUMAN BODY TO INFECTION

Approximately 90% of infected individuals recover from Hepatitis B infection and 50% this group have had no symptoms (**Figure 39.2**). Absent HBsAg in blood indicates recovery from the disease. Hepatitis B Antibody (Anti HBsAb) is present and is usually persists for long time after recovery.

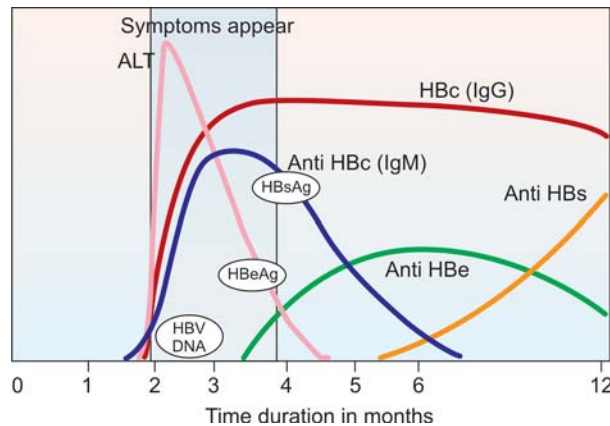


Figure 39.2: Showing the time of appearance of different antibodies, HBV DNA and HBsAg

ANTIBODIES TO HBc (HBcAb/ANTI-HBc)

These are the antibodies to the HBV core protein. It is the first detectable antibody to appear around 8 weeks after infection. The initial antibodies are of IgM and IgG class; usually appear after the appearance of HBsAg but often before ALT elevations. HBc Ab is predominantly Ig G class and persists in serum after infection with HBV. Presence of strong IgM HBc Ab indicates acute phase infection. These antibodies to HBcAg do not neutralize the virus. The presence of IgG HBcAb with no IgM HBcAb indicates chronic and resolved cases of hepatitis B infection; this has been used to determine if the presence of HBsAb was due to vaccination or previous exposure to live virus.

ANTIBODIES TO HBe PROTEIN (HBeAb)

Antibodies to the 'e' antigen (HBeAb) normally appear a few weeks after HBeAg and their presence indicates a favorable prognosis.

Antibodies to HBs Protein (Anti HBsAb)

- HBsAb is the last antibody to appear and it can neutralize the HBV and is taken as an indicator that an initial infection is under control due to host immune response.
- HBsAb production can be induced by vaccination and provide protection against HBV.
- However the immune response produced by vaccination may not be 100%. Although
- In rare cases HBV infection has occurred in vaccinated individuals and is due to mutant strains that express different surface proteins.

INTERFERON

When a human cell is exposed to a new virus it usually produces interferon. It is believed that interferon's modulate immune system, alter cell membranes to reduce infection of surrounding uninfected cells and helps to fight HBV. However, the interferon response was deficient in infants/children with immature immune systems.

ALANINE AMINOTRANSFERASE (ALT) AND ASPARTATE AMINOTRANSFERASE (AST)

These are enzymes produced in liver cells, can be detected in the blood stream. In case of damage to liver cells, these enzymes are released and elevated in serum. Damage may occur with little or no elevation of ALT (particularly HCV infection and patients of ESLD). Alcohol, hepatotoxic drugs may elevate these enzymes.

After an initial infection and at around the same time as HBcAb appears in the blood stream, the level of ALT starts to rise sharply. The rise in ALT is due to damage to the liver cells. Damage to liver cells is caused by own immune system, causing hepatic necrosis. In immunocompromised patients, there is increased risk of the infection becoming chronic but damage done by the chronic infection appears mild in comparison to people with normal immunity. During acute infection ALT starts to drop at around the same time as when the 'e' antigen is no longer detectable and is down to normal, when antibodies to the surface antigen appear.

ACUTE HEPATITIS B INFECTION

During HBV infection, HBV DNA and DNA polymerase appear first in the blood stream. Several weeks later HBcAg and HBeAg are detectable. Then HBsAg appears in blood stream. HBcAb is the first detectable antibody to appear. Symptoms appear in 1 to 6 weeks. Patient's immune system continues to resist infection and HBeAg disappears from the blood stream and a few weeks later HBeAb's appear. The level of ALT starts declining in blood and HBsAg disappears from serum at about the same time as HBsAb's are first detected.

Symptoms

Clinical symptoms are anorexia, malaise, nausea and vomiting and fever and may range from no symptoms to severe symptoms and sometimes mortality due to hepatic failure. Mortality in elderly is approximately 10 to 15%. In 3-10 days jaundice, yellowish urine appear, itching, pale stool appear. Symptoms then gradually subside and the period of illness normally lasts between

4 to 8 weeks. Few cases may develop into fulminant hepatic failure.

Treatment

In majority of cases no specific treatment is required for acute hepatitis B infection. Alcohol should be avoided until the infection is resolved. Once HBsAb appear, the infection is considered to have been resolved and the person is considered immune from future hepatitis B infection.

Prognosis

In 90% of cases, prognosis is good and the individual recovers completely and be immune to subsequent hepatitis B infection. Approximately 10% of cases do not clear up completely and progress to chronic infection.

CHRONIC HBV INFECTION

There about 400 million carriers of hepatitis B virus (HBV) worldwide.¹ Approximately 10% of people with HBV infection, HBsAg persists and HBsAb do not appear. If HBsAg persists for > 6 months, the condition is termed chronic infection. These are asymptomatic carriers of HBV.

Individuals with HBsAg, HBeAg, and no HBsAb, no HBeAb are generally termed as having chronic active hepatitis B infection and around 50% of chronic cases are of the active form. Male gender, vertical transmission, homosexuals and infection at younger age nearly always result in chronic infection. In children the rate of risk of developing chronic infection in children is approximately 25% and in healthy adults it is around 2-5%.

Symptoms

Most of the patients with chronic persistent hepatitis B are asymptomatic carriers and do not develop progressive parenchymal liver disease and do not require treatment. Other group is at increased risk of progressive parenchymal liver disease and is infectious. This group requires treatment. Most of the people without symptoms are diagnosed following routine screening. Vague symptoms like general malaise, tiredness, fatigue, weakness, loss of appetite, nausea, abdominal discomfort or just feeling "unwell" are common. Low grade fever and jaundice are variable. Only minority develop cirrhosis, splenomegaly, ascities and signs of portal hypertension.

Extrahepatic manifestations of CHB

- Ulcerative colitis
- Pulmonary fibrosis
- Nephritis
- Acne
- Hemolytic anemia

Most people with chronic active hepatitis B are also asymptomatic carriers but are at increased risk of severe liver problems, very infectious and the treatment proven to be of benefit is the interferon. Some people with chronic hepatitis B have "flare ups" where they have the symptoms of acute hepatitis.

Treatment

Interferon: In the mid-1980s, IFN became the first approved therapy for Chronic HBV infection.² Interferon (IFN) has direct actions on viral replication and indirect actions via immune modulation.³ Wong et al. performed a meta-analysis on published trials using adequate dosage (3–5 Million Units/m², thrice a week) for 3–6 months.⁴ Interferon treatment is associated with flu-like symptoms in most patients during the early part of therapy. This is controllable with prophylactic paracetamol, acetaminophen. Few patients experience weight loss, bone marrow suppression, an increased risk of sepsis (particularly those with cirrhosis), alopecia, thyroid dysfunction, depression and other psychiatric disorders.^{5,6}

Different antiviral drugs used in HBV infection

- Lamivudine (Zeffix)
- Entecavir (Baraclude)
- Telbivudine (Sebivo)
- Adefovir dipivoxil
- Emtricitabine
- Tenofovir
- DAPD
- Clevudine (l-FMAU)¹⁶

Lamivudine: It is the first oral therapy for the treatment of Chronic HBV infection.^{8,9} After clinical assessment, lamivudine was shown to have significant clinical efficacy and a good safety profile.^{7,8} In 1998, FDA (USA) registered lamivudine for CHB therapy. HBeAg can be used as a serological marker of active viral replication. Loss of HBeAg, or seroconversion to anti-HBe, can be used as the end-point of antiviral therapy, but assay of serum HBV-DNA levels improves the assessment of therapeutic potency.

Quantitative polymerase chain reaction (PCR) assays (especially real-time PCR) refine the detection limit up to 100 copies/ml. The target serum HBV-DNA level may be 10^4 - 10^5 virus equivalents/ml which, in most instances, means that the therapy should be able to reduce serum HBV-DNA by 4-5 log units. Extended periods of monotherapy with lamivudine are complicated by emergence of drug-resistant YMDD mutants.

The annual cumulative emergence rates of YMDD genotypic mutation over 5 years are 17, 40, 55, 66 and 69%.¹⁰⁻¹³ YMDD mutant HBV has a diminished replication capacity. Chronic HBV patients who developed YMDD mutants had significantly lower serum HBV-DNA and ALT values during the first year after YMDD emergence relative to baseline values.¹³ Patients with YMDD mutants have a variable degree of ALT elevation. The ALT profile changes with time, but is unpredictable. Acute exacerbations (flares), sometimes with hepatic decompensation, have been observed and fatalities have been reported.¹⁴

Relapse is common after stopping therapy at 12 months.¹⁴ Extended therapy for 2 years or longer has been associated with difficulties of the emergence of drug-resistant YMDD mutants and recurrence of hepatitis activity.¹⁵ The current indications for treatment are focused on patients with active liver disease (i.e. with detectable HBV-DNA by DNA sensitive hybridization assays that have a lower limit of detection of 100 000 virus equivalents/mL, together with raised ALT). This applies both to HBeAg positive and negative patients.

Treatment summary¹⁶

- Chronic hepatitis B with normal or minimally elevated ALT ($2 \times$ ULN)
 - Responds poorly to IFN and lamivudine.
 - Monitor and watch for an opportunity to treat.
- Chronic hepatitis B with raised ALT
 - ALT $> 2 \times$ ULN: IFN or Lamivudine
 - The dose of IFN is 5-10 MU (3 MU/m^2) thrice a week for 4-6 months.
 - For IFN non-responders, consider treatment with lamivudine.
 - Patients with ALT > 5 times ULN are best treated with lamivudine 100 mg/day.

(Note: IFN is preferably confined to patients without cirrhosis with ALT 2–5 times ULN because ALT flare during treatment may precipitate liver failure) (ULN: Upper normal limit)

Duration of lamivudine therapy: Treatment is continued until 2–6 months after HBeAg seroconversion to secure durability of response. Stop lamivudine in patients who

have not achieved seroconversion, despite 1 to 1 and 1/2 years of therapy. This will minimize the chance of emergence of YMDD. Relapse occurs after discontinuation of treatment, which is almost inevitable unless HBeAg seroconversion is achieved. Patients can be successfully retreated with lamivudine until HBeAg seroconversion occurs.

Adefovir dipivoxil is potent, but is nephrotoxic at doses higher than 10 mg/day. It has the added advantage of efficacy on YMDD mutant HBV at a renal-tolerable dose of 10 mg daily.

Entecavir: It is effective in suppressing YMDD mutant chronic HBV. It can be used as first line replacing lamivudine in treatment of HBV infection

Telbivudine:⁷⁴ It is a specific inhibitor of HBV polymerase. It has no mutagenicity/carcinogenicity/teratogenic/mitochondrial toxicity. Telbivudine is the only antiviral agent with pregnancy category B label from FDA.

[Category B: Reproduction studies have been performed in different animal(s) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Telbivudine]

Evidence to date suggest that Telbivudine is effective in

- HBeAg positive and negative patients,
- Patients suboptimal treated with lamivudine
- Patients suboptimal Adefovir treated,
- Adefovir salvage for Telbivudine-resistant patients (preliminary studies)

Emtricitabine: It showed potent viral suppression and an increased HBeAg seroconversion rate with a good safety profile, but emergence of YMDD variants could be expected to be similar to the closely related to Lamivudine (Figures 39.3 and 39.4).

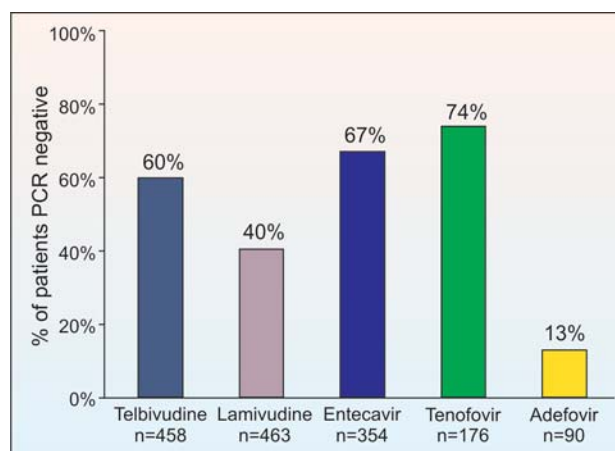


Figure 39.3: Showing percentage of PCR Negativity At 1-Year in HBeAg-Positive patients From Global Landmark Studies. (Data not from head-to-head studies. Design and inclusion criteria may differ)⁷⁶⁻⁷⁸

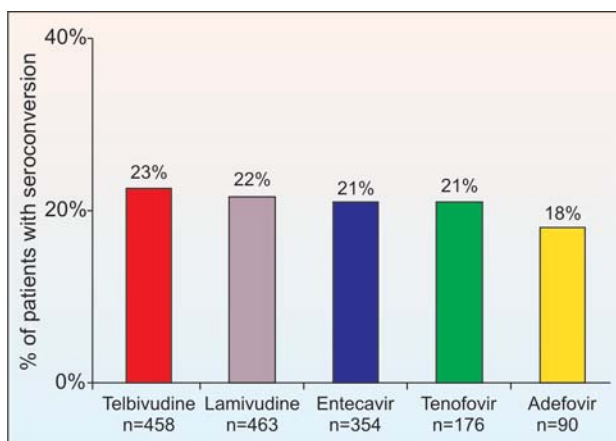


Figure 39.4: Shows percentage of HBeAg Seroconversion At 1-Year in HBeAg-Positive Patients from Global Landmark Studies. Data not from head-to-head studies. Design and inclusion criteria may differ⁷⁶⁻⁷⁸

Combination therapy in treatment of CHB: Two or more agents used together are more likely to suppress HBV, thereby both eradicating cccDNA in hepatocytes and decreasing the emergence of drug resistance. Pegylated IFN and Lamivudine or Adefovir and Lamivudine in combination will be of great interest.

Cirrhosis and antiviral therapy: In many patients with decompensated cirrhosis waiting for liver transplantation, treatment with lamivudine has been associated with improvement of liver function and some patients were even able to come off the transplant waiting list. Liver biopsy is the only way to firmly establish the exact extent of a HBV infection and to assess any damage done to the liver. A biopsy is often required before starting and on completion of any treatment so the effectiveness of the treatment can be assessed.

Active cirrhosis (Child's A): Prompt lamivudine treatment to halt the progression of the disease. YMDD mutation may emerge with reduced therapeutic benefit or worsening disease. Interferon has been used successfully in compensated Child's A cirrhosis with reduced dosage.

ALT flare, bone marrow suppression are major concerns with INF therapy. It is controversial regarding the use of lamivudine; it is not very clear whether it can be stopped or not after HBeAg seroconversion. It appears advisable to continue therapy in the long term based on available data.¹⁷

Active cirrhosis (Child's B and C): Start and continue lamivudine until liver transplantation is considered. If YMDD mutants are present, adefovir can be considered. Availability of adefovir, Entecavir and other agents effective against YMDD mutant HBV has altered the outcome.

Acute exacerbations (flares) of CHB: During an acute exacerbation and icteric decompensation, the prognosis is poor. Exclude other causes, especially acute hepatitis A, E and C, drugs (paracetamol) and herbs. Lamivudine should be started promptly, reported series show clinical benefit compared with historical controls.¹⁸ Long-term lamivudine therapy may be advisable. HBsAg-positive organ transplant recipients on immune suppressive agents often need long-term lamivudine or adefovir therapy after transplant.

COURSE OF THE DISEASE VARIES IN DIFFERENT PERSONS

- Progression to liver cirrhosis. (25%)
- HBV may clear up on it's own in 2-5% per year or remain infective for longtime.
- Risk of Hepatocellular carcinoma. (5%)
- Person may remain highly infectious and can infect other people.

HBV RESISTANCE

Antiviral drug resistance can be of 4 different types⁸⁴

- Phenotypic resistance
- Genotypic resistance
- Viral resistance
- Clinical resistance
 - **Phenotypic resistance** is defined as decreased susceptibility (i.e, increased concentrations of the drug are needed to achieve 50% or 90% inhibition) of an HBV polymerase to an antiviral drug in invitro assays.⁸⁴
 - **Genotypic resistance** is defined as the detection during antiviral therapy of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV polymerase gene that have been shown to confer resistance to antiviral drugs in phenotypic assays.⁸⁴
 - **Viral resistance or virologic breakthrough** is defined as an increase in serum HBV DNA by at least 1 log₁₀ (10-fold) above nadir or the reappearance of serum HBV DNA in the patient with previously undetectable HBV DNA on > 2 occasions at least 1 month apart while the patient is on treatment and after initial response is achieved in the medication-compliant patient.⁸⁴
 - **Clinical resistance** is often used synonymously with biochemical breakthrough and is defined as an elevation in serum alanine aminotransferase while the patient is on treatment and after normalization is achieved in the medication-compliant patient.⁸⁴

DIAGNOSIS OF DRUG RESISTANCE

Genotypic resistance may precede viral resistance by several months, and viral resistance may precede clinical resistance by months to years. Early diagnosis of antiviral drug resistance and prompt intervention are critical. Confirmation of virologic breakthrough on repeat testing is not necessary if there is a marked increase in serum HBV DNA or if there is accompanying biochemical breakthrough. Detection of virologic breakthrough requires knowledge of the pretreatment serum HBV DNA level, documentation of initial response, determination of nadir or lowest HBV DNA level achieved, and detection of a $> 1 \log_{10}$ increase (or reappearance) in the HBV DNA level.⁹⁰ Therefore, establishment of the baseline serum HBV DNA level and regular monitoring, preferably at 3-month intervals with the same HBV DNA assay at each measure, are necessary for the diagnosis of viral resistance. Without documentation of initial response, it is not possible to determine if a patient who has a high serum HBV DNA level after a long duration (> 6 months) of nucleos(t)ide analogue therapy has never achieved adequate viral suppression or instead has virologic breakthrough.⁹⁰

HBV drug resistance is detected by⁹⁰

- Direct sequencing
- Sequencing of multiple clones
- RFLP (Restriction fragment length polymorphism), line probe
- Single genome sequencing, MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) mass spectrometry-most sensitive method.

TREATMENT OF HBV DRUG RESISTANCE

Antiviral drug resistance has been reported in up to 70% of patients after 4 years of lamivudine, 29% after 5 years of adefovir, 1% after 5 years of entecavir, and 9 to 22% after 2 years of telbivudine.^{85-87,89} Resistance rates are substantially higher in patients with prior resistance to lamivudine, with rates of up to 20% after 2 years of switching to adefovir monotherapy and 51% after 5 years of switching to entecavir.^{88,89} The treatment of resistance is as follows⁹⁰

- Lamivudine/Telbivudine resistance: Add Adefovir, Depivoxil or Tenofovir or Change to Emtricitabine and Tenofovir.
- Adefovir resistance: Add Lamivudine or change to Emtricitabine and Tenofovir or add entecavir.
- Entecavir resistance: Add adefovir or tenofovir.

The treatment of multi drug HBV is still controversial.

PRE- AND POST-EXPOSURE PROPHYLAXIS OF HBV

HBV Vaccination is achieved by 3 dose regimen with the 2nd and 3rd doses given at 1 and 6 months interval. 5% of the vaccinations do not result in antibody response, so it is necessary that documentation of an anti HBs antibody response is necessary. Repeated vaccination is necessary for those who fail to respond initial vaccination. Hepatitis B vaccine is now recommended for all newborns before hospital discharge, regardless of maternal HBsAg status. Neonates born to mothers who are chronic HBsAg carriers should receive the first dose of vaccine within 12 hours of birth, accompanied by hepatitis B immune globulin (HBIG) at a different injection site.

Pre-exposure prophylaxis^{80,81}

- Universal prophylaxis in all Infants, children and adolescents who are not previously vaccinated
- High risk group
 - Illicit injection drug users
 - Sexual partners of HBV carriers
 - Homosexuals
 - Multiple sexual partners in the previous 6 months
 - History of sexually transmitted disease (STD)
 - Household contacts
 - Patients on hemodialysis
 - People in occupational contact with blood or body fluids
 - Recipients of clotting factor concentrates
 - Travel to endemic area for > 6 months
 - Clients and staff of institutions for the developmentally disabled.

HBV AND LIVER TRANSPLANTATION

HBV IN ASIA

Asian people are estimated to account for 75% of the 400 million individuals with chronic HBV infection worldwide.¹⁹ In Asian people, HBV is mostly acquired at birth by vertical transmission from CHB mothers or in infancy by close physical contact. In early life, immune tolerance to HBV is the rule, with normal serum alanine aminotransferase (ALT) levels, despite high HBV-DNA levels, followed by an immune reactive phase, with fluctuating viral levels and periodic or persistent elevation of serum ALT levels. Up to 3/4th of Asian CHB patients undergo spontaneous HBeAg seroconversion. This is followed by disease quiescence and a good prognosis. The remaining 1/4th of patients have a protracted immune clearance process, eventually resulting in cirrhosis. Without treatment, they will often succumb to

complications of cirrhosis or hepatocellular carcinoma. Adults, who acquire CHB, are more common among non-Asian patients, the routes of infection being parenteral or sexual. They tend to have active liver disease.

HBV PROPHYLAXIS

Without prophylaxis recurrence of the grafted liver with HBV is almost universal and is associated with CAH with rapid progression to cirrhosis and, in some patients, fulminant hepatitis.^{20,21} A retrospective study conducted at 17 European centers demonstrated that the 3-year actuarial risk of HBV recurrence among patients with HBV-related cirrhosis was $78 \pm 8\%$ without any prophylaxis.²²

Before effective prophylaxis was available, HBV reinfection often led to early graft cirrhosis with a 2-year mortality rate of 50%. Recurrent HBV was defined as the reappearance of HBsAg after its initial disappearance after orthotopic liver transplantation. HBV reinfection has a severe course after liver transplantation and fibrosing cholestatic hepatitis (FCH) is seen, caused by accumulation of large amounts of viral proteins in hepatocytes, which is characterized histopathologically as severe cholestasis, ballooning degenerations of hepatocytes, remarkable fibrosis and scant infiltration of

inflammatory cells. The prognosis of FCH is poor and the clinical course can involve progressive liver failure and death.⁶⁷⁻⁶⁹

Recurrence of HBV infection usually has a severe course and could result in graft failure leading to retransplantation or death.⁴⁴⁻⁴⁵ A study from North America, the overall 1-and 3-year HBV recurrence rates were 32 and 41%, respectively.³¹ In similar study from Hong Kong, the 2-year recurrence rate was 23%.³² Combination prophylaxis with HBIG and LAM seems to yield synergistic actions, remarkably reducing the overall 3-year recurrence rate to $<20\%$.^{33,34} Improved survival and reduced HCC recurrence with combination antiviral therapy is observed in patients undergoing OLT for HBV-associated disease.^{39, 40,41} It is widely accepted that viral load i.e. detectable HBV DNA before and during OLT shows a significant linear correlation with HBV recurrence after OLT.^{35,65} At present 5-year survival following OLT for HBV-related disease is similar to that for other indications.³⁶

It is safe to transplant anti-HBc-positive donors for HBsAg-negative recipients by using lamivudine prophylaxis.^{42,43} Treatment with alpha-interferon (IFN) has been shown to be beneficial in the non-transplant setting in patients with CHB.^{23,24} IFN alone given before

Post-exposure prophylaxis of HBV⁸⁰⁻⁸²

Vaccination status	Current antibody(Anti HBs) Status	
	Antibody +ve	Antibody -ve
a. Vaccinated and known responder	No treatment	Give HBIGx1 and booster dose of HBV vaccine
b. Vaccination and Nonresponder@	No treatment required, evaluate for HBsAg*	Give HBIGx1;start revaccination or give 2 more doses of HBIG**
c. Unvaccinated	No treatment required, evaluate for HBsAg #	Give HBIGx1 and initiate vaccination
d. Anti-HBs response unknown	Test exposed person for anti-HBs: If adequate, no treatment is necessary If inadequate, administer HBIG × 1 and vaccine booster, recheck anti-HBs level in 1 month	

(Anti-HBs, antibody to hepatitis B surface antigen;HBIG, hepatitis B immune globulin)

Anti HBs Antibody titers should be reconfirmed at every 10 years interval

@ Nonresponder: 5% of vaccinations do not result in an antibody response. Hence it is necessary to document anti HBs antibody response after vaccination. Repeat vaccination is necessary those who fail to show antibody response.

* A positive antibody test in a document nonresponder to vaccination implies that HBV infection has occurred . One should evaluate for HBV antigen because chronic infection may be present.

** If a nonresponder has undergone 2 successful full vaccination, Then 2 additional doses of HBIG should be given rather than vaccination.

An unvaccinated person with a positive antibody test has had prior HBV infection. then the person should be evaluate d for HBV antigen to determine whether chronic disease is present.

or after transplantation does not reliably prevent HBV reinfection.^{25,26} The introduction of hepatitis B immune globulin (HBIG) and lamivudine (LAM) combination prophylaxis led to a dramatic decrease in recurrent hepatitis B after transplant and improved both graft and patient survival.^{37,38} At present lamivudine and HBIG combination has become a standard prophylactic protocol to prevent post-transplant HBV recurrence and most of the studies have demonstrated the HBV recurrence rate at 1 and 2 years to be <10% with this combination treatment.^{47-51,70} Long-term use of high-dose intravenous HBIG monotherapy can reduce the overall 3-year recurrence rate to 20 to 35%.^{27,28} Administration of high doses of HBIG resulted in improved survival of HBV patients undergoing transplants with deceased donor livers in 1993.⁴⁶ Long-term use of LAM monotherapy can reduce the 3-year recurrence rate to 30 to 50%.³⁰⁻³²

Hepatitis B can relapse during HBIG therapy owing to inadequate doses or immune escape mutants of HBV S protein. YMDD mutants contribute to HBV recurrence after OLT. However, it is not entirely sufficient to prevent recurrence of HBV infection despite the administration of HBIG and lamivudine combination therapy. Adefovir dipivoxil (ADV) is a nucleotide analog that selectively inhibits viral polymerases and reverse transcriptase and is effective in both HBeAg-negative and HBeAg-positive patients.⁵²⁻⁵⁴ ADV is found to be effective versus both wild-type and lamivudine-resistant HBV strains in vivo and in vitro in a non-transplantation setting.^{55,56} ADV has been successful in patients with lamivudine-resistant HBV strains during the pretransplant period and in the treatment of post-transplant HBV recurrence despite HBIG and lamivudine combination prophylaxis.⁶¹⁻⁶⁶ Currently, it is being used in a liver transplantation setting to manage post-transplant HBV reinfection and lamivudine-resistant HBV infection.⁵⁷⁻⁵⁹

The patients with positive HBV-DNA were given lamivudine following their acceptance onto the liver transplant waiting list. Because the aim of the treatment is to ensure that all patients are HBV-DNA negative by the time of transplantation, the pretransplantation LAM/ADV treatment duration should be longer than 4 weeks. In patients with mutant viruses resistant to lamivudine, ADV 10 mg/day was added to treatment. Patients had prophylaxis with lamivudine and low-dose HBIG combination after liver transplantation. Lamivudine was maintained or initiated 100 mg/day before transplantation and continued indefinitely. Those patients who were treated with ADV before transplantation, continued to take ADV 10 mg/day after transplantation indefinitely. Post-transplant HBV prophylaxis is discussed in the earlier chapters. During follow up, check for Anti HBs Ab titer and viral load at an interval of 3-6 months. LAM

100 mg/day started 3-4 weeks before transplantation and continued post-operatively for long term. If mutant variety of HBV is detected, ADV 10 mg/day is added. HBV recurrence under ongoing HBIG prophylaxis was caused by escape mutations with reduced affinity to monoclonal or polyclonal anti-hepatitis B surface (anti-HBs) antibodies.²⁹ High dose HBIG prophylaxis with anti-HBs titers >500 U/l could reduce development of hepatitis B surface antigen (HBsAg) escape mutants, but not completely prevent the occurrence of mutations. 10-20% of patients show HBV recurrence even after use of high dose HBIG.⁶⁰

Dual infection of HBV and HCV all over the globe

Country	HBV carriers	HBV/HCV carriers	Country	HBV carrier	HBV/HCV carrier
America			Asia		
US	1.2 M	0.006 M	China	123.7 M	6.185 M
Brazil	3.7 M	0.2 M	India	40 M	2 M
Domingo	2.9 M	0.015 M	Indonesia	13.3 M	0.665 M
Mexico	1.0 M	0.005 M	Philippines	8.1 M	0.405 M
Europe			Thailand	5.0 M	0.25 M
Turkey	>6.7 M	0.135 M	Japan	3.7 M	0.019 M
Italy	1.5 M	0.075 M	South Korea	2.8 M	0.14 M
Spain	0.6 M	0.003 M	Taiwan	2.6 M	0.13 M
Germany	0.5 M	0.0025 M	Vietnam	12.5 M	0.63 M
Greece	0.3 M	0.0015 M	Singapore	0.2 M	0.01 M
France	0.3 M	0.0015 M	Africa		
UK	0.6 M	0.003 M	Egypt*	2.9 M	0.348 M

Total: 1 Millions (Abbreviation-M: Millions)

HBV endemic areas: 5% dual infection rate: non-endemic areas: 0.5% dual infection rate.

*HCV endemic areas: 12% dual infection rate.

(Adapted from Presentation in Taipei 2008 conference on Hepatitis B and C dual infection: Chun-Jen Liu, Pei-Jer Chen, Ding-Shinn Chen. Management of Patients with Dual Chronic Hepatitis B and C. National Taiwan University College of Medicine and Hospital, Taiwan)

COMBINATION ANTIVIRAL THERAPY AFTER TRANSPLANT

ADV in combination with LAM effectively suppressed viral replication and was efficacious in LAM-resistant patients with CHB. Genotypic analysis indicated that the emergence of ADV-resistant mutants was rare in patients on ADV + LAM combination therapy at least for 2 years. Virological analysis showed that the substitution at rt181, which was associated with both LAM and ADV resistance, is needed for careful monitoring before and during combination therapy.⁷⁵ The long-term survival for each of the 3 therapeutic approaches, namely, for the patients who did not receive any treatment, for the HBIG group, and for the LAM-HBIG group, were 20%, 50%, and 84%, respectively.⁹¹ LAM-HBIG combination is recommended treatment.⁹¹

HBcAb +ve GRAFT IN HBV INFECTED LIVER DISEASE

Hepatitis B core antibody +ve (HBcAb) grafts can be used in patients who have been vaccinated against HBV and have developed Anti HBs Ab and in patients who are HBV carriers. Patient and graft survival are comparable to patients who did not receive HBcAb +ve grafts. With present immunopro-phylaxis HBcAb+ve grafts are acceptable.^{71,72} HBcAb +ve grafts are used in recipients who are HBsAb negative and the risk of transmission of HBV infection is considered acceptable in patients who are critically ill or stage I/II HCC.⁷³

REFERENCES

- Nair S, Perrillo RP, et al. Hepatology. 4th edn. Philadelphia: Saunders 2003, P 959.
- Lok ASF, Wu PC, et al. Long-term follow-up in a randomised controlled trial of recombinant [alpha]₂-interferon in Chinese patients with chronic hepatitis B infection. *Lancet* 1988;ii:298-302.
- Dianzani F. Biological basis for the clinical use of interferon. *Gut* 1993;34(Suppl. 2):S74-6.
- Wong DKH, Cheung AM, et al. Effect of alfa-interferon treatment in patients with hepatitis B e antigen-positive hepatitis B: Meta-analysis. *Ann. Intern. Med* 1993;119:312-23.
- de Man RA, Marcellin P, et al. A randomized, placebo-controlled study to evaluate the efficacy of 12-month famciclovir treatment in patients with chronic hepatitis B e antigen-positive hepatitis B. *Hepatology* 2000;32:413-17.
- Chan HLY, Leung NWY, et al. Hepatitis B e antigen-negative chronic hepatitis B in Hong Kong. *Hepatology* 2000;31:763-58.
- Leung NWY. Liver disease: Significant improvement with lamivudine *J Med Virol* 2000;61:380-85.
- Leung N. Management of chronic hepatitis B. Nucleoside analogues in the treatment of chronic hepatitis BJ *Gastroenterol Hepatol* 2000;15:E53-60.
- Dienstag J, Perillo R, et al. A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995;333:1657-61.
- Liaw YF, Leung NWY, et al. Efficacy and tolerability of two years of lamivudine therapy in Asian patients with chronic hepatitis B *Gastroenterology* 2000;119:172-80.
- Leung NWY, Lai CL, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis e antigen seroconversion rates: Results after three years of therapy. *Hepatology* 2001;33:1527-32.
- Guan R, Lai CL, et al. Efficacy and safety of 5 years lamivudine treatment of Chinese patients with chronic hepatitis BJ *Gastroenterol Hepatol* 2001;16(Suppl.):A60.
- Allen M, Gauthier J, et al. Two sensitive PCR-based methods for the detection of hepatitis B virus variants associated with reduced susceptibility to lamivudine *J Clin Microbiol* 1999;37:3338-47.
- Liaw YF, Chien RN, et al. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology* 1999;30:567-72.
- Leung N, Lai CL, et al. The effect of longer duration of harbouring lamivudine resistant hepatitis B virus (YMDD mutants) on liver histology during 3 years lamivudine therapy in Chinese patients. *Hepatology* 2001;34:248A.
- Leung, Nancy, et al. Treatment of chronic hepatitis B: Case selection and duration of therapy *Advances in Liver Disease: Hepatitis B; Volume* 2002;17(4):pp 409-14.
- Villeneuve JP, Condreay LD, Willems B, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B *Hepatology* 2000;31:207-10.
- Tsang SW, Chan HL, Leung NW, et al. Lamivudine treatment for fulminant hepatic failure due to acute exacerbation of chronic hepatitis B infection. *Aliment. Pharmacol. Ther* 2001;15:1737-44.
- Gust ID. Epidemiology of hepatitis B infection in the Western Pacific and South East Asia. *Gut* 1996;38(Suppl. 2):S18-23.
- Todo S, Demetris AJ, et al. Orthotopic liver transplantation for patients with hepatitis B related liver disease. *Hepatology* 1991;13:619-26.
- O'Grady JG, Smith M, et al. Hepatitis B virus reinfection after orthotopic liver transplantation, serological and clinical implications *J Hepatol* 1992;14:104-11.
- D Samuel, R Muller, et al. Investigators of The European Concerted Action on Viral Hepatitis Study: Liver transplantation in European patients with the hepatitis B surface antigen, *N Engl J Med* 1993;329:1842.
- McGory RW, Ishitani MB, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996;61:1358-64.
- Marcellin P, Samuel D, Areias J, et al. Pretransplantation interferon treatment and recurrence of hepatitis B virus infection after liver transplantation for hepatitis B-related end-stage liver disease. *Hepatology* 1994;19:6-12.
- White M, Brunt EM, et al. Effect of alpha-Interferon and immune globulin therapy on hepatitis B viral infection in transplanted liver recipients (Abstract) *Hepatology* 1990;12:867.
- Lavine JE, Lake JR, et al. Persistent hepatitis B virus following Interferon alpha therapy and liver transplantation. *Gastroenterology* 1991;100:263-67.
- RG Sawyer, RW McGory, et al. Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization, *Ann Surg* 1998;227:841.
- McGory RW, Ishitani MB, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. *Transplantation* 1996;61:1358-64.
- NA Terrault, S Zhou, et al. Incidence and clinical consequences of surface and polymerase gene mutations in liver transplant recipients on hepatitis B immunoglobulin, *Hepatology* 1998;28:555.
- RP Perrillo, T Wright, et al and The Lamivudine North American Transplant Group: A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B, *Hepatology* 2001;33:424.
- CM Lo, ST Cheung, et al. Liver transplantation in Asian patients with chronic hepatitis B using lamivudine prophylaxis, *Ann Surg* 2001;233:276.
- SH Han, P Martinm, et al. Conversion from intravenous to intramuscular hepatitis B immune globulin in combination with lamivudine is safe and cost-effective in patients receiving long-term prophylaxis to prevent hepatitis B recurrence after liver transplantation, *Liver Transplant* 2003;9:182.

33. M Buti, A Mas, et al. A randomized study comparing lamivudine monotherapy after a short course of HBIG and lamivudine with long-term lamivudine plus HBIG in the prevention of hepatitis B virus recurrence after liver transplantation. *J Hepatol* 2003;38:811.
34. A Marzano, S Gaia, et al. Viral load at the time of liver transplantation and risk of hepatitis b virus recurrence, *Liver Transplant* 2005;11:402.
35. DM Anselmo, RM Ghobrial, et al. New era of liver transplantation for hepatitis B: A 17-year single-center experience, *Ann Surg* 2002;235:611.
36. T Steinmuller, D Seehofer, N Rayes, et al. Increasing applicability of liver transplantation for patients with hepatitis B-related liver disease, *Hepatology* 2002;35:1528.
37. SH Han, J Ofman, et al. An efficacy and cost-effectiveness analysis of combination hepatitis B immune globulin and lamivudine to prevent recurrent hepatitis B after orthotopic liver transplantation compared with hepatitis B immune globulin monotherapy, *Liver Transpl* 2000;6:741.
38. PW Angus, EJ Gane, et al. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against post-transplantation hepatitis B, *Liver Transpl* 2000;6:429.
39. WR Kim, JJ Poterucha, et al. Outcome of liver transplantation for hepatitis B in the United States, *Liver Transpl* 2004;10:968.
40. MA Zimmerman, RM Ghobrial, et al. Antiviral prophylaxis and recurrence of hepatocellular carcinoma following liver transplantation in patients with hepatitis B transplant proceed 2007;39(10):3276-80.
41. Celebi K, Z Karasu, et al. Living donor liver transplantation from hepatitis B core antibody positive donors; Transplantation Proceedings 2007;39(5):1488-90.
42. Murat Akyildiz, et al. Adefovir dipivoxil therapy in liver transplant recipients for recurrence of hepatitis B virus infection despite lamivudine plus hepatitis B immunoglobulin prophylaxis. *Journal of Gastroenterology and Hepatology* 2007;22(12):2130-34.
43. Shouval D, Samuel D. Hepatitis B immune globulin to prevent HBV graft reinfection following liver transplantation: A concise review *Hepatology* 2000;32:1189-95.
44. Rosenau J, Bahr MJ, et al. Lamivudine and low-dose hepatitis B immune globulin for prophylaxis of hepatitis B infection after liver transplantation: possible role of mutations in the YMDD motif before transplantation as a risk factor for reinfection *J Hepatol* 2001;34:895-902.
45. Samuel D, Muller R, et al. Liver transplantation in European patients with the hepatitis B surface antigen *N Engl J Med* 1993;329:1842-47.
46. Lok ASF. Prevention of recurrent hepatitis B post-liver transplantation. *Liver Transpl* 2002;8:S67-S73.
47. Marzano A, Salizzoni M, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with Lamivudine and passive immunoprophylaxis *J Hepatol* 2001;34:903-10.
48. Angus PW, McCaughan GW, et al. Combination low-dose hepatitis B immune globulin and lamivudine therapy provides effective prophylaxis against posttransplantation hepatitis B. *Liver Transpl* 2000;6:429-33.
49. Han SH, Ofman J, et al. An efficacy and cost-effectiveness analysis of combination hepatitis B immune globulin and lamivudine to prevent recurrent hepatitis B after orthotopic liver transplantation compared with hepatitis B immune globulin monotherapy. *Liver Transpl.* 2000;6:741-8.
50. Karasu Z, Ozacar T, et al. Low-dose hepatitis B immune globulin and higher-dose lamivudine combination to prevent hepatitis B virus recurrence after liver transplantation. *Antiviral Ther* 2004;9:921-27.
51. Marcellin P, Chang T-T, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen positive chronic hepatitis BN *Engl J Med* 2003;348:808-16.
52. Hadziyannis SJ, Tassopoulos NC, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis BN *Engl J Med* 2003;348:800-07.
53. Perrillo R, Schiff E, Yoshida E, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. *Hepatology* 2000;32:129-34.
54. Perillo R, Hann HW, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus *Gastroenterology* 2004;126:81-90.
55. Peters MG, Hann HW, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B *Gastroenterology* 2004;126:91-101.
56. Schiff EU, Lai CL, et al. Adefovir dipivoxil therapy for lamivudine resistant hepatitis B in pre-and post-liver transplantation patients. *Hepatology* 2003;38:1419-27.
57. Walsh KM, Woodall T, et al. Successful treatment with adefovir dipivoxil in a patient with fibrosing cholestatic hepatitis and lamivudine resistant hepatitis B virus. *Gut* 2001;49:436-40.
58. Tillmann HL, Bock CT, et al. Successful treatment of fibrosing cholestatic hepatitis using adefovir dipivoxil in a patient with cirrhosis and renal insufficiency. *Liver Transpl* 2003;9:191-16.
59. Protzer-Knolle U, Naumann U, et al. Hepatitis B virus with antigenically altered hepatitis B surface antigen is selected by high-dose HBIG after liver transplantation. *Hepatology* 1998;27:254-63.
60. Beckebaum S, Malago M, et al. Efficacy of combined lamivudine and adefovir dipivoxil treatment for severe HBV graft reinfection after living donor liver transplantation. *Clin Transplant* 2003;17:554-59.
61. Papatheodoridis GV, Sevastianos V, et al. Prevention of and treatment of hepatitis B virus infection after liver transplantation in the nucleoside analogues era. *Am J Transplant* 2003;3:250-58.
62. Vierling JM. Management of HBV infection in liver transplantation patients. *Int J Med Sci* 2005;2:41-49.
63. Marzano A, Lampertico P, et al. Prophylaxis of hepatitis B virus recurrence after liver transplantation in carriers of lamivudine-resistant mutants. *Liver Transpl* 2005;11:532-38.
64. Samuel D. Management of hepatitis B in liver transplantation patients *Semin Liver Dis* 2004;24:55-62.
65. Murat Akyildiz, et al. Adefovir dipivoxil therapy in liver transplant recipients for recurrence of hepatitis B virus infection despite lamivudine plus hepatitis B immunoglobulin prophylaxis. *Journal of Gastroenterology and Hepatology* 2007;22(12):2130-34.
66. Thabut D, Ratzu V, et al. Unsuccessful rescue therapy with adefovir dipivoxil for lamivudine resistant HBV in a patient with liver failure. *Gut* 2003;52:614.
67. Terault NA. Treatment of recurrent hepatitis B infection in liver transplant recipients. *Liver Transpl* 2002;8(Suppl.1):S74-81.
68. Lo CM, Cheung ST, et al. Fibrosing cholestatic hepatitis secondary to precore/core promoter hepatitis B variant with lamivudine resistance: Successful retransplantation with combination adefovir dipivoxil and hepatitis B immunoglobulin. *Liver Transpl* 2004;10:557-63.

69. Jiao Z Y, et al. Prophylaxis of recurrent HBV in Chinese patients after liver transplantation using lamivudine combined with HBIG according to the titre of antibody to HBsAg. *Transplantation proceedings* 2007;39:1533-39.
70. Nery JR, Gedaly R, et al. Are liver grafts from HBsAg-ve/HBcAb+ve donors suitable for transplantation? *Transpl proceed* 2001;33:1521-22.
71. Anslemo D, Ghobrial R, et al. New era of liver transplantation for hepatitis B: A 17 year single centre experience. *Ann Surg* 2002;235:611-20.
72. Dodson SF, Bonhom CA, et al. Prevention of de novo hepatitis B infection in recipients of hepatic allografts from anti HBc positive donors *Transpl* 1999;68:1058.
73. Lai CL, Leung N, Teo EK, et al. Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B *Gastroenterology* 2005;129(2):528-36.
74. Lai CL, et al. *Gastroenterology* 2005;129:528-36.
75. Adriano M, Pellicelli GB, et al. Adefovir for lamivudine resistant HBV: More than meets the eye. *Journal of Hepatology* 2007;47(4):618-19.
76. Lai CL, Gane E, Liaw YF, et al. Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B *N Engl J Med* 2007;357(25):2576-88.
77. Chang TT, Gish RG, de Man R, Gadano A, et al. BEHoLD A1463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B *N Engl J Med* 2006;354(10):1001-10.
78. Heathcote J, et al. Abstract #LB6 AASLD 2007. Approved for Tx. of CHB, EMEA 2008.
79. Chun-Tao Wai, Robert J Fontana. Clinical significance of hepatitis B virus genotypes, variants, and mutants. *Clin Liver Dis* 2004;8:321-52.
80. AS Yu, RC Cheung, EB Keeffe. Hepatitis B vaccines. *Clin Liver Dis* 2004;8:283-300.
81. Weinbaum C, Lyster R, Margolis HS. Centers for Disease Control and Prevention. Prevention and control of infections with hepatitis viruses in correctional settings. *Recomm Rep MMWR* 2003;52(RR-1):1-36.
82. Fry DE, et al. Occupational risks of blood exposure in the operating room *Am Surg* 2007;73(7):637-46.
83. P Gaglio, S Singh, B Degertekin, et al. Impact of the hepatitis B virus genotype on pre- and post-liver transplantation outcomes liver transplantation 2008;14:1420-27.
84. Lok AS, Zoulim F, Locarnini S, et al. Antiviral drug-resistant HBV: Standardization of nomenclature and assays and recommendations for management *Hepatology* 2007;46:254-65.
85. Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714-22.
86. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743-51.
87. Lai CL, Gane E, Hsu CW, et al. Two-year results from the globe trial in patients with hepatitis B: Greater clinical and antiviral efficacy for telbivudine (LDT) vs. lamivudine. *Hepatology* 2006;44:222A.
88. Fung SK, Chae HB, Fontana RJ, et al. Virologic response and resistance to adefovir in patients with chronic hepatitis B *J Hepatol* 2006;44:283-90.
89. Tenney DJ, Pokorowski KA, Fang J, et al. Entecavir at five years shows long term maintenance of high genetic barrier to hepatitis B virus resistance. Paper presented at: Conference of the Asia-Pacific Association for the Study of the Liver (APASL); 2008; Seoul, Korea.
90. Anna SF Lok. How to diagnose and treat hepatitis B virus antiviral drug resistance in the liver transplant setting. *Liver transplantation* 2008;14:S8-S14.
91. AW Avolio, E Nure, M Pompili, et al. Liver transplantation for hepatitis B virus patients: Long-term results of three therapeutic approaches. *Transplantation Proceed* 2008;40:1961-64.

Hepatitis C Virus and Liver Transplantation

HEPATITIS C VIRUS

Hepatitis C virus (HCV) belongs to hepacivirus genus in the family flaviviridae, was initially called non-A, non-B hepatitis virus (NANBH). It was discovered in 1989, re-named as hepatitis C virus.^{1,2} It is a single-stranded, positive sense RNA virus of 50 nm in size.

MODE OF TRANSMISSION

HCV infection is transmitted by blood products and sexual contact. The rate of perinatal transmission is 6%, which depends on maternal HCV RNA level. Efficiency of sexual transmission is considered to be very low. It is more during acute hepatitis phase.

STRUCTURE

HCV consists of a core of RNA, surrounded by an icosahedral protective shell of protein, and covered encased in a lipid envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope³ (Figure 40.1).

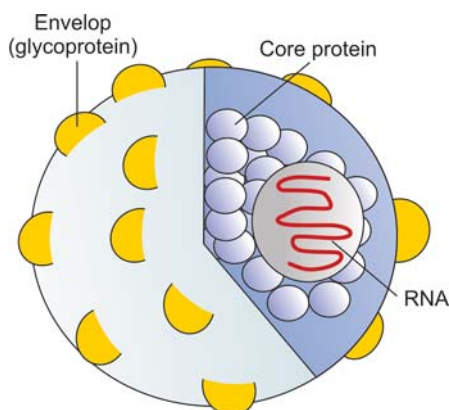


Figure 40.1: Hepatitis C virus

GENOTYPES

Based on genetic differences, HCV is classified into six genotypes (numbered as 1 to 6, with several subtypes within each genotype.⁴ Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes.⁴

Genotypes in different geographical areas:

North America: Genotype 1a followed by 1b, 2a, 2b, and 3a.

Europe: Genotype 1b is predominant followed by 2a, 2b, 2c, and 3a.

Taiwan and rest of Asia: Genotype 1 and 2 are common.

Africa: Genotypes 4 and 5

Replication⁵⁻⁷

HCV has a high replication rate of one trillion particles/day in an infected individual. Due to lack of proof reading by the HCV RNA polymerase, HCV has high mutation rate, which helps to tide over host's immune response. HCV mainly replicates within hepatocytes in the liver. Some evidence of replication is seen in lymphocytes or monocytes. Host tropism helps them to reach the proper site for replication. Circulating HCV bind to receptors on surface of hepatocytes to enter the cells and initiates lytic cycle. 2 HCV receptors are known such as CD81 and human scavenger receptor class B1 (SR-BI). HCV genome is translated to form a polyprotein of around 3011 amino acids which is proteolytically processed by viral and cellular proteases to produce three structural (virion-associated) and seven nonstructural (NS) proteins. A frame shift may occur in the core region to produce an Alternate Reading Frame Protein (ARFP). HCV encodes two proteases such as NS2 cysteine autoprotease and NS3-4A serine protease. NS proteins then recruit the viral

genome into an RNA replication complex. RNA replication takes place via the viral RNA-dependent RNA polymerase of NS5B, which produces a negative-strand RNA intermediate, which serves as a template for the production of new positive-strand viral genomes and are translated, further replicated, or packaged within new virus particles. New virus particles presumably bud into the secretory pathway and are released at the cell surface.

PRESENTATION

- Acute hepatitis
- Chronic hepatitis leading to cirrhosis and hepatocellular carcinoma

Acute Hepatitis C

Acute HCV hepatitis is seen first 6 months after infection. In the acute phase 60 to 70% of infected individuals do not develop symptoms. HCV is detectable in the blood within 1-3 weeks after infection. Anti HCV antibodies are detectable within 3 to 12 weeks. Spontaneous viral clearance occurs in 15-40% of patients and is indicated by normalization in liver function tests and HCV-RNA clearance.

Symptoms of acute HCV hepatitis

- Fatigue
- Reduced appetite
- Dull aching abdominal pain
- Icterus
- Flu-like symptoms

Chronic Hepatitis C

60-85% of patients with HCV develop chronic hepatitis C, i.e. infection lasting > 6 months. Symptoms specifically suggestive of liver disease are typically absent in the initial stage. Generalized signs and symptoms such as fatigue, weight loss, myalgia, arthralgia, low grade fevers, right upper abdominal pain, loss of appetite, nausea, diarrhea, dyspepsia, depression, headaches, and mood swings are seen.

Factors associated with rapid progression of HCV disease

- Age (increasing age: more rapid progression)
- Gender (males > females)
- Alcohol consumption (rapid progress in alcoholics)
- HIV coinfection
- Fatty liver (more rapid progression).

SPECIFIC SYMPTOMS RELATED TO ADVANCED LIVER DISEASE

- Cirrhosis
- Portal hypertension
- Ascites
- Esophageal varices
- Jaundice
- Hepatic encephalopathy

Extrahepatic manifestations associated chronic HCV infection

- Thyroiditis
- Porphyria cutanea tarda
- Cryoglobulinemia
- Glomerulonephritis—Membranoproliferative glomerulonephritis (MPGN)
- Sicca syndrome
- Thrombocytopenia
- Lichen planus
- Diabetes mellitus
- B-cell lymphoproliferative disorders

DIAGNOSIS

Abnormal Liver Function Tests

Abnormal liver function tests are used as one of the indicators of active disease. High ALT levels can be a sign of hepatitis C, but other conditions can also cause an increase in ALT, including hepatitis due to other causes, heart attacks and high triglyceride levels.

Anti-HCV Antibody

Anti-HCV antibody in serum is seen in 2-3 months after infection but may be negative for longer period. Anti-HCV antibodies can be detected in 80% of patients within 15 weeks after exposure, in > 90% within 5 months after exposure, and in > 97% by 6 months after exposure. These antibodies are detected by enzyme-linked immunosorbent assay (ELISA) or recombinant Immunoblot assay (RIBA).

Factors predictive of response to IFN and RBV in chronic hepatitis C

Baseline Predictors

- Viral
 - Genotype 2/3
 - Viral load = 1 million IU/ml
- Host
 - Fibrosis F0–F1
 - Age < 40 years
 - Female gender
- On-treatment factors: Viral kinetics
 - RVR
 - EVR

Adherence (compliance)

Rapid viral response (RVR): HCV RNA negative (< 50 IU/ml) at 4th week.

Early viral response (EVR): >2 log₁₀ drop from baseline or HCV RNA negative at 12th week.

HCV RNA Levels

HCV RNA levels are measured by RT-PCR (reverse transcriptase polymerase chain reaction: most commonly used), transcription mediated amplification (TMA), or branched DNA (b-DNA). HCV RNA can be detected within 1-2 weeks of exposure. It indicates viral load and genotypes like type 1, 2a, 2b, 3 and 4. It is not routine; restricted for liver transplant patients and research purpose. Repeat hepatitis C serology may be offered in 6 months to exclude recent seroconversion.

TREATMENT

- Alcohol consumption should be avoided
- Avoid donation of blood, semen or other body tissues or organs to reduce transmission. Avoid sharing syringes.
- Hepatotoxic drugs are avoided.

Treatment is indicated for patients with abnormal LFT for more than 6 months. Drugs used to control HCV infection are a combination of Interferon and Ribavirin. Other less commonly used drugs are Amantadine and Viramidine. Duration of standard interferon-based therapy for genotypes 1b and 4 is 48 weeks. 24 weeks' treatment may be recommended for patients with an RVR and low viral load. Treatment should be stopped in patients without an EVR. Treatment for genotypes 2 and 3 is completed in 24 weeks.

A shorter treatment duration with suboptimal dose of Ribavirin may be associated with an increase in the rate of relapse with subsequently decrease in SVR rate. Critical issue for achieving an SVR is to maintain an optimal dose of Ribavirin throughout the course of treatment and it prevents breakthrough and relapse.

INDICATION OF TREATMENT OF CHRONIC HEPATITIS C (NATIONAL TAIWAN HEALTH POLICY, 2008)

(Duration of treatment: 24 weeks of PEG-IFN or IFN + RBV for all genotypes)

Criteria

- Anti-HCV (+) ,
- ALT > 2X, 3 M apart, within 6 M
- Fibrosis > F1

Side effects of INF + Ribavirin therapy

- Nonspecific: Fatigue, headache, fever
- Skin: Pruritus, rash, dryskin, loss of hair
- GI: Anorexia, nausea, vomiting
- Respiratory: Cough, Dyspnea
- Neuropsychiatric: Irritability, anxiety, insomnia

FOLLOW-UP

Monitor LFT, and α -fetoprotein once in three months.

Patients requires attention if:

- Elevated LFT , particularly ALT values over a period of six months
- Signs of chronic hepatitis or liver failure
- Elevated α -fetoprotein level, exclude hepatocellular carcinoma.

If LFT are normal, regular 12 monthly testing and clinical assessment for symptoms or signs of liver disease is recommended. Risk of chronic active hepatitis and cirrhosis are more in patients positive for both HBV and HCV.

PROPHYLAXIS

Hepatitis A and hepatitis B vaccinations are recommended for individuals who are hepatitis C positive. Currently no vaccine is available to prevent hepatitis C infection.

HCV AND LIVER TRANSPLANTATION

There is rapid increase in the number of patients with HCV infection undergoing LTX. HCV is currently accounting for >50% of liver transplants both in USA and Europe. In Asian countries, Japan has more incidence of HCV as compared to others like China, Taiwan or Korea where HBV is more.

POST-TRANSPLANT RECURRENT HCV

Chronic HCV infection with cirrhosis is now the most common indication for OLT in the USA and Western Europe.^{8,9} Recurrence of HCV infection after LTX, is almost universal and thus measurement of serum HCV RNA is not helpful. Reinfection of the allograft may occur either from extra hepatic sites or from circulating virus perioperatively. Recurrent infection commonly leads to hepatitis, and is less aggressive than the recurrent hepatitis B after transplant. Increased risk of graft loss is noticed following recurrent hepatitis C infection. Genotype 1b and 4 are more virulent as compared to others. Recurrent HCV infection presenting as acute lobular hepatitis is documented in 75% of liver biopsy

by 4 months after transplantation. 70 to 80% of recurrent HCV infection develops as mild disease. Progression to cirrhosis occurs in 6 to 23% of patients at a median of 3 to 4 years post-LTX.⁴⁵ 20 to 30% of patients can have rapidly progressive disease, cirrhosis and decompensation at 5 years follow-up leading to allograft failure and need for retransplantation in 10 % of patients.^{10,11} Recurrent HCV infection can develop anytime during the first year after LTX, but rejection is more common in the first 2 months. Ghobrial et al.⁴¹ reported that the time interval to HCV recurrence is significantly shorter in LDLT patients than in patients after DDLT.

Gaglio et al.⁴² reported that the overall incidence of severe sequelae of hepatitis C recurrence either cholestatic hepatitis or grade III-IV inflammation or hepatitis C induced graft failure requiring retransplantation are not different between cadaveric grafts and those grafts from living liver donors. However, the morbidity of cholestatic hepatitis C was more severe in LDLT patients. A liver biopsy must be performed to differentiate recurrent hepatitis C from rejection. Liver biopsy samples were staged according to the original HAI (histological activity index) fibrosis score: 0, none; 1, fibrous portal expansion; 3, bridging fibrosis; and 4, cirrhosis.¹² Methods to identify individuals at risk for rapid fibrosis progression are histological assessment of allograft biopsies, measurement of liver stiffness and hepatic venous pressure gradient (HVPG).⁴⁶⁻⁵¹

Risk Factors for recurrence of HCV after transplantation

- **Virus related**
 - Genotype 1b
 - High pre LTX HCV RNA level
 - Early high post LTX HCV RNA level
- **Graft related**
 - Prolonged WIT
 - Episodes of rejection
 - Early evidence of post transplant histological proven injury
 - Recently transplanted allograft
- **Host related**
 - Advanced age
 - Noncaucasians
 - HLA matching
 - Absence of pretransplant viral infection (HBV/CMV)
 - Positive Anti HCV antibody (Ig M core Ab)
- **Immunosuppression related**
 - Use of OKT3 or MMF
 - Bolus high dose of corticosteroids
 - High immunosuppression levels.

Recently Surakit et al⁵³ reported that serum levels of markers of extracellular matrix metabolism such as serum Hyaluronic acid and YKL-40, measured in the first 8 months after LTX, could accurately predict those subjects at risk for rapid fibrosis progression after LTX for chronic HCV infection, performing significantly better than conventional histology assessments of inflammation and fibrosis, standard biochemical testing, or assessment of hepatic stellate cell activity.

Determinants of hepatic fibrosis after LTX^{13,14}

- Viral load,
- Donor factors
- Age > 50
- Sex
- Steatosis
- Host factors-HLA type
- Alcohol
- Immunosuppression
- Co-infection with other virus (HBV/CMV)
- Long warm ischemic time

The lack of HCV-specific T-cell responses is a crucial underlying pathology that results HCV-related graft injury after transplantation. Humoral immunity does not play a role in preventing recurrent HCV after LTX. Reinfection with HCV after transplantation is universal in patients with detectable serum HCV RNA before transplantation. Up to 70% of patients with pre-transplantation viremia can develop graft hepatitis after transplantation. Data from programs with annual protocol liver biopsies suggest that 20 to 28% patients will develop HCV related cirrhosis by 5 years after transplantation.

Causes of decompensation, retransplantation, and mortality

- Child-Pugh score B or C
- Low serum albumin
- Short interval between transplantation and post-transplantation cirrhosis.

TREATMENT

Recurrent hepatitis C may be accelerated in immuno-suppressed recipients. In 8-16% patients, recurrent HCV cause progression to cirrhosis, within 5 years. Rapid progression to liver failure has been observed in a subset of recipients who develop a cholestatic pattern of liver injury.

3 issues need to be addressed, related to treatment of recurrent HCV after LTX:

- Pre-transplant prophylaxis
- Post-transplant prophylaxis
- Treatment when a patient develops chronic disease.

Pre-transplant Prophylaxis

Patient intolerance and high incidence of side effects due to interferon therapy, limit the use in seriously ill patient in pretransplant period.³² Pre-transplant interferon therapy may delay/prevent post transplant recurrence of HCV infection.³³

Everson et al.⁴⁴ reported the result of preoperative low-dose regimen for HCV. The regimen consisted of Interferon alfa-2b (1.5 MU three times a week) or Peg-Interferon alfa-2b (0.5 µg/kg/week) plus Ribavirin (600 mg/day). 124 patients (70% genotype 1) were treated with the regimen. The mean Child Turcotte Pugh score was 7.4 and 23 of them were Child class C. Of these, 15 patients (12%) were negative for HCV at liver transplantation among which 12 remained (six of them received LDLT) negative 6 months or more after liver transplantation.

Sugawara et al in Kyoto university hospital⁴³ had performed pre-emptive therapy for LDLT patients for HCV. 23 patients underwent LDLT for HCV cirrhosis. All the patients pre-emptively received antiviral therapy consisting of interferon-α 2b and Ribavirin, which was started ~1 month after the operation. The therapy continued for 12 months after the first negative HCV-RNA test. The subjects were removed from the protocol if they could not continue the therapy for 12 months due to adverse effects or could not start the therapy due to early death. Eight patients were removed from the protocol. The sustained virologic response ratio was 39% (9/16). The ratio of genotype 1b patients was 32% and that of non-1b was 75%. The cumulative 3-year survival rate of the HCV-positive patients was 85%, comparable with that of patients negative for HCV (n = 93, 90%). The significance of preoperative regimen for HCV has remained unclear.

Post-transplant Prophylactic Treatment

Post-transplant prophylactic treatment should begin 2-8 weeks after transplantation. Early treatment with AVT causes rejection.³⁴

Post-transplant Antiviral Therapy

- Pre-emptive (prophylactic) therapy: Disadvantages of pre-emptive interferon-based therapy is that the immuno-modulatory effect of interferon that will increase the risk for acute allograft rejection by 35%.^{15,16}
- Histologically documented recurrent hepatitis C infection

Combination therapy of Interferon and Ribavirin for HCV infection after LTX

Interferon (INF): Pegylated Interferons are preferred.

- Interferon alfa-2b: 3 million IU/thrice a week (or)
- Pegylated Interferon α-2a: 180 µg once weekly (or)
- Pegylated Interferon α-2b: 1-1.5 µg/kg once weekly subcutaneously

Monitor neutrophil count during Interferon therapy

- Neutrophil count < 750/µl: Reduce dose of Pegylated-IFN to 0.75 µg/kg/week.
- Neutrophil count < 500/µl: Discontinue interferon treatment

Ribavirin: Start 600 mg oral dose, gradually increases 800 to 1000 mg/day (if tolerated)

Monitor creatinine clearance and hemoglobin during Ribavirin therapy

Dose adjusted according to creatinine clearance, measured every 3 months.

- Creatinine clearance = 70 mL/mn: 800 mg/day
- Creatinine clearance >40 mL/mn and <70 mL/mn: 600 mg/day

Hemoglobin < 10 gm/dL: Reduce dose of Ribavirin to 600 mg or 400 mg/day,

Erythropoietin-a (Epoietin-a): Dose of 40,000–60,000 units/once weekly subcutaneously, to prevent hemoglobin drop and discontinuation of Ribavirin.

Ribavirin is to be continued for another 6 months after discontinuation of INF therapy

Duration of treatment for combined therapy:

- 48 weeks for genotype 1 and 4 (SVR 35-45%)
- For other genotypes 24 weeks (SVR 60-80%)

Pregnancy: Ribavirin and Interferons are contraindicated during pregnancy.

Interferon and Ribavirin Combination Therapy

Interferon and Ribavirin combination therapy has improved efficacy as compared with interferon monotherapy, in recurrent HCV infection after transplantation. It is now appropriate to consider whether retreating previous nonresponders or relapsers with this new combination will be effective in the transplant setting.^{17,18} Interferons are usually given for 24 weeks; duration may be prolonged up to 48 weeks, depending on the viral load, genotypes (1 and 4) and patient tolerance. Combination of Pegylated interferon + Ribavirin is standard treatment with superior results. Sustained viral response (SVR) with this combination is 26-50%.^{19,20}

RESPONSE TO TREATMENT

Qualitative HCV-RNA by PCR

Check HCV RNA levels at baseline, at 4 weeks and then every 12 weeks to see the sustained viral response (SVR). Reduction of HCV RNA <1% of initial titer has 80% chance of cure rate. Patients who do not show >99% reduction in RNA titer at 12 weeks, chances of achieving SVR is almost nil.

Genotyping

Genotyping should be performed.²¹

Histological Confirmation

Liver biopsy specimens are obtained at inclusion and 24 weeks after the end of antiviral therapy. Histological benefit is seen in most nonresponders, retreated with Pegylated Interferon-Ribavirin combination.²² SVR is monitored by return of LFT particularly ALT to normal and disappearance of serum HCV RNA (PCR). SVR is long lasting from 3-5 years after discontinuation of therapy in responders.^{23,24,25,27} A recent Italian study showed that the SVR improves patient survival. In this study, SVR was achieved in 28% of 61 patients treated with Peg-Interferon/Ribavirin.²⁵ There is decrease in progression of fibrosis after antiviral therapy from 0.75 to 0.15.²⁶

HCV +ve Recipients, after LTX

- Proper Immunosuppressive therapy should be maintained along with antiviral therapy.
- Allograft rejection should be treated on histological proof (liver biopsy).
- Trial of antirejection therapy must be avoided in inconclusive liver biopsies.
- Least aggressive antirejection therapy is given to patients with documented rejection.

Risk for rapidly progressive HCV recurrence in allograft recipients is related to frequent use of steroid bolus doses, mycophenolate mofetil, ATG, ALG or OKT3 use.

Ascites in HCV Recipients

Post-transplant ascites is frequently common problem and it occurs in the absence of allograft fibrosis. The factors influencing are female gender, prolonged cold ischemic time and serum creatinine level.²⁸

Indications of Retransplantation in HCV +ve recipients with allograft cirrhosis and decompensation

- Recurrence of HCV
- Chronic rejection
- Biliary complications
- Hepatic artery thrombosis

Retransplantation is associated with decreased patient and graft survival regardless of HCV status. Sepsis and postoperative complications account for the majority of early morbidity and mortality.^{29,30} After retransplantation, 1 year survival rate is less than 50% in patients who developed allograft failure due to recurrent HCV infection. Severe hyperbilirubinemia and renal failure are associated with poor graft survival after retransplantation. As per the UNOS data base, HCV positive patients has high mortality after transplant as compared to HCV negative patients.³¹ HCV is superseded by multiple donors, operative and recipient factors as predictors of retransplantation graft survival, and should not contraindicate retransplantation.³⁵

Spontaneous Clearance of HCV

Spontaneous clearance of HCV occurs in 10 to 50% of patients with acute hepatitis C but is a rare event in immunocompetent individuals once chronic hepatitis C has been established.⁵⁴ Nearly all HCV-infected patients develop HCV reinfection after liver transplantation, and spontaneous clearance of HCV in the context of immunosuppression is frequently considered to be almost impossible. However, HCV-specific CD₄ and CD₈ T cell responses can be detected after liver transplantation and are thought to play a critical role in controlling HCV replication and graft damage.^{55,56}

HCV Antibody Positive Grafts

These grafts may be used in HCV related liver cirrhosis and there is no difference in patient and graft survival as compared to non HCV related liver disease.³⁶⁻³⁸ However, this type of transplantation is less practiced, usually during emergency situation. According to UNOS data base, patient survival was in fact significantly higher in HCV+ grafts.⁴⁰

HBcAb Positive Grafts in HCV Patients³⁹

HBcAb+ve allografts can be used for both HCV +ve and -ve recipients who are:

Precautionary measures to reduce HCV related liver injury after LTX⁵²

<i>Risk factors</i>	<i>Precautionary measure</i>
Donor age	Use of young donors
Graft steatosis	Avoid use of grafts with significant steatosis
Pre LTX high viremia level	Pretransplantation IFN therapy
Preservation/Ischemic injury	Reduce ischemic time
	High immunosuppression levels Individualize immunosuppression
	Treat only moderate to severe episodes of rejection
	Avoid bolus doses of methyl-prednisolone
	Avoid high dose combination immunosuppressive agents
CMV infection	Prophylaxis against CMV infection
Abrupt change of immune status	Avoid sudden change in dose and type of immunosuppression
Profibrogenic state	Promote antifibrogenic agents, such as angiotensin blockers
PTDM	Adequate blood sugar control
(Post LTX diabetes mellitus)	Promote hyperglycemic-sparing immunosuppression
HIV co-infection	HAART for adequate control of HIV replication

- Critically ill
- Early HCC
- Past exposure to HBV infection

However post-transplant prophylaxis against HBV should be continued.

Nudo et al⁵⁷ reported that the The 1-and 5-year survivals were 87.8%/75.6% and 89.6%/77.8% for pre-transplant RNA+ ve and -ve groups, respectively. RNA negative transplanted patients displayed lower virological response (VR) and longer time to histological response (HR). The SVR patients showed lower VR and HR compared to end of treatment response and RNA(+) patients.

REFERENCES

1. Choo Q, Kuo G, Weiner A, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989;244(4902):359-62.
2. Kuo G, Choo Q, Alter H, et al. "An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis." *Science* 1989;244(4902):362-64.
3. Beeck A, Dubuisson J. "Topology of hepatitis C virus envelope glycoproteins" *Rev Med Virol* 2003;13(4):233-41.
4. Simmonds P, Bukh J, Combet C, et al. "Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes." *Hepatology* 2005;42(4):962-73.
5. Lindenbach B, Rice C. "Unraveling hepatitis C virus replication from genome to function." *Nature* 2005;436(7053):933-38.
6. Watashi K, et al. *Molecular cell* 2005;(19):111-22.
7. Nakagawa M, et al. *Gastroenterology* 2005;129:1031-41.
8. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994 *N Engl J Med* 1999;341:556-62.
9. Kiyosawa K, Sodeyama T, Tanaka E, et al. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. *Hepatology* 1990;12:671-75.
10. Samuel D, Forns X, Berenguer M, et al. Report of the monothematic EASL conference on liver transplantation for viral hepatitis (Paris, France, January 12-14, 2006). *J Hepatol* 2006;45:127-43.
11. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplant Society consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003;9(Suppl.3):S1-S9.
12. Berenguer M, Palau A, Fernandez A, et al. Efficacy, predictors of response, and potential risks associated with antiviral therapy in liver transplant recipients with recurrent hepatitis C. *Liver Transpl* 2006;12:1067-76.
13. Berenguer M, Prieto M, San Juan F, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. *Hepatology* 2002;36:202-10.
14. Wali M, Harrison RF, Gow PJ, et al. Advancing donor liver age and rapid fibrosis progression following transplantation for hepatitis C *Gut* 2002;51:248-52.
15. Stanca CM, Fiel MI, Kontorinis N, et al. Chronic ductopenic rejection in patients with recurrent hepatitis C virus treated with pegylated interferon alfa-2a and ribavirin. *Transplantation* 2007;84:180-86.
16. Kugelmas M, Osgood MJ, Trotter JF, et al. Hepatitis C virus therapy, hepatocyte drug metabolism, and risk for acute cellular rejection. *Liver Transpl* 2003;9:1159-65.
17. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C virus. *N Engl J Med* 2000;343:1666-72.
18. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for patients with chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
19. Berenguer B. Treatment of hepatitis C after liver transplantation. *Clinics Liver Disease* 2005;9:579-600.
20. Kornberg A, Küpper B, Tannapfel A, et al. Antiviral treatment withdrawal in viremic HCV-positive liver transplant patients: Impact on viral loads, allograft function and morphology. *Liver Int* 2006;26:811-16.

21. Simmonds P. Variability of hepatitis C virus. *Hepatology* 1995;21:570-83.
22. T Bizollon, P Pradat, JY Mabrut, et al. Histological Benefit of Retreatment by Pegylated Interferon Alfa-2b and Ribavirin in Patients with Recurrent Hepatitis C virus Infection Posttransplantation. *Am J of Transpl* 2007;7(2):448-53.
23. Bizollon T, Ahmed SN, Radenne S, et al. Long-term histologic improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplant patients with hepatitis C recurrence. *Gut* 2003;52:283-87.
24. Abdelmalek MF, Firpi RJ, Soldevila-Pico C, et al. Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. *Liver Transpl* 2004;10:199-207.
25. M Berenguer, A Palau, V Aguilera, et al. Clinical benefits of Antiviral Therapy in Patients with Recurrent Hepatitis C Following Liver Transplantation *AmJ of Transplan* 2008;8(3):679-87.
26. Bahra M, Neumann UP, Jacob D, et al. Fibrosis progression in hepatitis C positive liver recipients after sustained virologic response to antiviral combination therapy (interferon-ribavirin therapy). *Transplantation* 2007;83:351-53.
27. Picciotto FP, Tritto G, Lanza AG et al. Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation. *J Hepatol* 2007;46:459-65.
28. Lan YB, Landry GM, Tan VO, et al. Ascites in Hepatitis C liver transplant recipients frequently occurs in the absence of advanced fibrosis. *Am J Transpl* 2008;8:366-76.
29. Watt KD, Lyden ER, McCashland TM. Poor survival after liver retransplantation: Is hepatitis C to blame? *Liver Transpl* 2003;9:1019-24.
30. Ghobrial RM. Retransplantation for recurrent hepatitis C. *Liver Transpl* 2002;8:S38-S43.
31. Forman LM, Lewis JD, et al. The association between Hepatitis C infection and survival after orthotopic liver transplantation; *Gastroenterology* 2002;122:889-96.
32. Saab S, Wang V. Recurrent hepatitis c following liver transplant, diagnosis, natural history and therapeutic options; *J Clin gastroentrol* 2003;37:155-63.
33. Forns x et al; Antiviral therapy of patients with decompensated cirrhosis to prevent recurrent hepatitis c after liver transplantation; *J Hepatol* 2003;39:389-96.
34. Chalasani N, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation. *Hepatology* 2005;41(2):289-98.
35. Ghabril M, Dickson R, Wiesner R. Improving Outcomes of Liver Retransplantation: An Analysis of Trends and the Impact of Hepatitis C Infection. *Am J of Transpl* 2008;8(2):404-11.
36. Salizzoni M, Lupo F, et al. Outcome of patients transplanted with liver for HCV positive donors. *Transpl proceed* 2001;33:1507-08.
37. Vargas HE, Laskus T, et al. Outcome of liver transplant in hepatitis C infected patients who receive HCV infected grafts. *Gastroenterology* 1999;117:149-53.
38. Validedeoglu E, Desai N, et al. Effect of donor Hepatitis C on graft survival. *Transpla proceed* 2001;33:3795-96.
39. Jain A, Orloff M, et al. Use of HBcAb positive grafts in HCV positive and negative recipients with the use of short course of HBIG and Lamivudine. *Transpl proceed* 2005;37:3187-89.
40. Morroquin CE, Marino G, et al. Transplantation in hepatitis C positive liver in hepatitis C positive C patients is equivalent to hepatitis C negative patients. *Liver transpl* 2001;7:762-68.
41. Ghobrial RM, Amersi F, Farmer DG, et al. Rapid and severe early HCV recurrence following adult living donor liver transplantation. *Am J Transplant* 2002;2(Suppl 3):163.
42. Gaglio PJ, Malireddy S, Levitt BS, et al. Increased risk of cholestatic hepatitis C in recipients of grafts from living versus cadaveric liver donors. *Liver Transpl* 2003;9:1028-35.
43. Sugawara Y, Kaneko J, Akamatsu N, et al. Living donor liver transplantation for end-stage hepatitis C. *Transplant Proc* 2004;36:1481-82.
44. Everson GT, Trotter J, Forman L, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005;42:255-62.
45. Rodriguez-Luna H, Vargas HE. Management of hepatitis C virus infection in the setting of liver transplantation. *Liver Transpl* 2005;11:479-89.
46. Garcia-RM, Forns X, Llovet JM, et al. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. *Hepatology* 2004;40:699-707.
47. Neumann UP, Berg T, Bahra M, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis CJ *Hepatol* 2004;41:830-36.
48. Carrion JA, Navasa M, Bosch J, et al. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. *Liver Transpl* 2006;12:1791-98.
49. Blasco A, Forns X, Carrion JA, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. *Hepatology* 2006;43:492-99.
50. Yilmaz N, Shiffman ML, Stravitz RT, et al. A prospective evaluation of fibrosis progression in patients with recurrent hepatitis C virus following liver transplantation. *Liver Transpl* 2007;13:975-83.
51. Samonakis DN, Cholongitas E, Thalheimer U, et al. Hepatic venous pressure gradient to assess fibrosis and its progression after liver transplantation for HCV cirrhosis. *Liver Transpl* 2007;13:1305-1311.
52. Marina Berenguer. Management of Hepatitis C Virus in the Transplant Patient. *Clin Liver Dis* 2007;11:355-76
53. Surakit P, David PN, Murali K, et al. Serum Fibrosis Markers Can Predict Rapid Fibrosis Progression After Liver Transplantation. for Hepatitis C. *Liver transplantation* 2008;14(9):1294-302.
54. Potthoff A, Sarhaddar J, Wiegand J, et al. Spontaneous resolution of chronic hepatitis C virus infection after antiviral treatment and relapse. *Hepatol Res* 2005;31:18-23.
55. Gruener NH, Jung MC, Ulsenheimer A, et al. Analysis of a successful HCVspecific CD8+ T-cell response in patients with recurrent HCV-infection after orthotopic liver transplantation. *Liver Transpl* 2004;10:1487-96.
56. Weston SJ, Leistikow RL, Reddy KR, et al. Reconstitution of hepatitis C virus-specific T-cell mediated immunity after liver transplantation. *Hepatology* 2005;41:72-81.
57. CG Nudo, RA Cortes, D Weppeler, et al. Effect of Pretransplant Hepatitis C Virus RNA Status on Posttransplant Outcome. *Transplant Proceed* 2008;40:1449-55.

Alcoholism and Liver Transplantation

INTRODUCTION

Alcoholic cirrhosis is one of the common causes of hepatic failure. Liver transplantation is the treatment of choice for patients with severe liver failure (Childs B and C). Relation between OLT and psychoactive substance abuse is an issue of increasing interest. An active substance use or dependency disorder has absolute contraindications for the placement of a patient on the waiting list.¹ Adults with alcoholism and substance abuse in remission should not be excluded from transplantation.² Many authors believe that 6 full months of abstinence in using psychoactive substances is essential to be placed on the transplantation wait list.³⁻⁵ While other authors reported that such criteria has no guarantee to predict or exclude a post-transplantation relapse^{6,7} to set the period of abstinence to 6 months seems excessively rigid, and in some cases it does not completely safeguard the health of the patient being assessed.^{8,9}

Chronic alcoholism is a direct cause of fatty liver, hepatitis, cirrhosis of liver and hepatocellular carcinoma. It contributes to the development of hepatitis B and C, uncovering of congenital hepatic disorders and predisposes to toxic liver injury.^{8,7} Alcohol does not produce end-stage liver disease in all chronic alcoholics.¹⁰ Previously treatment of alcoholic cirrhosis was limited to the control of complications of portal hypertension, but at present liver transplantation has become an acceptable option of treatment of alcoholic cirrhosis and its complications and transplanted patients have a better overall survival rate.¹¹⁻¹³ There are certain issues such as progressive alcoholic hepatitis^{14,15} and patients who are likely to continue to consume alcohol after transplantation, where indication and decision for liver transplantation are not clearly defined.

SOCIAL ISSUES RELEVANT TO ALCOHOLISM

Few reports mention that patients with ESLD due to alcohol are unworthy candidates for liver transplantation

as they are responsible for the cause of their liver disease.^{16,17} Even if they are considered for liver transplantation, they should have a lower priority on the waiting list for cadaver donor liver than others.^{18,19} Concern about live donation is that few potential donors believe that alcoholics are unworthy recipients and they will not donate their organs to an alcoholic.^{20,21} No matter what the social issue, it is clear that patients with alcoholic liver disease (ALD) tend to do well following liver transplantation and returns to work as frequently as other liver recipients.^{8,7}

RECIPIENT SELECTION

Selection criteria for the alcoholic recipient vary from center to center.²² It is always better to refer a patient too early for liver transplantation than too late when transplantation is no longer an option due to the severity of illness. Patients are usually referred to transplant center for evaluation when they develop complications such as variceal bleeding, ascites, or hepatic encephalopathy.^{8,7} Hypersplenism in the presence of decompensated alcoholic cirrhosis is associated with a greater likelihood of subsequent spontaneous bacterial peritonitis and variceal hemorrhage and should be included as an indication for referral.²³ Each patient is carefully evaluated for other risk factors such as HCV infection. When patients with HCV are evaluated for liver transplantation, a careful history will reveal that up to 35% are chronic alcoholics.²⁴ Perhaps the most difficult and still unresolved issue in the transplantation of alcoholic patients is what to do with the patient with alcoholic hepatitis. At present, most programs still refuse to transplant those with acute, decompensated alcoholic hepatitis.²⁶ Furthermore, the overall outcome of liver transplantation of patients with alcoholic hepatitis may be similar to patients with end-stage alcoholic liver disease lacking evidence of alcoholic hepatitis.²⁶

A multidisciplinary team including a psychologist and psychiatrist should carefully evaluate each and every alcoholic cirrhotic patient before being considered for liver transplantation.^{27,28} A psychiatrist is an important constituent of the team, as those with substance abuse have been identified to have more distress, less adaptive behavior skills, and more character pathology.²⁹ Although some have questioned the reliability of an alcoholic patient's history of alcohol consumption, at least one study indicates that such history obtained at the time of consideration of liver transplantation tends to be reliable.³⁰ The specific criteria used to determine candidacy typically includes a period of sobriety.³¹ The American Association for the Study of Liver Diseases guideline suggests it should be at least 6 months,³² and this interval is commonly followed by most of the centers. In spite of such recommendations, there is little evidence that length of pretransplant sobriety correlates with the likelihood of post-transplant recidivism.^{33,34} Some programs have also indicated that patients must go through outpatient treatment programs or attend and document attendance at Alcoholics Anonymous meetings.⁸⁷

LIVER TRANSPLANTATION

Although patients with end-stage ALD tend to have more advanced clinical liver disease at transplantation than patients transplanted for other end-stage liver diseases,^{35,36} the early outcome, survival rate and retransplantation rate is similar to that of other liver diseases.³⁷ Alcoholic cirrhosis patients over 50 years of age, who tend to have a longer initial hospitalization during post-transplantation and are at a higher risk of early mortality.³⁸ Longterm psychological and physical health in recipients is good.³⁹

Pretransplant psychiatric evaluation will determine what additional treatment and support is needed for the patient after transplantation. Some pretransplant problems such as spur cell anemia⁴¹ and polyneuropathy⁴² will resolve following liver transplantation, while others such as hypersplenism often persist. Cognitive function may also improve following transplantation of the alcoholic, although memory typically does not.⁴³ Alcoholic patients transplanted for ESLD have been reported to develop an acute postoperative confusional state lasting for 2-3 days leading to longer ICU stay. The mechanism of development of confusional state is not clear.⁴⁴ Post-transplant short and long term programs are needed to support continued abstinence in the recipient.⁴⁰

Patients transplanted for ESLD due to alcohol have a greater prevalence of post-transplant diabetes mellitus⁴⁵ and often require initial insulin therapy. Intensive insulin

management early during post-transplant care is crucial, and can contribute to a reduction of both intensive care and hospital length of stay. Bacterial infections also are more frequent in the alcoholic after transplantation.⁴⁶

The initial survival of patients transplanted for alcohol related ESLD is excellent,^{35,47-51} and appears to be unaffected by the return of the patient to modest drinking.^{38,49,50} Early postoperative clinical health status is similar in alcoholics and nonalcoholic patients.⁵² Longer pretransplant abstinence may improve long-term post-transplant outcomes.⁵⁰ According to UNOS data base, the overall long-term outcome in alcoholics may be poorer, in part explained by the greater severity of pretransplant illness⁵³ and an increase in late complications such as tumors, infections, and age-related disease.⁵⁴

RECURRENT DISEASE

Post-transplant alcohol drinking causes recurrent ALD specially includes fatty liver and pericellular fibrosis.^{49,55,56} Most of the patients do not return to the severity of drinking they experienced pretransplantation and recurrent ESLD is uncommon, although alcoholic hepatitis and cirrhosis have been reported,^{25,57} but graft loss from recidivism is uncommon.⁵⁴ Allograft cellular rejection is less common in the alcoholic than the nonalcoholic patients following OLT as the chronic alcoholics are intrinsically immunosuppressed.^{45,46,59} A return to alcohol consumption may or may not further reduce the risk of acute cellular rejection.^{58,60} Similarly, the incidence of chronic rejection in ALD also appears to be less,⁶¹ and may be further reduced in likelihood by alcohol consumption.⁶⁰

SOCIAL ISSUES AFTER TRANSPLANTATION

RECIDIVISM

Return of alcohol addiction following liver transplantation is considered a serious problem. History is not always useful and there may be few clues to its occurrence. Liver function tests are routinely done in all transplant patients but these tests are a poor indicator of recidivism.⁶² Detection of carbohydrate-deficient transferrin levels has been proposed as a marker of alcohol consumption,⁶³ but it does not appear to be reliable.⁶⁴ Patients transplanted for ESLD due to alcohol typically drink less alcohol than they did before transplantation,⁶⁵ recidivism is prevalent ranging from 8% to 33%.^{49,50,55,70,74} Other studies with short abstinence period report recidivism rates of 34%, 45%, and 66%⁶⁶ with relapse rates of 30 to 54% during a 1 to 3-year post-transplantation period.⁶⁷⁻⁶⁹

It is not related to the length of pretransplant sobriety.⁵⁴ However, some correlation has been reported between recidivism with shorter intervals of pretransplantation sobriety in some studies.^{71,72} Hence most transplant centers use a minimum of 6 months sobriety before transplantation. Other studies reported that the patients transplanted with acute alcoholic hepatitis, and consequently a shorter interval of pretransplantation sobriety, does not cause an unequivocal likelihood of recidivism.⁵⁷ The overall prevalence of drinking among alcoholic liver disease patients post-transplantation is similar to those transplanted for other liver diseases.^{65,70} Still it is controversial that alcohol consumption by the transplantation recipient has any significant effect on long-term outcome.⁷⁴ Fostering candor between the transplant team and the alcoholic patient seems crucial to care and a reduction of recidivism.⁷³

High risk of recidivism include:⁸⁷

- Family history of alcohol ingestion⁷⁵
- Male gender with an inadequate social environment⁴⁷
- Female gender with unemployment⁷⁸
- Poor living conditions associated with a history of suicide ideation
- Failure to participate in alcohol rehabilitation
- Past history of hospitalization for deaddiction of alcoholism⁷⁶
- Abuse of other drugs⁷⁷
- Earlier age for initial onset of drinking⁷¹
- Alcoholism with dual diagnosis.²⁹

COMPLIANCE

Compliance is rarely an issue in the post-transplantation period for alcoholic liver disease.⁶² Regular use of medication and OPD visits, overall general compliance is typically good and unaffected by recidivism, even if it should develop.⁷⁹ Quality of life usually improves post-transplantation,⁷¹ in conjunction with good social rehabilitation although there is more likelihood of post-transplantation marital separation.⁴⁵ Return to regular work varies in different studies. Few studies report it as less^{50,70} while others report it as comparable to those transplanted for nonalcoholic liver disease.^{80,81}

OTHER ISSUES

OSTEOPENIA

Osteopenia is common problem in almost all recipients and are at an increased risk of hepatic osteodystrophy, typically seen in the 1st 6 months to one year of transplant due to corticosteroids and nutritional issues.^{84,85} But the incidence is coming down after early withdrawal of

steroids in most transplant programs. Patients transplanted for alcoholic liver disease have an increased fracture risk in part due to alcoholism,⁸⁶ with up to 17% reporting fractures (often lumbar spine) during the first postoperative year.⁸⁷

MALIGNANCIES

Hematological and cutaneous malignancies are increased in prevalence in post-transplant period. Solid tumors are generally squamous cell type and are common in esophagus, oropharynx, lung and vulva. Recipients with predisposing conditions such as ulcerative colitis have an increased risk of colorectal cancer when transplanted for sclerosing cholangitis.^{82,83} Regular surveillance by dental, oropharyngeal examinations, pap smears, careful investigation and follow-up of new respiratory and esophageal symptoms is mandatory.⁸⁷

Gallimberti reported that the use of a time criteria alone for the selection of OLT patients with substance abuse disorder seems to be excessively rigid and restrictive. Strict adherence and a valid surrounding environment induce greater flexibility and improve the efficacy of the evaluation in selecting patients for transplantations.⁸⁸

REFERENCES

1. Jansen PL. New criteria for liver transplantation in adults: the combined Groningen and Rotterdam protocol. *Neth J Med* 1998;52:53.
2. Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. *Lancet* 1999;354:1636.
3. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: A report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997;3:628.
4. Bird GL, O'Grady JG, Harvey FA, et al. Liver transplantation in patients with alcoholic cirrhosis: Selection criteria and rates of survival and relapse. *Br Med J* 1990;301:15.
5. Miguet M, Monnet E, Vanlemmens C, et al. Predictive factors of alcohol relapse after orthotopic liver transplantation for alcoholic liver disease. *Gastroenterol Clin Biol* 2004;28:845.
6. Mackie J, Groves K, Hoyle A, et al. Orthotopic liver transplantation for alcoholic liver disease: A retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. *Liver Transpl* 2001;7:418.
7. Foster PF, Fabrega F, Karademir S, et al. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. *Hepatology* 2007;25:1469.
8. Alleman P, Burckhardt B, Dufour JF. Transplantation for alcoholic liver disease: The wrong arguments. *wiss Med Wkly* 2002;132:296.
9. Webb K, Neuberger J. Transplantation for alcoholic liver disease. *BMJ* 2004;329:63.
10. Maddrey WC. Alcohol-induced liver disease. *Clin Liver Dis* 2000;4:115-31.

11. Starzl TE, Van Thiel D, Tzakis AG, et al. Orthotopic liver transplantation for alcoholic liver disease. *JAMA* 1988;260:2542-44.
12. Van Thiel DH, Carr B, Iwatsuki S, et al. Liver transplantation for alcoholic liver disease, viral hepatitis and hepatic neoplasms. *Transplant Proc* 1991;23:1917-21.
13. Kumar S, Stauber RE, Gavalier JS, et al. Orthotopic liver transplantation for alcoholic liver disease. *Hepatology* 1990;11:159-64.
14. Morgan MY. The prognosis and outcome of alcoholic liver disease. *Alcohol Alcohol Suppl* 1994;2:335-43.
15. Haber PS, Warner R, Seth D, et al. Pathogenesis and management of alcoholic hepatitis. *J Gastroenterol Hepatol* 2003;18:1332-44.
16. Martens W. Do alcoholic liver transplantation candidates merit lower medical priority than nonalcoholic candidates? *Transpl Int* 2001;14:170-75.
17. Beresford T. The limits of philosophy in liver transplantation. *Transpl Int* 2001;14:176-79.
18. Neuberger J. Transplantation for alcoholic liver disease: a perspective from Europe. *Liver Transpl Surg* 1998;5(S 1):S51-7.
19. Glannon W. Responsibility, alcoholism, and transplantation. *J Med Philos* 1998;23:31-49.
20. Ubel PA, Jepson C, Baron J, et al. Allocation of transplantable organs: do people want to punish patients for causing their illness? *Liver Transpl* 2001;7:600-07.
21. Rudow DL, Russo MW, Hafliger S, et al. Clinical and ethnic differences in candidates listed for liver transplantation with and without potential living donors. *Liver Transpl* 2003;9:254-59.
22. Snyder SL, Drooker M, Strain JJ. A survey estimate of academic liver transplant teams' selection practices for alcohol-dependent applicants. *Psychosomatics* 1996;37:432-37.
23. Liangpunsakul S, Ulmer BJ, Chalasani N. Predictors and implications of severe hypersplenism in patients with cirrhosis. *Am J Med Sci* 2003;326:111-16.
24. Levy MT, Chen JJ, McGuinness PH, et al. Liver transplantation for hepatitis C-associated cirrhosis in a single Australian centre: referral patterns and transplant outcomes. *J Gastroenterol Hepatol* 1997;12:453-59.
25. Mohanty SR, La Brecque DR, Mitros FA, et al. Liver transplantation for disulfiram-induced hepatic failure. *J Clin Gastroenterol* 2004;38:292-95.
26. Tome S, Martinez-Ray C, Gonzalez-Quintela A, et al. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002;36:793-98.
27. Zibari GB, Edwin D, Wall L, et al. Liver transplantation for alcoholic liver disease. *Clin Transplant* 1996;10:676-79.
28. Stilley CS, Miller DJ, Gayowski T, et al. Psychological characteristics for liver transplantation: Differences according to history of substance abuse and UNOS listing. *J Clin Psychol* 1999;55:1287-97.
29. Tripp LE, Clemons JR, Goldstein RR, et al. Drinking patterns in liver transplant recipients. *Psychosomatics* 1996;37:249-53.
30. Yates WR, Labrecque DR, Pfab D. The reliability of alcoholism history in patients with alcohol-related cirrhosis. *Alcohol Alcohol* 1998;33:488-94.
31. Krom RA. Liver transplantation and alcohol: Who should get transplants? *Hepatology* 1994;20:28S-32S.
32. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg* 1997;3:628-37.
33. Di Martini A, Jain A, Irish W, et al. Outcome of liver transplantation in critically ill patients with alcoholic cirrhosis: Survival according to medical variables and sobriety. *Transplantation* 1998;66:298-302.
34. Yates WR, Martin M, Labrecque D, et al. A model to examine the validity of the 6-month abstinence criterion for liver transplantation. *Alcohol Clin Exp Res* 1998;22:513-17.
35. Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000;69:1873-81.
36. Stell DA, McAlister VC, Thorburn D. A comparison of disease severity and survival rates after liver transplantation in the United Kingdom, Canada, and the United States. *Liver Transpl* 2004;10:898-902.
37. McCurry KR, Baliga P, Merion RM, et al. Resource utilization and outcome of liver transplantation for alcoholic cirrhosis. A case-control study. *Arch Surg* 1992;127:772-76.
38. Gerhardt TC, Goldstein RM, Urschel HC, et al. Alcohol use after liver transplantation for alcoholic cirrhosis. *Transplantation* 1996;62:1060-63.
39. Beresford TP, Schwartz J, Wilson D, et al. The short-term psychological health of alcoholic and non-alcoholic liver transplant recipients. *Alcohol Clin Exp Res* 1992;16:996-1000.
40. DiMarini A, Weinrieb R, Fireman M. Liver transplantation in patients with alcohol and other substance use disorders. *Psychiatr Clin N Am* 2002;25:195-209.
41. Malik P, Bogetti D, Sileri P, et al. Spur cell anemia in alcoholic cirrhosis: cure by orthotopic liver transplantation and recurrence after liver graft failure. *Int Surg* 2002;87:201-04.
42. Spahn TW, Lohse AW, Otto G, et al. Remission of severe alcoholic polyneuropathy after liver transplantation. *Z Gastroenterol* 1995;33:711-14.
43. Aria AM, Tarter RE, Starzl TE, et al. Improvement in cognitive functioning of alcoholics following liver transplantation. *Alcohol Clin Exp Res* 1991;15:956-62.
44. Buis CI, Wiesner RH, Krom RA, et al. Acute confusional state following liver transplantation for alcoholic liver disease. *Neurology* 2002;59:601-05.
45. Abosh D, Rosser B, Kaita K, et al. Outcomes following liver transplantation for patients with alcohol-versus nonalcohol-induced liver disease. *Can J Gastroenterol* 2000;14:851-55.
46. Farges O, Saliba F, Farhamant H, et al. Incidence of rejection and infection after liver transplantation as a function of primary disease: possible influence of alcohol and polyclonal immunoglobulins. *Hepatology* 1996;23:240-48.
47. Platz KP, Mueller AR, Spree E, et al. Liver transplantation for alcoholic cirrhosis. *Transpl Int* 2000;13(Suppl 1):S127-30.
48. Osorio RW, Friesse CE, Ascher NL, et al. Orthotopic liver transplantation for end-stage alcoholic liver disease. *Transpl Proc* 1993;25:1133-34.
49. Burra P, Mioni D, Cecchetto A, et al. Histological features after liver transplantation in alcoholic cirrhotics. *J Hepatol* 2001;34:716-22.
50. Pageauz GP, Michel J, Coste V, et al. Alcoholic cirrhosis is a good indication for liver transplantation, even for case of recidivism. *Gut* 1999;45:421-26.
51. Mackie J, Groves K, Hoyle A, et al. Orthotopic liver transplantation of alcoholic liver disease: a retrospective

- analysis of survival, recidivism, and risk factors predisposing to recidivism. *Liver Transpl* 2001;7:418-27.
52. Knechtle SJ, Fleming MF, Barry KL, et al. Liver transplantation for alcoholic liver disease. *Surgery* 1992;112:694-701.
 53. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database. *Liver Transpl* 2004;10:886-97.
 54. Jain A, DiMartini A, Kashyap R, et al. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. *Transplantation* 2000;70:1335-42.
 55. Yusoff IF, House AK, De Boer WB, et al. Disease recurrence after liver transplantation in Western Australia. *J Gastroenterol Hepatol* 2002;17:203-07.
 56. Tang H, Boulton R, Gunson B, et al. Patterns of alcohol consumption after liver transplantation. *Gut* 1998;43:140-45.
 57. Conjeevaram HS, Hart J, Lissos TW, et al. Rapidly progressive liver injury and fatal alcoholic hepatitis occurring after liver transplantation in alcoholic patients. *Transplantation* 1999;67:1562-68.
 58. Lucey MR, Carr K, Beresford TP, et al. Alcohol use after liver transplantation in alcoholics: A clinical cohort follow-up study. *Hepatology* 1997;25:1223-47.
 59. Bathgate AJ, Hynd P, Sommerville D, et al. The prediction of acute cellular rejection in orthotopic liver transplantation. *Liver Transpl Surg* 1999;5:475-79.
 60. Van Thiel DH, Bonet H, Gavalier J, et al. Effect of alcohol use on allograft rejection rates after liver transplantation for alcoholic liver disease. *Alcohol Clin Exp Res* 1995;19:1151-55.
 61. Berlakovich GA, Steininger R, Herbst F, et al. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. *Transplantation* 1994;58:560-65.
 62. Berlakovich GA, Steininger R, Herbst F, et al. Transplantation for alcoholic cirrhosis: how does recurrence of disease harm the graft? *Transpl Int* 1994;7(Suppl 1):S123-27.
 63. Berlakovich BA, Windhager T, Freundorfer E, et al. Carbohydrate deficient transferrin for the detection of alcohol relapse after orthotopic liver transplantation for alcoholic cirrhosis. *Transplantation* 1999;67:1231-35.
 64. Heinemann A, Sterneck M, Kuhlencordt R, et al. Carbohydrate-deficient transferrin: diagnostic efficacy among patients with ESLD before and after liver transplantation. *Alcohol Clin Exp Res* 1998;22:1806-12.
 65. Pereira SP, Howard LM, Mulesan P, et al. Quality of life after liver transplantation for alcoholic cirrhosis. *Liver Transpl* 2000;6:762-68.
 66. Maldonado JR. *Clin Liver Dis* 1997;1:305.
 67. Tomas S, Martinez-Rey G, Gonzalez-Quintela A, et al. *Hepatol* 2002;36:793.
 68. Gish RG, Lee A, Brooks L, et al. *Liver Transplant* 2001;7:581.
 69. Pageaux GP, Michel J, Coste V. *Gut* 1999;45:421.
 70. Keefe EB, Esquivel CO. Controversies in patient selection for liver transplantation. *West J Med* 1993;159:586-93.
 71. Bravata DM, Olkin I, Barnato AE, et al. Employment and alcohol use after liver transplantation for alcoholic and nonalcoholic liver disease: A systematic review. *Liver Transpl* 2001;7:191-203.
 72. Foster PF, Fabrega F, Karademir S, et al. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. *Hepatology* 1997;25:1469-77.
 73. Weinrieb RM, Van Horn DH, McLellan AT, et al. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. *Liver Transpl* 2000;6:769-76.
 74. Beresford TP, Martin B, Alfors J. Developing a brief monitoring procedure for alcohol-dependent graft recipients. *Psychosomatics* 2004;45:220-23.
 75. Jauhar S, Talwalkar JA, Schneekloth T, et al. Analysis of factors that predict alcohol relapse following liver transplantation. *Liver Transpl* 2004;10:408-11.
 76. Karman JF, Sileri P, Kamuda D, et al. Risk factors for failure to meet listing requirements in liver transplant candidates with alcoholic cirrhosis. *Transplantation* 2001;71:1210-13.
 77. DiMartini A, Day N, Dew MA, et al. Alcohol use following liver transplantation: a comparison of follow-up methods. *Psychosomatics* 2001;42:55-62.
 78. Tringali RA, Trzepacz PT, DiMartini A, et al. Assessment and follow-up of alcohol-dependent liver transplantation patients. A clinical cohort. *Gen Hosp Psychiatry* 1996;18(6 Suppl):70S-77S.
 79. Fabrega E, Crespo J, Casafont F, et al. Alcoholic recidivism after liver transplantation for alcoholic cirrhosis. *J Clin Gastroenterol* 1998;26:204-06.
 80. Cowling T, Jennings LW, Goldstein RM, et al. Societal reintegration after liver transplantation: Findings in alcohol-related and nonalcohol-related transplant recipients. *Ann Surg* 2004;239:93-98.
 81. Cowling T, Jennings LW, Jung GS, et al. Comparing quality of life following liver transplantation for Laennec's versus non-Laennec's patients. *Clin Transplant* 2000;14:115-20.
 82. Benloch S, Berenguer M, Prieto M, et al. De novo internal neoplasms after liver transplantation: Increased risk and aggressive behavior in recent years? *Am J Transplant* 2004;4:596-604.
 83. Kenngott S, Gerbes AL, Schaure R, et al. Rapid development of esophageal squamous cell carcinoma after liver transplantation for alcohol-induced cirrhosis. *Transpl Int* 2003;16:639-41.
 84. Ng TM, Bajjoka IE. Treatment options for osteoporosis in chronic liver disease patients requiring liver transplantation. *Ann Pharmacother* 1999;33:233-35.
 85. Carey EJ, Balan V, Kremers WK, et al. Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. *Liver Transpl* 2003;9:1166-73.
 86. Mays E, Fontanges E, Fourcade N, et al. Bone loss after orthotopic liver transplantation. *Am J Med* 1994;97:445-50.
 87. Rowen K Zetterman. Liver Transplantation for Alcoholic Liver Disease. *Clin Liver Dis* 2005;9:171-81.
 88. L Gallimberti, G Forza, P Angeli, et al. Alcohol- and substance-dependent subjects: The correlated factors in qualifying for liver transplantation. *Transplant Proceed* 2007;39:1861-63.

Autoimmune Liver Diseases

CHAPTER 42

INTRODUCTION

The disease progression is slow in autoimmune liver diseases and episodes of decompensation are less frequent. Outcome after liver transplantation is good.

AUTOIMMUNE LIVER DISEASES

- Autoimmune hepatitis (AIH)
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)

AUTOIMMUNE HEPATITIS (AIH)

Autoimmune hepatitis

- Autoimmune disease
- M/F: 3.6:1
- Progressive fatigue, jaundice
- 30-40% of patients present with acute symptoms
- Some patients have associated with PBC or PSC (overlap syndrome)
- Elevated AST and ALT
- Elevated Ig G
- Elevated antinuclear antibody (type 1)
- Elevated liver-kidney antimicrosomal antibody (type 2) Histology
 - Mononuclear portal tract infiltration with more plasma cells
 - Interface hepatitis with varying degrees of portal and bridging fibrosis
- Associated with HLA-A1,B8,DR3,DR4¹
- Liver biopsy helps in diagnosis and for assessing the severity of the disease.
- HCV Hepatitis and Wilson's disease have to be ruled out.²

TREATMENT

Before the introduction of steroids, 5 year survival was 5-10%. At present > 80% survive for 20 years with recent drugs and liver transplantation.

Drugs

- Prednisolone
- Azathioprine
- Cyclosporine
- Tacrolimus (FK-506)
- Mycophenolate mofetil (MMF)

Indication of Medical Treatment³

Medical treatment controversial for milder form of disease. It is indicated in the following conditions:

- AST and ALT >10 times elevated
- AST and ALT >5 times and Gamma globulins > 2 times elevated
- Acute onset with complications
- Liver biopsy shows bridging necrosis

Standard Therapy

Prednisolone is used in patients with diabetes mellitus and patients with less bone density. Combination of prednisolone and azathioprine is used in patients with portal hypertension, thrombocytopenia or leukopenia. Treatment response is seen within 3-4 weeks. AST and ALT decreases to < 2 times, then gradual tapering of drugs may be attempted and maintenance dose is continued. Drugs should be maintained for long time when the liver biopsy shows continued presence of portal and interface hepatitis. Resolution of histological changes in liver takes 3 to 4 months.

Rescue Therapy

20% of the patients fail to respond to standard therapy, 10-12% have incomplete response and 8-9% patients, disease progresses during treatment. These patients require addition of immunosuppressive agents like cyclosporine, FK-506 or mycophenolate mofetil (MMF).

LIVER TRANSPLANTATION IN AIH

AIH is a good indication for liver transplantation.

INDICATION FOR LIVER TRANSPLANTATION

- Presented as cirrhosis with complication like portal hypertension and variceal bleeding.
- Failure to respond to standard and rescue therapy
- Patients with deteriorating clinical, laboratory and histological course.

RECURRENCE OF DISEASE AFTER TRANSPLANTATION

Significance of recurrent autoimmune hepatitis (AIH) after transplantation remains controversial. Exclusion of acute rejection, viral hepatitis, drug effects, and biliary obstruction is imperative before making a diagnosis of recurrent disease. Risk of recurrence is increased over time as immunosuppression is reduced, and longer follow-up is required to assess the impact of recurrent disease upon patient and graft survival. Recurrent disease is defined by sustained elevation of transaminases of at least 1-month duration, consistent histopathology, and positive autoimmune markers.⁴ Recurrence of symptoms is

Primary Biliary Cirrhosis (PBC)

- Autoimmune disease
- F/M:9:1
- Prevalence 1 in 4000 in USA and UK.
- PBC in the first degree relatives is 500 times more, but exact data is lacking regarding the familial predisposition.
- Association of viral etiology in PBC basing on the response to lamivudine and zidovudine.⁵
- No clear association of HLA genotypes, But HLA – B8 was found in Japanese patients.
- Antimitochondrial antibodies (AMA) are present in 95% of patients. Correlation between AMA and bile duct injury is unclear, but immune attack of aberrantly expressed antigenic molecules on biliary epithelial cells is possible.
- Lymphocytic destruction of medium-sized bile ducts expressing increased amounts of Class I and II antigens is characteristic.⁶

associated with abnormal liver chemistry tests and positive serology. Liver biopsy reveals periportal inflammation and interface hepatitis. Clinical, biochemical, and histologic parameters may improve after increasing corticosteroid dose and introduction of antimetabolites.

Reported recurrence rates are up to 33% and are based on well-defined criteria. Recurrence rate is influenced by differences in the immunosuppression and length of follow-up. Weaning of immunosuppression should be approached with caution, but recurrent disease appears to respond to an increase in corticosteroids with or without antimetabolites in most cases. The potential benefit of tacrolimus over cyclosporine in the prevention of recurrent disease is not clear. The incidence of acute rejection and steroid-resistant rejection is higher in patients transplanted for autoimmune hepatitis than in patients transplanted for diseases without an autoimmune basis. Few patients may require retransplantation.

PRIMARY BILIARY CIRRHOSIS (PBC)

PBC (**Figures 42.1A and B**) is manifested commonly in middle age females, presenting as fatigue, jaundice, portal hypertension and hypercholesteremia

Diagnosis of PBC

- Elevated IgM level
- Antimitochondrial antibody (AMA) positive in 95% cases.

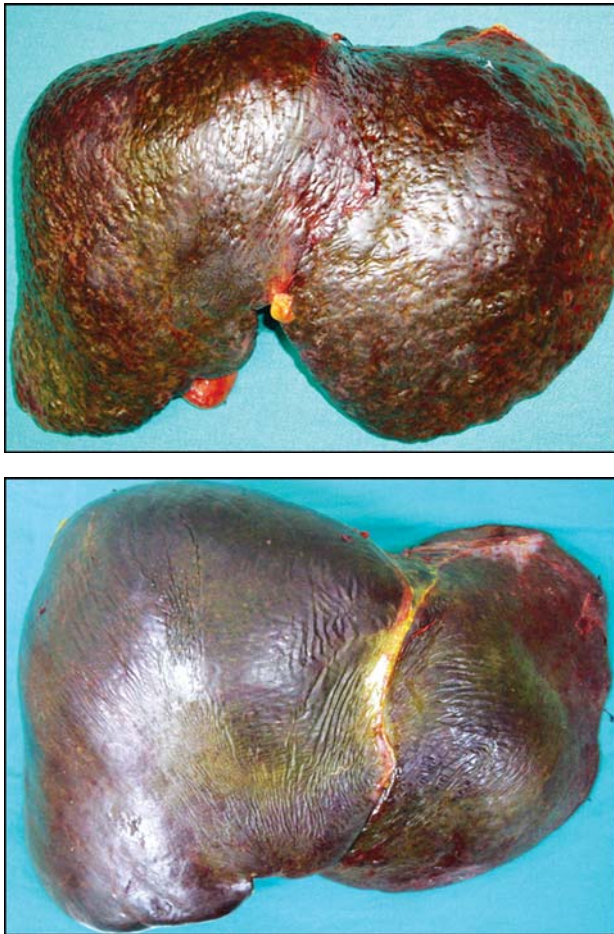
Liver biopsy in unnecessary and reserved for:

- Uncertainty in diagnosis
- Lack of AMA
- PBC overlap syndrome with AIH⁷
- Poor response to treatment
- Histology-chronic non-suppurative inflammation, fibrosis and eventual destruction of interlobular bile ducts.

TREATMENT

Medical Management

UDCA (Ursodeoxycholic acid), at a dose of 12-15 mg/kg/day⁸ is given in multiple doses (three or four daily). Improvement is noticed in symptoms and liver function tests.¹⁹ It causes release of bile acids from hepatocytes into biliary canaliculi and has some immunomodulatory effect.⁹ Other drugs like Colchicine (may be useful in combination with UDCA), prednisolone, azathioprine, cyclosporine, methotrexate and pencillamine were tried, but failed to show any improvement.



Figures 42.1A and B: Enlarged recipient liver in primary biliary cirrhosis

Surgical Management

Liver transplantation is the definite surgical treatment for PBC. The timing of liver transplantation is important as the disease progression is slow and decompensation is less frequent.

INDICATIONS FOR LIVER TRANSPLANTATION IN PBC

- Serum bilirubin > 5.9 mg/dl
- Index liver biopsy shows cirrhosis
- Presence of HCC
- Complications of cirrhosis like variceal bleeding or recurrent cholangitis.

Recurrence of PBC can occur after liver transplantation. Recurrent form cannot be caused by a process that is directly HLA restricted.¹⁰ Recurrent disease is manifested as granulomatous disruption of bile ducts, mononuclear infiltrates, lymphoid aggregates, portal tract granuloma, and ductopenia. Long term cyclosporine/azathioprine

and MMF may modify expression of recurrent disease within the graft. Low dose tacrolimus is inadequate to suppress the underlying immunologic abnormalities in PBC. Cyclosporine may be preferable to tacrolimus in patients transplanted for PBC.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Primary sclerosing cholangitis (PSC)

- Unknown etiology
- Most common in males
- Incidence: 1.3 and prevalence: 8.5 per 100,000 population¹¹
- M/F: 2.5-3/1
- Commonly associated with inflammatory bowel disease (IBD) in 70-90% cases particularly ulcerative colitis.
- 5-10% of patients of Ulcerative colitis are associated with IBD¹²
- Progressive liver disease is seen in ¾ of the patients and median survival is 18 years.¹³
- Long standing cases develop cholangiocarcinoma
- 2 types: Small duct and large duct type.
- Small duct type has better survival rates.¹⁴

MAYO CLINIC RISK SCORE FOR ASSESSING PROGNOSIS OF PSC¹³

$R = 0.03 \times \text{age (years)} + \text{Log bilirubin mg/dl} + 0.54 \times \text{logAST IU/L} + 1.24 \times \text{H/O variceal bleeding} - 0.84 \times \text{albumin g/dl}.$

DIAGNOSIS

- Pruritus, fatigue, jaundice and recurrent cholangitis
- Increased alkaline phosphatase and GGT
- ERCP/MRCP—Localized or multifocal strictures with intervening dilated or normal bile duct segments of intrahepatic and extrahepatic bile ducts
- Liver biopsy-histology: inflammation, fibrosis and obliterated bile ducts.

MANAGEMENT

- No specific treatment.
- UDCA: 10-15 mg/kg/day even higher doses have given better improvement in liver function in one series.¹⁵
- Infection—Usually E.coli, Pseudomonas, Enterococci, bacteroides
 - Treated with broad spectrum antibiotics
 - Long-term prophylaxis with ampicillin or ciprofloxacin in recurrent infections

Recurrent autoimmune and metabolic diseases after LTX¹⁸

Disease	Diagnosis	5 years incidence	Effect on graft survival	Risk factors	Treatment	Response to treatment
AIH	Autoantibodies IG elevated histology	30%	moderate	HLA absence of steroids	Steroids	Variable
PBC	AMA histology	40%	minimal	tacrolimus	UDCA	Unknown
PSC	Exclude non-anastomotic strictures	30%	significant	Intact colon	UDCA	Poor
Cryptogenic Alcohol	— History blood tests	40% 20% graft damage	Small Small	Uncertain Alcoholism Substance abuse	Nil specific Abstinence	Good
NASH	Clinical ultrasound	—	Moderate	Obesity Drugs Diabetes Small bowel surgery	Weight loss correction of bowel anatomy	Good

(**Abbreviations:** AMA, antimitochondrial antibodies; UDCA, ursodeoxycholic acid; IG, immunoglobulin; HLA, human leukocyte antigen; NASH, nonalcoholic steatohepatitis.) (Copyright: "Reprinted with permission of John Wiley and Sons, Inc.")

- Bile for culture should be obtained during endoscopic procedures
- Biliary strictures: Endoscopic or percutaneous dilatation and drainage by placing plastic stents or temporary ENBD in case of acute cholangitis.
- Sometimes endoscopic procedure is difficult due to dense and fibrotic strictures.
- Surgical drainage is controversial in modern era unless isolated extrahepatic segment of bile duct involved.
- Chronic recurrent cholangitis: liver transplantation
- 5 years survival is >80% for liver transplantation after PSC.¹⁶
- PSC can recur in the graft after many years.

Complications of PSC

- Inflammatory bowel disease
- Cholangiocarcinoma
- Hepatocellular carcinoma
- Colorectal cancers
- Osteoporosis
- Portal hypertension

In a retrospective study of 100 patients transplanted for PSC, Jeyarajah et al. found recurrent disease in 15.7% and chronic rejection in 13%.¹⁷

OVERLAP SYNDROME

The term "overlap syndrome" is used to describe variant forms of autoimmune hepatitis (AIH) which present with characteristics of AIH and primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Standardization

of diagnostic criteria for overlap syndromes has not been achieved so far, since these disorders are uncommon. It remains unclear whether these overlap syndromes form distinct disease entities or are only variants of the major immune hepatopathies.^{20,21} The AIH-PBC overlap syndrome is the most common form, affecting almost 10% of adults with AIH or PBC. Single cases of AIH and autoimmune cholangitis (AMA-negative PBC) overlap syndrome have also been reported. The AIH-PSC overlap syndrome is predominantly found in children, adolescents and young adults with AIH or PSC. Overlap syndromes show a progressive course towards liver cirrhosis and liver failure without treatment.²² Therapy for overlap syndromes is empiric, since controlled trials are not available in these rare disorders. Anticholestatic therapy with ursodeoxycholic acid is usually combined with immunosuppressive therapy with corticosteroids and/or azathioprine in both AIH-PBC and AIH-PSC overlap syndromes.²² In end-stage disease, liver transplantation is the treatment of choice.

REFERENCES

1. Donaldson PT, Doherty DG, Hayllar KM, et al. Susceptibility to autoimmune chronic active hepatitis: Human Leukocyte antigens DR4 and A1-B8-DR3 are independent risk factors. *Hepatology* 1999;13:701-06.
2. Czaja AJ, Carpenter HA. Histological findings in chronic hepatitis C with autoimmune features. *Hepatology* 1997;26:459-66.
3. Henegan MA, McFarlane IG. Current and Novel immunosuppressive therapy for autoimmune hepatitis. *Hepatology* 2002;35:7-13.

4. Prados E, Cuervas-Mons V, De La Mata M, et al. Outcome of autoimmune hepatitis after liver transplantation. *Transplantation* 1998;66:1645.
5. Mason AL, Far GH, Xu L, et al. Pilot studies of single and combination anti retroviral therapy in patients with primary biliary cirrhosis. *Am J of gastroenterology* 2004;99:2348-55.
6. Lee YM, Kaplan MM. Primary biliary cirrhosis. In Friedman LS, Keefe EB (eds): *Handbook of Liver Disease*. Edinburgh, Churchill Livingstone 1998,197.
7. Zein CO, Angulo P, Lindor KD. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis? *Clin Gastroenterol Hepatol* 2003;1:89-95.
8. Lindor KD, Dickson ER, Baldus WP, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. *gastroenterol* 1994; 106:1284-90.
9. Heathcote EJ. Management of primary biliary cirrhosis. *Hepatology* 2000;31:1005-13.
10. Liermann GRF, Evangelista GC, McMaster P, et al. Transplantation for primary biliary cirrhosis:retrospective analysis of 400 patients in a single centre. *Hepatology* 2001;33:22-27.
11. Boberg KM, Aadland E, Jahnsen J, et al. H.Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol.* 1998;33(1):99-103.
12. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. *Semin Liver Dis* 1991;11(1):31-39.
13. Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut.* 2002;51(4):562-66.
14. Björnsson E, Boberg KM, Cullen S, et al. Patients with small duct primary sclerosing cholangitis have a favourable long term prognosis. *Gut* 2002;51(5):731-35.
15. Mitchell SA, Bansl DS, Hunt N, et al. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology* 2001;121(4):900-07.
16. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database. *Liver Transpl* 2004;10(7):886-97.
17. Jeyarajah DR, Netto GJ, Lee SP, et al. Recurrent primary sclerosing cholangitis after orthotopic liver transplantation. *Transplantation* 1998;66:1300.
18. J Neuberger. Chronic allograft dysfunction: Diagnosis and management. Is it always progressive? *Liver Transplantation* 2005;11:63-68.
19. A Crosignani, PM Battezzati, P Invernizzi, et al. Clinical features and management of primary biliary cirrhosis. *World J Gastro-enterol* 2008;14(21):3313-27.
20. Czaja AJ. The variant forms of autoimmune hepatitis. *Ann Intern Med* 1996;125:588-98.
21. Poupon R. Autoimmune overlapping syndromes. *Clin Liver Dis* 2003;7:865-78.
22. C Rust, U Beuers. Overlap syndromes among autoimmune liver diseases. *World J Gastroenterol* 2008;14(21):3368-73.

Acute Liver Failure

Synonym: Fulminant Hepatic Failure

INTRODUCTION

Acute liver failure results when loss of liver function, caused by rapid death or injury to a large proportion of hepatocytes, leaves insufficient parenchymal mass to sustain life. ALF is defined as the development of hepatic encephalopathy within 8 weeks of jaundice in a patient who has no prior history of liver disease.

ALF accounts for approximately 5% of all LTXs in United States and 11% in Europe. ALF was 1st described in 1950 as a distinct clinical entity.¹ ALF can be divided into 3 subgroups such as **Hyperacute** (develop encephalopathy within 7 days of onset of jaundice) **Acute** (develop encephalopathy within 8-28 days of onset of jaundice) and **Subacute**: (develop encephalopathy within 5-12 weeks of onset of jaundice).

Course of the disease is very aggressive as a result of the rapid cellular damage that can lead to coma and death caused by multiorgan failure.² It is a major challenge to hepatic team as possibility of multiorgan failure and death can be prevented from early intervention.

EPIDEMIOLOGY OF ALF

ALF IN ASIAN COUNTRIES

In USA, ALF accounts for less than 10% of all liver transplantations. In contrary it accounts for more than two third of transplants in Asia.³ ALF is most commonly drug-induced in the West, but in Asia it is caused by viral hepatitis. Most common cause is acute exacerbations of chronic HBV, which is endemic in countries including Hong Kong, Taiwan, China and Hepatitis E endemic in India.⁴

Acute exacerbation of Chronic HBV may occur:⁵

- Spontaneously
- Due to mutant virus

- Superinfection with other viruses like HCV and HDV

In Western case series of HCV (non-A non-B) fulminant hepatitis, less than 12% were positive for HCV-RNA.⁶ But in Taiwan and China, this figure was 50% and above 50%, respectively.⁷ Similarly the incidence of HCV is increasing in Japan.

Flares of chronic HBV may be spontaneous, represent a secondary response to increased levels of replicating wild-type or mutant virus, occur after immuno-suppressive and cytotoxic therapy, or occur following superinfection with other hepatotropic viruses such as hepatitis D and HCV. Particularly severe exacerbations have been reported in patients who have pre-core mutant HBV infection.^{4,5}

ALF IN USA AND UK

In USA, ALF affects approximately 2000 people per year^{8,88} and 39% of ALF are caused by reported to be caused by acetaminophen (paracetamol) poisoning, and only a minority was caused by viral hepatitis.^{9,88} In USA, acetaminophen poisoning was unknown before 1980 but now it is the commonest cause of ALF and is most commonly seen in middle aged women.¹⁰

In United Kingdom, ALF is relatively uncommon as compared to USA, causing fewer than 500 deaths and less than 5% of liver transplantations per year.¹¹ According to the UK National Transplant Database, between 1995 and 1998 there was an almost 80% increase in the number of patients who had acetaminophen-induced ALF listed for a liver transplant.¹² Acetaminophen poisoning is the commonest cause of ALF accounting for 70% of cases.¹² Most cases of acetaminophen overdose in the UK are due to deliberate self-harm rather than unintentional as in USA.¹³ In fact, the UK has the highest rate of deliberate self harm by acetaminophen use in the world.¹⁴ Up to 10% of cases

of acetaminophen self-poisoning develop severe liver damage, and less than 2% will develop ALF, the worst outcomes being in patients with concurrent alcohol use.¹⁵

Common causes of ALF^{10,19,20,88}

- Drug induced: In USA, Acetaminophen (paracetamol) is the most common cause
- Other drugs:
 - Bromfenac and Troglitazone
 - Trimethoprim, Propylthiouracil,
 - Antitubercular drugs-INH, Rifampin, Disulfiram,
 - Anticonvulsants: Phenytoin, Carbamazepine, Phenobarbital,
 - Halothane, NSAIDs, Ketoconazole
 - Herbal medicines (chaparral and Teucrium polium)
 - Recreational drugs Ecstasy (3,4-methylene-dioxymethamphetamine) Cocaine
- Infection: Viral etiology: HBV, HAV, HCV and HEV Unusual viral causes: HSV, EBV, CMV and Varicella-zoster.
- Inherited/metabolic: Wilson's disease, Tyrosinemia, Galactosemia, Fatty acid oxidation defect
- Vascular: Budd-Chiari syndrome, Ischemic hepatitis
- Autoimmune hepatitis
- Idiopathic
- Malignancy/Leukemia
- Amanita phylloides
- Pregnancy

In 1998, UK Medicines Control Agency introduced legislation to reduce availability of acetaminophen and aspirin at the counters.⁸⁸ Under this legislation, pharmacies were limited to selling a maximum of 32 tablets of paracetamol (total 16 g) per sale and maximum allowable sale for other retailers was reduced from 24 to 16 tablets.¹⁶ In the 2 years immediately after the legislation (i.e., between 1998 and 2000) total acetaminophen sales in the United Kingdom fell by 41%.¹⁷ During 2001-2002, the percentage of emergency liver transplantations performed for acetaminophen-induced ALF decreased from 38 to 16%. In the same period, the number of patients listed for seronegative hepatitis rose by more than 60%.¹⁸

PATHOPHYSIOLOGY

ALF occurs when the rate of hepatocyte death is more than the rate of hepatocyte regeneration as a result of varied etiology that lead to a combination of apoptosis or necrosis.²¹

APOPTOSIS

It is associated with nuclear shrinkage but without cell membrane rupture. Therefore there is no release of intracellular content and no subsequent secondary inflammation.²¹ Apoptosis follows activation of caspases (cysteine proteases) (after oxidative mitochondrial damage). The caspase cascade is activated by various cytokines such as tumor necrosis factor-alpha and Fas ligand through receptors on the hepatocyte cell membrane.²² Example of necrotic ALF is acetaminophen (paracetamol) toxicity. Any insult that can induce apoptosis may also lead to cell death by necrosis, especially if the level of mitochondrial damage is such that ATP stores are depleted.²¹

NECROSIS

It causes ATP exhaustion resulting in cellular swelling that eventually lyses with release of intracellular content and consequent secondary inflammation.¹ Ischemia due to any etiology results in necrosis. Any process resulting in marked oxidative stress tend to produce necrotic rather than apoptotic cell death, because of severe mitochondrial damage and also inhibition of the proapoptotic caspase cascade.²³⁻²⁵

Other Factors

Regulating pathway of hepatocyte death^{21,88}

- Nitric oxide
- Antioxidants such as glutathione, tyrosine kinases, transcription factors
- Interferon, interleukins (IL-10 and IL-12) and natural killer cell-derived IL-5.

Presentation^{26,88}

- Encephalopathy and raised intracranial pressure
- Coagulopathy
- Renal impairment
- Hemodynamic instability and Hypotension
- Sepsis
- Multiorgan failure like respiratory failure and cardiac arrhythmias.

Death in ALF is usually related to sepsis, multiorgan failure, and intracranial hypertension.²⁸ Multiorgan failure can be particularly severe in acetaminophen-associated ALF.²⁷

LABORATORY INVESTIGATIONS

Laboratory investigations that have prognostic value in ALF and are used widely include coagulation parameters,

serum bilirubin, serum transaminases, serum creatinine, arterial pH, and serum lactate. Others like α -fetoprotein, ammonia, arterial ketone body ratio, galactose elimination, Gc-globulin, and serum Phosphate are less frequently used. The core laboratory data that are used widely are parameters of coagulation, serum bilirubin, arterial pH, (particularly in acetaminophen induced ALF), and serum creatinine.⁸⁸

PROGNOSTIC CRITERIA IN ALF: CLICHY CRITERIA AND KING'S COLLEGE

CLICHY CRITERIA (1986)

These criteria were the first described by Clichy^{29,30} basing on analysis of prognostic factors in 115 patients with fulminant HBV, managed medically in the pre-liver transplantation era between 1972 and 1981. It was initially widely used in Europe. ALF patients should undergo transplantation if:

- Grade 3 or 4 encephalopathy.
- Factor V < 20%, and patient age < 30 years.
- Factor V < 20%, and patient age > 30 years.

Limitations^{31,32}

- Limited availability of factor V measurement
- Lack of good prospective validation
- Study based on which these criteria were designed was based on single etiology (Fulminant HBV).

The King's College Criteria (1989)

These criteria were derived from a retrospective study of 588 patients medically treated managed between 1973 and 1985.³⁴ The King's College criteria are widely used, reason being that they take into account the cause of ALF. Basing on King's College criteria, the sensitivity and specificity of prognostic criteria for acetaminophen-induced ALF is 92 and 69% respectively, indicating that a proportion of patients will die without fulfilling the criteria.^{33,35} There are fewer studies relating to non-acetaminophen criteria. When both sets of criteria were applied to a non-acetaminophen study population, the King's College criteria performed better than the Clichy criteria.³⁶

Both King's College and the Clichy criteria have low negative predictive value leading to inappropriate use of LTX in patients of ALF who would have recovered without transplantation.³⁷ The time interval from fulfilling a set of criteria to becoming medically unsuitable for LTX may be very short, hence there is a need to develop a more sensitive criteria with greater negative predictive value without loss of specificity.³³

King's College criteria for transplantation in ALF⁸⁸

• Non-acetaminophen induced ALF

INR (International normalized ratio) > 6.7 (PT > 100s)

or

Any three of

- Unfavorable cause (e.g. drug-induced)
- Age < 10 or > 40 years
- Acute/Subacute presentation
- Bilirubin level > 300 mmol/l
- INR > 3.5 (PT>50s)

• Acetaminophen induced ALF

Arterial pH < 7.3 after volume resuscitation

or

Concurrent findings of

- Grade III/IV Encephalopathy
- Creatinine > 300 mmol/L
- INR > 6.5 (PT>100s)

Both the above criteria when compared with MELD score in patients of ALF seemed to be an excellent predictor of outcome in both adults and children with a diagnostic accuracy of 95%.³⁸ Several markers (Lactate,³⁹ Phosphate⁴⁰ Factor VIII and V ratios,⁴¹ Serial prothrombin times,⁴² Arterial ketone body ratio,⁴³ Liver size on CT (< 1 L),⁴⁴ Liver histology (necrosis)⁴⁵ and Circulating interleukins (IL-6 and 8] have been proposed, when added with King's criteria, the result is improved sensitivity without significant reduction in specificity.^{39,40} Blood lactate and hyperphosphatemia are significant in acetaminophen-related ALF.

CRITERIA IN PEDIATRIC AGE GROUP

The criteria for diagnosis of ALF in adults can't be applied to diagnose ALF in children. PALFSG (Pediatric Acute Liver Failure Study Group) defined ALF in children as:

- Biochemical evidence of liver injury
- No history of known chronic liver disease
- Coagulopathy not corrected by vitamin K administration
- INR > 1.5 if the patient had encephalopathy or > 2.0 if the patient does not have encephalopathy

PALFSG staging of encephalopathy for children younger than 4 years

Stage	Clinical signs	Reflexes	Neurologic signs
Early (Grade I and II)	Inconsolable crying, sleep reversal, inattention to task	Hyper-reflexic	Unstable
Mid (Grade III)	Somnolence, stupor, combativeness	Hyper-reflexic	Most likely untestable
Late (Grade IV)	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate

LIVER TRANSPLANTATION IN ALF

Emergency LTX is the definitive treatment for ALF, but it is associated with a worse outcome than transplantation for chronic liver disease due to high postoperative mortality caused by sepsis and multiorgan failure.^{46,47} Other factors associated with poor outcome include small-size grafts and ABO incompatibility.

ROLE OF APOLT (AUXILIARY PARTIAL ORTHOTOPIC LIVER TRANSPLANTATION)

In APOLT, a partial liver graft is placed and the native liver is left in situ. Indications for APOLT are due to⁸⁸

- The ability of the native liver to regenerate to normal morphology with time
- The absence of clinical need for the immediate benefits of total removal of the diseased liver.

Theoretically, when the insult causing ALF resolves, the native liver subsequently regenerates and immunosuppressive drugs may be discontinued and the graft is allowed to atrophy or is surgically removed. Currently it is difficult to predict which patients will regenerate the native liver.⁸⁸

APOLT in acute hepatitis B is controversial, as even small amounts of virus in the remaining native liver may increase the risk of reinfection despite the use of antiviral therapy and immunoglobulin. APOLT is not suitable for Wilson's disease, autoimmune hepatitis, and Budd-Chiari syndrome causing ALF.

Favorable factors for regeneration are^{33,51}

- Young age
- Etiology of ALF (Acetaminophen/Virus)
- Mode of presentation (Hyperacute Liver failure)
- Limited extrahepatic organ involvement

Poor prognostic factors

- Grade IV encephalopathy
- Cerebral edema
- Renal failure
- Subacute liver failure

ROLE OF LDLT

LDLT is popular in Far East in contrary to DDLT in the West, due to the lack of availability of cadaver donors because of cultural beliefs. LDLT is being increasingly used for adults with ALF in countries like Japan, Taiwan, China, Hong Kong and Singapore.⁴⁸⁻⁵⁰ Most successful reported cases of LDLT in ALF have involved right lobe graft. Complications are more common in those donating

a right than a left lobe. In the present era of liver transplantation, right lobe grafts are the first choice in LDLT irrespective of the etiology of transplantation. Considering that patients with ALF have little chance to survive without transplantation and that cadaveric grafts are still a limited resource, LDLT is a valid option for these patients, as well as a safe procedure for donors.⁹⁰

MEDICAL MANAGEMENT OF ACUTE LIVER FAILURE

Emergency LTX is the only definitive treatment. Early liaison with a LTX unit is clearly important, and any contraindications to transplantation should be identified with available history from the family, friends, and the primary care physicians, if necessary. General supportive measures and close clinical monitoring in ICU is important.

FLUID BALANCE

Liberal volume expansion is likely to be required in most cases, usually with a mixture of crystalloids and colloids. Correction of acid-base disturbances and hyperlactatemia is important because of their impact on circulatory function and increasing cerebral hyperemia.⁵² A pulmonary capillary wedge pressure of 12-14 mm of Hg is desirable. Episodes of hypotension usually avoided.

HYPOGLYCEMIA

It occurs due to impaired gluconeogenesis. Glucose levels must be monitored 4-6 hourly and adequately maintained to prevent the cerebral and systemic effects of hypoglycemia while avoiding hyperglycemia, which worsens cerebral edema.⁵³

NUTRITION

Patients of ALF are usually fed via nasogastric tubes

ELECTROLYTES

Close monitoring of Na⁺, Ca²⁺, Mg²⁺ levels is required. Hyponatremia is a negative prognostic sign and can worsen brain edema.^{54,55} Sodium values <125 mmol/l are a contraindication for transplantation.

HYPERCAPNIA

Hypercapnia should be avoided, because it can lead to cerebral hyperemia and increases intracranial pressure (ICP).⁵⁶

PROPHYLACTIC ANTIBIOTICS AND ANTIFUNGAL DRUGS

Prophylactic antibiotics and antifungal drugs are used in ALF who are at high risk of sepsis, and there is increasing suspicion that the systemic inflammatory response is important in the pathogenesis of increased ICP in ALF.^{57,58} Common organisms are staphylococcus aureus, E. coli and Pseudomonas.

N-ACETYLCYSTEINE

Role of this drug in ALF due to acetaminophen overdose is proved. Progression to grade III-IV encephalopathy and mortality is less when patients are treated with N-Acetylcysteine.^{59,60} Hence in acetaminophen poisoning, irrespective of when the patient presents, administration of N-Acetylcysteine is recommended as it may prevent the progression to full-blown ALF.⁶¹

INTRACRANIAL HYPERTENSION

Cerebral edema leading to rise in intracranial hypertension occurs in 50-80% of cases of ALF in grade III or IV encephalopathy. In grade 1 and 2 encephalopathy, sedatives should be avoided, and the patient should be observed closely in a quiet intensive care setting. In patients who have grade 3 and 4 encephalopathy, the head should be elevated to 30 degrees, and endotracheal intubation should be performed.⁸⁸

Aim of treatment is to maintain the cerebral perfusion pressure (CPP) > 40 mm of Hg and mean arterial pressure > 60 mm of Hg. CPP < 40 mm of Hg is usually considered as relative contraindication for transplantation.

Pathogenesis of intracranial hypertension in ALF is not clear. Factors contributing to raised ICP are:

- Ammonia-related cerebral edema is an early insult.⁶²
- Autoregulation of cerebral blood flow is lost in ALF, resulting in cerebral hyperemia.⁶³
- Systemic inflammatory response is important in the pathogenesis of increased ICP in ALF.^{57,58,64}

Use of ICP monitors seems to be justified in controlling ICP, but routine monitoring needs to be balanced against the risk of bleeding. Insertion of ICP monitors based on measurements using jugular bulb oxygen saturation is an option.⁴³ The emergence of new methods such as continuous EEG and microdialysis techniques are useful in monitoring ICP. ICP is usually measured in patients of grade III and IV encephalopathy with papillary abnormalities who are to undergo transplantation.⁸⁸

REDUCTION OF CEREBRAL EDEMA

Mannitol is used to treat cerebral edema and raised ICP in ALF. It increases the osmolarity of capillaries in the brain. ICP > 20 mm of Hg for more than 5 mins or papillary changes usually treated with mannitol 0.5-1 gm/kg, 20% solution. Reduction of blood volume with hemofiltration is also effective in reducing the ICP.⁴³

Hyperthermia should be prevented, because it worsens intracranial hypertension.

Hypertonic saline (30%) also significantly decreased ICP relative to baseline over the first 24 hours.⁶⁵ Adverse effects of hypertonic saline are multiple small hemorrhages, venous thrombosis, pons demyelination and aggravation of coagulopathy and shrinkage of the brain.⁶⁶

Intravenous indomethacin also reported to reduce ICP due to cerebral vasoconstriction and reduction in cerebral temperature by inhibition of the endothelial cyclo-oxygenase pathway.^{67,68} But due to its renal and GI toxicity, it cannot be recommended for routine use in ALF.⁸⁸

Reduction of ammonia level: Although lactulose is often used to reduce ammonia, studies have not shown any benefit in ALF.⁶¹

ROLE OF HYPOTHERMIA

Hypothermia is also associated with significant improvement in cardiovascular hemodynamics, manifested by increased mean arterial pressure and systemic vascular resistance and reduced requirement of inotropic agents.⁷⁰

Moderate hypothermia (32° C–33°C) is known to reduce ICP in ALF by.⁶⁹

- Affecting ammonia level through its brain metabolism, cerebral blood flow, and autoregulation
- Reduction in the inflammatory response and its mediators such as nitric oxide, pro-inflammatory cytokines and products of oxidative stress.⁷⁰

Corticosteroids should be considered only if the underlying cause of ALF is an exaggerated immune response or autoimmune hepatitis, not for treatment of intracranial hypertension.⁸⁸

COAGULOPATHY

Correction of coagulopathy is required only with hemorrhage or in preparation for invasive procedures. Vitamin K is given to correct any reversible coagulopathy. Administration of fresh frozen plasma and recombinant

factor VIIa produces temporary correction of coagulopathy and might be useful in the setting of renal insufficiency in which volume overload is a concern.^{71,72}

METABOLIC AND RENAL PROBLEMS

Metabolic acidosis is common in ALF and is due to tissue hypoxia and increased peripheral lactate production. Extracorporeal renal support will be required in up to 80% of cases of advanced ALF complicated by cerebral edema.⁷³ The circulatory disturbances in ALF, which contribute to the often-associated renal failure, are characterized by a generalized vasodilatation that results in increased cardiac output and reduced systemic vascular resistance and mean arterial pressure.^{75,76} Initial management is aggressive volume replacement. If no response, should be treated with renal dose of dopamine, furosemide. Early consideration of renal replacement therapy in the form of CVVHD (continuous venovenous hemodiafiltration) or high volume hemofiltration as they cause a lower rise in ICP, greater cardiovascular stability, and better cerebral perfusion.⁷⁴ Intermittent hemodialysis is avoided as episodes of hypotension causes fall in CPP.

LIVER-SUPPORTING DEVICES FOR ALF

These are used as a bridge to transplantation or to help recovery of the ailing liver. There are 2 categories of liver supporting devices such as bioartificial and artificial.⁷⁷ ALF reduces the liver's ability for synthesis and detoxification. This reduced ability results in declining albumin and clotting factor synthesis, urea cycle dysfunction (with subsequent increase in ammonia), and reduced metabolism of other protein breakdown products.⁷⁷ Toxins such as amino acids, bile acids, bilirubin, endogenous benzodiazepines, nitric oxide, and phenols accumulate and may contribute to multiorgan failure. These toxins are mostly bound to albumin in the plasma and therefore are not removable by hemofiltration or dialysis. These are the potential targets of liver supporting devices.⁸⁸

BIOARTIFICIAL LIVERS (BAL)

In BAL, hepatocytes are used to reproduce the synthetic, detoxifying, and excretory function of the failing liver. An estimated 10^{10} hepatocytes are necessary to provide the equivalent function of 10 to 30% of the normal liver mass.⁷⁸ But human hepatocytes are difficult to grow in culture and are inherently unstable.⁷⁷ Hence devices in current use rely on animal, particularly porcine, hepatocytes that can be cryopreserved much more readily or use genetically engineered human hepatocytes designed to retain specific functions.⁷⁹

The term BAL has been used generically and in respect to a specific hybrid device that used 50 g of porcine hepatocytes attached to collagen-coated microcarriers and charcoal columns in an extracorporeal circuit. Charcoal columns were incorporated to reduce the toxic load in plasma being exposed to the hepatocytes with a view to preserving their functionality, but the possibility of a more proactive contribution to the overall efficacy of the device cannot be excluded. Safety concerns regarding BAL include immune reactions to foreign antigens, xenozoonosis, and the escape of tumorigenic cells into the recipient.⁷⁷ Use of stem cells for BAL is also been described.

ARTIFICIAL: EXTRACORPOREAL LIVER ASSIST DEVICE (ELAD) SYSTEM

A major advance in artificial extracorporeal devices that has helped fuel this interest is the use of albumin dialysis with a membrane containing pores small enough to increase the selectivity of the detoxifying process. The system can be specific for albumin-bound substances, which include most of the toxins that accumulate in liver failure, whereas larger and more useful molecules (such as immunoglobulins) cannot cross over.⁷⁷

MARS (MOLECULAR ADSORBENTS RECIRCULATING SYSTEM)

It is the most recently developed system.⁸⁰ MARS significantly improves in encephalopathy and reduction in ammonia, bilirubin, bile acids, aromatic amino acids, and creatinine and is useful in ALF particularly if the underlying cause is toxins,⁸¹ fulminant Wilson's disease.⁸¹ Following acute hypoxic liver injury after cardiogenic shock⁸² and as a bridge to liver transplantation after amanita phalloides (toxic mushroom) intoxication and Wilson's disease.⁸³ Complications of MARS are thrombocytopenia and disseminated intravascular coagulation.

MARS treatment improved the clinical picture of these patients, increasing the available time for obtaining an urgent liver graft. Moreover, the patients could undergo transplantation in a more favorable clinical condition. But MARS did not lead to an improvement of coagulation function. There is much interest in the application of MARS as a bridge to transplantation that remains the only effective treatment for therapy of acute liver failure.⁸⁹

PLASMAPHERESIS

It has been used periodically to provide artificial support in acute liver failure. Improvement in encephalopathy, cerebral blood flow, and cerebral perfusion pressure

without any deleterious change in intracranial pressure is documented.

EX-VIVO PERFUSION

Ex-vivo perfusion using pig or human livers that are unsuitable for transplantation also is described as a bridge to transplantation in a small number of patients. Cell-based therapies also are attracting interest as a method of augmenting liver function.⁸⁷

HEPATOCYTE TRANSPLANTATION

Hepatocyte transplantation, in which human hepatocytes are infused into splenic or portal vascular beds, has shown early promise with reduction in encephalopathy, ammonia levels, and prothrombin times in small case series.⁸⁴

SURVIVAL

Liver transplantation has significantly improved the prognosis of ALF. Selection of recipient and timing of transplantation are important in ALF to achieve better results.³³ The overall survival rates after transplantation are 63% in the United States and 61% in Europe. Postoperative survival rates in the West and Far East are roughly equivalent i.e. 60-80%, compared with 15 to 20% survival rates in patients who do not receive grafts.^{85,86} ALF secondary to idiosyncratic reactions and HBV had the poorest outcome (i.e., less than 25% spontaneous survival). Acetaminophen-related ALF had the best transplant-free survival rate (68%).¹⁹ According to European registry, the graft survival rate for ABO-incompatible liver grafts used for emergency transplantation was only 32% at 1 year, compared with 54 and 49% for matched and unmatched but compatible grafts, respectively. The best results were achieved for transplantation for Wilson's disease and the worst for idiosyncratic drug reactions. In a series of 141 pediatric cases undergoing liver transplantation for acute liver failure, the 6-month survival rate was 74.5%, and mortality was associated with age under 1 year and grade 4 encephalopathy and renal failure before transplantation.

REFERENCES

1. Trey C, Davidson CS. The management of fulminant hepatic failure. In: Popper H, Schaffner F, editors. *Progress in liver disease*. New York: Grune and Stratton 1970:282-98.
2. Lee WM, Schiodt FV. Fulminant hepatic failure. In: Schiff ER, Sorrell MF, Maddrey WC, editors. *Schiff's diseases of liver*. 8th edition. Philadelphia: Lippincott-Raven 1999:879-95.
3. Bowen DG, Shackel NA, McCaughan GW. East meets West: Acute liver failure in the global village. *J Gastroenterol Hepatol* 2000;15:467-69.
4. Cheng V. Current issues and treatment of fulminant hepatic failure including transplantation in Hong Kong and the Far East. *Semin Liver Dis* 2003;23:239-50.
5. Brunetto MR, Giarin MM, Oliveri F, et al. Wild-type and e antigen-minus hepatitis B viruses and course of chronic hepatitis. *Proc Natl Acad Sci USA* 1991;88:4186-90.
6. Baliga P, Alvarez S, Lindblad A, et al. Posttransplant survival in pediatric fulminant hepatic failure: The SPLIT experience. *Liver Transpl* 2004;10:1364-71.
7. Demetriou AA, Brown RS, Busuttil RW, et al. Prospective, randomised multicenter controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg* 2002;239:660-70.
8. Hoofnagle JH, Carithers RL, Shapiro C, et al. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995;21:240-52.
9. Ritt DJ, Whelan G, Werner DJ, et al. Acute hepatic necrosis with stupor or coma. An analysis of thirty-one patients. *Medicine* 1969;48:151-72.
10. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005;42(6):1364-72.
11. UK National Transplant Database. Bristol, UK: UK Transplant Support Service Authority; 2002.
12. Ellis A, Rhodes A, Jackson N, et al. Acute liver failure (ALF) in a specialist intensive care unit; A 7 year experience. *Crit Care* 1998;2(Suppl 1):150.
13. Makin A, Williams R. Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. *QJM* 2000;93:341-49.
14. Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. *Suicide Life Threat Behav* 2000;30:313-26.
15. Bowles J. Suicide prevention in western Samoa: An example of a suicide prevention program in a developing country. In: Diekstra R, Gulbinat W, Kienhorst I, et al, editors. *Preventative strategies in suicide*. Leiden (The Netherlands): EJ Brill 1995:173-206.
16. Sheen CL, Dillon JF, Bateman DN, et al. Paracetamol toxicity: epidemiology, prevention and costs to the health-care system. *QJM* 2002;95:609-19.
17. Sheen CL, Dillon JF, Bateman DN, et al. Paracetamol pack size restriction: The impact on paracetamol poisoning and over-the-counter supply of paracetamol, aspirin and ibuprofen. *Pharmacoepidemiol Drug Saf* 2002;11:329-31.
18. William R. Classification, etiology, and considerations of outcome in acute liver failure. *Semin Liver Dis* 1996;16:343-48.
19. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947-54.
20. Ellis A, Rhodes A, Jackson N, et al. Acute liver failure (ALF) in a specialist intensive care unit; A 7 year experience. *Crit Care* 1998;2(Suppl 1):150.
21. Riordan SM, Williams R. Mechanisms of hepatocyte injury, multiorgan failure and prognostic criteria in acute liver failure. *Semin Liver Dis* 2003;23(3):203-15.
22. Galle P, Krammer P. CD95-induced apoptosis in human liver disease. *Semin Liver Dis* 1998;18:141-51.

23. Kaplowitz N. Mechanism of liver cell injury. *J Hepatol* 2000;32(Suppl 1):39-47.
24. Lemaire C, Andreau K, Souvannavong V, et al. Inhibition of caspase a switch from apoptosis to necrosis. *Febs Lett* 1998;425:266-70.
25. Leist M, Single B, Castoldi AF, et al. Intracellular adenosine triphosphate (ATP) concentration: A switch in the decision between apoptosis and necrosis. *J Exp Med* 1997;185:1481-86.
26. Ellis A, Rhodes A, Jackson N, et al. Acute liver failure (ALF) in a specialist intensive care unit; A 7 year experience. *Crit Care* 1998;2(Suppl 1):150.
27. Bernal W, Wendon J, Rela M, et al. Use and outcome of liver transplantation in acetaminophen induced acute liver failure. *Hepatology* 1998;27:1050-55.
28. Larsen FS. Optimal management of patients with fulminant hepatic failure: targeting the brain. *Hepatology* 2004;39:299-301.
29. Bemuan J, Goudau A, Poynard T, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986;6:648-51.
30. Bismuth H, Samuel D, Castaing D, et al. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. *Ann Surg* 1995;23:1507-11.
31. Nevens F, Schepens D, Wilmer A. Evaluation of the Kings and Clichy criteria for the selection of OLTx in patients with non-paracetamol induced acute liver failure. *Hepatology* 1998;28:223A.
32. Jalan R. Gc-globulin to predict outcome in acute liver failure: a panacea? *Liver Transpl* 2005;10:1169-71.
33. Bernal W, Wendon J. Liver transplantation in adults with acute liver failure. *J Hepatol* 2004;40:192-97.
34. O'Grady J, Alexander G, Hayllar K, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439-45.
35. Bailey B, Amre D, Gaudreault P. Fulminant hepatic failure secondary to acetaminophen poisoning: A systematic review and meta-analysis of prognostic criteria determining the need for liver transplantation. *Crit Care Med* 2003;31:299-305.
36. Pauwels A, Mostefa-Kara N, Florent C, et al. Emergency liver transplantation for acute liver failure. *J Hepatol* 1993;17:124-27.
37. Wiesner RH. MELD/PELD and the allocation of deceased donor livers for status 1 recipients with acute fulminant hepatic failure, primary nonfunction, hepatic artery thrombosis, and acute Wilson's disease. *Liver Transpl* 2004;10(Suppl 2):S17-22.
38. Yantorno SET, Trentadue JJ, Ruf AE, et al. The model for end-stage liver disease (MELD): A useful tool to access prognosis in fulminant hepatic failure. *Liver Transpl* 2004;10:C36.
39. Bernal W, Donaldson N, Wyncoll D, et al. Blood lactate as an early predictor of outcome in paracetamol-induced hepatic failure. *Lancet* 2002;359:558-63.
40. Bernal W, Wendon J. More on serum phosphate in acute liver failure. *Hepatology* 2003;38:533-34.
41. Pereira LM, Langley PG, Hayllar KM, et al. Coagulation factor V and VIII/V ratio as predictors of outcome in paracetamol induced fulminant hepatic failure. *Gut* 1992;33:98-102.
42. Harrison PM, O'Grady JG, Keays RT, et al. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *BMJ* 1990;301:964-66.
43. Saibara T, Onishi S, Sone J, et al. Arterial ketone body ratio as a possible indicator for liver transplantation in fulminant hepatic failure. *Transplantation* 1991;51:782-86.
44. Itai Y, Sekiyama K, Ahmadi T, et al. Fulminant hepatic failure: observation with serial CT. *Radiology* 1997;202:379-82.
45. Shakil AO, Jones BC, Lee RG, et al. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. *Dig Dis Sci* 2000;4:334-39.
46. Farmer D, Anselmo D, Ghobrial R, et al. Liver transplantation for fulminant hepatic failure. Experience with more than 200 patients over a 17 year period. *Ann Surg* 2003;237:666-76.
47. Devlin J, Wendon J, Heaton N, et al. Pretransplant clinical status and outcome of emergency transplantation for acute liver failure. *Hepatology* 1995;21:1018-24.
48. Uemoto S, Inomata Y, Sakurai T, et al. Living donor liver transplantation for fulminant hepatic failure. *Transplantation* 2000;70:152-57.
49. Wang SH, Chen CL, Chen YS, et al. Living donor liver transplantation: The Kaohsiung experience. *Transplant Proc* 2000;32:2137-38.
50. Wai CT, Lo SK, Lee KH, et al. Ten years of experience of liver transplantation in Singapore. *Transplant Proc* 2000;32:2139.
51. Chenard-Neu MP, Boudjema K, Bemuau J, et al. Auxiliary liver transplantation: Regeneration of the native liver and outcome in 30 patients with fulminant hepatic failure: a multicentre European study. *Hepatology* 1996;23:1119-27.
52. Zwingmann C, Chatauret N, Leibfritz D, et al. Selective increase of brain lactate synthesis in experimental acute liver failure: results of $[H1-C13]$ nuclear magnetic resonance study. *Hepatology* 2003;37:420-28.
53. Kodakar SK, Gopal PB, Wendon JA. Hyperglycaemia is associated with intracranial hypertension in patients with acute liver failure. *Liver Transpl* 2001;7:C21.
54. Cordoba J, Gottstein J, Blei AT. Chronic hyponatremia exacerbates ammonia induced brain oedema in rats after portocaval anastomosis. *J Hepatol* 1998;29:589-94.
55. Jalan R, Dabos K, Redhead DN, et al. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol* 1997;27:928-33.
56. Van Hulst RA, Hasan D, Lachmann B. Intracranial pressure, brain, pCO₂, pO₂, and pH during hypo and hypertension at constant mean airway pressure in pigs. *Intensive Care Med* 2002;28:68-73.
57. Ronaldo N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000;32:734-39.
58. Jalan R, Pollok A, Shah S, et al. Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure. *J Hepatol* 2002;37:536.
59. Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990;30(335):1572-73.
60. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991;303:1026-29.
61. Jalan R. Acute liver failure: current management and future prospects. *J Hepatol* 2005;42(Suppl1):S115-23.
62. Blei AT, Olafsson S, Therrein G, et al. Ammonia-induced brain oedema and intracranial hypertension in rats after portocaval anastomosis. *Hepatology* 1994;19:1437-44.
63. Jalan R, Olde SW, Hayes PC, et al. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. *J Hepatol* 2004;41:613-20.
64. Jalan R, Williams R. The inflammatory basis of intracranial hypertension in acute liver failure. *J Hepatol* 2001;34:940-42.

65. Murphy N, Auzinger G, Bernel W, et al. The effect of hypertonic sodium chloride intracranial pressure in patients with acute liver failure. *Hepatology* 2004;39:464-70.
66. Larsen FS. Optimal management of patients with fulminant hepatic failure: targeting the brain. *Hepatology* 2004;39:299-301.
67. Jensen K, Ohrstrom J, Cold GE, et al. Indomethacin (Confortid) in severe head injury and elevated intracranial pressure (ICP). *Acta Neurochir Suppl (Wien)* 1992;55:47-48.
68. Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab* 2004;24:798-804.
69. Jalan R, Olde Damink SWM, Deutz NEP, et al. Treatment of uncontrolled intracranial hypertension in acute liver failure with moderate hypothermia. *Lancet* 1999;354:1164-68.
70. Jalan R, Olde Damink SWM, Deutz NEP, et al. Moderate hypothermia in patients with acute liver failure and uncontrolled hypertension. *Gastroenterology* 2004;127:1338-46.
71. Brown JB, Emerick KM, Brown DL, et al. Recombinant factor VIIa improves coagulopathy caused by liver failure. *J Pediatr Gastroenterol Nutr* 2003;37(3):268-72.
72. Pavese P, Bonadona A, Beaubien J, et al. FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: a report of four cases. *Can J Anaesth* 2005;52(1):26-29.
73. Davenport A, Will EJ, Davison AM, et al. Changes in intracranial pressure during hemofiltration in oliguric patients with grade IV encephalopathy. *Nephron* 1989;53:142-46.
74. Davenport A, Will EJ, Davison AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit Care Med* 1993;21:328-38.
75. Shawcross D, Davies NA, Mookerjee RP, et al. Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with hepatic encephalopathy. *Hepatology* 2004;39:471-75.
76. Jalan R. Intracranial hypertension in acute liver failure: pathophysiological basis of rational management. *Semin Liver Dis* 2003;23:271-82.
77. Sen S, Williams R. New liver support devices in acute liver failure. A critical evaluation. *Semin Liver Dis* 2003;23:283-93.
78. Strain AJ, Neuberger JM. A bioartificial liver-state of the art. *Science* 2002;295:1005-09.
79. McCloskey P, Tootle R, Selden C, et al. Modulation of hepatocyte function in an immortalized human hepatocyte cell line following exposure to liver-failure plasma. *Artif Organs* 2002;26:340-48.
80. Stange J, Ramlow W, Mitzner S, et al. Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. *Artif Organs* 1993;17:809-13.
81. Hassanein T, Tofteng F, Brown RS, et al. Efficacy of albumin dialysis (MARS) in patients with cirrhosis F and advanced grades of hepatic encephalopathy: A prospective, controlled, randomized multicenter trial. *Hepatology* 2004;40(Suppl.1):726.
82. El Banayosy A, Kizner L, Schueler V, et al. First use of the Molecular Adsorbent Recirculating System technique on patients with hypoxic liver failure after cardiogenic shock. *ASAIO J* 2004;50:332-37.
83. Sein Anand J, Chodorowski Z, Hydzik P. Molecular adsorbent recirculating system-MARS as a bridge to liver transplantation in Amanita phalloides intoxication. *Przegl Lek* 2005;62:480-81.
84. Bilir BM, Guinette D, Karrer F, et al. Hepatocyte transplantation in acute liver failure. *Liver Transpl* 2000;6:32-40.
85. Chapman RW, Forman D, Peto R, et al. Liver transplantation for acute hepatic failure. *Lancet* 1990;335:32-35.
86. Lo CM, Fan ST, Liu CL, et al. Ten-year experience with liver transplantation at Queen Mary Hospital: Retrospective study. *Hong Kong Med J* 2002;8:240-44.
87. Lo CM, Fan ST, Chan JK, et al. Minimum GV for successful adult-to-adult living donor liver transplantation for fulminant hepatic failure. *Transplantation* 1996;62:696-98.
88. Shahid A. Khan, Naina Shah, Roger Williams, et al. Acute Liver Failure: A Review. *Clin Liver Dis* 2006;10:239-58.
89. F Pugliese, F Ruberto, SM Perrella, A, et al. Modifications of intracranial pressure after molecular adsorbent recirculating system treatment in patients with acute liver failure: Case Reports. *Transplant Proceed* 2007;39:2042-44.
90. M Uribe, G Gonzalez, A Alba, et al. Living Donor Liver Transplantation in Pediatric Patients With Acute Liver Failure: Safe and Effective Alternative. *Transplant Proceed* 2008;40(9):3253-55.

Metabolic Liver Diseases

INTRODUCTION

Metabolic liver diseases are a group of disorders which usually present in childhood with a wide-range of effects on the liver. Incidence is approximately 20% of pediatric and 4% of adult liver transplants performed for metabolic diseases.^{1,2} Metabolic disorders can be divided into 4 different groups according to the etiology.⁴⁵

A. Primary metabolic defect is in the liver such as Wilson disease, α 1-Antitrypsin deficiency, neonatal hemochromatosis, galactosemia, glycogen storage disease type I, IV and alagille syndrome. **B.** Primary metabolic defect is in the liver and liver function is preserved such as familial amyloid polyneuropathy, primary hyperoxaluria type I, Crigler-Najjar syndrome type I, familial hypercholesterolemia, and urea cycle defects. **C.** Primary metabolic defect is extrahepatic such as nonalcoholic steatohepatitis (NASH), gaucher disease, hereditary hemochromatosis, and porphyria. **D.** Systemic metabolic defect, liver also involved such as cystic fibrosis

ALPHA 1-ANTITRYPSIN DEFICIENCY

Alpha-1-antitrypsin (α 1AT) is a glycoprotein primarily synthesized in the liver and secreted into the serum, where its function is to inhibit nonspecific, neutrophil protease-induced host tissue damage.³ α 1-Antitrypsin deficiency is one of the most common inherited autosomal recessive metabolic liver diseases.⁴ Homozygosity for the autosomal codominant Z mutant allele of α 1AT ("PIZZ" in World Health Organization [WHO] nomenclature) represents the classical form of α 1AT deficiency.⁵ It affects 1 in 2,000 live births.⁶ But only 10 to 15% of patients with PiZZ phenotype develop significant liver disease.^{7,8}

CLINICAL PRESENTATION

It affects lung and liver disease.

PULMONARY SYMPTOMS

Emphysema develops due to systemic loss of antitrypsin function leading to uninhibited proteolytic destruction of the pulmonary connective tissue matrix.⁴⁵

HEPATIC SYMPTOMS

Presents with jaundice and cirrhosis. In infants, the most common presentation of α 1-AT deficiency is cholestasis, which usually resolves by 6 months of age.^{9,10} Nearly 10% of these patients may develop paucity of intrahepatic bile ducts and develop prolonged jaundice and cirrhosis.¹¹ In most of the cases, jaundice gradually resolves; however, cirrhosis may develop in up to 25%, and 10% go on to require liver transplantation.^{12,13} Cirrhosis can present in the neonatal period in the absence of jaundice, but it is usually rare.¹⁴ In adults, hepatic manifestations present in the fourth decade of life. Patients usually present with chronic active hepatitis, cirrhosis, portal hypertension, or hepatocellular carcinoma.¹⁵ Male patients are at increased risk for developing hepatocellular carcinoma.¹⁶

Liver disease in α 1-AT deficiency develops because of a gain of toxic function from accumulation and decreased clearance of polymerized mutant α 1-AT molecules in the endoplasmic reticulum of hepatocytes. Precipitating factors, such as alcohol, viral hepatitis, or iron overload, may contribute to liver disease among heterozygotes.⁴⁵

DIAGNOSIS

Phenotyping

The gold standard for the diagnosis of α -1AT deficiency is the phenotype (PI or PI-type) of the α -1AT protein present in a sample of the patient's serum as determined by isoelectric focusing gel electrophoresis.¹⁷

α -1AT Level

Its level in the in peripheral blood can be used as a complementary test to compare the phenotype result.

Liver biopsy

Periodic Acid Schiff +ve globules can be seen in both homozygous and heterozygous patients.¹⁸

Treatment

No specific treatment for the liver disease associated with α -1AT deficiency.

- Supportive medical treatment.
- Avoid smoking
- Exogenous α -1AT protein replacement is available as a treatment for the adult emphysema associated with α -1AT deficiency, although replacement has no effect on the development of liver disease because liver injury is not related to a lack of circulating anti-protease activity
- Liver transplantation is the only effective treatment for decompensated liver disease.
- Overall 1-year survival is more than 75%. Improved surgical techniques and ICU management may explain this improvement in outcome. After LTX, α 1-AT phenotype converts to that of the donor with normalization of serum α 1-AT level within weeks.¹²

CYSTIC FIBROSIS

Synonyms: Mucoviscoidosis

Cystic fibrosis (CF) is an autosomal recessive metabolic disorder. Prevalence is approximately 1 in every 3000 white live births. CF affects the exocrine (mucus) glands of the lungs, liver, pancreas, and intestines, causing progressive disability due to multisystem failure.⁴⁵

DEFECT

The mutations in cystic fibrosis transmembrane regulator (CFTR) (cAMP-dependent chloride channel) lead to inability to maintain luminal hydration of ducts leading to ductal blockage.³⁰

CLINICAL PRESENTATION

Liver

Prevalence of liver disease ranges from 2 to 37% in patients with CF.^{31,32} CFTR is predominantly expressed on the apical surface of the biliary epithelium.³³ Liver disease is caused by plugging of intrahepatic bile ducts by inspissated bile resulting in biliary obstruction and multilobular biliary cirrhosis.³⁴ Meconium ileus and pancreatic disease seem to be risk factors for liver disease.³² 1.8 to 7.8% of patients with CF develop cirrhosis, peaking age group between 16-20 years.^{35,36} Common manifestations are biliary cirrhosis and portal hypertension related complications. Onset of portal hypertension carries a poor prognosis, with a mean survival of 4.5 years.³⁷ These patients are also at risk for malnutrition, osteoporosis, diabetes, and deterioration of pulmonary status.³⁰

Other systems

Thick mucus plugs result in frequent lung infections. Decrease in the secretion of pancreatic enzymes result in poor growth, fatty diarrhea and deficiency in fat-soluble vitamins. Males can be infertile due to the condition congenital bilateral absence of the vas deferens. Often, symptoms of CF appear in infancy and childhood. Meconium ileus is a typical finding in newborn babies with CF.⁴⁵

DIAGNOSIS⁴⁵

- Genetic testing
- Newborn screening tests are increasingly common and effective
- Sweat test: High level of salt is found in sweat

Role of LTX

The optimal timing of liver transplantation is debated. Some have suggested that liver transplantation should be considered early because portal hypertension may contribute to the deterioration of pulmonary status. Gooding et al. reported that liver transplantation should be reserved for patients with significant synthetic dysfunction and variceal bleeding alone should not be an indication for transplantation.³⁸ Other studies reported encouraging results after liver transplantation, with improved pulmonary function, prolonged survival, and improved quality of life.³⁹⁻⁴¹ Perioperative care should focus on aggressive chest physiotherapy, nutritional support, nebulized bronchodilator and DNase treatment, and individualized antibiotic and antifungal therapy. Pulmonary status initially improves and then stabilizes

after liver transplantation.⁴² Biliary complications are frequent because of involvement of common bile duct. For this reason, some authors have advocated routine use of Roux-en-Y choledochojejunostomy for patients with CF undergoing liver transplantation.⁴¹

It has been suggested that liver transplantation seems to improve nutritional status in patients with CF. Colombo et al. reported that BMI, bone density, and plasma vitamin A and E levels were significantly improved at 5 years after liver transplantation compared with patients who did not undergo transplant.⁴³

Role of Multi-organ Transplantation in CF

Combined lung–liver or heart–lung–liver transplantation have been reported. Combined transplantation poses technical difficulties with a 1 year survival rate up to 85.7%.⁴⁴

Gene Therapy

Gene therapy holds promise as a potential avenue to cure cystic fibrosis. Gene therapy attempts to place a normal copy of the CFTR gene into affected cells. Studies have shown that to prevent the lung manifestations of cystic fibrosis, only 5–10% the normal amount of CFTR gene expression is needed. Several clinical trials have been initiated but the successful gene therapy is yet to come.⁴⁵

HEREDITARY HEMOCHROMATOSIS (HHC)

It is one of the most common inherited autosomal recessive metabolic diseases causing liver cirrhosis. Prevalence of this disease is approximately 1:200 to 1:400.¹⁹ Most patients who have clinical manifestations of HHC are either homozygous for the C282Y mutation or compound heterozygous for C282Y/H63D.²⁰ Since the discovery of the HFE gene, several studies have shown that most of the patients who have iron overload in the setting of cirrhosis do not have classic HHC based on genotype analysis.^{21,22}

PRESENTATION

HHC is due to dysregulation of iron absorption leading to increased intestinal absorption of iron. Excessive iron deposits in various organs results in cirrhosis, hepatocellular carcinoma, diabetes, cardiomyopathy, arthropathy, hypogonadism and skin hyperpigmentation.⁴⁵

HEPATIC IRON OVERLOAD

Hepatic iron overload is seen in⁴⁵

- Hereditary hemochromatosis

- Chronic hepatitis C
- Alcoholic liver disease.

TREATMENT

- Early diagnosis and phlebotomy is essential. Once cirrhosis develops, there is an increased risk for hepatocellular carcinoma and premature mortality despite iron depletion therapy.²³ Patients with iron depletion therapy before liver transplant had a better survival rates.
- Liver transplantation is indicated in patients with decompensated cirrhosis and/or presence of hepatocellular carcinoma.

SURVIVAL RATES

1-year and 5-years post-transplant survival rates in patients with HHC is less than other indications (54% and 43% vs. 79.4% and 69.2%).²⁴ Similar results were reported UNOS Liver Transplant Registry.² It indicates that hepatic iron overload is associated with decreased survival after liver transplant. Kowdley et al. reported that in HFE-associated HHC patients, 1-, 3-, and 5-year post-transplant survival rates were 64%, 48%, and 34%, respectively, significantly lower than in patients who did not have HHC²⁵ and the patients who did not have HHC who had hepatic iron overload also had significantly decreased 5-year post-transplant survival compared with the overall population (63% versus 72%).⁴⁵

The decreased survival and increased mortality rates in HHC is due to:^{25–27}

- Iron over load
- Infectious complications
- Cardiac complications

Patients who have HHC undergoing evaluation for liver transplantation should have a thorough cardiac evaluation. There is an increased incidence of hepatocellular carcinoma in patients with HHC.

DISEASE RECURRENCE AFTER LTX

Limited data are available regarding iron reaccumulation after LTX. If the primary site of metabolic defect is in the small intestine, hepatic iron reaccumulation in the transplanted liver would be expected. There is no conclusive evidence of significant hepatic iron accumulation in patients who have HHC after liver transplantation, however. One study reported that there was no evidence of iron overload in 10 of the 11 surviving patients in 4 years after LTX. Only 1 patient had increased serum ferritin and grade 1 to 2 siderosis on liver biopsy.²⁸ Absence of iron accumulation after LTX in follow-up period suggests that the liver may play an important role in regulating iron metabolism in HHC.²⁹

ALAGILLE SYNDROME

It is an autosomal dominant disorder involving affects the liver, heart, and other systems of the body, named after Daniel Alagille.⁴⁶

INCIDENCE

1 in every 100,000 live births.

PATHOGENESIS

Mutations in JAG1 and NOTCH2 disrupt the signaling pathway, causing defective development of bile ducts in liver, heart, spinal column, and facial appearance.^{47,48} JAG1 primary gene that is involved in signaling between adjacent cells during embryonic development.⁴⁷ The affected person may inherit the mutation from one affected parent or it may result from new mutations in the gene. It may occur with no family history of the disease.

CLINICAL PRESENTATION

Presentation is in infancy or early childhood. Clinical manifestations vary from clinically asymptomatic to severe liver and/or heart disease ending in organ transplantation. Other systems like renal and central nervous systems can also be affected. The patients has broad, prominent forehead, deep-set eyes, small pointed chin. Clinically presents with pruritus, jaundice, cholesterol xanthomas and congenital heart diseases like Tetralogy of Fallot.

DIAGNOSIS

Radiological examination reveals butterfly shaped bones are seen in the spinal column; Liver biopsy reveals paucity of bile duct and Doppler study reveals cardiac defects.

Treatment

No specific treatment for this disease. Aim of treatment includes functional improvement of the organs involved like liver, heart and kidney. Here we focus on treatment of liver disease.

1. Various drugs like UDCA (Ursodeoxy cholic acid), Cholestyramine, Hydroxyzine, Rifampicin, and Phenobarbitol can be used in intractable pruritus and jaundice.
2. Nutritional support and high dose of vitamins A, D, E and K.
3. Antibiotics and other supportive care in case of cholangitis.

4. Surgical treatment: Transient external biliary diversion with PTCB may be helpful in improving jaundice. If there is severe degree of atrophy of bile ducts and recurrent attacks of cholangitis, liver transplantation is the ultimate treatment. Cardiac defects also require surgical correction.

REFERENCES

1. Tung BY, Kowdley KV, et al. Liver transplantation for hemochromatosis, Wilson disease, and other metabolic disorders. *Clin Liver Dis* 1997;1(2):341-60.
2. Belle SH, Beringer KC, Detre KM. Liver transplantation in the United States: Results from the national Pitt-UNOS liver transplant registry. *Clin Transpl* 1994;19-35.
3. Vennarecci G, Gunson BK, Ismail T, et al. Transplantation for end stage liver disease related to α 1-antitrypsin. *Transplantation* 1996;61:1488-95.
4. Marcus N, Techman JH, Perlmutter DH. Alpha 1-antitrypsin deficiency: From genotype to childhood disease. *J Pediatr Gastroenterol Nutr* 1998;27:65-74.
5. Alpha 1-antitrypsin deficiency: Memorandum from a WHO meeting. *Bull World Health Organ* 1997;75:397-415.
6. Perlmutter DH. Clinical manifestations of alpha(1)-antitrypsin deficiency. *Gastroenterol Clin North Am* 1995;24:27-43.
7. Silverman EK, Miletich JP, Pierce JA, et al. α 1-antitrypsin deficiency. High prevalence in the St Louis area determined by direct population screening. *Am Rev Respir Dis* 1989;140:961-66.
8. Sveger T, Eriksson S. The liver in adolescents with α 1-antitrypsin deficiency. *Hepatology* 1995;22:514-17.
9. Moroz SP. Liver disease associated with α 1-antitrypsin deficiency in childhood. *J Pediatr Gastroenterol Nutr* 1976;88:19-25.
10. Sveger T. Liver disease in α 1-antitrypsin deficiency detected by screening in 200,000 infants. *N Engl J Med* 1976;294:1316-21.
11. Ibarguen E. Liver disease in α 1-antitrypsin deficiency and prognostic indicators. *J Pediatr Gastroenterol Nutr* 1990;117:864-70.
12. Filippini F, Soubrane O, Labrousse F, et al. Liver transplantation for end stage liver disease associated with α 1-antitrypsin deficiency in children: Pretransplant natural history, timing, and results of transplantation. *J Hepatol* 1994;21(1):72-78.
13. Esquivel CO, Vicente E, Van-Thiel D, et al. Orthotopic liver transplantation for α 1-antitrypsin deficiency: An experience in 29 children and ten adults. *Transplant Proc* 1987;19(5):3798-802.
14. Gishan FK. α 1-antitrypsin deficiency presenting with ascites and cirrhosis in the neonatal period. *Gastroenterology* 1983;85:435-38.
15. Perlmutter DH. α 1-antitrypsin deficiency: Diagnosis and treatment. *Clin Liver Dis* 2004;8:839-59.
16. Eriksson S, Carlson J, Velez R. Risk of cirrhosis and primary liver cancer in α 1-antitrypsin deficiency. *N Engl J Med* 1986;314(12):736-39.
17. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med* 2003;168:818-900.

18. Triger DR, Millward-Sadler GH, Czaykowski AA, et al. Alpha-1 antitrypsin deficiency and liver disease in adults. *Q J Medicine* 1976;178:351-72.
19. DuBois S, Kowdley KV. Review article: Targeted screening for hereditary haemochromatosis in high-risk groups. *Aliment Pharmacol Ther* 2004;20:1-14.
20. Bacon BR, Powell LW, Adams PC, et al. Molecular medicine and hemochromatosis: At the crossroads. *Gastroenterology* 1999;116:193-207.
21. Deugnier Y, Turlin B, le Quilleuc D, et al. Are appraisal of hepatic siderosis in patients with end-stage cirrhosis practical implications for the diagnosis of hemochromatosis. *Am J Surg Pathol* 1997;21:669-75.
22. Brandhagen DJ, Alvarez W, Therneau TM, et al. Iron overload in cirrhosis-HFE genotypes and outcome after liver transplantation. *Hepatology* 2000;31:456-60.
23. Fargion S, Mandelli C, Peiperno A, et al. Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. *Hepatology* 1992;15:655-59.
24. Kilpe VE, Krakauer H, Wren RE. An analysis of liver transplant experience from 37 transplant centers as reported to medicare. *Transplantation* 1993;56:554-61.
25. Kowdley KV, Brandhagen DJ, Gish RG, et al. Survival after liver transplantation in patients with hepatic iron overload: The national hemochromatosis transplant registry. *Gastroenterology* 2005;129(2):494-503.
26. Kowdley KV, Hassanein T, Kaur S, et al. Primary liver cancer and survival in patients undergoing liver transplantation for hemochromatosis. *Liver Transpl Surg* 1995;1:237-41.
27. Tung BY, Farrell FJ, McCashland TM, et al. Long-term follow-up after liver transplantation in patients with hepatic iron overload. *Liver Transpl Surg* 1999;5(5):369-74.
28. Crawford DHG, Fletcher LM, Hubscher SG, et al. Patient and graft survival after liver transplantation for hereditary hemochromatosis: Implications for pathogenesis. *Hepatology* 2004;39:1655-62.
29. Kowdley KV. Liver transplantation: An "in vivo" model for the pathophysiology of hemochromatosis? *Hepatology* 2004;39:1495-98.
30. Colombo C, Russo MC, Zazzaron L, et al. Liver disease in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2006;43(1):S49-55.
31. Feranchak AP, Sokol RJ. Cholangiocyte biology and cystic fibrosis liver disease. *Semin Liver Dis* 2001;21:471-88.
32. Colombo CBP, Podda M. Hepatobiliary disease in cystic fibrosis. *Semin Liver Dis* 1994;14: 259-69.
33. Cohn JA, Strong TV, Picciotto MR, et al. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. *Gastroenterology* 1993;105:1857-64.
34. Mauraage C, Lenaerts C, Weber AM, et al. Meconium ileus and its equivalent as a risk factor for the development of cirrhosis: An autopsy study in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1989;9:17-20.
35. Colombo C, Battezzati PM, Crosignani A, et al. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. *Hepatology* 2002;36:1374-82.
36. Lamireau T, Monnereau S, Martin S, et al. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. *J Hepatol* 2004;41(6):920-25.
37. Feigelson J, Anagnostopoulos C, Poguet M, et al. Liver cirrhosis in cystic fibrosis-the therapeutic implications and long term follow up. *Arch Dis Child* 1993;68:653-57.
38. Gooding I, Dondos V, Gyi KM, et al. Variceal hemorrhage and cystic fibrosis: Outcomes and implications for liver transplantation. *Liver Transpl* 2005;11:1522-26.
39. Milkiewicz P, Skiba G, Kelly D, et al. Transplantation for cystic fibrosis outcome following early liver transplantation. *J Gastroenterol Hepatol* 2002;17:208-13.
40. Noble-Jamieson G, Valente J, Barnes ND, et al. Liver transplantation for hepatic cirrhosis in cystic fibrosis. *Arch Dis Child* 1994;71:349-52.
41. Chaves-Cartaya R, Drage M, Jamieson NV. Biliary complications in liver transplantation for cystic fibrosis. *Transplant Proc* 1999;31(6):2411-12.
42. Couetil JP, Soubrane O, Houssin DP, et al. Combined heart-lung-liver, double lung-liver, and isolated liver transplantation for cystic fibrosis in children. *Transpl Int* 1997;10(1):33-39.
43. Mack DR, Traystman MD, Colombo JL, et al. Clinical denouement and mutation analysis of patients with cystic fibrosis undergoing liver transplantation for biliary cirrhosis. *J Pediatr* 1995;127:881-87.
44. Colombo C, Crosignani A, Rocchi A, et al. Effects of liver transplantation on the nutritional status of patients with cystic fibrosis. *Transpl Int* 2005;18:246-55.
45. Kristine YZ, Bruce YT, Kris VK. Liver transplantation for metabolic liver diseases. *Clin Liver Dis* 2007;11:265-81.
46. D Alagille, M Odièvre, M Gautier, JP Dommergues. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *Journal of Pediatrics*, St. Louis, 1975;86:63-71.
47. Oda T, Elkahoul AG, Pike BL, et al. "Mutations in the human Jagged1 gene are responsible for Alagille syndrome". *Nat Genet* 1997;16 (3):235-42.
48. Samejima H, Torii C, Kosaki R, et al. "Screening for Alagille syndrome mutations in the JAG1 and NOTCH2 genes using denaturing high-performance liquid chromatography". *Genet Test* 2007;11(3):216-27.

Non-alcoholic Fatty Liver Disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver disease in the world. Absence of significant amount of alcohol consumption (<40 g of ethanol/week) is essential for diagnosis of NAFLD. It includes a spectrum of conditions with hepatic steatosis in the absence of significant alcohol use. The spectrum of NAFLD includes:

- Fatty liver/hepatic steatosis (FL)
- Fatty liver with nonspecific inflammation (FL-N)
- Non-alcoholic steatohepatitis (NASH)

Fatty liver with or without nonspecific inflammation is believed to have a benign course. Non-alcoholic steatohepatitis (NASH) can progress to cirrhosis, leading to liver failure and hepatocellular carcinoma (HCC).

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

It is the most extreme form of NAFLD, which is regarded as a major cause of cirrhosis of the liver of unknown cause.¹ NASH was first reported described in 1980 from Mayo Clinic.²

NASH is histologically indistinguishable from alcoholic liver disease and is characterised by:

- Hepatic steatosis
- Necroinflammation: Lobular inflammation predominantly with neutrophils, balloon degeneration.
- Presence of fibrosis and/or Mallory bodies.

PREVALENCE OF NAFLD

In unselected populations, the estimated prevalence of NAFLD ranges from 3 to 36.9%.³⁻⁹ The prevalence of NAFLD increases with increase in prevalence of its associated risk factors (e.g. obesity or diabetes mellitus).¹⁰ In patients with various components of metabolic

syndrome, the prevalence of NAFLD ranges from 63% in diabetics to as high as 96% in subjects with morbid obesity.¹¹⁻¹³ In patients who have abnormal liver enzymes in the absence of serologic or biochemical markers of liver disease, the prevalence of NASH ranges from 34 to 40%.^{14,15}

AGE

The prevalence of NAFLD increases with age.^{16,17} Peak prevalence of NAFLD was earlier in men (fourth decade) than women (sixth decade).³ The prevalence of NAFLD seemed lowest in the elderly.¹⁸

GENDER

NAFLD affects both genders equally or slightly higher in men.^{3,16,19,20}

RACIAL AND ETHNIC DIFFERENCES

Higher prevalence of NAFLD is seen in Hispanics and a lower prevalence in non-Hispanic blacks than in non-Hispanic whites.^{5,19-21}

RISK FACTORS FOR NAFLD^{22,23,68}

- Weight gain
- Presence of the metabolic syndrome (obesity, diabetes or hypertriglyceridemia)
- Age (in women only)
- Surgical procedures: Intestinal bypass surgery
- Polycystic ovarian syndrome
- Rapid weight loss
- Abetalipoproteinemia
- Total parenteral nutrition (TPN)

Patients with NASH are more likely to have the metabolic syndrome (obesity, dyslipidemia,

hypertension, and insulin resistance) than are those who have simple steatosis. Presence of the metabolic syndrome confers a 4- to 11-fold increased risk for future development of NAFLD and the presence of the metabolic syndrome is less likely to be associated with regression of NAFLD.²² Association of NAFLD with metabolic syndrome is known as "Syndrome X."

Table below shows prevalence of metabolic syndrome in patients of NAFLD.²⁴⁻³¹

Metabolic syndrome	Association with NAFLD
Obesity	25 to 93%
Diabetes	30 to 50%
Hyperlipidemia	92%

DIAGNOSIS

There are no accurate and sensitive noninvasive markers for NAFLD and NASH.

- Liver biopsy is the current gold standard in the diagnosis of NAFLD and NASH is
- Hepatic enzymes may be normal.
- Hepatic imaging can detect hepatic steatosis but generally lacks sensitivity in those who have minimal steatosis.³²
- Proton magnetic resonance spectroscopy is a promising noninvasive imaging modality to detect and quantify hepatic steatosis; however, it is expensive and, thus, difficult to use as a screening tool.⁵

None of these tests can differentiate between FL or FL-N and NASH.^{32,33}

The ratio of NASH to NAFLD of 1:3 in liver biopsy studies, the prevalence of NASH in the general population was estimated to be 5.7% and that of NAFLD was estimated to be 17%.³⁴

NATURAL HISTORY OF NAFLD³⁵⁻⁴⁰

The natural course of NAFLD has been studied using paired biopsy studies and cohort studies.⁶⁹ The figure below shows the natural course of NAFLD. Those who have FL or FL-N have a generally benign prognosis, whereas those who have NASH can have progressive fibrosis leading to cirrhosis and then complications leading to death or timely liver transplantation. The patients with FL or FL-N may develop NASH, but the rate of progression of fibrosis is slow and the development of cirrhosis or complications of cirrhosis is uncommon.^{28,36,38,41,45} Conversely, those with NASH on initial presentation lack this ability and can progress to varying degrees of fibrosis and cirrhosis.²⁸ There is a higher proportion of subjects who were obese in the studies and they showed progression to cirrhosis.^{35,36}

An important issue in the management of patients who have NAFLD is the identification of patients who have risk factors associated with progressive disease. High BMI and diabetes are found to be risk factors for progression to fibrosis and cirrhosis.³⁵ Obesity and diabetes mellitus are also shown in cohort studies leading to excess deaths from cirrhosis and its complications, including HCC.^{42,43} In persons who did not consume alcohol, obesity was associated with a fourfold-increased risk for cirrhosis-related death or hospitalization.⁴⁴

PRETRANSPLANT EVALUATION OF NASH RELATED CIRRHOSIS PATIENT

Careful evaluation of such patients in the pretransplant period is essential to rule out metabolic syndrome. More aggressive investigations like exercise stress test, dobutamine stress echocardiography and cardiac catheterization may be necessary to rule out ischemic heart disease. In case of diabetic patients strict control of blood sugar is essential and 24 hour urine collection for protein and creatinine to look for the evidence of diabetic nephropathy.

CLINICAL OUTCOME IN NAFLD

In majority of the patients with FL and FL-N, a benign prognosis is seen, although progression to NASH and cirrhosis can occur.^{41,45} Patients who had FL embedded within a cohort that included all histologic subtypes of NAFLD likewise showed similar benign long-term outcomes.³⁸ Patients who have NASH have a different clinical outcome from patients who have FL or FL-N and development of fibrosis and cirrhosis is comparatively high.²⁸

Cardiovascular disease is a leading cause of death in cohorts of patients with NAFLD.^{28,38} Several recent studies have high lighted the association NAFLD with increased atherogenesis that seems to be independent of insulin resistance or the presence of metabolic syndrome.⁴⁶⁻⁴⁸ Hence NAFLD patients might require aggressive evaluation and management of cardiovascular risk factors in addition to management of chronic liver disease.⁴⁹

CLINICAL OUTCOME IN NASH

The development of cirrhosis in patients with NASH alters the prognosis significantly. Hui et al. reported that nearly 40% patients with NASH-related cirrhosis develop complications of cirrhosis after a median follow-up of 5 years.⁵¹ Once cirrhosis develops in patients with NASH, the prognosis is poor and seems no different from patients with HCV-related cirrhosis.^{50,51}

CORRELATION OF NAFLD AND HCC

The association of HCC and NAFLD was described first in case reports.⁵²⁻⁵⁴ Serial liver biopsies in patients who had NASH show loss of steatosis as progression occurs from steatohepatitis to cirrhosis, which then can be interpreted as cryptogenic cirrhosis.^{26,37} Earlier studies have reported that patients with cryptogenic cirrhosis resemble patients with NASH more closely than patients with HCV-related cirrhosis.⁵⁵⁻⁵⁷ Bugianesi et al.⁵⁸ reported that patients with HCC associated with cryptogenic cirrhosis were more likely to have features suggestive of NASH than those who had HCC resulting from alcohol- or viral-associated cirrhosis. Marrero et al. in their series reported that at least one half of the patients with cryptogenic cirrhosis had histologic or clinical features of NASH and estimated that NASH accounted for at least 13% of all cases of HCC.⁵⁹ Adam et al reported that 10% of patients who had NASH-related cirrhosis developed HCC after a median follow-up of 7 years.³⁸ This shows that increased risk for HCC in patients with obesity or diabetes, both established risk factors for NASH.^{42,43}

HCC does develop in patients who have NASH-related cirrhosis, although the exact carcinogenic risk has yet to be determined. In patients who have NAFLD with progression to cirrhosis, it seems that it is reasonable to screen for HCC, as is done in cirrhosis from other causes.⁶⁸

Role of NAFLD donors on organ function: The cause of suboptimal performance of transplanted fatty livers is not clearly known. Probably the decreased mitochondrial ATP synthesis during cold preservation and significant reperfusion injury are the causes for suboptimal graft function.^{66,67}

TREATMENT OF NAFLD

Treatment of NAFLD is not well established.

- **Exercise and Lifestyle modification** significantly improves insulin sensitivity, reduce blood pressure, lipid levels, and decrease cardiovascular mortality. Lifestyle modifications such regular exercise and weight reduction should be combined with medication to control diabetes, hypertension, and hypercholesterolemia after liver transplantation and is necessary to decrease the incidence of recurrent NAFLD.
- **Antioxidants** such as vitamin E and betaine have some role.
- Few studies have used glitazones.^{62,63}
Glitazones (Pioglitazone, Rosiglitazone): In normal population, rosiglitazone has improved liver histology in 59% of patients in 2 years treatment⁶² and improvement in serum liver biochemical tests and histology is seen with pioglitazone.⁶³

LIVER TRANSPLANTATION IN NAFLD

Liver transplant survival rate seems to be similar to the recipients with other chronic liver diseases.^{60,61} More importantly, recurrence of FL and NASH after liver transplantation occurs and can be severe enough to lead to allograft failure.⁶¹ In USA, approximately 7% of liver transplantations are undertaken for cryptogenic cirrhosis.^{64,65} The patients transplanted for cryptogenic cirrhosis, steatosis is likely to develop if the underlying cause is NASH.⁶⁵

Recurrent of NASH after LTX is reported to be as 11% to 38%.⁷⁰ Increased prevalence of recurrent steatosis and NASH may be explained in terms of the metabolic derangements and immunosuppression related dyslipidemia commonly seen after liver transplantation.⁶⁸

REFERENCES

1. Clark JM, Diehl AM (2003). "Nonalcoholic fatty liver disease: An underrecognized cause of cryptogenic cirrhosis". JAMA 2003;289:3000-04.
2. Ludwig J, Viggiano TR, McGill DB, Oh BJ (1980). "Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease". Mayo Clin Proc 55.
3. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterol 2003;124(1):71-9.
4. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. Gastroenterology 2002;124(1):71-79.
5. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the united states: impact of ethnicity. Hepatology 2004;40(6):1387-95.
6. Omagari K, Kadokawa Y, Masuda J, et al. Fatty liver in non-alcoholic non-overweight japanese adults: Incidence and clinical characteristics. J Gastroenterol Hepatol 2002;17(10):1098-105.
7. Ground KE. Liver pathology in aircrew. Aviat Space Environ Med 1982;53(1):14-18.
8. Hilden M, Christoffersen P, Juhl E, et al. Liver histology in a 'normal' population: examinations of 503 consecutive fatal traffic casualties. Scand J Gastroenterol 1977;12(5):593-7.
9. Nomura H, Kashiwagi S, Hayashi J, et al. Prevalence of fatty liver in a general population of Okinawa, Japan. Jpn J Med 1988;27(2):142-49.
10. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: From steatosis to cirrhosis. Hepatology 2006;43(2 Suppl 1):S99-112.
11. Ong JP, Elariny H, Collantes R, et al. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. Obes Surg 2005;15(3):310-15.
12. Kemmer NM, McKinney KH, Xiao SY, et al. High prevalence of NASH among Mexican-American females with Type II diabetes mellitus. Philadelphia: WB Saunders 2001. p.A117.
13. Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: Predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121(1):91-100.
14. Daniel S, Ben-Menachem T, Vasudevan G, et al. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. Am J Gastroenterol 1999;94(10):3010-4.

15. Skelly MM, James PD, Ryder SD. Findings on liver biopsy to investigate abnormal liver function tests in the absence of diagnostic serology. *J Hepatol* 2001;35(2):195-9.
16. Shen L, Fan JG, Shao Y, et al. Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: An epidemiological survey. *World J Gastroenterol* 2003;9(5):1106-10.
17. Fan JG, Zhu J, Li XJ, et al. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. *J Hepatol* 2005;43(3):508-14.
18. Kagansky N, Levy S, Keter D, et al. Non-alcoholic fatty liver diseased a common and benign finding in octogenarian patients. *Liver Int* 2004;24(6):588-94.
19. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003;98(5):960-7.
20. Weston SR, Leyden W, Murphy R, et al. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. *Hepatology* 2005;41(2):372-9.
21. Caldwell SH, Harris DM, Patrie JT, et al. Is NASH under diagnosed among African Americans? *Am J Gastroenterol* 2002;97(6):1496-500.
22. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005;143(10):722-28.
23. Falck-Ytter Y, Younossi ZM, Marchesini G, et al. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001;21(1):17-26.
24. Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980;55(7):434-38.
25. Lee RG. Nonalcoholic steatohepatitis: A study of 49 patients. *Hum Pathol* 1989;20(6):594-98.
26. Powell EE, Cooksley WG, Hanson R, et al. The natural history of nonalcoholic steatohepatitis: A follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990;11(1):74-80.
27. Cortez-Pinto H, Camilo ME, Baptista A, et al. Non-alcoholic fatty liver: another feature of the metabolic syndrome? *Clin Nutr* 1999;18(6):353-58.
28. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;116(6):1413-19.
29. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology* 1999;30(6):1356-62.
30. Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002;35(2):373-79.
31. Diehl AM, Goodman Z, Ishak KG. Alcohollike liver disease in nonalcoholics. A clinical and histologic comparison with alcohol-induced liver injury. *Gastroenterology* 1988;95(4):1056-62.
32. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002;123(3):745-50.
33. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003;37(6):1286-92.
34. McCullough AJ. The epidemiology and risk factors of NASH. In: Farrell GC, George J, de la M Hall P, et al, editors. *Fatty liver disease: NASH and related disorders*. Malden (MA): Blackwell Publishing 2005 p 23-37.
35. Adams LA, Sanderson S, Lindor KD, et al. The histological course of nonalcoholic fatty liver disease: A longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005;42(1):132-38.
36. Harrison SA, Torgerson S, Hayashi PH. The natural history of nonalcoholic fatty liver disease: A clinical histopathological study. *Am J Gastroenterol* 2003;98(9):2042-47.
37. Day CP. Pathogenesis of steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002;16(5):663-78.
38. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. *Gastroenterology* 2005;129(1):113-21.
39. Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. *Hepatology* 2004;39(3):770-8.
40. Fassio E, Alvarez E, Dominguez N, et al. Natural history of nonalcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. *Hepatology* 2004;40(4):820-26.
41. Dam-Larsen S, Franzmann M, Andersen IB, et al. Long term prognosis of fatty liver: Risk of chronic liver disease and death. *Gut* 2004;53(5):750-55.
42. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348(17):1625-38.
43. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004;126(2):460-68.
44. Ioannou GN, Weiss NS, Kowdley KV, et al. Is obesity a risk factor for cirrhosis-related death or hospitalization? A population-based cohort study. *Gastroenterology* 2003;125(4):1053-59.
45. Teli MR, James OF, Burt AD, et al. The natural history of nonalcoholic fatty liver: a followup study. *Hepatology* 1995;22(6):1714-19.
46. Villanova N, Moscatiello S, Ramilli S, et al. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. *Hepatology* 2005;42(2):473-80.
47. Targher G. Associations between liver histology and early carotid atherosclerosis in subjects with nonalcoholic fatty liver disease. *Hepatology* 2005;42(4):974-75.
48. Brea A, Mosquera D, Martin E, et al. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: A case-control study. *Arterioscler Thromb Vasc Biol* 2005;25(5):1045-50.
49. McPherson DD. Circulatory dysfunction in NAFLD which is first, which is last, and what do we do in between? *Hepatology* 2005;42(2):270-2.
50. Ratzl V, Bonyhay L, Di Martino V, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology* 2002;35(6):1485-93.
51. Hui JM, Kench JG, Chitturi S, et al. Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. *Hepatology* 2003;38(2):420-27.
52. Cotrim HP, Parana R, Braga E, et al. Nonalcoholic steatohepatitis and hepatocellular carcinoma: natural history? *Am J Gastroenterol* 2000;95(10):3018-19.
53. Zen Y, Katayanagi K, Tsuneyama K, et al. Hepatocellular carcinoma arising in non-alcoholic steatohepatitis. *Pathol Int* 2001;51(2):127-31.

54. Shimada M, Hashimoto E, Taniai M, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Hepatol* 2002;37(1):154-60.
55. Caldwell SH, Oelsner DH, Iezzoni JC, et al. Cryptogenic cirrhosis: Clinical characterization and risk factors for underlying disease. *Hepatology* 1999;29(3):664-69.
56. Poonawala A, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: A case-control study. *Hepatology* 2000;32(4 Pt 1):689-92.
57. Ong J, Younossi ZM, Reddy V, et al. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl* 2001;7(9):797-801.
58. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: From cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;123(1):134-40.
59. Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. *Hepatology* 2002;36(6):1349-54.
60. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2001;7(4):363-73.
61. Charlton M, Kasparova P, Weston S, et al. Frequency of nonalcoholic steatohepatitis as a cause of advanced liver disease. *Liver Transpl* 2001;7(7):608-14.
62. Neuschwander-Tetri BA, Brunt E, Wehmeier KR, et al. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology* 2003;38:1008-17.
63. Promrat K, Lutchman G, Uwaifo GI, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004;39(1):188-96.
64. Liver transplant waiting list. UNOS database 2000. Available at: <http://www.optn.org/.com>
65. Cantos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl* 2001;7:363-73.
66. Fukumori T, Okhohchi N, Tsukamoto S et al. Why is the fatty liver unsuitable for transplantation? Detioration of mitochondrial ATP synthesis and sinusoidal structure during cold preservation of a liver with steatosis. *Transpl proceed* 1997;29:412-15.
67. Gao W, Connor HD, Lamestars JJ, et al. Primary nonfunction of fatty liver produced by alcohol is associated with a new, antioxidant insensitive free radical species. *Transplant.* 1995;15:674-79
68. Janus P Ong, Zobair M Younossi. Approach to the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease. *Clin Liver Dis* 2005;9:617-34
69. JP Ong, ZM Younossi. Epidemiology and Natural History of NAFLD and NASH. *Clin Liver Dis* 2007;11:1-16.
70. Kotlyer DS, Campbell MS, Reddy KR, et al. Recurrence of diseases following orthotopic liver transplantation. *Am J Gastroenterol* 2006;101:1370-78.

Wilson's Disease

Synonym: Hepatolenticular degeneration

INTRODUCTION

The disease was named after British neurologist, Dr Samuel Alexander Kinnier Wilson (1878-1937), who described the disease in 1912. It is characterized by of copper in tissues like liver, kidney, cornea, central nervous system, heart, skin and blood. It is an autosomal recessive disorder.¹ The Wilson's disease gene (ATP7B) has been mapped to chromosome 13 (13q14.3) which codes for a P-type ATPase that transports copper into bile and incorporates it into ceruloplasmin.^{2,3} Female/Male ratio is 4:1. Presents in the age group of 6-20 years. Its incidence in the Western populations is 1 per 30,000. Rate of carriers is 1 in 100, meaning that 1 in 100 people are unaffected carriers of heterozygous mutation. Presentation before 5 years and after 40 years rare in spite of biochemical defect present since birth.

SIGNS AND SYMPTOMS^{4,5}

- **CNS:** Copper deposits in the basal ganglia, particularly in lenticular nucleus (putamen+ globus pallidus) causing cell death and Parkinson's disease.
- **Hepatic symptoms:** 40-50% cases, 10- 14 years of age
- **Neurologic symptoms:** 40-50% cases, 20-22 years of age
- **Hepatic:** Chronic active hepatitis leading to cirrhosis
- Fulminant liver failure (which is characterized by low alkaline phosphatase, low ceruloplasmin and high bilirubin levels), Rarely Hepatocellular carcinoma
- **Neuropsychiatric symptoms:**⁶ Dementia, mood disorders, asterixis (a flapping tremor of the hands), Parkinsonism, Psychiatric symptoms (Behavioral, Affective, Schizophrenia like symptoms, Cognitive).
- **Renal:** Renal tubular acidosis, kidney stones,
- **Ophthalmic:** Kayser-Fleischer rings (brown rings around the cornea in the eye that result from copper deposition in Descemet's membrane of the cornea.⁷

- Sunflower cataracts (brown or green pigmentation of the anterior and posterior lens capsule).
- **Cardiac:** Cardiomyopathy, cardiac arrhythmias
- **Cutaneous:** Hidradenitis suppurate
- **Hematological:** Anemia, present only in severe cases.
- Musculoskeletal
 - *Skeletal involvement:* Osteopenia on conventional radiologic examination.
 - Arthropathy occurs in 20-50% of patients after age of 20 years frequently involves the spine and large appendicular joints, such as knees, wrists, and hips.

DIAGNOSIS⁸⁻¹⁰

- **LFT:** Low serum alkaline phosphatase¹¹
- Low ceruloplasmin level (<30%) in over 80% of patients (Normal level 20-60 mg/dl)
- 24 hour Urinary copper elevated usually >100 ug/dl (Normal 15-50 micro gm/day)
- Blood copper level elevated (Normal: Males: 70-140 ug/dl, Females: 80-153 ug/dl)

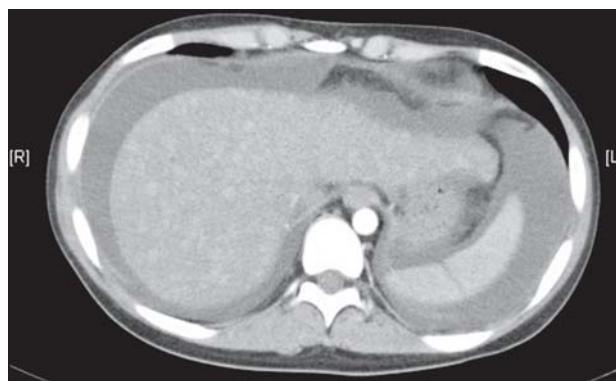


Figure 46.1: CT scan image of wilson's disease

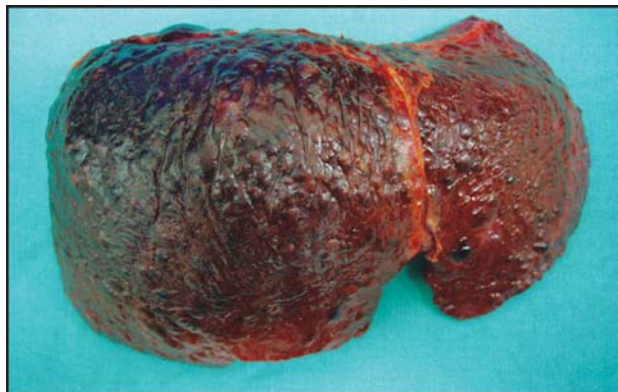


Figure 46.2: Liver in a Wilson's disease patient

- **Liver biopsy:** Increased copper (normal <10 ug/gm dry weight of liver). Usually > 20 times the normal level in Wilson's disease.

RADIOLABELLED COPPER

- It directly assays hepatic copper metabolism.
- Blood sample collected at 1, 2, 4, 24, and 48 hours after oral ingestion of radiolabelled copper (Cu64 or Cu67) to see radioactivity in serum.
- In normal people radioactivity immediately appears after absorption followed by hepatic clearance and reappearance of the radioactivity in serum occurs as the labeled copper is incorporated into newly synthesized ceruloplasmin and released into the circulation.
- Heterozygotes exhibit a slow lower-level reappearance of radioactivity rather than the continued fall in radioactivity in those with Wilson disease.
- Patients with Wilson disease, even those with normal ceruloplasmin levels, do not exhibit the secondary rise in radioactivity.

GENETIC DIAGNOSIS

- Linkage analysis has been used in family studies for presymptomatic testing
- Multiplicity of mutations (>200 mutations of ATP7B are identified) that require screening in individuals without affected family members^{12,13}
- Molecular testing is currently limited to screening of family members for an identified mutation detected in the index patient.

IMAGING STUDIES

- Cranial CT scan findings are typically bilateral
 - Well-defined, slit like, low-attenuation foci involving basal ganglia, particularly the putamen

- Larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus.
- Widening of the frontal horns of the lateral ventricles and diffuse cerebral and cerebellar atrophy and histologically proven neuronal loss.
- Brain MRI
 - More sensitive than CT scan in detecting early lesions.
 - MRI studies show bilateral focal abnormalities of 3-15 mm diameter, in the white matter, pons, and deep cerebellar nuclei, appearing with low signal intensity on T1-weighted images and with high signal intensity on T2-weighted images, representing cell loss and gliosis.
 - A characteristic "face of the giant panda" sign has been described, formed by high signal intensity in the tegmentum (except for the red nucleus), preserved signal intensity of the lateral portion of the pars reticulata of the substantia nigra, and hypointensity of the superior colliculus.

POSITRON EMISSION TOMOGRAPHY SCAN (PET SCAN)

- PET scan reveals a significantly decreased cerebral metabolic rate of glucose consumption in the cerebellum, striatum, cortex and thalamus.
- PET analyses of patients of Wilson disease have marked reduction in the activity of dopa-decarboxylase indicating impaired function of the nigrostriatal dopaminergic pathway.
- All these abnormalities improve with chelation therapy, indicating a reversible component of striatal neuron injury.
- CT scan, MRI, ultrasound, and nuclear medicine studies are neither specific nor sensitive for Wilson disease.

ELECTRON MICROSCOPY

- The electron microscopic detection of copper-containing hepatocytic lysosomes is helpful for the diagnosis of early stages of Wilson disease in addition to the quantification of hepatic copper by atomic absorption spectrophotometry.

TREATMENT^{14,15}

- Avoid mushrooms, nuts, chocolate, dried fruit, liver, legumes and shellfish (especially lobster).
- Restrict copper < 1 mg/day.
- Lifelong treatment
- **Chelating agents:** Remove the copper from the tissues
 - D-penicillamine (16)

Dose: 1 gm/day (adults), 20 mg/kg/day for children
maintenance: 750 mg to 1 g/d PO QD 30 min after meals

C/I: hypersensitivity, renal insufficiency, aplastic anemia

- *Trientine (Triethylene tetramine hydrochloride)*: Useful in patients who can not tolerate penicillamine.

Dose: 250-500 mg TID or 0.5-2 gms/day (adults), 20 mg/kg/day (children) indicated if initial presentation is hepatic related and is administered with zinc.

C/I: hypersensitivity, biliary cirrhosis, rheumatoid arthritis, cystinuria

- *Ammonium tetrathiomolybdate*: 120 mg/day

- **Pregnancy in Wilson's disease**: Can have a successful pregnancy while undergoing chelation therapy at a reduced dosage, particularly in the third trimester. Some studies say its safety is not established in pregnancy.

- **Vitamin B₆ (Pyridoxine)**: Involved in synthesis of GABA.

Dose: 25 mg QD

- **Zinc acetate**: 150-300 mg QD.

- It blocks the intestinal absorption of copper from the diet and endogenous secretions.

- It also acts by producing metallothionein, a protein that binds with copper to prevent its release into the blood, and facilitates elimination via the stool.

- **Dimercaprol**: used for refractory wilson disease not responding to routine treatment

Dose: 3-5 mg/kg IM q4h

C/I: Hypersensitivity, G-6-PD deficiency, concurrent iron supplementation therapy

- Fulminant Wilson disease leads to rapidly progressive hepatic failure, hepatic encephalopathy, coagulopathy and death if emergent liver transplantation is not performed.
- Liver transplantation is effective in patients with fulminant hepatic failure. These patients are listed as status 1 in the waiting list, as per UNOS.
- Transplantation is reserved for patients with fulminant liver failure, end-stage liver cirrhosis which progresses despite chelation therapy.
- In the absence of severe hepatic disease, liver transplantation is generally not recommended for treatment of refractory extrahepatic manifestations.
- Transplantation is curative, but as it is only undertaken in severely ill patients the prognosis is still mediocre.
- Dystonia and parkinsonian: Anticholinergics, Tizanidine, Baclofen, Levodopa, or (GABA) γ -aminobutyric acid agonists—particularly clonazepam.

PROGNOSIS¹⁷

- **Prognostic index**: Wilson disease with Fulminant Hepatitis

Score	0	1	2	3	4
Serum bilirubin (range, 3-20 mmol/l)	< 100	100-150	151-200	201-300	> 300
Serum AST (range, 7-40 IU/l)	< 100	100-150	151-200	201-300	> 300
Prolonged pro-thrombin time (seconds)	< 4	4-8	9-12	13-20	> 30

- Patients with score > 7 must be considered for liver transplantation.
- Patients who exceeded this score die within 2 months of diagnosis inspite of medical treatment.
- Prognosis after liver transplantation is relatively good and comparable to other causes of liver transplantation.

FOLLOW-UP

- **First 4-6 weeks after chelation therapy**: Weekly 24-hour urinary copper, CCB count, urinalysis, serum free copper, LFT and renal function tests following initiation of chelation therapy.

- **Monitor efficacy as follows**:

- Measure serum non-ceruloplasmin bound copper:

Formula: Total serum copper (mcg/dL) - 3 [ceruloplasmin (mg/dL)]. (Normal <15 mcg/dL).

- Measure urinary copper excretion. Urinary chelator levels usually measure 200-500 mcg/day. Urinary zinc levels usually measure <75 mcg/day.

- Bimonthly evaluations are recommended through the first year, followed by yearly examinations thereafter.
- In patients with Kayser-Fleischer rings: Slit-lamp examination once in a year.
- Lifelong, uninterrupted chelation therapy is necessary in all patients with Wilson disease.
- Frequent follow-up with patients is necessary, secondary to patient decompensation and Fulminant hepatic failure due to noncompliance.
- Patients should avoid alcohol and hepatotoxic drugs.
- First-degree relatives of any patient newly diagnosed with Wilson disease must be screened for the condition
- Wilson disease with Pregnancy
- Excessive intrauterine copper concentrations may be responsible for the high rate of spontaneous abortions.
- D-penicillamine at a lower dose (0.75-1.5 g/d) appears to pose no risk to the fetus and must be continued throughout pregnancy.

REFERENCES

1. Sternlieb I, Twedt DC, Johnson GF, et al. "Inherited copper toxicity of the liver in Bedlington terriers". *Proc. R. Soc. Med.* 1977;70(Suppl 3):8-9.
2. Bowcock AM, Farrer LA, Hebert JM, et al. Eight closely linked loci place the Wilson disease locus within 13q14-q21. *Am J Hum Genet* Nov 1988;43(5):664-74.
3. de Bie P, Muller P, Wijmenga C, et al. "Molecular pathogenesis of Wilson and Menkes disease: Correlation of mutations with molecular defects and disease phenotypes" *J Med Genet* 2007;44 (11):673-88.
4. Cuthbert JA. Wilson's disease. Update of a systemic disorder with protean manifestations. *Gastroenterol Clin North Am* Sep 1998;27(3):655-81.
5. Walshe JM. Copper: Its role in the pathogenesis of liver disease. *Semin Liver Dis.* Aug 1984;4(3):252-63.
6. Grubenbecher S, Stüve O, Heffter H, et al. "Prion protein gene codon 129 modulates clinical course of neurological Wilson disease". *Neuroreport* 2006;17(5):549-52.
7. Kinnier Wilson SA. "Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver". *Brain* 1912;34(1):295-507.
8. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000;223(1):39-46.
9. Perri RE, Hahn SH, Ferber MJ. Wilson Disease—keeping the bar for diagnosis raised. *Hepatology.* Oct 2005;42(4):974.
10. Schilsky ML. Wilson disease: new insights into pathogenesis, diagnosis, and future therapy. *Curr Gastroenterol Rep* Feb 2005;7(1):26-31.
11. Shaver WA, Bhatt H, Combes B. "Low serum alkaline phosphatase activity in Wilson's disease". *Hepatology* 1986;6(5):859-63.
12. Thomas GR, Forbes JR, Roberts EA, et al. The Wilson disease gene: spectrum of mutations and their consequences. *Nat Genet* Feb 1995;9(2):210-17.
13. Tanzi RE, Petrukhin K, Chernov I, et al. "The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene". *Nat Genet* 1993;5(4):344-50.
14. Ala A, Walker AP, Ashkan K, et al. "Wilson's disease". *Lancet* 2007;369(9559):397-408.
15. Roberts EA, Schilsky ML. "A practice guideline on Wilson disease". *Hepatology* 2003;37(6):1475-92.
16. Walshe JM. "Penicillamine, a new oral therapy for Wilson's disease". *Am J Med* 1956;21(4):487-95.
17. Merle U, Schaefer M, Ferenci P, et al. "Clinical presentation, diagnosis and long-term outcome of Wilson's disease: A cohort study". *Gut* 2007;56(1):115-20.

Budd-Chiari Syndrome

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare disorder that is characterized by hepatic venous outflow obstruction, usually associated with a prothrombotic state. Obstruction can occur at any level from the hepatic venules to the right atrium of the heart. It occurs predominantly in young adults and affects more women than men.¹ The expert panels have defined BCS as hepatic venous outflow obstruction between the hepatic veins and the right atrium.² Venocclusive disease as nonthrombotic

Most common causes of Budd-Chiari syndrome⁶⁻⁸

- Congenital caval membranes (Eastern countries)¹
- Myeloproliferative disorders (MPD) (50%) (Western countries)
 - Polycythemia vera
 - Essential thrombocytosis
- Dysfunction of the coagulation cascade (Western countries)
 - Factor V Leiden mutation
 - Protein C and S deficiency
 - antithrombin III deficiency
- Hypercoagulable states (10-20 %) (2)
 - use of estrogen/oral contraceptives
 - pregnancy (10%)
 - tumors (10%)
- Paroxysmal nocturnal hemoglobinuria (5%)
- Antiphospholipid syndrome
- Idiopathic 20%
- Other causes
 - Trauma
 - Hepatitis
 - Hepatic abscess
 - Inflammatory bowel disease
 - Polycystic liver disease

obstruction of sinusoids is excluded from this definition. This obstruction causes venous stasis, centrilobular congestion, and hepatocyte necrosis, which leads to centrilobular fibrosis, nodular regenerative hyperplasia, and ultimately cirrhosis of the liver.³ Spontaneous resolution has been reported,⁴ and up to 25% of patients remain asymptomatic.⁵

PRESENTATION

It varies from completely asymptomatic patient to fulminant hepatic failure. Common manifestations are -

- Right upper quadrant pain
- Hepatomegaly
- Abdominal ascites

Three forms of presentation:^{9,10}

- *Acute/fulminant form*: Presents with rapidly worsening encephalopathy and ascites
- *Subacute form*: It is the most common form and presents with minimal ascites and hepatic necrosis because of sinusoidal decompression through the collateral venous circulation.
- *Chronic form*: Present with the end-stage liver disease and portal hypertension.

HCC in BCS patients:¹¹ Hepatocellular carcinoma can cause hepatic vein or IVC obstruction by direct vascular invasion of the tumor, resulting in secondary outflow occlusion. Alternatively, HCC can develop de novo in patients with BCS and cirrhosis.

DIAGNOSTIC WORK UP

- Duplex ultrasound: First modality of investigation with an accuracy of 70%¹²
- CT scan: Assessment of
 - Patency of hepatic veins
 - Parenchymal abnormalities

- Caudate lobe hypertrophy¹³
- Ascites

Caudate lobe hypertrophy is due to compensatory mechanism following hepatic venous outflow obstruction. It has an important surgical relevance.

- Magnetic resonance imaging:¹⁴ It is useful in
 - Differentiating acute from chronic disease.
 - Detailed evaluation of vascular anatomy, and patency of the supra and infrahepatic vena cava¹⁵
 - Distinguishing benign from malignant disease
- Angiography/Venography may also be considered.
- Liver biopsy is usually is needed as part of the evaluation for liver transplantation. Patients who have bridging fibrosis and cirrhosis are suitable candidates for liver transplantation and have an excellent post-transplantation prognosis.
- Bone marrow biopsy is required in patients with suspected myeloproliferative disorders

TREATMENT

MEDICAL TREATMENT

- **Heparin** is started, followed by addition of Warfarin for long-term therapy.
- **Control of ascites**
 - Fluid and sodium restriction (sodium-60 to 90 mEq/day = 1500 to 2000 mg of salt) for control of ascites
 - Diuretics: furosemide (20-40 mg/d) and/or spironolactone (50-200 mg/d)
 - Regular abdominal paracentesis in tense ascites
- **Control of variceal bleeding**
 - β -blockers
 - Endoscopic therapy

Treatment failure is defined as worsening liver function, refractory ascites, hepatorenal syndrome, or hepatic encephalopathy despite optimal therapy.¹⁶ Medical treatment alone is associated with a high mortality rate of more than 80%.¹⁷

Thrombolytic Therapy

Streptokinase or tissue plasminogen activator can be used. Tissue plasminogen activator is the preferred agent because it has a very short half-life (5 minutes), and systemic therapy is of little value.¹⁸

Contraindications to thrombolysis:

- History of a bleeding disorder
- Previous cerebrovascular accident
- Hypertension.

Interventional Therapy¹⁹⁻²³

Hepatic vein recanalization and stenting.²² Balloon angioplasty and stent placement in the IVC and hepatic veins are useful adjuncts to medical therapy in acute setting. Stent placement is recommended because reocclusion occurs frequently after angioplasty.¹⁹ Zhang et al²⁰ reported his series of 115 patients with BCS treated successfully by stent placement in the IVC and hepatic veins in 94 and 87%, respectively. Stent patency with a mean follow-up of more than 45 months was greater than 90%.

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective method and is useful in patients who present late and already have intrahepatic shunt formation.^{21,23} TIPS is preferable to a surgical shunt in most instances, especially if patients have caudate lobe compression of the inferior vena cava or are candidates for liver transplantation.

For the minority of patients who continue to deteriorate despite TIPS, liver transplantation may be considered.

SURGICAL MANAGEMENT

Surgical shunts provide good long-term patency rates.²⁵ The first report of a portocaval shunt in BCS was presented by Blakemore in 1948.²⁴ Published data indicated that surgical portosystemic shunting provides good patency rates, showing long 5-year survival ranging from 69% to 94%.^{1,25-28}

Survival rates after liver transplantation in BCS^{16, 33-40}

Author	year	5 years	10 years	Recurrence	Thrombotic events
Halff et al	1980	~ 50%	-	9	13
Jameieson et al	1991	~ 50%	-	7	18
Srinivasan et al	2002	95%	78%	11	11
Fisher	1999	> 80%	-	-	-
Roselle et al	2004	> 80%	-	-	-
ELTR*	2005	84%	68%	-	-
Cruz et al	2005	65%	65%	27	27
Mentha et al	2006	71%	68%	2	14
Plessier et al	2006	-	-	9	36
Frank et al	2008	89%	84%	7	12

(*ELTR- European liver transplant registry)

In 2004, Murad et al¹ reported a large multicenter study in which a prognostic model, assessing longterm transplantation-free survival, was developed.¹ This model, later referred to as the Rotterdam BCS index, was able to distinguish 3 classes of patients. The equation is as follows:

$$1.27 \times \text{encephalopathy} + 1.04 \times \text{ascites} + 0.72 \times \text{prothrombin time} + 0.004 \times \text{bilirubin}$$

Ascites and hepatic encephalopathy were scored as present (score-1) or absent (score-0).

Prothrombin time was scored as higher (score-1) or lower (score-0) than 2.3 INR. Bilirubin was a continuous variable for which the risk increased with 0.004 per $\mu\text{mol/l}$.

The total score (*i.e.*, the sum of item scores) ranged from 0.02 to 4.03. Three classes of patients could be distinguished such as:

- Class I - Total score between 0 and 1.1
- Class II - Score between 1.1 and 1.5
- Class III - Score of 1.5 and higher

The overall survival rates in this study were 82%, 69%, and 62% at 1, 5, and 10 years, respectively. The 5-year survival rate was 89% for class I, 74% for class II, and 42% for class III.¹

Different shunts procedures such as side-to-side portocaval shunt, mesocaval and mesoatrial (use of Goretex graft in between SMA and right atrium) shunts can be performed in BCS. Synthetic H Grafts can also be used for shunt reconstruction. Side to side portocaval shunts are most preferred. Mesoatrial shunts are discouraged due to an unacceptable incidence of graft thrombosis and death.²⁹

LIVER TRANSPLANTATION

First report of a successful liver transplantation for BCS was reported in 1976.³⁰ Fulminant BCS with irreparable necrosis of liver parenchyma and chronic forms with established cirrhosis and progressive hepatic decompensation are the indications for orthotopic liver transplantation (OLT).³¹ Life long anticoagulation is required after LTX to avoid recurrence of BCS.

Technical concerns at the time of transplantation are prior shunt placement and caudate lobe hypertrophy. Pre-existing portacaval shunts can make the hilar dissection particularly challenging. Caudate lobe enlargement may make mobilization of the liver extremely difficult. Optimal exposure is mandatory. Patients with significant portal hypertension and prior shunt surgery are placed on venovenous bypass (both peripheral and portal). This bypass allows portal decompression during the dissection, thus reducing blood loss and preserving hemodynamic stability.

Vascular complications in the form of thrombosis in portal vein/hepatic vein/IVC²¹ are more after LTX for BCS. Hence the patients are on long term anticoagulation therapy. Mentha et al.²¹ reported that mortality rate ranges upto 40% after recurrence of BCS or other vascular complications. Nearly, 40% of early deaths occurred among patients who had a creatinine $> 160 \mu\text{mol/l}$ at the time of LTX, while patients with a normal renal function did well, with a survival of 77% at 10 years.

Liver transplantation for BCS is a safe treatment option in patients who fail to respond to conventional therapies including thrombolysis, angioplasty, TIPS, or shunt surgery, and should be considered before renal failure occurs.^{32,38}

RECURRENCE

Rate of recurrence of BCS after transplantation ranges from 2-27%.^{16,33-35,38,39}

Thrombotic events after LTX range from 11-36%.^{16, 33-35,38,40}

REFERENCES

1. Murad SD, Valla DC, de Groen PC, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. *Hepatology* 2004;39:500-08.
2. Janssen HL, Garcia-Pagan JC, Elias E, et al. Budd-Chiari syndrome: A review by an expert panel. *J Hepatol* 2003;38:364-71.
3. Tanaka M, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. *Hepatology* 1998;27:488-96.
4. Mahmoud AE, Mendoza A, Meshikhes AN, et al. Clinical spectrum, investigations and treatment of Budd-Chiari syndrome. *QJM* 1996;89(1):37-43.
5. Bismuth H, Sherlock DJ. Portosystemic shunting versus liver transplantation for the Budd-Chiari syndrome. *Ann Surg* 1991;214(5):581-89.
6. Singh V, Sinha SK, Nain CK, et al. Budd-Chiari syndrome: our experience of 71 patients. *J Gastroenterol Hepatol* 2000;15:550-54.
7. Olzinski AT, Sanyal AJ. Treating Budd-Chiari syndrome: Making rational choices from a myriad of options. *J Clin Gastroenterol* 2000;30:155-61.
8. MA Zimmerman, AM Cameron, RM Ghobrial. Budd-Chiari Syndrome. *Clin Liver Dis* 2006;10:259-73.
9. HemmingAW, Langer B, Greig P, et al. Treatment of Budd-Chiari syndrome with portosystemic shunt or liver transplantation. *Am J Surg* 1996;171(1):176-80.
10. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. *N Engl J Med* 2004;350(6): 578-85.
11. Takayasu K, Muramatsu Y, Moriyama N, et al. Radiological study of idiopathic Budd-Chiari syndrome complicated by hepatocellular carcinoma. A report of four cases. *Am J Gastroenterol* 1994;89(2):249-53.

12. Stanley P. Budd-Chiari syndrome. *Radiology* 1989;170(3 Pt 1):625-27.
13. McKusick MA. Imaging findings in Budd-Chiari syndrome. *Liver Transpl* 2001;7(8):743-44.
14. Noone TC, Semelka RC, Siegelman ES, et al. Budd-Chiari syndrome: Spectrum of appearances of acute, subacute, and chronic disease with magnetic resonance imaging. *J Magn Reson Imaging* 2000;11(1):44-50.
15. Maetani Y, Itoh K, Egawa H, et al. Benign hepatic nodules in Budd-Chiari syndrome: Radiologic-pathologic correlation with emphasis on the central scar. *AJR Am J Roentgenol* 2002;178(4):869-75.
16. Plessier A, Sibert A, Consigny Y, et al. Aiming at minimal invasiveness as a therapeutic strategy for Budd-Chiari syndrome. *Hepatology* 2006;44:1308-16.
17. McCarthy PM, van Heerden JA, Adson MA, et al. The Budd-Chiari syndrome. Medical and surgical management of 30 patients. *Arch Surg* 1985;120:657-62.
18. Sharma S, Texeira A, Texeira P, et al. Pharmacological thrombolysis in Budd Chiari syndrome: A single centre experience and review of the literature. *J Hepatol* 2004;40(1):172-80.
19. Fisher NC, McCafferty I, DolapciM, et al. Managing Budd-Chiari syndrome: A retrospective review of percutaneous hepatic vein angioplasty and surgical shunting. *Gut* 1999;44(4):568-74.
20. Zhang CQ, Fu LN, Xu L, et al. Long-term effect of stent placement in 115 patients with Budd-Chiari syndrome. *World J Gastroenterol* 2003;9(11):2587-91.
21. Eapen CE, Velissaris D, Heydtmann M. Favourable medium term outcome following hepatic vein recanalisation and/or transjugular intrahepatic portosystemic shunt for Budd-Chiari syndrome. *Gut* 2006;55:878-84.
22. Klein AS. Management of Budd-Chiari syndrome. *Liver Transpl* 2006;12(2):S23-S28.
23. Olliff SP. Transjugular intrahepatic portosystemic shunt in the management of Budd Chiari syndrome. *Eur J Gastroenterol Hepatol* 2006;18:1151-54.
24. Blakemore AH. Porto-caval anastomosis. *Surg Clin North Am* 1948;28:279-89.
25. Bachet JB, Condat B, Hagege H, et al. Long-term portosystemic shunt patency as a determinant of outcome in Budd-Chiari syndrome. *J Hepatol* 2007;46:60-68.
26. Pisani-Ceretti A, Intra M, Prestipino F, et al. Surgical and radiologic treatment of primary Budd-Chiari syndrome. *World J Surg* 1998;22:48-53.
27. Orloff MJ, Daily PO, Orloff SL, et al. A 27-year experience with surgical treatment of Budd-Chiari syndrome. *Ann Surg* 2000;232:340-352.
28. Slakey DP, Klein AS, Venbrux AC, et al. Budd-Chiari syndrome: Current management options. *Ann Surg* 2001;233:522-527.
29. Marshall J Orloff, Pat O Daily, Susan L Orloff, et al. A 27-Year Experience With Surgical Treatment of Budd-Chiari Syndrome. *Annals of surgery* 2000;232(3):340-52.
30. Putnam CW, Porter KA, Weil R 3rd, et al. Liver transplantation of Budd-Chiari syndrome. *JAMA* 1976;236:1142-43.
31. Klein AS, Molmenti EP. Surgical treatment of Budd-Chiari syndrome. *Liver Transpl* 2003;9:891-96.
32. Dorry LS, Geoffrey CN, Jayme EL, et al. Twenty Years of Liver Transplantation for Budd-Chiari Syndrome: A National Registry Analysis. *Liver transplantation* 2007;13:1285-94.
33. Halff G, Todo S, Starzl TE, et al. Liver transplantation for the Budd-Chiari syndrome. *Ann Surg* 1990;211:43-49.
34. Jamieson NV, Williams R, Calne RY. Liver transplantation for Budd-Chiari syndrome, 1976-1990. *Ann Chir* 1991;45:362-65.
35. Srinivasan P, Rela M, Prachalias A, et al. Liver transplantation for Budd-Chiari syndrome. *Transplantation* 2002;73:973-77.
36. Fisher NC, McCafferty I, Dolapci M, et al. Managing Budd-Chiari syndrome: A retrospective review of percutaneous hepatic vein angioplasty and surgical shunting. *Gut* 1999;44:568-74.
37. Rossle M, Olschewski M, Siegerstetter V, et al. The Budd-Chiari syndrome: Outcome after treatment with the transjugular intrahepatic portosystemic shunt. *Surgery* 2004;135:394-403.
38. Mentha G, Giostra E, Majno PE, et al. Liver transplantation for Budd-Chiari syndrome: A European study on 248 patients from 51 centres. *J Hepatol* 2006;44:520-28.
39. Cruz E, Ascher NL, Roberts JP, et al. High incidence of recurrence and hematologic events following liver transplantation for Budd-Chiari syndrome. *Clin Transplant* 2005;19:501-06.
40. F Ulrich, J Pratschke, U Neumann, et al. Eighteen Years of Liver Transplantation Experience in Patients with Advanced Budd-Chiari Syndrome. *Liver transplant* 2008;14:144-50.

Recent Advances in Liver Transplantation

INTRODUCTION

Liver transplantation has significantly improved the prognosis in patients with ESLD. The improvement in the techniques, better postoperative care and newer immunosuppressive agents has improved the longterm survival in liver transplantation. But it has several limitations such as the shortage of organ donors, complications and life long immunosuppression. In live donor transplantation donor complications are also significant. The incidence of chronic liver failure is expected to increase over the next 10 years as a result of the silent epidemic of hepatitis C. As a result of the

shortage of donor organs, potential liver transplant patients must often await a donor liver for years. Only about 5000 patients each year receive a solid liver transplantation. Clearly, the vast majority of patients with liver diseases cannot rely on organ transplantation as a solution. There is an urgent need for new technologies for acute and long-term support of patients with damaged livers.

Recent developments as alternative to liver transplantation options are:

- Hepatocyte transplantation
- Xenotransplantation
- Stem cell transplantation

(A) HEPATOCYTE TRANSPLANTATION

It is thought that the function of the liver can only be replaced by functioning liver cells, thereby requiring the availability of liver tissue from xenogenic or human sources. Hepatocyte transplantation (HT) may be a useful bridge to transplantation for selected patients with liver failure.¹⁻⁵ Mito et al (1992) reported the first clinical experience of hepatocyte transplantation in humans.²⁵ Unfortunately his trial did not show any clinical improvement in clinical status of his patients.

INDICATIONS

- Acute liver failure¹¹
- Inborn errors of metabolism
 - Glycogen storage disease, type 1 (Muraca et al⁶)
 - Crigler-Najjar syndrome type I⁹
- Urea cycle disorders
- Infantile Refsum disease, an autosomal recessive inborn error in peroxisomal metabolism of very-long chain fatty acids, bile acid metabolism, and pipecolic acid catabolism (Sokal et al⁷)
- Liver-based metabolic disorder characterized by a severe deficiency in the production and secretion of the coagulation factor VII. Dhawan et al. reported that after HT, the requirement for exogenous factor VII diminished to approximately 20%.⁸
- Fumaryl-lactate hydrolase deficiency¹¹
- Hereditary tyrosinemia type I¹¹
- **Chronic liver disease:** Kobayashi et al. results from studies in rats showed that intra-splenic HT could improve liver function in chronic liver diseases. They also suggested that hepatocytes transplanted into the

spleen could receive much better perfusion and be in closer contact with the portal circulation than those that are located in the peritoneum or the orthotopic cirrhotic liver.¹⁰

ROUTES OF HEPATOCYTE TRANSPLANTATION

- Transhepatic approach is commonly used. But when repeated cell infusions are required, Other approaches are used
- Umbilical vein; if it is patent, it can be elegantly used for portal vein access. During HT, the ductus venosus has to be blocked with a second balloon catheter to prevent shunting of the cells into the caval vein.^{12,13}
- Inferior mesenteric vein can also be used for portal vein access¹⁴
- Middle colic vein may be a good alternative in case of portal vein thrombosis⁵⁰

In virtually all human patients, HT has been associated with a clinical improvement of the patient. However, no complete correction of any metabolic disease in human patients by HT alone has been reported.

ADVANTAGES OF HT

Advantages of HT over whole liver transplantation:

- Whole livers can only be transplanted within a short time after procurement; isolated liver cells may be cryopreserved for later use in emergencies.¹⁶
- A single donor could potentially provide hepatocytes for several patients.
- It is a minimally invasive procedure carrying less morbidity and expense than whole organ transplantation.
- Hepatocyte transplantation should not interfere with subsequent OLT.

The most reliable sites for hepatocyte engraftment and function are:¹⁷

- Liver
- Spleen.
- Peritoneal cavity
- Portal vein
- Subcutaneous tissue

Portal vein infusion or injection of hepatocytes into the splenic pulp results in seeding of the transplanted cells into the liver parenchyma. Transplantation of hepatocytes has been shown to significantly improve the survival of animals with both chemically and surgically induced acute liver failure¹⁸ and to prevent the development of intracranial hypertension in pigs with acute ischemic liver failure.¹⁹ Studies using transgenic animals have indicated that massive repopulation of the host liver by engrafted hepatocytes requires that the transplanted cells undergo a proliferative stimulus to which the host hepatocytes cannot respond.²⁰

The proliferative stimulus may consist of the:

- Loss of hepatic mass, such as partial hepatectomy
- Reperfusion injury
- Massive apoptosis mediated by Fas-gene transfer
- Administration of stimulants of hepatocellular mitosis.

Conceptually, hepatocyte transplantation should be especially suitable for treating acute liver failure because the liver remains architecturally normal and has considerable potential for recovery.

CLINICAL STUDIES²¹

Habibulla et al.²² from India reported 7 patients who received a single intraperitoneal infusion of fetal hepatocytes harvested from 26 to 34 weeks gestational age fetuses. The overall survival of patients receiving hepatocytes was 43%, as compared with 33% in matched control subjects. All the patients in grade III hepatic encephalopathy, who received a liver cell transplant survived, whereas matched control subjects who did not receive transplants had a 50% mortality rate.

Strom et al.²³ reported the use of hepatocyte transplantation (mixture of between 107 and 109 freshly isolated and cryopreserved liver cells) via splenic arterial perfusion as a bridge to liver transplantation in 5 patients with grade IV hepatic encephalopathy and multisystem organ failure. All the patients maintained normal cerebral perfusion, cardiac stability and blood ammonia levels decreased significantly with withdrawal of medical support 2 to 10 days before liver transplantation. In contrast 4 patients with illness of equal severity were used as control subjects, all died within 3 days.

Bilir et al.²⁴ reported 5 patients with acute liver failure (grade III to IV encephalopathy and factor V levels less than 0.5 U/ml, ventilator and dialysis dependent) who underwent intrasplenic and/or intrahepatic hepatocyte transplantation. There was an initial improvement (in encephalopathy scores, arterial ammonia level, and prothrombin time) in 3 patients who survived for 12, 28, and 52 days, respectively. Postmortem examination showed the presence of transplanted hepatocytes in liver and spleen by light microscopy and fluorescent *in situ* hybridization (FISH).

Approximately 20% of patients with acute liver failure might survive without transplantation. Although transplanted hepatocytes may have provided clinical benefit, convincing evidence of engraftment and function of the transplanted cells is difficult to prove. Relatively less than optimal liver cell number, quality and viability after cryopreservation in some of the earlier transplants may have also been a factor. For better results may be seen in the future if multiple hepatocytes infusions are performed. Further prospective randomized control studies are needed to clarify the outcomes of patients who receive liver cell transplants for acute liver failure.²¹

SOURCES OF HEPATOCYTES

Liver Rejected for Transplantation

The most limiting factor in HT is a lack of livers to harvest hepatocytes. Usually the only source of livers to harvest hepatocytes is livers that are rejected for transplantation. Approximately 25% of livers²⁵ from multiorgan donors are refused for transplantation each year, mostly because of misdiagnosed cirrhosis or high-grade steatosis. Using this pool of organs as a source of human hepatocytes for transplantation purpose is an approach to save livers and improve long-term outcome of patients affected by terminal liver disease. But in liver with >20% steatosis, the hepatocytes do not have the metabolic capabilities of normal hepatocytes.

Fetal Hepatocytes

Fetal hepatocytes have several characteristics that make them potentially suitable as donor cells. They are highly proliferative, which may facilitate engraftment and expansion of transplanted cell population.²⁶

Bone Marrow-derived Cells

Many articles have been published mentioned the possibility that pluripotent stem cells reside in the bone marrow and can contribute to liver regeneration after noxious insults to the liver.²⁷⁻²⁹ These studies have been undertaken in both animal models of liver progenitor cell activation and in anecdotal cases of sex-mismatched human liver and bone marrow transplantation analyzing the expression of the Y chromosome in the livers of males transplanted from a female donor and in the hepatic tissue of females with a bone marrow transplant from a male donor. Lagasse et al.³⁰ reported the intravenous injection of adult bone marrow cells in the tyrosinemic mouse model and demonstrated rescue of the mouse and restoration of biochemical function of the liver.

Immortalized Cells

Several studies have investigated the use of conditionally immortalized hepatocytes for liver cell transplantation.^{31,32} These cell lines are based on the use of the SV40 large T antigen that can induce temperature-sensitive immortalization through the production of a protein that is active at 33°C, but is conformationally inactivated at 39°C. These conditionally immortalized hepatocytes become de-differentiated and would not therefore be suitable for clinical use because of the risk of tumorigenesis. Thereafter, cell lines have been constructed with an additional herpes simplex virus–thymidine kinase so that ganciclovir can be used to destroy any

simian virus 40 large T-antigen (SV40Tag) expressing cells should the control of these cells become unregulated.

Liver Resected for Malignancy

In a study from Australia, Haghighi et al. have demonstrated the successful initial stages of harvesting tumor-free hepatocytes from liver resected for metastatic tumors such as colorectal and pancreatic cancers. Tumor cells were removed using immunomagnetic technique.³³

Banking of Human Liver Cells

Primary isolated human hepatocytes are the best source of hepatic tissue for liver cell-based therapy. The major drawbacks to the use of primary isolated human hepatocytes are the difficulty to identify human livers suitable for cell isolation and

The important factors preventing the use of HT are:

- Limited availability of hepatocytes from human livers unsuitable for orthotopic liver transplantation.³⁴⁻³⁶
- Lack of development of a standardized and centralized method of cell isolation and conservation in many countries.

Hepatocyte Apoptosis during Rejection

Donor hepatocyte apoptosis is induced by recipient cytotoxic T lymphocytes during acute rejection episodes, representing a major impediment for the application of hepatocyte transplantation.³⁷ The mechanisms of transplant hepatocyte loss involve Fas-mediated pathways.^{38,39} BCL-2 genetic modification can protect liver cells from Fas-mediated apoptosis.^{40,41} Wang et al. reported that adenovirus-mediated BCL-2 gene transfer protects transplanted hepatocytes from Fas-mediated cytolysis, thus holding promise for a new avenue of acute liver failure treatment.⁴²

NATURAL COURSE OF THE TRANSPLANTED HEPATOCYTES

Transplantation of isolated syngeneic and allogeneic hepatocytes are rapidly disintegrated by recipient mechanisms of innate immunity, irrespective of origin or site of engraftment, namely, spleen, liver, portal vein, peritoneum, or subcutaneous tissue. The cell implantation procedure creates a wound which leads to local mobilization and activation of granulocytes and macrophages, as well as to deposition of complement and coagulation factors. The scavenging phase of wound healing is initiated. Transplanted cells become the victims of the wound healing process, being removed with wound debris. Only a few cells survive among the large number

of hepatocytes that had been transplanted in suspension into tissues and body cavities.⁴³⁻⁴⁶ Wesolowska et al. reported that elimination of recipient natural killer cells with irradiation and bone marrow transfusion prevents early destruction of transplanted hepatocytes.⁴⁷

FUTURE ALTERNATIVE SOURCES

Future alternative sources for HT are xenotransplants, immortalized human hepatocytes⁴⁸ and stem cell-derived hepatocytes.^{15,49}

REFERENCES

1. Fisher RA, Bu D, Thompson M, et al. Defining hepatocellular chimerism in a liver failure patient bridged with hepatocyte infusion. *Transplantation* 2000;69:303.
2. Fox IJ, Chowdhury JR. Hepatocyte transplantation. *Am J Transplant* 2004;4(Suppl 6):7.
3. Lee SW, Wang X, Chowdhury NR, et al. Hepatocyte transplantation: State of the art and strategies for overcoming existing hurdles. *Ann Hepatol* 2004;3:48.
4. Maruyama M, Totsugawa T, Kunieda T, et al. Hepatocyte isolation and transplantation in the pig. *Cell Transplant* 2003;12:593.
5. Mito M, Kusano M, Kawaura Y. Hepatocyte transplantation in man. *Transplant Proc* 1992;24:3052.
6. Muraca M, Gerunda G, Neri D, et al. Hepatocyte transplantation as a treatment for glycogen storage disease type 1a. *Lancet* 2002;359:317.
7. Sokal EM, Smets F, Bourgois A, et al. Hepatocyte transplantation in a 4-year-old girl with peroxisomal biogenesis disease: Technique, safety, and metabolic follow-up. *Transplantation* 2003;76:735.
8. Dhawan A, Mitry RR, Hughes RD, et al. Hepatocyte transplantation for inherited factor VII deficiency. *Transplantation* 2004;78:1812.
9. Fox IJ, Chowdhury JR, Kaufman SS, et al. Treatment of the Crigler-Najjar syndrome type I with hepatocyte transplantation. *N Engl J Med* 1998;338:1422.
10. N Kobayashi, M Ito, J Nakamura, et al. The role of hepatocyte transplantation to treat chronic liver failure. *Transplant Proceed* 2000;32:2287-88.
11. Overturf K, Al-Dhalimy M, Tanguay R, et al. Hepatocytes corrected by gene therapy are selected *in vivo* in a murine model of hereditary tyrosinaemia type I. *Nat Genet* 1996;12:266.
12. Horslen SP, McCowan TC, Goertzen TC, et al. Isolated hepatocyte transplantation in an infant with a severe urea cycle disorder. *Pediatrics* 2003;111:1262.
13. Mitry RR, Dhawan A, Hughes RD, et al. One liver, three recipients: Segment IV from split-liver procedures as a source of hepatocytes for cell transplantation. *Transplantation* 2004;77:1614.
14. Darwish AA, Sokal E, Stephenne X, et al. Permanent access to the portal system for cellular transplantation using an implantable port device. *Liver Transpl* 2004;10:1213.
15. Miki T, Lehmann T, Cai H, et al. Stem cells characteristics of amniotic epithelial cells. *Stem Cells* 2005;23:1549.
16. Moshage HJ, Rijntjes PJ, Hafkenscheid JC, et al. Primary culture of cryopreserved adult human hepatocytes on homologous extracellular matrix and the influence of monocytic products on albumin synthesis. *J Hepatol* 1998;7:34.
17. Demetriou AA, Levenson SM, Novikoff PM, et al. Survival, organization and function of microcarrier-attached hepatocytes transplanted in rats. *Proc Natl Acad Sci USA* 1998;83:7475.
18. Gupta S, Chowdhury JR. Hepatocyte transplantation: Back to the future. *Hepatology* 1992;15:156.
19. Arkadopoulos N, Chen SC, Khalili TM, et al. Transplantation of hepatocytes for prevention of intracranial hypertension in pigs with ischemic liver failure. *Cell Transplant* 1998;7:357.
20. Laconi S, Pillai S, Porcu PP, et al. Massive liver replacement by transplanted hepatocytes in the absence of exogenous growth stimuli in rats treated with retrorsine. *Am J Pathol* 2001;158:771.
21. U Baccarani, GL Adani, M Sainz, et al. Human hepatocyte transplantation for acute liver failure: State of the Art and Analysis of Cell Sources. *Transplant Proceed* 2005;37:2702-04.
22. Habibullah CM, Syed IH, Qamar A, et al. Human fetal hepatocyte transplantation in patients with fulminant hepatic failure. *Transplantation* 1994;58:951.
23. Strom SC, Chowdhury JR, Fox IJ. Hepatocyte transplantation for the treatment of human disease. *Semin Liver Dis* 1999;19:39.
24. Bilir BM, Guinette D, Karrer F, et al. Hepatocyte transplantation in acute liver failure. *Liver Transpl* 2000;6:32.
25. Piccolo G, Donini A, Baccarani U, et al. *Cell Transpl* 1999;8:202.
26. Lilja H, Blanc P, Demetriou AA, et al. Response of cultured fetal and adult rat hepatocytes to growth factors and cyclosporine. *Cell Transplant* 1998;7:257.
27. Alison M, Golding M, Lalani el N, et al. Wound healing in the liver with particular reference to stem cells. *Philos Trans R Soc Lond B Biol Sci* 1998;353:877.
28. Petersen BE, Bowen WC, Patrene KD, et al. Bone marrow as a potential source of hepatic oval cells. *Science* 1999;284:1168.
29. Theise ND, Nimmakayalu M, Gardner R, et al. Liver from bone marrow in humans. *Hepatology* 2000;32:11.
30. Lagasse E, Connors H, Al-Dhalimy M, et al. Purified hematopoietic stem cells can differentiate into hepatocytes *in vivo*. *Nat Med* 2000;6:1229.
31. Allen KJ, Reyes R, Demmler K, et al. Conditionally immortalized mouse hepatocytes for use in liver gene therapy. *J Gastroenterol Hepatol* 2000;15:1325.
32. N Kobayashi, H Noguchi, T Watanabe, et al. Role of immortalized hepatocyte transplantation in acute liver failure. *Transplant Proceed* 2001;33:645-46.
33. KS Haghighi, WWL Woon, J Akhter, et al. A new source of hepatocytes for transplantation. *Transplant Proceed* 2004;36:2466-68.
34. Bilir BM, Guinette D, Karrer F, et al. Hepatocyte transplantation in acute liver failure. *Liver Transpl* 2000;6:32.
35. Horslen SP, McCowan TC, Goertzen TC, et al. Isolated hepatocyte transplantation in an infant with a severe urea cycle disorder. *Pediatrics* 2003;111:1262.
36. Fisher RA, Bu D, Thompson M, et al. Defining hepatocellular chimerism in a liver failure patient bridged with hepatocyte infusion. *Transplantation* 2000;69:303.
37. Kawahara T, Kasai S, Yagita H, et al. Critical role of Fas/Fas ligand interaction in CD28-independent pathway of allogeneic murine hepatocyte rejection. *Hepatology* 1997;26(4):944-48.
38. Song E, Chen J, Lutz J, et al. FLIM58, a blocking peptide for FAS ligand, reduces apoptotic cell death of allogeneic-transplanted hepatocytes in spleen. *Transplant Proc* 2001;33(1-2):650.

39. Wang J, Li W, Min J, et al. Transplant Proc Fas siRNA reduces apoptotic cell death of allogeneic-transplanted hepatocytes in mouse spleen 2003;35(4):1594.
40. Lacronique V, Mignon A, Fabre M, et al. Bcl-2 protects from lethal hepatic apoptosis induced by an anti-Fas antibody in mice Nat Med 1996;2(1):80-6.
41. Song E, Chen J, Antus B, et al. Adenovirus-mediated Bcl-2 gene transfer inhibits apoptosis and promotes survival of allogeneic transplanted hepatocytes. Surgery 2001;130(3):502-11.
42. J Wang, W Li, J Min, Q Ou, et al. Intrasplenic transplantation of allogeneic hepatocytes modified by BCL-2 gene protects rats from acute liver failure. Transplant Proceed 2004;36:2924-26.
43. de Ross WK, von Geusau BA, Bouwman E, et al. Monitoring engraftment of transplanted hepatocytes in recipient liver with 5-bromo-2'-deoxyuridine. Transplantation 1997;63(4):513-18.
44. Olszewski WL, Interewicz B, Durlak M, et al. Early loss of transplanted autologous hepatocytes-lysis by leukocytes in vivo and in vitro. Transplant Proceed 2001;33(1-2):651-3.
45. Olszewski WL, Rudowska A, Mecner B, et al. Autologous transplanted hepatocytes: depletion of recipient leukocytes prevents in vivo lysis. Transplant Proceedings 2002;34(2):705-06.
46. Wanhg X, Moritini E, Al-Dhalimy M, et al. Kinetics of liver repopulation after bone marrow transplantation Am J Pathol 2002;161(2):565-74.
47. A Wesolowska, WL Olszewski, M Durlak. Transplantation of Hepatocytes: Elimination of Recipient Natural Killer Cells With Irradiation and Bone Marrow Reconstitution Prevent Early Graft Dysfunction. Transplant Proceed 2003;35:2358-60.
48. Cai J, Ito M, Nagata H, et al. Treatment of liver failure in rats with end-stage cirrhosis by transplantation of immortalized hepatocytes. Hepatology 2002;36:386.
49. Avital I, Feraresso C, Aoki T, et al. Bone marrow-derived liver stem cell and mature hepatocyte engraftment in livers undergoing rejection. Surgery 2002;132:384.
50. J Meyburg, F Hoerster, J Weitz, et al. Use of the Middle Colic Vein for Liver Cell Transplantation in Infants and Small Children. Transplantn Proceed 2008;40:936-37.

(B) XENOTRANSPLANTATION

Organ transplantation is a highly successful treatment modality, but its application is severely restricted by a worldwide shortage of organs. Xenotransplantation would eliminate this organ shortage. Xenotransplantation (Xeno: Greek word-foreign) is the transplantation of living cells, tissues or organs from one species to another such as from pigs to humans. Such cells, tissues or organs are called xenografts or xenotransplants. To overcome the shortage of human organs for transplantation, pigs are considered as xenogeneic donors.

Advances in immunology and genetics foretold the transplantation of animal tissues and cells into humans, which could become a reality in the future.¹⁻³ Thomas E. Starzl, wrote that: "History tells us that procedures that were inconceivable yesterday, and are barely achievable today, often become the routine of tomorrow." Today, Xenotransplantation is barely achievable; I am convinced that tomorrow, xenotransplantation will become routine.

Pig cells express a carbohydrate epitope called the α -gal-epitope which is also expressed on tissues of all mammals except humans and subhuman primates. Humans and primates have natural antibodies against this epitope. If a pig kidney is perfused with human blood, the preformed antibodies react with the α -gal-epitope. This antibody-antigen reaction elicits an activation of the complement and clotting systems, causing injury to the vascular thrombosis leading to hyperacute rejection.

In Europe during early 1990s, White et al. from Cambridge developed pigs that were transgenic for a human complement inhibitor known as h-DAF. When organs from such pigs were transplanted into primates, hyperacute rejection was usually avoided. If the primates were treated with immunosuppressive agents, the pig organs could, in some animals, function for several weeks.⁴ Following renal transplantation, post-operational function was obtained for 78 days in 1 recipient.⁵ However, many of the pig kidneys were lost within days or weeks due to rejection, whereas many of the primates died of adverse reactions related to the immunosuppressive treatment.

Zhong et al.⁶ reported orthotopic heart transplantations in baboons using organs from h-DAF transgenic pigs, with a maximum survival of 38 days. It indicates that the pig kidneys and hearts could function in primates for several weeks, but the results were inconsistent and many of the recipients died. There was the potential risk of transmitting porcine endogenous retroviruses (PERV). It was finally

concluded that progress had been made, but that the technology was not sufficiently developed for clinical application.

ADVANTAGES OF XENOTRANSPLANTATION¹⁸

- Allow wider indications
- Eliminates organ shortage
- Eliminate living donors
- Eliminate use of marginal donor organs
- Eliminate the waiting time
- Allow recipient pretreatment
- Allow immune modification of donors
- Protect from HLA and autoantibody
- Allow proper scheduling of organ transplant
- Inbred donors facilitate tolerance

Historical review of xenotransplantation of liver

Author	Country	Animal source	Survival	Year
Starzl	USA	Chimpanzee	9 days	1969
Bertoye and Marion	France	Baboon	>4 months	1969
Leger	France	Baboon	72 h	1970
Giles and Starzl	USA	Chimpanzee	26 h	1970
Pouyet and Berard	France	Baboon	<2 days	1971
Starzl	USA	Chimpanzee	14 days	1974
Makowka	USA	Pig	34 h	1992
Starzl	USA	Baboon	70 days	1992
Starzl	USA	Baboon	26 days	1993

(Source: Deschamps J-Y, Roux FA, Say P, Gouin E¹⁷ and Taniguchi and Cooper⁷⁻¹⁶)

MAJOR HURDLES FOR DEVELOPMENT IN XENOTRANSPLANTATION¹⁸

- Immune barriers
- Xenoviruses
- Ethical issues

Immunological Barrier

Highly effective immunological barriers, such as hyperacute rejection causes rapid destruction of the xenograft in the recipient.¹⁹⁻²³ Innate immunity seems to play a major role in rejection of pig xenografts in primate models. In particular, tumor necrosis factor (TNF), produced by natural killer cells and macrophages, contributes to xenograft rejection by promoting endothelial cell activation and the recruitment of

inflammatory cells. TNF binds to two distinct high-affinity receptors, TNF-Receptor 1 (TNFR1, p55) and TNF-Receptor 2, which are co expressed in most cell types.²⁴ TNFR1 mediates the majority of cytotoxic and proinflammatory TNF activities, whereas the effects of TNFR2 vary depending on the cell type.²⁴ Interestingly, TNF does not always function cross-species, as human TNF α (hTNF α) binds poorly to murine TNFR2.²⁵ Reports have shown that both pTNFR1 and pTNFR2 binds hTNF α with high affinity.^{26,27}

The current focus of the xenograft community is the genetic engineering of donor pigs to diminish the immunologic response encountered on graft reperfusion. At present, 2 transgenic strategies are used to diminish hyperacute rejection in porcine organs such as:

- Strategy 1 adds human complement-regulatory proteins (CRPs) to the surface of pig cells.
- Strategy 2 is α -gal down regulation that diminishes the major xenoepitope on the surface of porcine cells.²⁸⁻³²

The development of transgenic pigs with human CRPs has made hyperacute rejection more manageable.^{33,34} In 2002, research groups in Boston and Pittsburgh succeeded in cloning pigs. The genes that encode α -galactosyltransferase were eliminated, and the pigs did not express the α -gal-epitope.³⁵⁻³⁷ So it is possible to produce α 1, 3-galactosyltransferase gene-knockout (GT-KO) pigs by cloning.¹⁸ The tissue of such pigs is free from Gal (α 50 Gal knockout pigs), the epitope that induces hyperacute xenorejection.

When kidneys and hearts from such " α -gal-knockout" pigs were transplanted to baboons, hyperacute rejection was not seen, and in some immunosuppressed recipients the pig organs survived and functioned for a few months as compared to that seen previously with organs from pigs transgenic for human decay-accelerating factor (hDAF).²⁰ But, long-term function was prevented by graft rejection and thrombotic microangiopathy was seen on histological examination. These findings indicate that there are more pathways to xenograft failure than Gala1, 3Gal (Gal); anti-non-Gal Abs and coagulation incompatibilities may be implicated.¹⁸ Attempts are being made to introduce human genes that would induce complement inhibitors, or inhibitors of coagulation, into the GT-KO pigs. The results of organ transplantation from such pigs are eagerly awaited.

Ramirez, et al. in a study conducted to prevent hyperacute rejection in orthotopic Liver xenotransplantation performed from pigs to baboons, concluded that genetically modified pig livers expressing CD55 and CD59 are resistant to hyperacute rejection and able to maintain hemostasis xenotransplanted baboons.³⁸

Potential targets for prevention of acute vascular rejection³⁹

<i>Molecular Target</i>	<i>Consequence</i>
α -Gal	Binding of xenoreactive antibody
Tissue factor	Thrombosis
FGL2/fibroleukin	Thrombosis
CD39 (ATPDase)	Platelet activation
Tissue factor pathway inhibition	Inhibition of tissue factor-mediated thrombosis
Heme oxygenase 1 (HO-1)	Modulation of apoptosis

Xenoviruses

Virological barriers are mainly represented by infectious porcine endogenous retroviruses (PERV) that cause no harm in the pig itself but have the capacity to productively infect human cells in vitro.⁴⁰⁻⁴² However, the animal models used so far do not reflect transmission of PERV,⁴³ suggesting that an intact immune system is able to effectively suppress productive infections. To minimize this risk, the organs from pigs free of PERV shall be used for xenotransplantation. The use of strictly controlled animals will minimize the risk of transmitting infectious agents from pig to human.⁴⁸

PERV-free means the exclusion of infectious proviruses, But there are numerous truncated proviral sequences that can not be completely eliminated.⁴⁴ Even those defect PERV form a risk in terms of virological safety. If the truncation concerns the envelope (env) gene, it is possible that this mutated provirus acts like a long terminal repeat (LTR) retrotransposon, which amplifies itself intracellularly, a mechanism termed retrotransposition.⁴⁵ LTR retrotransposons belong to the transposable elements in eukaryotes that are acting like retroviruses but, due to the lack of env, they merely circulate intracellularly. This has been shown for gamma-type retrovirus Moloney Murine Leukemia Virus (MoMLV).⁴⁵⁻⁴⁷

Ethical Issues

Ethical issues⁴⁸ are important pertaining to the first patients who will be offered transplantation with xenogenic tissues. One such issue concerns defining the merit/demerits ratio in the context of the first clinical attempts. It might also be difficult to institute an appropriate informed consent procedure. The fact that the patients will have to be monitored for possible infectious diseases for an extended time, possibly for life,

is another ethical concern. There are a number of ethical issues with regard to society at large. It is important to achieve public acceptance of a novel medical technology such as xenogenic transplantation. Any new and unfamiliar treatment modalities are often met with scepticism. Such scepticism prevailed in the 1960s and 1970s when human organ transplantation was in its infancy. When it became apparent that transplantation could return a dying patient to a normal life, the scepticism, and the criticism, abated. The establishment of national guidelines and of an official surveillance system is prerequisites for clinical trials with xenotransplantation. A number of countries already have guidelines in place, whereas others are lagging behind. This raises concerns that some such countries might initiate xenotransplantation programs and attract desperate patients in need of a transplant. The World Health Organization has recently issued a statement against such practices.

XENOGENIC CELL TRANSPLANTATION

It has been shown that diabetes can be cured by the transplantation of human islets of langerhans, and the transplantation of neurons has been tested as a treatment for Parkinson's disease. In view long waiting list for transplantation, the supply of human cellular grafts is inadequate. An alternative would then be to use cellular grafts from pigs.⁴⁰ In the early 1990s, Carl Groth et al.⁴⁹ reported that fetal pig islets were injected into 10 diabetic patients. In 8 patients, islets were injected into the portal vein. These patients had undergone renal transplantation for diabetic nephropathy and were thus on immunosuppressive treatment. 4 patients showed evidence of function of the pig islets, in that there was porcine C-peptide excretion for several months, in 1 patient for more than 1 year. 2 patients had the islets placed under the kidney capsule of a simultaneously transplanted human kidney. A biopsy specimen taken 3 weeks after transplantation showed intact porcine cells. These were the first ever observations of pig cells surviving in the human body. This study indicates in future there is a role for xenogenic cell transplantation.

The main obstacle to hepatocyte transplantation is identifying an appropriate cell source.⁷⁻¹⁰ Human hepatocytes are too scarce. Although immortalized cell lines are plentiful, safety concerns make their use untenable. Porcine hepatocytes, on the other hand, are abundant, maintain their differentiated functions and metabolic activity, and do not present the tumorigenicity and de-differentiation risk of modified cells. The principle obstacle with transplanting porcine cells is rejection. This limitation can be overcome by immunoisolating or encasing the cells within a selectively permeable

polymeric membrane.¹¹⁻¹⁶ The selective membrane barrier admits oxygen and required nutrients and releases bioactive cell secretions, but restricts passage of larger cytotoxic agents from the host immune system. Immunoisolation eliminates the need for chronic immunosuppression and allows the cells to be obtained from human or nonhuman sources, thus avoiding the cell sourcing constraints that limit the clinical application of unencapsulated cell transplants.⁵⁰

SOURCES OF XENOGENIC HEPATOCYTES

There are 2 sources of pig hepatocytes, one from neonates and other from adult pigs. Maintaining and proliferating neonatal hepatocytes has many practical advantages such as:⁵⁰

- Pig liver cells, isolated by enzymatic digestion, were maintained *in vitro* for 3 weeks while the adult derived hepatocytes are difficult to culture.^{51,52} The survival of adult hepatocytes declines precipitously after 3 days in culture with virtually no surviving cells after 7 days.
- It provides time to determine cell viability, morphology, phenotype, and functions such as secreting albumin and factor VIII.
- It allows time for microbial, bacterial, and virologic testing without the need to cryopreserve the cells. Within the timeframe of the current studies, cells from the same herd of animals have been shown to be free of viruses including pig cytomegalovirus (PCMV), pig lymphotropic herpesvirus (PLHV), and pig circovirus (PCV).⁵³
- Maintaining liver cells *in vitro* provides the opportunity to proliferate the cells prior to transplantation. Whereas *in vitro* hepatocyte proliferation would have obvious benefits, it has been difficult to achieve.

Disadvantages of Pig Hepatocyte Transplantation⁵⁰

- Malignant cell lines such as the hepatoblastoma-derived HepG2 carry the risk of inducing hepatic cancer and their altered metabolic phenotype makes them unsuitable for restoring many liver functions.
- SV40 T-antigen immortalized hepatocytes also carry a potential for increased malignant transformation.
- Possibility of transmitting infectious agents such as PERV to the recipient.

XENOPERFUSION

Xenoperfusion¹⁷ via the liver of a pig was first proposed in 1965 by Eiseman et al. (Denver, USA),⁵⁴ 1 month after Sen et al. (Mumbai, India) reported the use of extracorporeal liver perfusion using human livers to treat five patients.^{55,56} Hume et al. (Richmond, USA) in 1967 first tested cross circulation between the arm of a woman

in deep hepatic coma and the leg of a 35-pound baboon, for clearing the human blood.⁵⁷ After 12 hour, the patient had excreted about 5 l of fluid through the baboon's kidney and regained consciousness. 22 days later the patient went home, and the baboon was alive and healthy. Several successful similar studies reported later.⁵⁸⁻⁶⁰

Extracorporeal xenogeneic liver perfusion has been regularly used in the treatment of hepatic encephalopathy^{61,62} but, because of the success of liver transplantation, this procedure was abandoned in the 1980s. Later, it was again used to support patients with fulminant hepatic failure and patients awaiting liver transplantation.⁶³ In spite of the interest elicited by this technique, which has been considered to be successful,⁶⁴ a recent and exhaustive retrospective study showed that long-term survival does not exceed that observed with conventional intensive care.⁶⁵

In 2000, Levy et al. (Dallas, TX, USA) reported the first two successful extracorporeal hepatic supports with transgenic (hDAF/hCD59) porcine livers used as a bridge to human liver transplantation.⁶⁶ The first patient was a 17-year old man with idiopathic acute hepatic failure; he was perfused for 6.5 hour, until the arrival of a human liver. During the perfusion, the porcine liver produced 115 ml of bile. The 2nd patient was an 18-year-old woman with Wilson's disease who was perfused for 10 hour; the porcine liver produced 270 ml of bile. In both cases, successful allotransplantation ensued, with excellent graft function and patients in good health.

PUBLIC OPINION ABOUT XENOTRANSPLANTATION

There was no overwhelming support for xenotransplantation, but over time it seemed as if lower proportions oppose it. Proportional differences in support and opposition between geographical regions remain. Opinions to xenotransplantation depend on many socioeconomic factors. The influence of gender, education and religion on opinions about xenotransplantation was similar as to what is usually the case with other related issues, like the use of animals in biomedical research and other biotechnology/genetic engineering applications.⁶⁷ The attitude toward xenotransplantation is not as favorable among hospital personnel as it is in the general public.⁶⁸ However, the level of acceptance of a transplant organ from an animal among the general population varies between 40 and 79%.⁶⁹⁻⁷²

REFERENCES

1. Weiss R. Science, medicine and the future. *Xenotransplantation*. *BJM* 1998;317:931.
2. Lambrijs D, Sachs DH, Cooper DKC. Discordant organ xenotransplantation in primates. *Transplantation* 1998;66:547.
3. Bach FH, Fishman JA, Daniels N, et al. Uncertainty in xenotransplantation: Individual benefit versus collective risk. *Nat Med* 1995;1:964.
4. Cozzi E, Vial C, Ostlie D, et al. Maintenance triple immunosuppression with cyclosporin A, mycophenolate sodium and steroids allows prolonged survival of primate recipients of hDAF porcine renal xenografts. *Xenotransplantation* 2003;10:300.
5. Schuurman HJ, Pino-Chavez G, Philips MJ, et al. Incidence of hyperacute rejection in pig-to-primate transplantation using organs from hDAF-transgenic donors. *Transplantation* 2002;73:1146.
6. Zhong R, Chen G, Sun F, et al. Pig-to-baboon transplantation using hDAF-transgenic donors: 4 years experience at a Canadian center. *Xenotransplantation* 2003;10:481.
7. Taniguchi S, Cooper DKC. Clinical xenotransplantation: Past, present and future. *Ann R Coll Surg Engl* 1997;79:13.
8. Starzl TE. Orthotopic Heterotransplantation, In *Experience in Hepatic Transplantation* Philadelphia: WB Saunders Co, 1969:408.
9. Bertoye A, Marion P, Mikaeloff P, et al. Essais de traitement de certaines insuffisances hépatiques graves aiguës par greffe hépatique temporaire hépatotrope hépatologique (foie de babouin) [Experiments for the treatment of various severe acute hepatic failures by temporary heterotopic heterologous liver graft (baboon liver)]. *Lyon Med* 1969;222:347.
10. Leger L, Chapuis Y, Lenriot JP. Transplantation hépatotrope d'un foie de babouin à un patient atteint d'hépatite fulminante [Heterotopic transplantation of a baboon liver to a patient with fulminating hepatitis]. *Chirurgie* 1970;96:249.
11. Giles GR, Boehmig HJ, Amemiya H, et al. Clinical heterotransplantation of the liver. *Transplant Proc* 1970;2:506.
12. Pouyet M, Berard P. Deux cas de transplantation hépatotrope vraie de foie de babouin au cours d'hépatites aiguës malignes [Two cases of true heterotopic transplantation of baboon livers in malignant acute hepatitis]. *Lyon Chir* 1971;67:288.
13. Starzl TE, Ishikawa M, Putnam CW, et al. Progress in and deterrents to orthotopic liver transplantation, with special reference to survival, resistance to hyperacute rejection, and biliary duct reconstruction. *Transplant Proc* 1974;6:129.
14. Makowka L, Cramer DV, Hoffman A, et al. The use of a pig liver xenograft for temporary support of a patient with fulminant hepatic failure. *Transplantation* 1995;59:1654.
15. Starzl TE, Fung J, Tzakis A, et al. Baboon-to-human liver transplantation. *Lancet* 1993;341:65.
16. Starzl TE, Valdivia LA, Murase N, et al. The biologic basis of and strategies for clinical xenotransplantation. *Immunol Rev* 1994;141:213.
17. Deschamps J-Y, Roux FA, Saý P, Gouin E. History of xenotransplantation. *Xenotransplantation* 2005;12:91-109.
18. Carl G Groth. Progress in xenotransplantation: A personal view. Honoured Member Lecture given at the 8th International Xenotransplantation Congress, Goteborg, Sept 14, 2005.
19. Platt JL, Fischel RJ, Matas AJ, et al. Immunopathology of hyperacute xenograft rejection in a swine-to-primate model. *Transplantation*. 1991;52(2):214-20.
20. Macchiarini P, Mazamarian GM, Oriol R: Ex vivo lung model of pig-to-human hyperacute xenograft rejection *J Thorac Cardiovasc Surg* 1997 ;114(3):315-25.

21. Bucher P, Morel P, Buhler LH: *Transpl Int* 18:894, 2005
22. Tai HC, Ezzelarab M, Hara H, et al. Progress in xenotransplantation following the introduction of gene-knockout technology. *Transpl Int* 2007;20(2):107-17.
23. Cooper DK, Dorling A, Pierson III RN, et al. Alpha1,3-galactosyltransferase gene-knockout pigs for xenotransplantation: Where do we go from here? *Transplantation* 2007;84(1):1-7
24. Barbara JAJ, Van Ostande X, Lopez AF: Tumor necrosis factor-alpha (TNF α): The good, the bad and potentially very effective. *Immunol Cell Biol* 1996;74:434.
25. Lewis M, Tartaglia LA, Lee A, et al. Cloning and expression of cDNAs for two distinct murine tumor necrosis factor receptors demonstrate one receptor is species specific. *Proc Natl Acad Sci U S A* 1991;88:2830.
26. Costa C, Bell NK, Stabel TJ, et al. Use of porcine tumor necrosis factor 1-Ig fusion protein to prolong xenograft survival. *Xenotransplantation* 2004;11:491.
27. C Costa, SR Casinghino, and WL Fodor. Characterization of porcine tumor necrosis factor receptor 2: Implications for Xenotransplantation. *Transplant Proceed* 2007;39:2443-46.
28. Byrne G, McCurry K, Martin M, McClellan S, Platt J, Logan J. Transgenic pigs expressing human CD59 and decay-accelerating factor produce an intrinsic barrier to complement-mediated damage. *Transplantation* 1997;63:149-55.
29. Diamond LE, McCurry KR, Martin MJ, McClellan SB, Oldham ER, Platt JL, et al. Characterization of transgenic pigs expressing functionally active human CD59 on cardiac endothelium. *Transplantation* 1996;61:1241-49.
30. Costa C, Zhao L, Burton WV, Bondioli KR, Williams BL, Hoagland TA, et al. Expression of the human alpha1,2-fucosyltransferase in transgenic pigs modifies the cell surface carbohydrate phenotype and confers resistance to human serum-mediated cytolysis. *FASEB J* 1999;13:1762-73.
31. Sharma A, Okabe J, Birch P, McClellan S, Martin M, Platt J, et al. Reduction in the level of Gal(a1,3) Gal in transgenic mice and pigs by the expression of an a(1,2) fucosyltransferase. *Proc Natl Acad Sci USA* 1996;93:7190-95.
32. Joseph Tector A, M Berho, Jonathan A, et al. Rejection of pig liver xenografts in patients with liver failure: Implications for Xenotransplantation. *Liver Transplantation* 2001;7(2):82-89.
33. Waterworth PD, Dunning J, Tolan M, Cozzi E, Langford G, Chavez G, et al. Life-supporting pig-to-baboon heart xenotransplantation. *J Heart Lung Transplant* 1998;17:1201-07.
34. Lin SS, Weidner BC, Byrne GW, Diamond LE, Lawson JH, Hoopes CW, et al. The role of antibodies in acute vascular rejection of pig-to-baboon cardiac transplants. *J Clin Invest* 1998;101:1745-16.
35. Yamada K, Yazawa K, Shimizu A, et al. Marked prolongation of porcine renal xenograft survival in baboons through the use of a1,3-galactosyltransferase gene-knockout donors and the cotransplantation of vascularized thymic tissue. *Nature Med* 2005;11:32.
36. Kuwaki K, Tseng Y-L, Dor F, et al. Heart transplantation in baboons using a1,3-galactosyltransferase gene-knockout pigs as donors: initial experience. *Nature Med* 2005;11:29.
37. Chen G, Qian H, Starzl T, et al. Acute rejection is associated with antibodies to non-Gal antigens in baboons using Gal-knockout pig kidneys. *Nature Med* 2005 ;11:1295.
38. P. Ram rez, M.J. Montoya, A. R os, et al. Prevention of Hyperacute Rejection in a Model of Orthotopic Liver Xenotransplantation From Pig to Baboon Using Polytransgenic Pig Livers (CD55, CD59, and H-Transferase). *Transplant Proceed* 2005;37:4103-4106.
39. G.A. Levy, A. Ghanekar, M. Mendicino, et al. The Present Status of Xenotransplantation. *Transplant Proceed* 2001;33:3050-3052.)
40. Patience C, Takeuchi Y, Weiss RA. *Nature Med* 1997;3:282.
41. Wilson CA, Wong S, Muller J, et al. *J Virol* 1998;72:3082.
42. Martin U, Kiessig V, Blusch JH, et al. *Lancet* 1998;352:692.
43. Blusch JH, Patience C, Martin U. Pig endogenous retroviruses and xenotransplantation. *Xenotransplantation* 2002;9(4):242-51.
44. Niebert M, Rogel-Gaillard C, Chardon P, et al. Characterization of chromosomally assigned replication-competent gamma porcine endogenous retroviruses derived from a large white pig and expression in human cells. *J Virol* 2002;76(6):2714-20.
45. Heidmann T, Heidmann O, Nicolas JF: An indicator gene to demonstrate intracellular transposition of defective retroviruses. *Proc Natl Acad Sci USA*. 1988;85(7):2219-23.
46. Tchenio T, Heidmann T. Defective retroviruses can disperse in the human genome by intracellular transposition *J Virol* 1991;65(4):2113-18.
47. Tchenio T, Heidmann T. High-frequency intracellular transposition of a defective mammalian provirus detected by an in situ colorimetric assay. *J Virol* 1992;66:1571-78.
48. CG Groth. Prospects in Xenotransplantation. A Personal View. *Transplant Proceed* 2007;39:685-87.
49. Groth CG, Korsgren O, Tibell A, et al. Transplantation of porcine fetal pancreas to diabetic patients. *Lancet* 1994;344:1402.
50. O Garkavenko, DF Emerich, M Muzina, et al. Xenotransplantation of Neonatal Porcine Liver Cells. *Transplant Proceed* 2005;37:477-80.
51. Gerlach J, Kloppel K, Schon MR. Comparison of pig hepatocyte isolation using intraoperative perfusion without warm ischemia and isolation of cells from abattoir organs after warm ischemia. *Artif Organs* 1993;17:950.
52. Koebe HG, Schildberg FW: Isolation of porcine hepatocytes from slaughterhouse organs. *Int J Artif Organs* 1996;19:53.
53. Garkavenko O, Muzina M, Muzina Z, et al. Monitoring for potentially xenozoonotic viruses in New Zealand pigs. *J Med Virol* 2004;72:338.
54. Eiseman B, Liem DS, Raffuci F. Heterologous liver perfusion in treatment of hepatic failure. *Ann Surg* 1965;162:329.
55. Sen PK, Bhalariao RA, Parulkar GP, et al. Use of isolated perfused cadaveric liver in the management of hepatic failure. *Surgery* 1966;59:774.
56. Pascher A, Sauer IM, Hammer C, et al. Extracorporeal liver perfusion as hepatic assist in acute liver failure: A review of world experience. *Xenotransplantation* 2002;9:309.
57. Hume DM, Gayle WE Jr, Williams GM. Cross circulation of patients in hepatic coma with baboon partners having human blood. *Surg Gynecol Obstet* 1969;128:495.
58. Saunders SJ, Bosman SC, Barnard CN, et al. [Exchange transfusion and cross circulation with baboons in the treatment of acute liver failure]. *Internist (Berl)* 1970;11:77.
59. Abouna GM, Fisher LM, Still WJ, et al. Acute hepatic coma successfully treated by extracorporeal baboon liver perfusions. *BMJ* 1972;1:23.
60. Abouna GM, Cook JS, Fisher LM, et al. Treatment of acute hepatic coma by ex vivo baboon and human liver perfusions. *Surgery* 1972;71:537.
61. Abouna GM, Kirkley JR, Hull CJ, et al. Treatment of hepatic coma by extra-corporeal pig liver perfusion. *Lancet* 1969;1:64.

62. Leger L, Chapuis Y, Lenriot JP, et al. Traitement du coma hépatique par épuration dans un foie hétérologue [Treatment of hepatic coma by purification in a heterologous liver]. *J Chir (Paris)* 1969;97:161.
63. Abouna GM. Extracorporeal xenogeneic liver perfusion for the treatment of hepatic failure. In: Cooper DKC, Kemp E, Platt JL, et al eds. *Xenotransplantation. The Transplantation of Organs and Tissues Between Species*, 2nd edn. Berlin: Springer Verlag, 1997:785.
64. Abouna GM. Ex vivo xenogeneic liver perfusion for hepatic failure. *Xenotransplantation* 1996;4:102.
65. Pascher A, Sauer IM, Hammer C, et al. Extracorporeal liver perfusion as hepatic assist in acute liver failure: a review of world experience. *Xenotransplantation* 2002;9:309.
66. Levy MF, Crippin J, Sutton S, et al. Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD55/hCD59) porcine livers: clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus. *Transplantation* 2000;69:272.
67. Hagelin J. Public opinion surveys about xenotransplantation. *Xenotransplantation* 2004;11:551-58.
68. Ríos A, Conesa C, Ramírez P, et al. Hospital personnel faced with organ xenotransplantation: An attitudinal survey in a hospital with a pre-clinical liver xenotransplantation program. *Xenotransplantation* 2006;13:447-54.
69. Ríos A, Conesa C, Ramírez P, et al. Actitud pública hacia el xenotrasplante: encuesta de opinión. *Transplant Proc* 2004;36:2901.
70. Omnell M, Persson NH, Ranstam J, et al. Attitudes towards xenotransplantation patients waiting for transplantation versus the general public. *Transplant Int* 2001;14:334.
71. Sanner MA. Giving and taking to whom and from whom? People's attitudes towards transplantation of organs and tissue from different sources. *Clin Transplant* 1998;12:530.
72. Hagelin J. Public opinion surveys about xenotransplantation. *Xenotransplantation* 2008;11:551.

(C) STEM CELL TRANSPLANTATION

A stem cell is an undifferentiated cell capable of renewing itself throughout its life and of generating one or more types of differentiated cells. While Embryonic stem cells (ESCs) are the only ones to be totipotent, adult tissues with high cellular turnover (e.g. skin, gut mucosa and bone marrow) retain a population of stem cells with restricted differentiation potential that constantly supply the tissue with new cells. ESCs hold much promise in the future. Circulating hematopoietic stem cells (HSCs) contribute to the repair of solid organs, like the liver, offering promise in the future. Stem cells within the adult hematopoietic system could potentially be clinically useful to generate hepatocytes to replace damaged or deficient liver tissue.

ROUTE OF IMPLANTATION

- Local (direct vascular delivery)
- Peripheral (injection in a peripheral vein)

Peterson et al. first reported that rodent bone marrow cells were able to give rise to oval cells and hepatocytes upon transplantation into lethally irradiated rats.¹ Later Wang et al.² showed that the human hematopoietic stem cell (HSCs) and progenitor cell populations had the capacity to generate cells within the recipient liver to synthesize and secrete human albumin into the sera of mice after transplantation. Esch et al. reported that portal administration of autologous CD₁₃₃⁺ HSCs accelerated liver regeneration.³ Lagasse et al.⁴ and by Wager's et al. have demonstrated the plasticity of hematopoietic stem cells to differentiate into hepatocytes. In another study, Sakaida et al. have demonstrated that bone-marrow stem cell transplantation reduced fibrosis in chemically induced liver cirrhosis. From a therapeutic point of view, chronic liver cirrhosis is one of the targets where bone marrow cell transplantation might be employed. In this condition, there is excessive deposition of extracellular matrix and hepatocytes necrosis.⁵

In two recently published studies, Gordon et al.⁶ and Terai et al.⁷ evaluated the effects of CD₃₄⁺ hematopoietic stem cell intrahepatic injection and whole bone marrow peripheral infusion in five and nine patients with liver cirrhosis, respectively. After examining the results, the authors concluded that bone marrow stem cells are able to improve the residual liver function in cirrhotic patients. In the study by Gordon et al., a decrease in serum bilirubin and an improvement in serum albumin were observed in three and four of the five patients, respectively, with the disappearance of ascites observed in one patient. In

the study by Terai et al., significant increases in albumin and total protein level and an improvement of the Child-Pugh score were observed in all of the nine patients, and a reduction in ascites was observed in six patients. Recently Khan et al. reported that autologous bone marrow stem cell transplantation through the hepatic artery is a safe and effective procedure.⁸

AUTOLOGOUS BONE MARROW STEM CELLS

Indication for autologous bone marrow stem cell transplantation is chronic hepatic failure with abnormal serum albumin, bilirubin, AST, PT, which are unsuitable for LTX.

CONTRAINDICATIONS⁸

- Active infection
- Serum creatinine concentrations >1.5 mg/dl
- Spontaneous bacterial peritonitis
- Recurrent gastrointestinal bleeding
- Liver tumors or past history of other cancers.
- Hepatopulmonary diseases
- Pregnancy or lactation.

PROCEDURE⁸

Bone Marrow Aspiration and Isolation of CD₃₄⁺ Cells

After 5 days of granulocyte colony-stimulating factor (G-CSF-300 µg/ml) injections, 100 ml of bone marrow is aspirated from iliac crest. After the collection, stem cells were enriched from the bone marrow using standard procedures. The viability of the cells was examined using the trypan blue dye exclusion test. The cells were constituted in 10 ml of normal saline.

Flow Cytometric Analysis

Isolated bone marrow cells (1X10⁴/ml) were labeled with primary antibody (CD₃₄) as per the standard protocol. Then phycoerythrin conjugated secondary antibody was labeled with unconjugated primary antibody. Stained cells were analyzed on a FACS Calibur flow cytometer to count the percentage of CD₃₄⁺ cells.

Infusion of Cells

Infusion of cells to the patient is done under local anesthesia via femoral arterial access. After evaluation of visceral arterial anatomy by angiography, selective

catheterization of the hepatic artery is performed with a 6Fr. guiding catheter. Through the guiding catheter a 3 to 4 mm balloon catheter was negotiated over the guide wire into the hepatic artery. The cells were infused through the distal lumen of the inflated catheter at the rate of 1 ml/min. Possible adverse effects are fever, chills, chest pain (cardiac ischemia), increase in ascites and renal failure. Patients are followed up regularly with routine LFTs, RFTs and hyaluronic acid assay by ELISA. Hyaluronic acid levels are directly proportional to the degree of fibrosis in the liver.

HUMAN CORD BLOOD STEM CELLS

The isolation of Hemopoietic stem cells (HSCs) and Mesenchymal stem cells (MSCs) from cord blood is a relatively new procedure and only few studies have been published.^{9,10} Cord blood contains different populations of embryonic like and other pluripotent stem cells capable of originating hematopoietic, epithelial, endothelial, and neural tissues both *in vitro* and *in vivo*. Cord blood cells have many advantages as a transplantable source of stem/progenitor cells, because of their immaturity and availability. Several studies showed that cord blood cells give rise to hepatocyte like cells (HLCs) after transplantation into an injured liver.¹¹⁻¹³ None of these studies are in human population.

Procedure in the earlier animals studies involves the collection of cord blood samples from full-term deliveries with prior informed consent followed by processing of these cells. Cell transplantation NOD/SCID mice is performed. Detection of cord blood derived hepatocyte like cells in the recipient mouse livers immunohistological analysis and reverse transcriptase-polymerase chain reaction (RT-PCR) analysis.

Sàez-Lara et al.¹⁴ transplanted CD₃₄₊ HSCs derived from human cord blood into rats with liver cirrhosis without achieving a significant rate of engraftment, as GFP-positive cells were clearly eliminated. By contrast,¹⁵ low-density mononuclear cells obtained from human cord blood transplanted *in utero* in fetal rats generated functional hepatocytes that persisted in the fetal recipient liver at least 6 months after birth. This humanized animal model provides a very interesting approach to *in vivo* investigation of human cord blood stem cell differentiation into hepatocytes.

Hong et al.¹⁶ described the ability of human umbilical cord blood MSCs (CD₃₄₊) to differentiate into hepatocytes when cultured in prohepatogenic conditions. Recently, Campard et al.¹⁷ demonstrated that human cord matrix stem cells cultured with growth factors show hepatocyte characteristics like cytochrome P450-3A expression, glycogen storage and urea production. In addition, when

transplanted into hepatectomized immune-deficient mice, small clusters of human cells expressing albumin and α -fetoprotein appear, thereby demonstrating the good engraftment and differentiation capacity of the transplanted cells.¹⁸

Placenta is another potential source of stem cells. Placenta-derived stem cells (PDSCs) are fibroblast-like cells that attach to a plastic surface. They can be expanded for more than 20 population doublings and induced to differentiate into cells of various mesenchymal tissues. Chien et al.¹⁹ recently cultivated PDSCs derived from human placenta in hepatic differentiation media, and obtained cells with hepatocyte morphology expressing specific hepatocyte functions.

EMBRYONIC STEM CELLS

Use of human embryonic stem cells (ESCs) is currently limited to *in vitro* and animal studies.²⁷

- Huge proliferative and differentiation potential of ESCs
- Major ethical concerns.

Effective protocols are needed not only to promote ESCs differentiation into hepatocytes, but also to determine the expression of hepatic functions such as albumin secretion, indocyanine green uptake and release, glycogen storage and p450 metabolism.²⁰ Cytokines and growth factors such as hepatocyte growth factor (HGF) and Fibroblast growth factor (FGF) have been shown to promote ESCs differentiation and growth.²¹ In addition, it has been demonstrated that sodium butyrate, a non-proteinaceous compound, supports the action of these factors.²²

Hay et al.²³ developed a multistage system in which HGF was used without the requirement of sodium butyrate, and human ESCs differentiated into hepatocyte-like cells without embryoid body formation. Use of an extracellular synthetic or natural matrix can be relevant, as shown by Ishizaka et al.²⁴ in a three-dimensional system in which hepatocytes developed from mouse ESCs transfected with the hepatocyte nuclear factor-3 beta on a 3-D matrix scaffold. 3-D matrix scaffolds have been reported to be superior to the more commonly used 2-D monolayer culture in inducing differentiation into hepatocytes.

The other effective way to obtain hepatic differentiation is genetic modulation. This can be achieved by transfecting stem cells with recombinant DNA encoding for hepatospecific proteins. Adding collagen, appropriate cytokines and growth factors has an important effect on hepatocyte differentiation.²⁵ Agarwal et al.²⁶ reported a new differentiation protocol for the generation of high-purity (70%) hepatocyte cultures: the

differentiation process was largely uniform, with cell cultures progressively expressing increasing numbers of hepatic lineage markers and functional hepatic characteristics. When transplanted in mice with acute liver injury, the human ESCs derived endoderm differentiated into hepatocytes and repopulated the damaged liver.

REFERENCES

- Petersen BE, Bowen WC, Patrene KD, et al. Bone marrow as a potential source of hepatic oval cells. *Science* 1999;284:1168.
- Wang X, Ge S, McNamara G, et al. Albumin expressing hepatocyte-like cells develop in the livers of immune-deficient mice that received transplants of highly purified human hematopoietic stem cell. *Blood* 2003;101:4201.
- Am Esch JS 2nd, Knoefel WT, Klein M, et al. Portal application of autologous CD133+ bone marrow cells to the liver: a novel concept to support hepatic regeneration. *Stem Cells* 2005;23:463.
- Lagasse E, Connors H, Al-Dhalimy M, et al. Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. *Nat Med* 2000;6:1229.
- Sakaida I, Terai S, Yamamoto N, et al. Transplantation of bone marrow cells reduces CC14-induced liver fibrosis in mice. *Hepatology* 2004;40:1304.
- Gordon MY, Levicar N, Pai M, et al. Characterisation and clinical application of human CD34+stem/progenitor cell populations mobilised into the blood by G-CSF. *Stem Cells* 2006;24:1822.
- Terai S, Ishikawa T, Omori K, et al. Improved liver function in liver cirrhosis patients after autologous bone marrow cell infusion therapy. *STEM CELLS* 2006;24:2292-98.
- AA Khan, N Parveen, VS Mahaboob, et al. Safety and efficacy of autologous bone marrow stem cell transplantation through hepatic artery for the treatment of chronic liver failure: A preliminary study. *Transplant Proceed* 2008;40 :1140-44.
- Soto-Gutierrez A, Kobayashi N, Rivas-Carrillo JD, et al. Reversal of mouse hepatic failure using an implanted liver-assist device containing ES cell-derived hepatocytes. *Nat Biotechnol* 2006;24:1412-19.
- Ruhnke M, Ungefroren H, Nussler A, et al. Differentiation of in vitro modified human peripheral blood monocytes into hepatocyte-like and pancreatic islet-like cells. *Gastroenterology* 2005;128:1774-86.
- Kakinuma S, Tanaka Y, Chinzei R, et al. Human umbilical cord blood as a source of transplantable hepatic progenitor cells. *Stem Cells* 2003;21:217.
- Tanabe Y, Tajima F, Nakamura Y, et al. Analyses to clarify rich fractions in hepatic progenitor cells from human umbilical cord blood and cell fusion. *Biochem Biophys Res Commun* 2004;324:711.
- Nonome K, Li XK, Takahara T, et al. Human umbilical cord blood-derived cells differentiate into hepatocyte-like cells in the Fas-mediated liver injury model. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G1091.
- Saez-Lara MJ, Frecha C, Martin F, et al. Transplantation of human CD34+ stem cells from umbilical cord blood to rats with thioacetamide induced liver cirrhosis. *Xenotransplantation* 2006;13:529-35.
- Sun Y, Xiao D, Zhang RS, et al. Formation of human hepatocyte-like cells with different cellular phenotypes by human umbilical cord blood derived cells in the human-rat chimeras. *Biochem Biophys Res Commun* 2007;357:1160-65.
- Hong SH, Gang EJ, Jeong JA, et al. In vitro differentiation of human umbilical cord blood-derived mesenchymal stem cells into hepatocyte-like cells. *Biochem Biophys Res Commun* 2005;330:1153-61.
- Campard D, Lysy PA, Najimi M, et al. Native umbilical cord matrix stem cells express hepatic markers and differentiate into hepatocyte-like cells. *Gastroenterology* 2008;134:833-48.
- Teramoto K, Asahina K, Kumashiro Y, et al. Hepatocyte differentiation from embryonic stem cells and umbilical cord blood cells. *J Hepatobiliary Pancreat Surg* 2005;12:196-202.
- Chien CC, Yen BL, Lee FK, et al. In vitro differentiation of human placenta derived multipotent cells into hepatocyte-like cells. *Stem Cells* 2006;24: 1759-68.
- Heng BC, Yu H, Yin Y, et al. Factors influencing stem cell differentiation into the hepatic lineage in vitro. *JGastroenterol Hepatol* 2005;20:975-87.
- Hu A, Cai J, Zheng Q, et al. Hepatic differentiation from embryonic stem cells in vitro. *Chin Med J (Engl)* 2003;116:1893-97.
- Rambhatla L, Chiu CP, Kundu P, et al. Generation of hepatocyte-like cells from human embryonic stem cells. *Cell Transplant* 2003;12:1-11.
- Hay DC, Zhao D, Ross A, et al. Direct differentiation of human embryonic stem cells to hepatocyte like cells exhibiting functional activities. *Cloning StemCells* 2007;9:51-62.
- Ishizaka S, Ouji Y, Yoshikawa M, et al. Derivation and characterization of hepatocytes from embryonic stem cells in vitro. *Methods Mol Biol* 2006;330:387-99.
- Tabei I, Hashimoto H, Ishiwata I, et al. New approach for the establishment of an hepatocyte cell line derived from rat early embryonic stemcells. *Hum Cell* 2003;16:39-46.
- Agarwal S, Holton KL, Lanza R. Efficient differentiation of functional hepatocytes from human embryonic stem cells. *Stem Cells* 2008;26:1117-27.
- S Lorenzini, S Gitto, E Grandini, et al. Stem cells for end stage liver disease: How far have we got? *World J Gastroenterol* 2008;14(29):4593-99.

Complications of ESLD

(A) ASCITES

Ascites (Greek word *Askos* means bag) is defined as the pathological accumulation of fluid in the peritoneal cavity. Ascites is seen in nearly 50% of long standing compensated cirrhosis patients and is the most common complication in cirrhosis. It increases the complications of cirrhosis like increased risk of spontaneous bacterial peritonitis and renal failure.¹ Survival rate in cirrhosis patients is approximately 50% in 2-5 years.^{2,3}

ETIOLOGY OF ASCITES

Etiology		
a. High serum-ascitic fluid albumin gradient (Transudate):^{4,5}		
Cirrhosis-81% (alcoholic 65%, viral 10%, cryptogenic 6%)		
Heart failure-3%		
Constrictive pericarditis		
Kwashiorkor		
Budd-Chiari syndrome/veno-occlusive disease		
b. Low serum-ascitic fluid albumin gradient (Exudate):		
Malignancy (primary/secondary)-10%		
Nephrotic syndrome		
Tuberculosis-2%		
Pancreatitis-1%		
Serositis		
Hereditary angioedema		
Difference between exudate and transudate:⁴		
Parameters	Exudate	Transudate
Protein	High	Low protein (<30 g/L)
LDH	High	Low
pH	Low (<7.30)	High (>7.30)
Glucose	Low	Normal
WBC count	More	Less (1 WBC/1000 mm ³)

Ascites can be divided into 3 grades according to severity:¹¹

Grade 1—Mild and detectable only on imaging studies

Grade 2—Moderate, manifested by symmetrical distension of abdomen

Grade 3—Large or gross with massive abdominal distension

SIGNS AND SYMPTOMS

Abdominal distension, discomfort, shortness of breath due to mechanical impingement on the diaphragm, decreased food intake, malnutrition, decreased quality of life and death. On examination visible bulging of the flanks, shifting dullness and fluid thrill. Other signs of ascites in cirrhosis patients with portal hypertension are pedal edema, gynecomastia, hematemesis and encephalopathy.

PATHOPHYSIOLOGY OF ASCITES IN CIRRHOSIS PATIENTS WITH PORTAL HYPERTENSION

Ascitic fluid accumulates in cirrhosis patients as a transudate which is the result of increased portal pressure (>8 mm Hg, usually around 20 mm Hg), e.g. due to cirrhosis, while exudates are actively secreted fluid due to inflammation or malignancy.⁶³ Portal hypertension plays an important role in the production of ascites by raising capillary hydrostatic pressure within the splanchnic bed. Sinusoidal portal hypertension is associated with a state of systemic arterial vasodilation.⁸ Increased nitric oxide activity is associated with arterial vasodilation.⁹ Splanchnic arterial bed is particularly

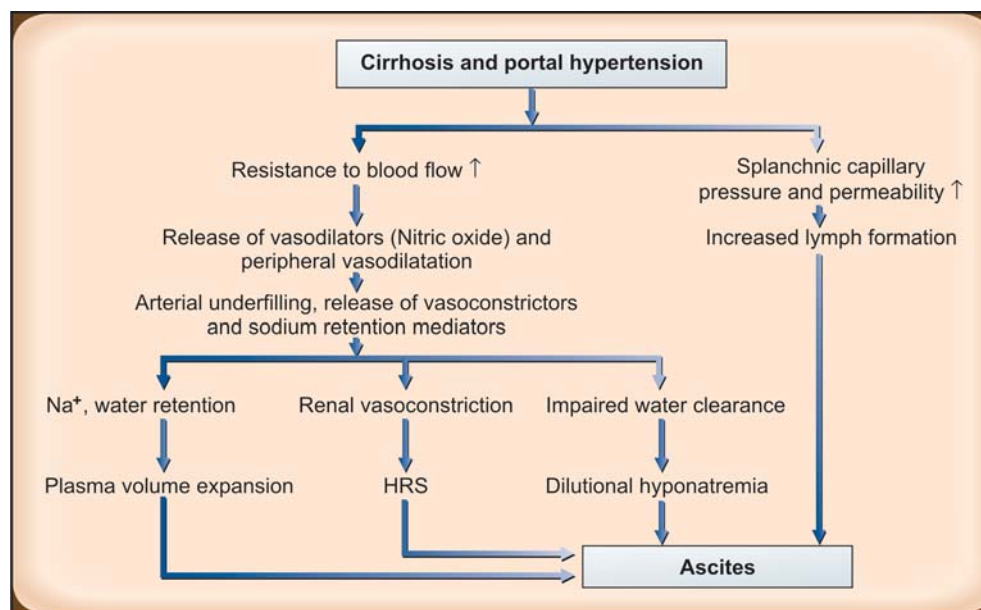


Figure 49.1: Schematic presentation of pathophysiology of ascites⁶³

susceptible to vasodilation. Redistribution of the circulating blood volume to the dilated vascular beds decreases the effective circulating volume that initially is compensated for by increased cardiac output and a hyperdynamic circulatory state.^{8,10}

Irrespective of the etiology, sequestration of fluid within the abdomen leads to additional fluid retention by the kidneys due to stimulatory effect on blood pressure hormones, notably aldosterone. The sympathetic nervous system is also activated, and renin production is increased due to decreased perfusion of the kidney. These results in decreased renal plasma flow, GFR and severe Na⁺ retention and development of functional renal failure called hepatorenal syndrome (HRS).^{6,8} Water retention also results from hypersecretion of antidiuretic hormone.^{10,11} When the water retention exceeds Na⁺ retention, hyponatremia develops. All of these mechanisms combine to cause Na and water retention. In cirrhosis patients the sinusoidal pressures increases leading to increased hepatic lymph production increases. Although this initially can be accommodated by increased thoracic duct flow, it eventually spills over from surface lymphatics to the peritoneal cavity when hepatic lymph production exceeds the ability to return the lymph to circulation by means of the thoracic duct, thus causing ascites.

INVESTIGATIONS IN CIRRHOSIS PATIENTS WITH ASCITES⁶³

- Complete hemogram
- **Liver function tests:** Serum bilirubin (direct and total), AST, ALT, alkaline phosphatase, serum albumin
- **Coagulation profile:** PT, APTT, INR
- **Renal function:** Blood Urea, Serum creatinine, 24 hour urinary sodium and protein
- **Electrolytes:** Sodium, potassium.
- **Ascitic fluid analysis:** Cell count, bacterial culture and sensitivity, glucose, albumin, total protein, Gram's stain for AFB, LDH level, amylase level
- Upper GI endoscopy
- USG of abdomen or CT scan

TREATMENT OF ASCITES

Aim of Treatment

- Improve sodium balance
- Enhance free water clearance
- Treat the underlying cause (liver disease)

General Measures

- Bed rest improves sodium excretion and response to diuretics.¹²

- **Sodium and fluid restriction:**

- Restricting sodium intake to 60 to 90 mEq/d, (salt 1.5 to 2.0 gm/day).¹³
- Fluid restriction to 1 liter/24 hours is helpful in patients with dilutional hyponatremia. Dilutional hyponatremia occurs due to water retention secondary to decreased effective intravascular volume and high levels of antidiuretic hormone. It is diagnosed by serum sodium level of less than 130 mEq/L in the presence of ascites and pedal edema.¹⁴

Drugs

Diuretics:

Aldosterone antagonists (Spironolactone) is commonly used diuretic, which blocks the effects of aldosterone. Dose of spironolactone: 100-400 mg/day.^{15,16} Diuretic effect of this drug is seen after 48 hours.¹⁷ Peak effects may be delayed till 7 to 10 days and dose adjustments should not be made earlier than a week.¹⁷ Side effects are painful gynecomastia, hyperkalemia and suboptimal diuresis. Addition of a loop diuretic (furosemide) has a synergistic effect with spironolactone and decreases the risk of hyperkalemia.^{15,16}

Amiloride, a distal diuretic and is not associated with gynecomastia. Dose 5-30 mg/day. It is faster acting than spironolactone but has a relatively weaker diuretic action and is more expensive.¹⁸

Loop diuretics (furosemide) are very effective and fast acting. Dose of furosemide: 40-60 mg/day.¹⁵ Diuretic effect of furosemide appears within 30 minutes, peaks at 1 to 2 hours, and wears off by 3 to 4 hours.²⁰ They act by inhibiting active chloride reabsorption in the ascending limb of the loop of Henle, thereby increasing the amount of Na, Cl, and water delivered to the distal tubule. Limitations of loop diuretics as a single agent are that, all the sodium delivered to the distal tubule is reabsorbed because of the unopposed action of aldosterone.¹⁹ If an aldosterone antagonist is administered simultaneously, reabsorption of Na⁺ load to the distal tubule is blocked, thereby producing a marked natriuresis. Side effects of furosemide are hypokalemia, hyponatremia, dehydration, azotemia and hepatic encephalopathy.^{21,22} Furosemide increases renal ammonia production and adds to the risk of development of hepatic encephalopathy in the presence of electrolyte disturbances.²³

Grade I ascites can be easily controlled with diuretics and sodium restriction. But grade II and III are difficult to control. Spironolactone is the diuretic of choice, as it achieves a negative sodium balance by enhancing sodium excretion. The recommended initial dose is either

spironolactone 100 to 200 mg/day. Combination therapy with furosemide is usually preferred. Initially, furosemide is added in low doses of 20 to 40 mg/day to enhance natriuresis, especially in the presence of peripheral edema.⁶³ Best combination of drugs for control of ascites is furosemide and spironolactone may be used in the ratio of 40:100 mg/day. This will have a good natriuretic and diuretic action and avoids potassium imbalance.^{24,25} The maximal dose of spironolactone is usually 400 mg/day, and that of furosemide is 160 mg/day. In nonazotemic subjects with moderate ascites, spironolactone monotherapy is as effective as combination therapy.²⁶ Response to diuretic treatment is assessed by the changes in clinical condition and body weight. The recommended weight loss in patients with or without peripheral edema is 800 to 1000 gm/day and 300 to 500 g/day, respectively. Urinary sodium excretion measurement is necessary when there is not adequate response to diuretic therapy. As only 10 mEq/d of sodium is lost by nonurinary sources, urinary sodium excretion should be greater than Na intake. If the urinary sodium excretion is more than the sodium intake in a patient with a poor diuretic response, compliance with the low sodium diet should be questioned. If the urine Na⁺ is very low in a patient who is compliant with Na⁺ restriction but has worsening ascites, an increase in diuretic dose is often helpful in inducing a natriuresis, unless overt renal failure already has set in. Urine Na⁺ measurement helps in dose modification.^{15,16}

Dilutional hyponatremia in cirrhosis is associated with a poor survival.²⁷ Volume restriction is the treatment but it may worsen renal function and is therefore suboptimal.²⁸ Vasopressin receptor 2 antagonists improve free water clearance, serum sodium levels, and commonality, and decrease the urine osmolality.^{29,30} Central opioid receptor agonists such as niravoline also have been used to decrease the hypothalamic release of vasopressin and thus improve water excretion. Aggressive treatment with diuretics leads to complications such as renal failure, electrolyte disturbances, hepatic dysfunction and hepatic encephalopathy. Free water clearance and GFR are decreased only mildly in most of these cases. The best approach in this situation is administration of antimineralocorticoids, because secondary hyperaldosteronism is responsible for sodium retention from the distal tubules and the collecting ducts.

Refractory ascites: It is defined as diuretic-resistant when there is a lack of response to the maximal permissible dose of diuretics (400 mg of spironolactone and 160 mg of furosemide), or diuretic-intractable when there is inability to reach the maximal dose of diuretics because of adverse effects such as hepatic encephalopathy,

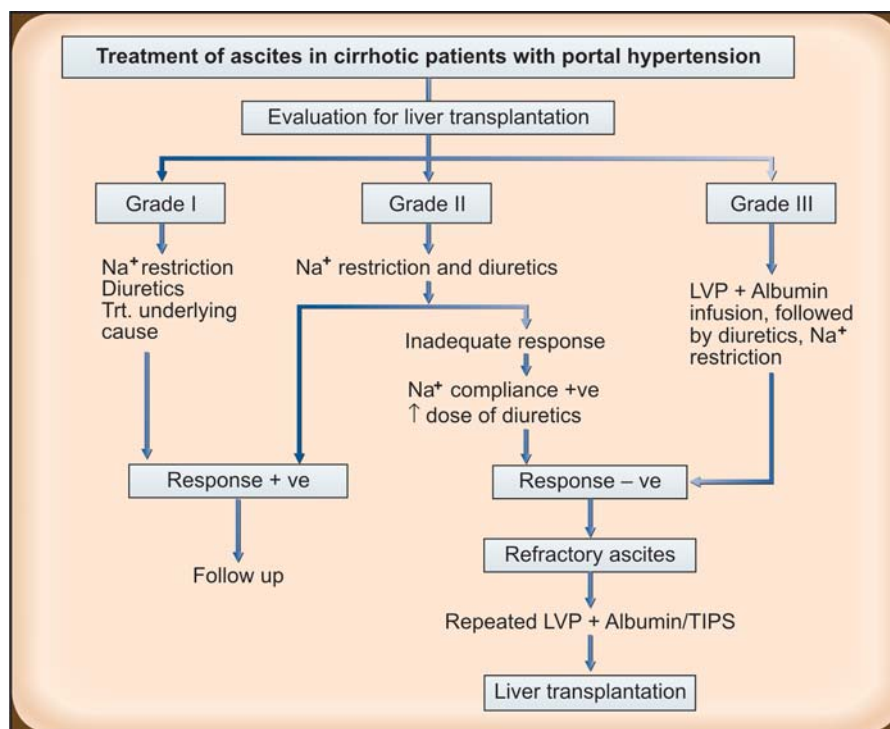


Figure 49.2: Schematic presentation of treatment of ascites in cirrhotic patients

hyponatremia, hypokalemia, or renal insufficiency.⁶ Incidence of refractory ascites is 5-10% and it has a poor prognosis with increased rate of complications like SBP and HRS.⁷

Large Volume Paracentesis (LVP)

It is defined as draining of about > 5 liters of ascitic fluid.

LVP: Indications

- Tense ascites
- Respiratory distress
- Poor response to medical therapy
- Impending rupture of an umbilical hernia

20% cases will develop post-paracentesis circulatory dysfunction (PPCD), characterized by the development of worsened hyponatremia and increased catecholamine levels and renin activity after LVP³¹⁻³⁴ after 24-48 hours resulting in increased risk of renal failure and mortality up to 30 days after the LVP.^{31,32} Treatment of PPCD: Albumin, intravenously at a dose of 6 to 8 g for each liter of ascites removed.³² Albumin is superior to polygeline, or dextran⁷⁰ for volume expansion and preventing PPCD.^{31,32} Albumin infusion is not required when less

than 4 to 5 L of ascites are removed. Total paracentesis, involving the drainage of all of the ascites, can be performed safely when albumin is infused.^{35-37,42}

Complications of Paracentesis^{38,41,43}

- Local infection
- Intestinal perforation
- Local bleeding
- Leak from the tap site

Compared with diuretic alone, LVP controls the ascites more rapidly and effectively than medical treatment and decreases the hospital stay with less complication rates.³⁸⁻⁴¹ But ascites recurs in 93% patients within 4 weeks without any medication. So diuretic therapy is required to prevent or delay reaccumulation of ascites after LVP.⁴³

Volume Expansion

Intravenous infusion of albumin improves the effective arterial volume and renal perfusion. Diuretics have a better response if combined with weekly albumin administration (25 g/week).^{44,45} The combination also shortens the hospital stay, decreases the probability of reaccumulation of ascites, and reduces the likelihood of readmission, but without any survival benefit.^{44,45}

Aquaretic Agents

Aquaretic agents are now found to be useful in the treatment of dilutional hyponatremia in cirrhosis patients with ascites. Mechanism of action: Enhance water clearance by antagonizing the effect of vasopressin in 2 different ways:^{29,30,46}

- Suppression of hypothalamic secretion of vasopressin with agonists of opioid k receptors has neurological side effects.
- Selectively blocking V2 receptors in the renal collecting tubules in the renal collecting tubule by VPA-985, however, improved free water clearance and serum sodium levels.

Role of Shunts

- **Surgical shunts** (rarely used)
- **Nonsurgical shunts:** TIPS

TIPS is created between the hepatic vein and an intrahepatic portal vein branch via jugular approach by deployment of a metallic stent. Stenosis and occlusion is a common problem in 40 to 75% of TIPS at 6 months to 1 year.⁵⁰⁻⁵² But the recent use of polytetrafluoroethylene-coated stents (e-PTFE) has further reduced the rate of TIPS stenosis.⁴⁷ TIPS take several weeks to control the ascites and are better than the LVP as it prevents the re-accumulation of ascites without any improvement in survival.⁵¹ Now a days it is used in patients who are on the waiting list in order to avoid undue complications of portal hypertension and to bridge the long waiting time due to organ shortage. TIPS acts by increasing the venous return to the heart from the splanchnic bed resulting in an increase in cardiac output. It can precipitate cardiac failure in patients with compromised cardiac function.⁴⁸ Improvement in effective hypervolemia results in an improvement in renal perfusion and decreased renal Na⁺ reabsorption in the proximal tubules.⁴⁹ Decreased Na⁺ reabsorption produces a natriuresis, helps to control sodium retention and ascites.⁵⁷ Mortality rate at 3 months is significant following TIPS.⁵³⁻⁵⁶ Hence it should be used selectively. Hepatic encephalopathy is seen in 30% of patients.⁵⁰⁻⁵²

Contraindications of TIPS⁵³⁻⁵⁶

- Bilirubin level > 3 mg/dL
- PT > 20 seconds
- Serum creatinine > 2 mg/dL

Treatment of Refractory Ascites

Therapeutic options for managing refractory ascites include repeated LVP or TIPS.⁵⁸⁻⁶¹ Repeated LVP and administration albumin for volume expansion are the first

line of therapy for refractory ascites. Diuretics should be continued as tolerated and should be stopped if there are complications or inadequate natriuresis (less than 30mEq/d).²⁸ Unfortunately, ascites recur in most subjects, necessitating repeated LVP. On the other hand, TIPS effectively controls ascites and prevents the reaccumulation, because it corrects portal hypertension, which is the basic abnormality leading to ascites.⁵⁹ TIPS should not be considered as a treatment to improve survival. TIPS should be used in subjects who repeatedly fail LVP and have relatively preserved liver functions.

Liver Transplantation

Liver transplantation provides definitive treatment for ESLD with ascites.⁶³ It improves the survival and quality of life. Any cirrhotic patient with ascites is a potential candidate for liver transplantation as ascites is associated with poor long term survival (30 to 40% survival at 5 years) and they should be thoroughly evaluated for liver transplantation.¹ MELD score is used widely to evaluate the prognosis of cirrhosis patients.⁶² Presence of SBP and HRS adds to the morbidity and mortality after transplantation.

REFERENCES

1. Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: Natural history and prognostic factors. *Hepatology* 1987;7:122-28.
2. D'Amico G, Morabito A, Pagliaro L, et al. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* 1986;31:468-75.
3. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: A retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-72.
4. Warrell DA, Cox TN, Firth JD, Benz ED. *Oxford textbook of medicine*. Oxford: Oxford University Press, 2003.
5. Branco-Ferreira M, Pedro E, Barbosa MA, et al. "Ascites in hereditary angioedema". *Allergy* 1998;53(5):543-45.
6. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 1996;23:164-76.
7. Gines P, Cardenas A, Arroyo V, et al. Management of cirrhosis and ascites. *N Engl J Med* 2004;350:1646-54.
8. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151-57.
9. Martin PY, Gines P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med* 1998;339:533-41.
10. Ring-Larsen H, Hesse B, Henriksen JH, et al. Sympathetic nervous activity and renal and systemic hemodynamics in cirrhosis: Plasma norepinephrine concentration, hepatic extraction, and renal release. *Hepatology* 1982;2:304-10.

11. Arroyo V, Planas R, Gaya J, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis. Relationship to functional renal failure and sodium and water excretion. *Eur J Clin Invest* 1983;13:271-78.
12. Gentilini P. Spironolactone and canrenoate: Different antialdosteronic diuretic agents. *Hepatology* 1991;13:999-1000.
13. Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology* 1998;27:264-72.
14. Gines P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: From pathogenesis to treatment. *Hepatology* 1998;28:851-64.
15. Runyon BA. Management of adult patients with ascites due to cirrhosis. *Hepatology* 2004;39:841-56.
16. Yu AS, Hu KQ. Management of ascites. *Clin Liver Dis* 2001;5:541-68.
17. Fogel MR, Sawhney VK, Neal EA, et al. Diuresis in the ascitic patient: A randomized controlled trial of three regimens. *J Clin Gastroenterol* 1981;3(Suppl 1):73-80.
18. Angeli P, Dalla PM, De Bei E, et al. Randomized clinical study of the efficacy of amiloride and potassium canrenoate in nonazotemic cirrhotic patients with ascites. *Hepatology* 1994;19:72-79.
19. Perez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology* 1983;84:961-68.
20. Yagi N, Kiuchi T, Satoh H, et al. Bioavailability and diuretic effect of furosemide following administration of tablets and retarded capsules to human subjects. *Biol Pharm Bull* 1996;19:616-22.
21. Bernardi M, De Palma R, Trevisani F, et al. Effects of a new loop diuretic (muzzolimine) in cirrhosis with ascites: Comparison with furosemide. *Hepatology* 1986;6:400-05.
22. Pockros PJ, Reynolds TB. Rapid diuresis in patients with ascites from chronic liver disease: The importance of peripheral edema. *Gastroenterology* 1986;90:1827-33.
23. Imler M, Bockel R, Peter B, et al. Importance of hyperammonemia of the renal origin in the pathogenesis of hepatic coma released in cirrhotic patients by diuretics generating hypokaliemia. *Pathol Biol (Paris)* 1969;17:5-19.
24. Gentilini P, Laffi G, La Villa G, et al. Torasemide in the treatment of patients with cirrhosis and ascites. *Cardiovasc Drugs Ther* 1993;7(Suppl 1):81-85.
25. Laffi G, Marra F, Buzzelli G, et al. Comparison of the effects of torasemide and furosemide in nonazotemic cirrhotic patients with ascites: A randomized, double-blind study. *Hepatology* 1991;13:1101-05.
26. Santos J, Planas R, Pardo A, et al. Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. *J Hepatol* 2003;39:187-92.
27. Porcel A, Diaz F, Rendon P, et al. Dilutional hyponatremia in patients with cirrhosis and ascites. *Arch Intern Med* 2002;162:323-28.
28. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: Report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258-66.
29. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: A randomized double-blind multicenter trial. *Gastroenterology* 2003;124:933-39.
30. Wong F, Blei AT, Blendis LM, et al. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: A multi-center, randomized, placebocontrolled trial. *Hepatology* 2003;37:182-91.
31. Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996;111:1002-10.
32. Gines P, Tito L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988;94:1493-502.
33. Luca A, Garcia-Pagan JC, Bosch J, et al. Beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. *Hepatology* 1995;22:753-58.
34. Ruiz-Del-Arbol L, Monescillo A, Jimenez W, et al. Paracentesis-induced circulatory dysfunction: Mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997;113:579-86.
35. Luca A, Feu F, Garcia-Pagan JC, Jimenez W, et al. Favorable effects of total paracentesis on splanchnic hemodynamics in cirrhotic patients with tense ascites. *Hepatology* 1994;20:30-33.
36. Tito L, Gines P, Arroyo V, et al. Total paracentesis associated with intravenous albumin management of patients with cirrhosis and ascites. *Gastroenterology* 1990;98:146-51.
37. Vila MC, Coll S, Sola R, et al. Total paracentesis in cirrhotic patients with tense ascites and dilutional hyponatremia. *Am J Gastroenterol* 1999;94:2219-23.
38. Gines P, Arroyo V, Quintero E, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 1987;93:234-41.
39. Pinto PC, Amerian J, Reynolds TB. Large-volume paracentesis in nonedematous patients with tense ascites: Its effect on intravascular volume. *Hepatology* 1988;8:207-10.
40. Salerno F, Badalamenti S, Incerti P, et al. Paracentesis: A re-evaluated procedure in the management of cirrhotic patients with ascites. *Ital J Gastroenterol* 1990;22:44-49.
41. Salerno F, Badalamenti S, Incerti P, et al. Repeated paracentesis and i.v. albumin infusion to treat tense ascites in cirrhotic patients. A safe alternative therapy. *J Hepatol* 1987;5:102-08.
42. Gines P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. *N Engl J Med* 1991;325:829-35.
43. Fernandez-Esparrach G, Guevara M, Sort P, et al. Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis. A randomized double-blind trial of spironolactone versus placebo. *J Hepatol* 1997;26:614-20.
44. Gentilini P, Casini-Raggi V, Di Fiore G, et al. Albumin improves the response to diuretics in patients with cirrhosis and ascites: Results of a randomized, controlled trial. *J Hepatol* 1999;30:639-45.
45. Laffi G, Gentilini P, Romanelli RG, et al. Is the use of albumin of value in the treatment of ascites in cirrhosis? The case in favour. *Dig Liver Dis* 2003;35:660-63.
46. Gadano A, Moreau R, Pessione F, et al. Aquaretic effects of niravoline, a kappa-opioid agonist, in patients with cirrhosis. *J Hepatol* 2000;32:38-42.
47. Bureau C, Garcia-Pagan JC, Otal P, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS:

- Results of a randomized study. *Gastroenterology* 2004;126:469-75.
48. Naritaka Y, Ogawa K, Shimakawa T, et al. Clinical experience of transjugular intrahepatic portosystemic shunt (TIPS) and its effects on systemic hemodynamics. *Hepatogastroenterology* 2004;51:1470-72.
 49. Colombato LA, Spahr L, Martinet JP, et al. Haemodynamic adaptation two months after transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients. *Gut* 1996;39:600-04.
 50. LaBerge JM, Somberg KA, Lake JR, et al. Two-year outcome following transjugular Intrahepatic portosystemic shunt for variceal bleeding: Results in 90 patients. *Gastroenterology* 1995;108:1143-51.
 51. Sanyal AJ, Freedman AM, Shiffman ML, et al. Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: Results of a prospective controlled study. *Hepatology* 1994;20:46-55.
 52. Somberg KA, Riegler JL, LaBerge JM, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: Incidence and risk factors. *Am J Gastroenterol* 1995;90:549-55.
 53. Freedman AM, Sanyal AJ, Tisnado J, et al. Complications of transjugular Intrahepatic portosystemic shunt: A comprehensive review. *Radiographics* 1993;13:1185-210.
 54. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864-71.
 55. Patch D, Nikolopoulou V, McCormick A, et al. Factors related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding. *J Hepatol* 1998;28:454-60.
 56. Ring EJ, Lake JR, Roberts JP, et al. Using transjugular intrahepatic portosystemic shunts to control variceal bleeding before liver transplantation. *Ann Intern Med* 1992;116:304-09.
 57. Wong W, Liu P, Blendis L, et al. Long-term renal sodium handling in patients with cirrhosis treated with transjugular intrahepatic portosystemic shunts for refractory ascites. *Am J Med* 1999;106:315-22.
 58. Gines P, Uriz J, Calahorra B, et al. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterol* 2002;123:1839-47.
 59. Ochs A, Rossle M, Haag K, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. *N Engl J Med* 1995;332:1192-97.
 60. Peltekian KM, Wong F, Liu PP, et al. Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. *Am J Gastroenterol* 1997;92:394-99.
 61. Shiffman ML, Jeffers L, Hoofnagle JH, et al. The role of transjugular intrahepatic portosystemic shunt for treatment of portal hypertension and its complications: A conference sponsored by the National Digestive Diseases Advisory Board. *Hepatology* 1995;22:1591-97.
 62. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with endstage liver disease. *Hepatology* 2001;33:464-70.
 63. B S Sandhu, A J Sanyal. Management of Ascites in Cirrhosis. *Clin Liver Dis* 2005;9:715-32.

(B) PORTAL HYPERTENSION AND VARICEAL BLEEDING

ANATOMY OF THE PORTAL VENOUS SYSTEM

Understanding the anatomy of portal venous system is very important in the management of variceal bleeding. Portal vein is formed behind the neck of the pancreas by the confluence of the SMV, which drains blood vessels perfusing the small bowel, and the splenic vein. Short gastric veins, which drain the gastric fundus, enter the spleen above the origin of the splenic vein. Left gastric vein (coronary vein) enters the portal venous system within a few centimeters from the confluence through the splenic vein or the portal vein itself. Portal flow in normal person is approximately 1 to 1.2 l/min with a low pressure of about 7 mm Hg. It constitutes two thirds of the hepatic blood flow and provides 30 to 60% of oxygen consumed by the liver. Blood vessels around gastroesophageal junction drain into the azygos vein before returning to the systemic circulation. The normal azygos venous blood flow is around 150 to 200 ml/min. Gastroesophageal varices arise from the lower esophagus and the cardiac end of the stomach.

FOUR ZONES OF ESOPHAGOGASTRIC JUNCTION

Vianna, et al,¹ divided the vasculature of esophagogastric (EG) junction into 4 zones basing on the radiologic imaging and corrosion casting study.

- **Gastric zone:** It is located just below the EG junction, identified by longitudinal veins draining into the short gastric and left gastric veins.
- **Palisade zone:** It extends 2 to 3 cm above the gastric zone and consists of uniformly distributed parallel veins running in four groups with multiple anastomoses lying in the lamina propria. Each of these groups corresponds to one esophageal mucosal fold. Blood flows in both caudal and cephalad directions in this zone depending on pressure above and below this level.
- **Perforating zone:** It lies above the palisade zone. It has lost the longitudinal structure but features venules penetrating through the muscle wall of the esophagus linking the submucosal vessels to the extra esophageal vessels.
- **Truncal zone:** It lies above the perforating zone. It consists of longitudinal veins and occasional perforating veins penetrating at irregular intervals.

PORTAL HYPERTENSION

Portal hypertension is a common clinical syndrome, which is hemodynamically defined by a pathological increase of the portal pressure gradient (the pressure difference between the portal vein and the IVC) and by the formation of portosystemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver.²

Normal values of the portal pressure gradient are of 1-5 mm Hg. Clinically significant portal hypertension is diagnosed when clinical manifestations of the disease appear or when portal pressure gradient or in case of cirrhosis determined by its equivalent, the hepatic venous pressure gradient (HVPG)³ exceeds a threshold value of 10-12 mm of Hg. Values of portal pressure gradient between 5 and 9 mm Hg correspond to preclinical portal hypertension.⁴⁻⁷ Cirrhosis of the liver determines about 90% of cases of portal hypertension. Other causes of portal hypertension account for approximately 10% of cases worldwide, which explains why these are frequently referred to as non-cirrhotic portal hypertension.

Causes of portal hypertension^{8,57} Prehepatic

- Portal vein thrombosis (most common prehepatic cause)
 - Umbilical sepsis (most common cause in children)
 - Thrombophilic syndromes
 - congenital (protein C and S deficiency)
 - acquired (latent myeloproliferative disease)
 - Other factors
 - Sepsis
 - Abdominal trauma
 - Post surgical
- Splenic vein thrombosis
- Congenital stenosis/external compression of portal vein
- Arteriovenous fistulae

Hepatic

- Cirrhosis (most common cause-90% cases)
- Idiopathic portal hypertension
- Acute fatty liver of pregnancy
- Hepatitis: viral/alcoholic/chronic active hepatitis
- Hepatocellular carcinoma
- Granulomatous diseases
 - Tuberculosis
 - Sarcoidosis
 - Schistosomiasis
- Hematological liver diseases
- Polycystic liver disease
- Nodular regenerative hyperplasia
- Congenital hepatic fibrosis
- Veno-occlusive diseases of liver

- Peliosis hepatis
- Hypervitaminosis A
- Metals and chemicals
 - Arsenic, copper sulfate
 - Vinyl chloride poisoning
 - Cyanamide toxicity
- Amyloidosis
- Mastocytosis
- Rendu-Osler-Weber syndrome

Posthepatic

- Budd-Chiari syndrome (most common cause)
- Congenital malformations of IVC
- IVC thrombosis
- Constrictive pericarditis
- Tricuspid valvular diseases

Intrahepatic causes of portal hypertension can be classified according to the results of hepatic vein catheterization, such as:^{9,57}

- **Presinusoidal PH:** Normal wedged and free hepatic venous pressure (WHVP and FHVP);
- **Sinusoidal PH:** Increased WHVP and normal FHVP;
- **Postsinusoidal PH:** Increased WHVP and FHVP. (WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure).

PATHOPHYSIOLOGY OF ESOPHAGEAL VARICES

Esophageal varices (EV) are the tortuous dilated venous plexus in the lamina propria of the lower esophagus. In cirrhosis, portal pressure increases as a result of distorted architecture of the liver due to fibrosis, regenerative nodule formation and intrahepatic vasoconstriction (due to decreased nitric oxide).¹⁰ When hepatic venous pressure gradient (HVPG) is >10-12 mmHg, it causes dilation and high pressures in the periesophageal veins, rendering the valves in the perforating veins incompetent and allowing retrograde flow into the deep intrinsic veins and its tributaries. The dilated deep intrinsic veins displace the superficial venous plexus and assume a subepithelial position forming the tortuous variceal columns in the esophageal lumen.¹¹ The high-pressure dilated vessels in the perforating zone force blood to flow caudally into the palisade zone where these thin parallel vessels run within the mucosal fold in a longitudinal manner. Esophageal plexus in this region is more superficial and has poor connective tissue support. Commonly the palisade zone is the most common site of bleeding. Varices at the perforating and truncal zones are connected to periesophageal varices by the perforators. It has been suggested that these perforators are the cause of failed endoscopic treatment and early recurrence of varices after endoscopic therapy.¹²⁻¹⁵

Gastroesophageal varices (GV) are present in 50% of cirrhotic patients and in up to 70% of those with decompensated cirrhosis.¹⁶ In patients with large varices,

the risk for hemorrhage is at least 30% within the first 2 years of diagnosis.¹⁷ Variceal hemorrhage has a mortality of at least 20% at 6 weeks, despite improvements in therapy.¹⁸⁻²⁰

SURVEILLANCE POLICY

Routine universal screening for EV is recommended because the development of varices cannot be prevented with medical treatment.²¹ Only patients with medium or large gastroesophageal varices get the benefit of prophylactic treatment.²² For subjecting the patients for endoscopic screening, diagnosis of cirrhosis with portal hypertension must be established. Clinical signs and symptoms along with proven laboratory investigations including liver function tests, coagulation profile and abdominal imaging such as abdominal USG and CT scan will establish the diagnosis.⁵⁶ In case of doubtful diagnosis, liver biopsy should be considered. Practice guidelines recommend that all patients with cirrhosis should have endoscopic screening for esophageal varices,^{22,23} because there is no noninvasive way to assess their presence reliably.²⁴

Portal hypertension is a progressive condition and rate of esophageal varices formation is approximately 7% per year in cirrhosis patients and even higher in decompensated cirrhotic patients.²⁵ Screening endoscopy should be repeated performed once in every 1 to 2 years in case of small varices, once every 2 to 3 years in those who have no varices, and yearly in patients who have decompensated cirrhosis to monitor the formation and progression of varices.²³

PROPHYLACTIC TREATMENT

Patients without any EVs, recent data do not support the use of prophylactic medical treatment.²¹ A reduction of >10% of hepatic venous pressure gradient (HVPG)

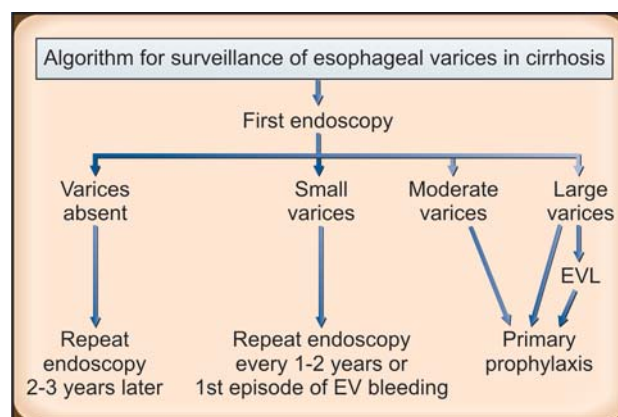


Figure 49.3: Surveillance for esophageal varices^{9,56}

significantly decreases the development of varices and risk for bleeding.^{21,27} Reduction of HVPG to < 12 mm Hg eliminates the risk for hemorrhage and improves the survival rate.²⁶

Small EVs

No routine prophylaxis recommended except in few studies which showed that prophylactic treatment has a role in preventing them. Presence of "red wale sign" and ESLD is an indication for prophylaxis.^{28,29} Medium or large EVs (> 5 mm): Usually benefitted from prophylaxis and prevent first episode of variceal bleeding.¹⁹ In patients with large esophageal varices, nonselective β -adrenergic blockers (propranolol or nadolol) reduce the risk 1st episode of bleeding in from 30 to 14% in 2 years.¹⁹

Role of β -blockers

They reduce the portal pressure by decreasing the cardiac output (β_1 effect) and causing α -adrenergic-induced splanchnic vasoconstriction (β_2 effect), thereby reducing portal blood flow. Important side effect is bradycardia. Dose of nonselective β -blockers (propranolol, nadolol) is adjusted to keep the resting pulse rate at around 55/minute. Carvedilol with non-selective α and β blocker activity can also be used. Duration of treatment is long for primary and secondary prophylaxis. Propranolol, nadolol and carvedilol can be used as monotherapy. Other drugs like nitrates further decrease the portal pressure. Combination therapy has more side effects and is not recommended.^{30,31}

Endoscopic Variceal Ligation (EVL)

It is a very useful tool in preventing first variceal bleeding even though there is no difference in the mortality rates in EVL and medical treatment.^{32,33} EVL is indicated in patients who are intolerant to therapeutic doses of β -blockers (10-15%) or patients with contraindications to β -blockers. (15%) Combination therapy of EVL and β -blockers when compared with EVL did not show any difference in outcome.³⁴ There is no role for endoscopic sclerotherapy, shunt surgery, or TIPS in the primary prophylaxis of variceal hemorrhage.

Primary and secondary prophylaxis for esophageal varices

Drug	Maximum dose (mg/day)
1. Propranolol 20 mg BID, oral; increase the dose	320
2. Nadolol 40 mg BID, oral; increase the dose	160
3. Carvedilol 6.25 mg BID, oral; increase the dose	50
4. Isosorbide mononitrate 10-20 mg BID, oral; increase the dose	20-40
Isosorbide mononitrate is used in combination with β -blocker	

(Presented in a modified form with permission of Jaime Bosch⁵⁷) (J Bosch, A Berzigotti, JC Garcia-Pagan, et al. The management of portal hypertension: Rational basis, available treatments and future options. *J of Hepatology* 2008;48:S68-S92).

TREATMENT OF BLEEDING ESOPHAGEAL VARICES

General Care

Variceal hemorrhage is a life threatening complication in ESLD patients with portal hypertension. It presents with hematemesis or melena, and may be the first manifestation of cirrhosis in patients with previously unknown liver disease.⁹ Spontaneous stoppage of bleeding is observed in upto 30-40% of patients. These patients should be admitted to an ICU for early resuscitation and management. Initial resuscitation includes care of airway, breathing and circulation. Access with a large IV cannula is important to infuse fluid and blood components to replace the volume loss. Volume expansion should be performed with care to prevent "overexpansion" of the plasma volume can increase portal pressure and precipitate recurrent variceal bleeding.⁵⁶ Use of isotonic saline usually avoided as this can worsen or precipitate the formation of ascites or other extra vascular fluid accumulation. Blood volume resuscitation should be undertaken to maintain the hemoglobin around 8 gm/dl. Transfusion of fresh frozen plasma and platelets may be considered, in case of significant coagulopathy or thrombocytopenia.⁹

Endotracheal intubation may be required in case of aspiration of blood to protect the airway particularly in case of associated hepatic encephalopathy. Role of antibiotics is controversial. But studies have reported that use of prophylactic antibiotics decrease the risk for bacterial infections, reduces the risk for early rebleeding, and increases survival.³⁵⁻³⁷ Oral fluoroquinolones like norfloxacin 400 mg for 7 days is preferable. IV access may be used in case of patient not tolerating oral medication.³⁷ Reports suggest that IV ceftriaxone is more effective than is oral norfloxacin in preventing bacterial infections in EV bleeding.³⁸ Aminoglycosides are avoided due to nephrotoxicity.³⁹

Definitive Treatment

Endoscopic treatment combined with medical treatment is the preferred approach.⁴⁰ First line treatment is to start vasoconstrictor group of drugs like terlipressin, somatostatin or somatostatin analogues (octreotide, vapreotide) before endoscopic procedure. They control bleeding by temporarily lowering the portal pressure due to splanchnic vasoconstriction.⁵⁶

Endoscopic Treatment

Endoscopic treatment is the gold standard in treatment of acute variceal bleeding.⁹ After hemodynamically stabilizing the patient, emergency therapeutic endoscopic procedure should be undertaken to control active hemorrhage and to prevent early rebleeding. EVL is the preferred endoscopic approach in controlling active hemorrhage from EVs and is associated with fewer complications, low rates of rebleeding, and low mortality rate.^{41,42} Endoscopic sclerotherapy is preferred when banding is technically difficult due to obscure field due to hemorrhage.⁵⁶

PHARMACOTHERAPY

Terlipressin is a longer-acting vasopressin analogue. It is safe and effective in controlling acute variceal hemorrhage with less side effects and reduced mortality. The list of drugs used in treatment of esophageal varices is shown in the box below:

Treatment of bleeding esophageal varices (duration of treatment: 2-5 days)		
Drug		Dose
1. Terlipressin	IV; Bolus dose	2 mg/4 hour for 24-48 hour then 1 mg/4 hour
2. Vasopressin+ NTG:	VP-IV infusion, 0.4 units/min+NTG	Percutaneous 20 mg
3. Somatostatin	IV; Bolus dose, later infusion	250 µg followed by 250-500 µg/h
4. Octreotide	IV; Bolus dose, later infusion	50 µg followed by 50 µg/h
5. Vapreotide	IV; Bolus dose, later infusion	50 µg followed by 50 µg/h

(Abbreviation: IV—intravenous; VP—Vasopressin; NTG—Nitroglycerine)

(Presented in a modified form with permission of Jaime Bosch⁵⁷) (J Bosch, A Berzigotti, JC Garcia-Pagan, et al. The management of portal hypertension: Rational basis, available treatments and future options. *J of Hepatology* 2008;48:S68-S92).

Role of TIPS

Role of TIPS 10 to 20% patients with variceal hemorrhage will have uncontrolled hemorrhage or early rebleeding

within 1-3 days which can be treated with repeated attempts of therapeutic endoscopy. TIPS remains the last option in case of failure all these measures.⁴³ TIPS effectively control bleeding by reducing the portal pressure. It acts as a side-to-side porto-caval shunt. Disadvantages of TIPS is worsening of encephalopathy in decompensated cirrhotic patients and occlusion of TIPS in 50-70% at the end of one year. But recent use of PTFE (polytetrafluoroethylene)-covered stents have improved primary and secondary TIPS patency rates and decreased the rates of stent occlusion and stenosis.⁴⁴

Role of Balloon Tamponade

Use of Sengstaken Blackmore tube is limited. It is a temporary method of variceal bleeding control in case of failure of endoscopic and pharmacologic therapies, but deflation of the balloon may lead to rebleeding. It can be used in a patient who has failed repeated endoscopy and waiting for TIPS and shunt surgery in emergency. Complication of tamponade is esophageal ulcerations due to pressure necrosis of the esophageal wall that can be lethal.⁵⁶

Recurrent Variceal Hemorrhage

Risk for recurrent variceal hemorrhage after an episode of 1st variceal hemorrhage is 50-60% in the first year.⁴⁵ EVL and nonselective β -blocker (propranolol and nadolol) treatment reduces the rebleeding rates to around 15 to 23% at 16 months.^{46,47} Lowest rebleeding rate is less in patients by reducing HVPG < 12 mm of Hg or > 20% from the baseline.⁴⁵

Role of EVL

Repeated EVL at an interval of 2-4 weeks may be required to prevent rebleeding. One study reported that repeated EVL once in every 2 months increases the possibility of eradication of EVs and decreases the recurrence of EVs.⁴⁸ Once complete eradication is achieved, patients should be kept under surveillance endoscopy for recurrent EVs, once in every 6 months-1 year depending upon the severity of chronic liver disease.⁵⁶

Role of TIPS/Surgical Shunts

In case of recurrent bleeding from EVs in spite of EVL and pharmacotherapy, decision should be taken to consider TIPS or shunt surgery (Distal splenorenal shunt preferred). Both the procedures have a similar rates of rebleeding, encephalopathy and mortality rates.⁴⁹ Role of shunt surgery is declining in the control of recurrent variceal bleeding with the growing experience in TIPS placement by the interventional radiologist. TIPS is not

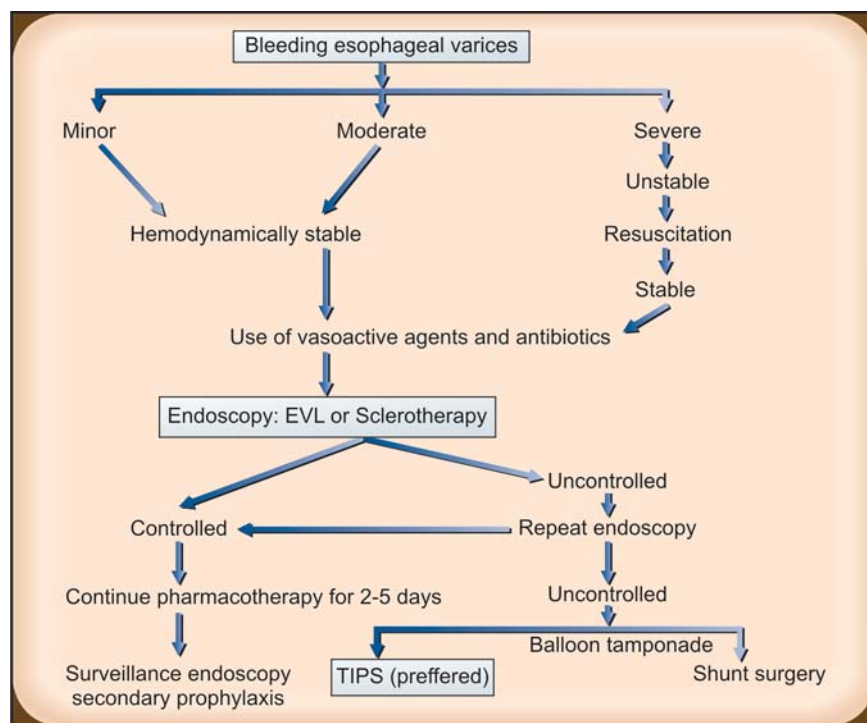


Figure 49.4: Algorithm for treatment of esophageal varices (Presented in a modified form with permission of Jaime Bosch)⁵⁷ (J Bosch, A Berzigotti, JC Garcia-Pagan, et al. *The management of portal hypertension: Rational basis, available treatments and future options. J of Hepatology* 2008; 48:S68-S92)

a permanent treatment. Role of TIPS is to bridge the time gap between appearance of complications and liver transplantation. All these patients should be evaluated for liver transplantation.⁹

Administration of Recombinant Activated Factor VII

Early control of bleeding is crucial and is a key factor influencing survival. Active bleeding at endoscopy is an independent prognostic factor of mortality. For this reason, new ways to optimize coagulation are currently under evaluation. Recombinant activated factor VII (rFVIIa) has been reported to achieve immediate control of bleeding in 100% (a total of eight) patients with refractory bleeding.⁵⁰ A recent randomized controlled trial investigated the administration of rFVIIa in addition to standard medical and endoscopic therapy. Exploratory analyses showed a beneficial effect of rFVIIa for the control of bleeding in patients with variceal bleeding and impaired liver function (Child Pugh B and C).⁵¹

Hence rFVIIa can be proposed in patients with refractory bleeding to avoid TIPS when this procedure is contra-indicated; rFVIIa can also be used to stabilize patients before the TIPS procedure, although the ideal dosage of rFVIIa for this purpose is not known.⁵²

Gastric Varices

In cirrhotic patients, gastric varices (GV) are an extension of esophageal varices and less prevalent (20%) than esophageal varices (50-70%). Gastric varices are classified commonly based on their relationship with esophageal varices as well as their location in the stomach.^{53,56}

- **Type 1 GV (GEV1):** They extend along the lesser curve and are similar to esophageal varices. They are the most common type of GVs and treatment is same as for esophageal varices.
- **Type 2 GV (GEV2):** They extend along the fundus and tend to be longer and more tortuous.

Isolated GV (IGVs) occur in absence of esophageal varices; can be classified into 2 subgroups: Type 1 and Type 2 IGVs:^{9,56}

- Type 1 IGVs (IGV1) are located in the fundus and tends to be tortuous and complex.
- Type 2 IGVs (IGV2) are located in the body, antrum, or around the pylorus.

Type 2 GV and Type 1 IGV (GEV2 and IGV1) constitute the fundal varices. There is limited literature available for treatment guidelines of fundal varices. No reported studies indicating role of pharmacotherapy in GV. Splenectomy is indicated in Type 1 IGV, if the etiology

is splenic vein thrombosis.⁹ GV bleeding is diagnosed on endoscopy as “snake skin” or “reticulated” appearance. Different treatment options are endoscopic sclerotherapy or band ligation or variceal obscuration with tissue adhesives like N-butyl-cyanoacrylate, isobutyl-2-cyanoacrylate and thrombin.^{54,55} Use of tissue adhesives and sclerotherapy are more favored in GV rather than banding. Role of TIPS or surgical shunts are rarely required for repeated episodes of bleeding GVs. β blockers can be used to prevent recurrent episodes of bleeding GVs.⁹

REFERENCES

- Vianna A, Hayes PC, Moscoso G, et al. Normal venous circulation of the gastro-esophageal junction. *Gastroenterology* 1987;93:876.
- Garcia-Pagan JC, Groszmann RJ, Bosch J. Portal hypertension. In: Weinstein WM, Hawkey CJ, Bosch J, editors. *Clinical gastroenterology and hepatology*. Philadelphia: Elsevier Mosby;2005:707-16.
- Bosch J, Garcia-Pagan JC, Berzigotti A, et al. Measurement of portal pressure and its role in the management of chronic liver disease. *Semin Liver Dis* 2006;26:348-62.
- Bosch J, Navasa M, Kravetz D, et al. Diagnosis and evaluation of portal hypertension. *Z Gastroenterol* 1988;26:8-14.
- Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254-61.
- Casado M, Bosch J, Garcia-Pagan JC, et al. Clinical events after transjugular intrahepatic portosystemic shunt: Correlation with hemodynamic findings. *Gastroenterology* 1998;114:1296-303.
- Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401-07.
- Valla DC, Condat B. Portal vein thrombosis in adults: Pathophysiology, pathogenesis and management. *J Hepatol* 2000;32:865-71.
- V Longacre, G Garcia-Tsao A Commonsense Approach to Esophageal Varices. *Clin Liver Dis* 2006;10:613-25.
- Wiest R, Groszmann RJ. Nitric oxide and portal hypertension: Its role in the regulation of intrahepatic and splanchnic vascular resistance. *Semin Liver Dis* 1999;19:411-26.
- Kitano S, Terblanche J, Kahn J, et al. Venous anatomy of the lower oesophagus in portal hypertension: Practical implications. *Br J Surg* 1986;73:525.
- Dhiman RK, Choudhuri G, Saraswat VA, et al. Role of para-esophageal collaterals and perforating veins on outcome of endoscopic sclerotherapy for esophageal varices. *Gut* 1996;38:759.
- Leung VKS, Sung JY, Ahuja A, et al. Large para-oesophageal varices on endosonography predicts recurrent oesophageal varices and rebleeding. *Gastroenterology* 1997;112:1811.
- Nagamine N, Ueno N, Tomiyama T, et al. A pilot study on modified endoscopic variceal ligation using endoscopic ultrasonography with color Doppler function. *Am J Gastroenterol* 1998;93:150.
- Sakai T, Iwao T, Oho K, et al. Influence of extra-variceal collateral channels pattern on recurrence of esophageal varices after sclerotherapy. *J Gastroenterol* 1997;32:715.
- Madhotra R, Mulcahy HE, Willner I, et al. Prediction of esophageal varices in patients with cirrhosis. *J Clin Gastroenterol* 2002;34(1):81-85.
- D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: An evidence-based approach. *Semin Liver Dis* 1999;19(4):475-505.
- El-Serag HB, Everhart JE. Improved survival after variceal bleeding over an 11-year period in the Department of Veterans Affairs. *Am J Gastroenterol* 2000;95:3566-73.
- Carbonell N, Pauwels A, Serfaty L, et al. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology* 2004;40:652-59.
- D'Amico G, DeFranchis R, Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;38:599-612.
- Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent esophageal varices in patients with cirrhosis. *N Engl J Med* 2005;353:2254-61.
- Grace ND, Groszmann RJ, Garcia-Tsao G, et al. Portal hypertension and variceal bleeding: An AASLD single topic symposium. *Hepatology* 1998;28:868-80.
- de Franchis R. Updating consensus in portal hypertension: Report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33:846-52.
- D'Amico G, Morabito A. Noninvasive markers of esophageal varices: Another round, not the last. *Hepatology* 2004;39(1):30-34.
- Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatol* 2003;38(3):266-72.
- Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99(5):590-92.
- Aracil C, Lopez-Balaguer JM, Monfort D, et al. Hemodynamic response to beta-blockers and prediction of clinical efficacy in the primary prophylaxis of variceal bleeding in patients with cirrhosis [abstract]. *Hepatology* 2003;38:296A.
- de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;43:167-76.
- Merkel C, Marin R, Angeli P, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology* 2004;127(2):476-84.
- Spanish Variceal Bleeding Group. Propranolol p placebo vs propranolol p isosorbide-5-mononitrate in the prevention of the first variceal bleeding. A multicenter double-blind randomized trial. *J Hepatol* 1999;30(Suppl 1):50.
- D'Amico G, Pasta L, Politi F, et al. Isosorbide mononitrate with nadolol compared to nadolol alone for prevention of the first bleeding in cirrhosis. A double-blind placebocontrolled randomized trial. *Gastroenterology International* 2002;15:40-50.
- Khuroo MS, Khuroo NS, Farahat KL, et al. Meta-analysis: Endoscopic variceal ligation for primary prophylaxis of

- oesophageal variceal bleeding. *Aliment Pharmacol Ther* 2005;21:347-61.
33. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2004;40(1):65-72.
 34. Sarin SK, Wadhawan M, Agarwal SR, et al. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. *Am J Gastroenterol* 2005;100:797-804.
 35. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: A meta-analysis. *Hepatology* 1999;29:1655-61.
 36. Hou MC, Lin HC, Liu TT, et al. Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: A randomized trial. *Hepatology* 2004;39(3):746-53.
 37. Blaise M, Pateron D, Trinchet JC, et al. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology* 1994;20(1):34-38.
 38. Planas R, Fernandez J, del Arbol LR, et al. Randomized, multicenter controlled trial comparing oral norfloxacin vs intravenous ceftriaxone in the prevention of bacterial infection in cirrhotics with severe liver failure and gastrointestinal bleeding. *Gastroenterology* 2005;128(4):687-88.
 39. Hampel H, Bynum GD, Zamora E, et al. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. *Am J Gastroenterol* 2001;96(7):2206-10.
 40. Banares R, Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: A meta-analysis. *Hepatology* 2002;35(3):609-15.
 41. Lo GH, Lai KH, Cheng JS, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology* 1997;25:1101-04.
 42. Avgerinos A, Armonis A, Stefanidis G, et al. Sustained rise of portal pressure after sclerotherapy, but not band ligation, in acute variceal bleeding in cirrhosis. *Hepatology* 2004;39(6):1623-30.
 43. Chau TN, Patch D, Chan YW, et al. "Salvage" transjugular intrahepatic portosystemic shunts: Gastric fundal compared with esophageal variceal bleeding. *Gastroenterology* 1998;114:981-87.
 44. Bureau C, Garcia-Pagan JC, Ota P, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: Results of a randomized study. *Gastroenterology* 2004;126(2):469-75.
 45. Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. *Lancet* 2003;361:952-54.
 46. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sulcrilate compared with ligation alone for the prevention of variceal rebleeding: A prospective, randomized trial. *Hepatology* 2000;32(3):461-65.
 47. de la Pena J, Brullet E, Sanchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: A multicenter trial. *Hepatology* 2005;41(3):572-78.
 48. Yoshida H, Mamada Y, Tanai N, et al. A randomized control trial of bimonthly versus biweekly endoscopic variceal ligation of esophageal varices. *Am J Gastroenterol* 2005;100:2005-09.
 49. Henderson M, Boyer TD, Kutner MH, et al. DSRs vs. TIPS for refractory variceal bleeding: A prospective randomized controlled trial [abstract]. *Hepatology* 2004;40(4):725A.
 50. Jimenez-Saenz M, Romero-Castro R. [Recombinant factor VII in the treatment of acute hemorrhage due to esophageal varices.]. *Gastroenterol Hepatol* 2005;28(6):333-36.
 51. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: A randomized, double-blind trial. *Gastroenterology* 2004;127(4):1123-30.
 52. D Thabut, B Bernard-Chabert management of acute bleeding from portal hypertension. Best practice and research clinical gastroenterology 2007;21(1):19-29.
 53. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: A long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-49.
 54. Sarin SK, Jain AK, Jain M, et al. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002;97:1010-15.
 55. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001;33:1060-64.
 56. Anna V. Longacre, Guadalupe Garcia-Tsao. A commonsense approach to esophageal varices. *Clin Liver Dis* 2006;10:613-25.
 57. J Bosch, A Berzigotti, JC Garcia-Pagan, et al. The management of portal hypertension: Rational basis, available treatments and future options. *Journal of Hepatology* 2008;48:S68-S92.

(C) HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is a functional renal failure occurring in the absence of parenchymal kidney disease, is the most frequent cause of renal dysfunction in patients who have cirrhosis,¹ but it occasionally occurs in patients who have alcoholic hepatitis or acute liver failure.¹⁻⁴ Acute renal injury is a common occurrence among patients with advanced liver failure.⁵ These patients are at increased risk due to prerenal factors such as diuretic use and typical causes of intravascular volume depletion such as diarrhea secondary to lactulose use.⁶ Furthermore, patients with advanced liver disease are at higher risk for the development of intrarenal causes, such as acute tubular necrosis (ischemia, nephrotoxins) and acute interstitial nephritis. Cirrhotic patients with ascites and marked sodium retention as well as dilutional hyponatremia and are at a high risk of developing HRS.⁷ Probability of developing HRS in cirrhotic patients is 18% at 1 year and increased to 39% at 5 years.⁷ The development of HRS portends a notably worse prognosis for patients who ultimately undergo orthotopic liver transplantation (5-year survival 60% vs. 68%), leading to increasingly complicated hospitalizations with associated morbidity and mortality.⁸⁻¹²

Despite the complications associated with kidney dysfunction among patients awaiting OLT, combined liver-kidney transplants are not routinely performed. The basis for this practice was the initial realization in 1969 that transplanted cadaveric kidneys from patients with HRS were fully functional when transplanted into recipients.¹³ Four years later, Iwatsuki, et al. observed that patients with HRS showed resolution of renal dysfunction after receiving a liver transplantation and do not develop subsequent chronic renal disease.¹⁴ More recently, in 1991, Gonwa, et al. noted significant improvement in kidney function for the majority of patients with HRS after LTX.¹⁵ Seu, et al. (1991) reported no significant difference in serum creatinine measurements at 24 weeks post-transplant between patients with and without HRS.¹⁶ They concluded that kidney transplantation should not be performed in patients with HRS, thus allowing organ allocation to a person would obtain a survival benefit from the renal transplant.

PATHOGENESIS OF HRS AND ACTION OF VASOCONSTRICTOR DRUGS IN HRS

Renal vasoconstriction is the main hemodynamic derangement that occurs in HRS during the late stage of cirrhosis.^{17,18} Portal hypertension is the factor responsible

for hemodynamic derangements and splanchnic arterial vasodilatation, due to production of nitric oxide as a consequence of endothelial stretching and possibly bacterial translocation.¹⁹

CHANGES IN LATE STAGE CIRRHOSIS WITH HRS

- Changes in systemic arterial circulation
- Increased portal pressure
- Activation of systemic and renal vasoconstrictor factors that modulate renal circulation
- Renal dysfunction without any histological damage in the kidneys

Plasma accumulation in the splanchnic bed causes a compensatory response activation of systemic vasoconstrictor and antinatriuretic systems such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and arginine vasopressin (AVP) accounting for sodium and water retention as well as renal vasoconstriction as the kidney senses a relative hypovolemic state. Constant activation of vasoconstrictor factors on the kidney are compensated by renal vasodilators but with time circulating vasoconstrictors overcome the effect of renal vasodilators, leading to severe renal vasoconstriction and reduction in glomerular filtration rate.^{18,21}

Bacterial infections worsen circulatory dysfunction and aggravate renal vasoconstriction.^{20,22} Recent studies suggest that the development of HRS occurs in the setting of a reduction in cardiac output, indicating that the progression of circulatory and renal dysfunction in cirrhosis is caused not only by splanchnic vasodilation but also by a reduction in cardiac output.^{23,24}

CLINICAL FEATURES

HRS for the most part exhibit clinical features of advanced cirrhosis along with

- Low arterial blood pressure
- Low urine volume
- Severe urinary sodium retention
- Spontaneous dilutional hyponatremia is almost always present because of an increased solute-free water retention related to elevated levels of arginine vasopressin.²⁵
- Serum creatinine levels are elevated, but less than noncirrhotics with acute renal failure due to less muscle mass and low endogenous production of creatinine.^{26,27}

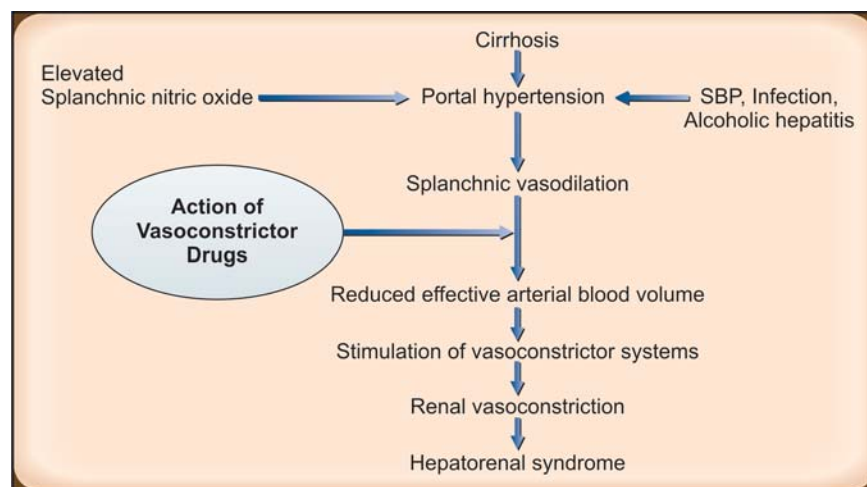


Figure 49.5: (Ref: Modified from Gine's and Arroyo, Hepatorenal syndrome.. J Am Soc Nephrol 10:1833-1839, 1999)

Types of HRS: 2 types of HRS were defined by the International Ascites Club (IAC):²³ Type I and II

Type I HRS: Rapidly progressive renal failure with a doubling of serum creatinine to a level >2.5 mg/dl ($220 \mu\text{mol/L}$) or a 50% reduction of creatinine clearance to < 20 ml/min in < 2 weeks.⁵⁵

MEDIAN SURVIVAL

2 weeks:^{14,28}

- 80% mortality at 2 weeks
- 10% surviving more than 3 months

It is associated with poor prognosis. If not treated early. These patients usually have a MELD score of 20 or higher and a Child score of 12 or higher.²⁸ Type 1 HRS may develop spontaneously, but it can be precipitated by bacterial infections such as spontaneous bacterial peritonitis (SBP) or sepsis, acute alcoholic hepatitis, or large-volume paracentesis without albumin expansion.^{3,22,30} It can be precipitated in 30% cases by bacterial infections and SBP, despite appropriate treatment and resolution of the infection.^{22,31} and in 20% cases due to therapeutic paracentesis without albumin expansion.¹⁵ Renal failure may occur in up to 10% of cirrhotic patients who have gastrointestinal bleeding, but in most cases this renal failure is caused by acute tubular necrosis and not HRS.¹⁷

TYPE II HRS

Serum creatinine level is > 1.5 mg/dl (132 micromole/L) and/or creatinine clearance is < 40 ml/min.⁵⁵ Renal failure is more slowly progressively and it has a better

prognosis. It is a steady form that develops slowly over weeks with better survival.²³ It has a subtler course, and serum creatinine levels range between 1.5 and 2.5 mg/dl (132 - $220 \mu\text{mol/L}$).^{1,28,29} Most patients with type 2 HRS usually have diuretic-resistant ascites and have a median survival time of approximately 6 months without transplantation.^{5,28,29}

DIAGNOSTIC CRITERIA

A. Diagnostic criteria consensus conference, Chicago (1994)

- Hepatic failure and portal hypertension
- Creatinine >1.5 mg/dl ($132 \mu\text{mol/L}$) or GFR < 40 ml/min
- No improvement after diuretic withdrawal and IV saline infusion (1500 ml)
- No shock, no ongoing bacterial infection, nephrotoxic agents or fluid losses
- Proteinuria < 500 mg/dl, normal renal US

B. Diagnostic criteria of HRS proposed by IAC (1996)

- Low GFR, as indicated by serum creatinine levels greater than 1.5 mg/dL or $132 \mu\text{mol/L}$
- Absence of shock, volume depletion and use of nephrotoxic drugs (NSAIDs)
- No improvement in serum creatinine level despite stopping use of diuretics for at least 4 to 5 days and volume repletion with 40 g intravenous albumin
- Absence of
 - Proteinuria
 - Sonographic evidence of obstructive uropathy
 - Parenchymal renal disease,

- Prerenal renal failure secondary to volume depletion
- ATN secondary to shock
- Drug-induced renal failure
- Glomerulopathies in cirrhosis patients due to alcohol or hepatitis viruses

C. New diagnostic criteria, San Francisco (2005)

- Cirrhosis with ascites
- Creatinine > 1.5 mg/dl
- No improvement after diuretic withdrawal and IV albumin infusion (1 g/kg/d) 48 h
- Absence of shock
- No recent nephrotoxic agents
- Proteinuria < 500 mg/day, microhematuria (< 50 RBC/field), normal renal US

MANAGEMENT

In type 1 HRS, hospitalization is recommended and type 2 HRS can be managed as outpatients.

Initial work up of the patient with type 1 HRS⁵⁵

- Measurement of
 - Pulse
 - Blood pressure
 - Intake and output
 - Daily weight
- Blood tests: Complete blood cell count
 - Liver function tests
 - Coagulation studies,
 - Serum BUN
 - Serum creatinine level
 - Serum electrolytes
 - Serum albumin
- Abdominal USG to rule out any
 - Parenchymal nephropathy
 - Mass lesion
 - Obstructive uropathy
- 24 hour urine volume
 - Urine sodium
 - Urine sediment
 - Urine analysis
 - Urine culture
- Diagnostic paracentesis to rule out SBP
 - Cell count
 - Culture
 - Albumin measurement

TREATMENT

Supportive Treatment

- Sodium restricted diet
- Discontinue diuretics
- Plasma expansion with albumin

- If dilutional hyponatremia present, fluid restriction of 1 L/d is recommended.¹⁸
- Nutrition support
- Evaluation for liver transplantation

Specific Treatment

Type 1 HRS: Splanchnic vasoconstrictors or TIPS

Type 2 HRS: Large-volume paracentesis and albumin expansion or TIPS

Type 1 HRS

Splanchnic vasoconstrictors

- Vasopressin analogues (ornipressin and terlipressin)
- Somatostatin analogues (octreotide)
- Alpha-adrenergic agonists (midodrine and noradrenaline)

Combination of vasoconstrictors and albumin^{34-37,39} is important to obtain an optimal response. Albumin expands the circulating blood volume, increase cardiac preload and cardiac output resulting in improvement of effective arterial blood volume leading to increased GFR.³⁷

Goals of Therapy

Goals of therapy is to reduce serum creatinine level to < 1.5 mg/dl (132 µmol/l) and influencing the outcome following transplantation by

- Providing a successful bridge to liver transplantation by reversing renal failure
- Allowing the patients to undergo transplantation with less morbidity and mortality
- Achieving survival rates similar to the patients without HRS.

Patients treated successfully with terlipressin and albumin before liver transplantation have similar outcome after transplantation with those who did not have HRS. Patients who responded to therapy of HRS with terlipressin and albumin and octreotide, midodrine, and albumin had a better survival rate than patients who did not respond to therapy.³⁸⁻⁴⁰

Terlipressin and other vasoconstrictors: Vasopressin analogues are potent vasoconstrictors in the splanchnic circulation. Ornipressin and vasopressin are not used in HRS due to ischemic side effects.^{28,29,42,43,46} Terlipressin is a newer and safer synthetic analogue of vasopressin with fewer side effects and has been used successfully in type 1 HRS.^{33,36,38,39} Administration of terlipressin and intravenous albumin improves renal function with a reduction of serum creatinine and improvement in GFR in 75% of patients with type 1 HRS.^{30-33,35-41,46}

First sign of response is improvement in urine volume in 48 hours. Treatment can be withdrawn once desired

serum creatinine level (< 1.5 mg/dL or $132 \mu\text{mol/L}$) is achieved, but changes in serum creatinine may take up to 3 days. One-month survival among most studies has ranged from 40 to 80%.^{33,36,38,39} Use of midodrine (alpha-adrenergic agonist) in association with Octreotide (an inhibitor of release of glucagon) and albumin also improve the renal function in cirrhotic patients with HRS.^{33,40}

Gine's P, et al.⁵¹ reported an algorithm for treatment of hepatorenal syndrome. The aim of the treatment is to reduce serum creatinine to < 1.5 mg/dL ($132 \mu\text{mol/L}$). The first lines of drugs are the combination of Vasoconstrictors + Albumin (1 gm/kg on first day, followed by intravenous albumin 20-40 gm/day). Vasoconstrictors such as Terlipressin or a combination of Midodrine and Octreotide or Noradrenaline can be used in a combination with albumin. Duration of treatment is 5 days to 2 weeks. TIPS is considered in patients with Child score less than 12 and not responding to vasoconstrictors.

Dose of vasoconstrictors:

1. **Terlipressin:** 0.5 mg IV every 4 hours; increase dose to 1 mg/4h, then up to 2 mg/4h or 2-12 mg/day, IV continuous infusion.
2. **Combination of Midodrine and Octreotide.**
Midodrine: 2.5-7.5 mg p.o. t.i.d, increase upto 12.5 mg TID daily depending upon the response to treatment and
Octreotide: 100 ug s.c. TID with an increase to 200 ug TID, if needed.
3. **Noradrenaline:** 0.5-3 mg/hour continuous IV infusion.

Transjugular intrahepatic portosystemic shunt (TIPS): It has been successfully used in treatment of refractory ascites. TIPS also used in HRS, improves renal function and GFR as well as reduces the activity of RAAS and SNS in cirrhotic patients,^{40,44-46} with 60 to 70% success rate. If used in patients with a child score > 12 , has increased risk of mortality. Recent approach is to use a combination of vasoconstrictors with TIPS in treatment of type 1 HRS to achieve improvement and completely normalized renal function.⁴⁰

Dialysis: It is not routinely recommended in HRS

Indications of Dialysis⁵⁵

- No response to first line treatment (vasoconstrictors + albumin or TIPS)
- Severe volume overload and metabolic acidosis
- Refractory hyperkalemia

Side Effects

Hypotension, coagulopathy, and GI bleeding.^{47,48}

Extracorporeal Liver Supporting Systems

They are also used in type 1 HRS in cirrhotic patients to decrease in bilirubin and creatinine, an improvement in serum sodium levels, urine volume, and mean arterial blood pressure, and decreased mortality.^{49,50}

Liver Transplantation

Liver transplantation is the best treatment option for HRS. The 1- and 3-years survival rate in cirrhotic patients with HRS after liver transplantation is 85 and 73%, respectively. Presence of HRS is associated with increased morbidity and early mortality after transplantation. Transplantation for type 1 HRS is limited, as significant proportion of patients die before the transplantation as a result of short survival and prolonged waiting time.⁵¹ LDLT in present scenario is a good option in these patients instead of long waiting period. Campbell, et al demonstrated a predictive value of the duration of pre-transplant creatinine elevation to determine post-transplant renal function, that is, those patients with the longest duration pre-OLT showed the greatest chance of nonresolution.⁵²

OUTCOME AND PREVENTION

Patients with pre-OLT renal dysfunction have an excellent chance of renal recovery after transplantation⁵⁶ and prevention of conditions which precipitate HRS like SBP, alcoholic hepatitis and bacterial infections is important in cirrhotic patients. HRS carried an approximately 95% mortality among untreated patients within 30 days.⁵⁴

Role of Pentoxifyllin

This drug in a dose of 400 mg three times daily for 1 month in patients of acute alcoholic hepatitis have shown to reduce the incidence and mortality of HRS.³

Role of Albumin

Intravenous albumin (dose-1.5 g/kg at diagnosis of infection and 1 g/kg 48 hours later) helps in preventing HRS in SBP patients as it counteracts the enhanced arterial splanchnic vasodilation causing under filling and subsequent activation of vasoconstrictor systems that might occur in the setting of bacterial infections in cirrhosis patients. Incidence of HRS in cirrhosis patients with SBP without albumin administration is 33 and 10% in those who received albumin and inhospital mortality in albumin receiving group is 10% compared to 29% in those not receiving albumin.²⁰ Plasma expanders like hydroxyethyl starch and others are not effective in preventing renal failure in SBP patients.⁵³

REFERENCES

- Arroyo V, Ginés P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
- Ginés P, Cárdenas A, Arroyo V, et al. Management of cirrhosis and ascites. *N Engl J Med* 2004;350:1646-54.
- Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: A double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637-48.
- Moore K. Renal failure in acute liver failure. *Eur J Gastroenterol Hepatol* 1999;11:967-75.
- Eknoyan G. Glomerular abnormalities in liver disease. In Epstein (Med): *The Kidney in Liver Disease*. Philadelphia: Hanley and Z Belfus;1996:123.
- Cassinello C, Moreno E, Solis-Herruzo, et al. Effects of orthotopic liver transplantation on vasoactive systems and renal function in patients with advanced liver cirrhosis. *Dig Dis Sci* 2003;48:179.
- Ginés A, Escorsell A, Ginés P, et al. Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. *Gastroenterology* 1993;105:229-36.
- Davis C, Gonwa T, Wilkinson A: Pathophysiology of renal disease associated with liver disorders: Implications for liver transplantation. Part 1. *Liver Transplant* 2002;8:91.
- Pham PTT, Pham PCT, Rastogi A, et al. Review article: Current management of renal dysfunction in the cirrhotic patient. *Aliment Pharm Therapy* 2005;21:949.
- Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1998;8:1151, 1998.
- Platt JF, Ellis JH, Rubin JM, et al. Renal duplex doppler ultrasonography: A noninvasive predictor of kidney dysfunction and hepatorenal, failure in liver disease. *Hepatology* 1994;10:362.
- Gonwa T, Klintmalm G, Levy M, et al. Impact of pretransplantation renal function on survival after liver transplantation. *Transplantation* 1995;59:361.
- Koppel M, Coburn J, Mims M, et al. Transplantation of cadaveric kidneys from patients with hepatorenal syndrome. *N Engl J Med* 1969;280:1367.
- Iwatsuki S, Popovtzer M, Corman J, et al. Recovery from "hepatorenal syndrome" after orthotopic liver transplantation. *N Engl J Med* 1973;289:1155.
- Gonwa T, Morris C, Goldstein R, et al. Long-term survival and renal function following liver transplantation in patients with and without hepatorenal syndrome—experience in 300 patients. *Transplantation* 1991;51:428.
- Seu P, Wilkinson A, Shaked A, et al. The hepatorenal syndrome in liver transplant recipients. *Am Surg* 1991;12:806.
- Moreau R, Lebrec D. Hepatorenal syndromedefinitions and diagnosis. *Aliment Pharmacol Ther* 2004;20(Suppl 3):24-8.
- Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151-57.
- Iwakiri Y, Groszmann R. The hyperdynamic circulation of chronic liver diseases: From the patient to the molecule. *Hepatology* 2006;43:S121-31.
- Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;5:403-09.
- Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: Pathophysiological basis of therapy and current management. *J Hepatol* 2003;38(Suppl 1):S69-89.
- Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis. Value of MELD score. *Gastroenterology* 2005;129:1944-53.
- Ruiz del Arbol L, Monescillo A, Arocena C, et al. Circulatory function and HRS in cirrhosis. *Hepatology* 2005;42:439-47.
- Ruiz-del-Arbol W, Urman J, Fernandez J, et al. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 2003;38:1210-18.
- Cárdenas A, Ginés P. Management of hyponatremia in cirrhosis. In: Ginés P, Arroyo V, Rodés J, et al, editors. *Ascites and renal dysfunction in liver disease*. Oxford (UK): Blackwell Publishing;2005:305-14.
- Caregaro L, Menon F, Angeli P, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med* 1994;154:201-05.
- Sherman D, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: Problems and pitfalls. *Am J Kidney Dis* 2003;41:269-78.
- Alessandria C, Ozdogan O, Guevara M, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: Relevance to liver transplantation. *Hepatology* 2005;41:1282-89.
- Cárdenas A. hepatorenal syndrome: A dreaded complication of end-stage liver disease. *Am J Gastroenterol* 2005;100:1-8.
- Ginés P, Titó L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 1988;94:1493-502.
- Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: Incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495-501.
- Cárdenas A, Ginés P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis. Incidence, clinical course, predictive factors and short-term prognosis. *Hepatology* 2001;34:671-76.
- Mulkay JP, Louis H, Donckier V, et al. Long-term terlipressin administration improves renal function in cirrhotic patients with type 1 hepatorenal syndrome: A pilot study. *Acta Gastroenterol Belg* 2001;64:15-19.
- Angeli P, Volpin R, Gerunda G, et al. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690-97.
- Duvoux C, Zanditenas D, Hezode C, et al. Effects of noradrenaline and albumin in patients with type 1 hepatorenal syndrome: A pilot study. *Hepatology* 2002;36:374-80.
- Arroyo V, Terra C, Torre A, et al. Hepatorenal syndrome in cirrhosis: Clinical features, diagnosis, and management. In: Ginés P, Arroyo V, Rodés J, et al, editors. *Ascites and renal dysfunction in liver disease*. Oxford (UK): Blackwell Publishing;2005:341-59.
- Arroyo V, Ruiz del Arbol, Ginés P. Circulatory dysfunction in cirrhosis. In: Arroyo V, Navasa M, Forns X, et al, editors. *Update in treatment of liver disease*. Barcelona (Spain): Ars Medica;2005:19-28.

38. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. *Gastroenterology* 2002;122:923-30.
39. Ortega R, Ginés P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome. Results of a prospective, non-randomized study. *Hepatology* 2002;36:941-48.
40. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55-64.
41. Restuccia T, Ortega R, Guevara M, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. *J Hepatol* 2004;40:140-6.
42. Guevara M, Ginés P, Fernandez-Esparrach G, et al. Reversibility of hepatorenal syndrome by prolonged administration of ornipressin and plasma volume expansion. *Hepatology* 1998;27:35-41.
43. Gulberg V, Bilzer M, Gerbes AL. Long-term therapy and retreatment of hepatorenal syndrome type 1 with ornipressin and dopamine. *Hepatology* 1999;30:870-75.
44. Guevara M, Ginés P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: Effects on renal function and vasoactive systems. *Hepatology* 1998;28:416-22.
45. Brensing KA, Textor J, Perz J, et al. Long-term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: A phase II study. *Gut* 2000;47:288-95.
46. Testino G, Ferro C, Sumberaz A, et al. Type-2 hepatorenal syndrome and refractory ascites: Role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003;50:1753-55.
47. Kapling RK, Bastani B. The clinical course of patients with type 1 hepatorenal syndrome maintained on hemodialysis. *Ren Fail* 2004;26:563-68.
48. Keller F, Heinze H, Jochimsen F, et al. Risk factors and outcome of 107 patients with decompensated liver disease and acute renal failure (including 26 patients with hepatorenal syndrome): The role of hemodialysis. *Ren Fail* 1995;17:135-46.
49. Mitzer SR, Stange J, Klammt S, et al. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: Results of a prospective, randomized, controlled clinical trial. *Liver Transpl* 2000;6:277-86.
50. Rifai K, Ernst T, Kretschmer U, et al. The Prometheus device for extracorporeal support of combined liver and renal failure. *Blood Purif* 2005;23:298-302.
51. Cárdenas A, Ginés P. Management of complications of cirrhosis in patients awaiting liver transplantation. *J Hepatol* 2005;42:S124-33.
52. Campbell MS, Kotlyar DS, Brensinger CM, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. *Liver Transpl* 2005;11:1048-55.
53. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatology* 2005;42:627-34.
54. Marik PE, Wood K, Starzl T. The course of type 1 hepatorenal syndrome post liver transplantation. *Nephrol Dial Transplant* 2006;21:478.
55. Andrés Cárdenas, Pere Gines Hepatorenal Syndrome. *Clin Liver Dis* 2006;10:371-85.
56. B Shusterman, G Mchedishvili, and M.H. Rosner. Outcomes for hepatorenal syndrome and acute kidney injury in patients undergoing liver transplantation: A single-center experience. *Transplant Proceed* 2007;39:1496-500.

(D) HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is defined as a complex of reversible neuropsychiatric syndrome due to portosystemic shunting, with or without intrinsic parenchymal liver disease. The presence of hepatic encephalopathy, whether it occurs in patients with acute or chronic liver injury, indicates liver failure, is a serious complication, and is often considered a clinical indication for evaluation for liver transplantation.¹ 30-50% of hospitalizations for cirrhosis are related to HE.²

CLASSIFICATION (DEPENDING ON THE ETIOLOGY)⁴

- **Type A:** Encephalopathy due to acute liver failure
- **Type B:** Encephalopathy due to portosystemic shunting, no intrinsic liver disease
- **Type C:** Encephalopathy due to cirrhosis with portosystemic shunting:
 - Episodic: precipitated, spontaneous, or recurrent
 - Resistant: mild, severe, treatment-dependent
 - Minimal. also known as “subclinical”

PATHOGENESIS

The neurologic impairment in HE is believed to be caused by multiple factors. This complex syndrome results due to:⁵⁻⁷

- Ammonia, derived from protein breakdown in the gut is the key toxin. Ammonia affects a number of neurotransmitter systems and exerts its effect through its products of metabolism (e.g. glutamate and glutamine). In HE
 - Cerebral glutamine levels are increased
 - Cerebral glutamate levels decreased
 - Glutamate re-uptake mechanisms are abnormal
 - Glutamate-binding sites on post-synaptic neurons are down regulated
- Failure of detoxification of gut-derived toxins, which are normally cleared by the liver.
- Intra- and extrahepatic shunting in liver failure.
- Abnormal blood brain barrier in HE, exacerbates the crossover of high levels of circulating systemic toxins into the CNS.
- Oxidative stress due to generation of reactive oxygen species
- Endogenous benzodiazepine like ligands
- Subclinical intracellular astrocytic edema
- GABA like molecules that act as GABA agonists
- Abnormal histamine and serotonin neurotransmission

- Endogenous opiates, neurosteroids, inflammatory cytokines
- Manganese toxicity

CLINICAL PRESENTATION

Clinical features ranging from life-threatening coma with cerebral edema (in acute liver failure) to subclinical, occult or minimal confusion/disorientation. An abrupt onset of a confusional state, neuromuscular abnormalities and fetor hepaticus (a sweet, musty smell on the breath from exhalation of unmetabolized mercaptans) and may progress within a matter of hours from a mild confusional state to deep coma. Asterixis (liver flap) should be sought and tendon reflexes tested; the latter are often increased, unlike in many patients who are drowsy. In fulminant liver failure, presentation of HE is same as those seen in patients with cirrhosis but as cerebral edema is more common. Signs of raised intracranial pressure (bradycardia, hypertension, dilated pupils, decerebrate posturing) may also be seen. Chronic persistent encephalopathy is used to describe patients with chronic liver disease that previously have had recurrent episodes of acute encephalopathy who then develop persistent neurological manifestations which may range from dysarthria and ataxia to dementia, parkinsonism and myelopathy. Subclinical encephalopathy is the term used to describe the mild brain dysfunction that is commonly overlooked during cursory clinical examination, but may affect visuospatial and psychomotor abilities and interfere with quality of life (e.g. driving may be impaired). It can present with focal neurologic signs, hemiplegia and hemiparesis were the most common focal neurologic signs, but hemiagnosia and monoplegia were also observed.⁸

RISK FACTORS

Seizures were more common in patients with focal neurologic signs. The focal neurologic deficits resolved, without sequelae, in parallel with the resolution of the HE.¹ The development of focal neurologic signs or seizures in a patient with encephalopathy should lead to appropriate brain imaging, however, because structural brain lesions, such as subdural hematomas, can cause the focal neurologic signs. Cerebral edema or even fatal uncal herniation have rarely been described in cirrhotic patients with HE.⁹⁻¹¹

Risk factors for encephalopathy

1. Increased protein load Upper GI hemorrhage Large protein meal 3. Electrolyte disturbance Hypokalemia Hyponatremia Dehydration Paracentesis 5. Portacaval shunts/TIPS Acute hepatitis Drug-induced liver injury 7. Drugs Sedatives Antidepressants 9. Terminal liver disease 11. Surgery 13. Diabetes mellitus	2. Decreased excretion of ammonia Renal failure, Hepatorenal syndrome Constipation 4. Infection Spontaneous bacterial peritonitis Pulmonary infection Urinary tract infection Cutaneous infection 6. Superimposed acute liver injury 8. Hepatocellular carcinoma 10. Severe hyperammonemia 12. Acute liver failure 14. Malnutrition

Hepatic encephalopathy: West Haven criteria for grading mental state³**West Haven criteria for grading mental state**

Grade	Clinical findings
Grade 0	No abnormality detected
Grade 1 (Mild)	Trivial lack of awareness, euphoria, anxiety, reduced attention span, impaired performance in addition or subtraction
Grade 2 (Moderate)	Lethargy, apathy, disorientation for time and place, personality change, Inappropriate behavior
Grade 3 (Severe)	Somnolence to semi-stupor, but responsive to stimuli, confusion and gross disorientation
Grade 4 (Coma)	Coma, little or no response to stimuli Mental state not testable

Conn H, Lieberthal M, et al. The hepatic coma syndromes and lactulose. Williams and Wilkins;1979:73).

DIAGNOSIS

- **Blood ammonia level:** Blood sample should be drawn in a nonheparinized container, immediately kept on ice and ammonia measured in 30 minutes. Arterial blood is more favorable for its measurement. Venous and arterial blood ammonia levels are closely similar when properly assayed without any technical errors.¹¹ Technical errors occur during the biochemical assay of ammonia levels. Ammonia is a labile compound. Evaporation and spontaneous deamination can occur during storage and transport at room temperature. There is a difference in assessing the venous and arterial blood for ammonia. Blood ammonia levels may be moderately elevated in patients with cirrhosis without HE. Elevated ammonia levels are seen in HE. Its level correlates with the severity of HE.^{12,13} Normal blood ammonia levels do not support the diagnosis

of HE. An increased ammonia level in a comatose patient does not exclude other coexistent conditions. Significant rise in ammonia level i.e. >150-200 μ mol/L in a comatose patient strongly favor HE.

- **Electroencephalogram (EEG):** It classically shows bilateral, synchronous slowing of frequency from alpha to theta (4-7 Hz) or even to the delta range (<4 Hz) and triphasic spikes, but these abnormalities are not specific for HE particularly in presence of convulsions.
- **Electrophysiological tests:** They are of research interest.

Visual evoked potentials	Brain stem auditory evoked potentials
Somatosensory evoked potentials	P300 event-related potentials

- **Psychometric tests:** Number connection test, useful in assessing the clinical course of HE and assess response to therapy.
- **PET Scan**
- **Head CT or MRI Scan:** To rule out other organic lesions causing abnormal mental status.

DIFFERENTIAL DIAGNOSIS

- Metabolic encephalopathy
Hypoglycemia, hypoxia, hypercapnia, hyponatremia, hypernatremia, ketoacidosis, uremia and thyroid dysfunction
- Drugs/toxins
Alcohol, sedatives, e.g. benzodiazepines
- Intracranial lesions
Subdural hematoma, subarachnoid hemorrhage, stroke, transient ischemic attack, intra-cranial hemorrhage, space occupying lesion
- Infection
Meningitis and encephalitis (bacteria/virus/fungus)
- Miscellaneous
Seizures, Wernicke's encephalopathy, delirium tremens, post-ictal state
- Trauma
Head injury

TREATMENT

Correction of Precipitating Factors

Dehydration should be corrected with infusion of isotonic saline. Discontinuation of diuretics and free water restriction is important even in presence of ascites and reintroduced cautiously. Restriction of protein diet and sedative drugs is necessary. Gastrointestinal blood loss should be replaced with blood transfusion. Broad-spectrum antibiotics are initiated after obtaining samples for culture when infection is suspected and later changed of antibiotics, based on the culture and sensitivity reports. Electrolyte disturbances in sodium and potassium levels should be corrected. Limited infusions of hypertonic saline (3% NaCl, 150 mL intravenous) may be needed for very severe hyponatremia. The new vasopressin receptor antagonists have shown promising results in treating severe hyponatremia with cirrhosis. They can be considered for patients with severe HE and severe hyponatremia.^{27,28} Renal failure, hepatorenal syndrome and urinary tract obstruction due to stones or prostatic hyperplasia should be corrected. Hypoxia due to pulmonary infections, ARDS, massive pleural effusions and other causes should be appropriately treated.

Dietary Protein Restriction

The traditional dietary measures aim to reduce protein intake from the normal 80 gm/day to about 40-60 gm/day or, in severe cases, 20 gm/day. The current recommended protein diet for with a history of HE is 0.8 to 1.5 g/kg/d. In chronic HE branched chain amino acids (valine, leucine and isoleucine) and vegetable protein diet is advised.¹²⁻¹⁴

Lactulose

Lactulose is nonabsorbable disaccharide, which acts by inducing diarrhoea, change the intestinal bacterial flora, can decrease ammonia production and increase ammonia excretion. It is given orally or via nasogastric tube depending upon the level of consciousness, at a dose of 30 ml 2-4 times/day. It cannot be given orally in patients with paralytic ileus and is inadvisable in presence of tense ascites. Patients with advanced HE, severe ascites, and spontaneous bacterial peritonitis, lactulose is administered as colonic retention enema (300 mL of lactulose plus 700 mL of tap water).¹⁵ Dose requirement is variable from patient to patient. Lactulose enemas causes less abdominal distention. Adverse effects of lactulose are sweet taste, intestinal gas production, abdominal pain, distension and diarrhea.^{16,17} Inadequate compliance due to its side effects is a major problem.

Antibiotics

Antibiotics like neomycin (neomycin sulfate: 4-12 grams/day), metronidazole, vancomycin, and rifaximin (nonabsorbable rifamycin) inhibit the production of ammonia or other neurotoxins by intestinal bacteria.¹⁸⁻²⁰ Neomycin is commonly used drug. However, in recent days rifaximin at a dose of 1200 mg/day has gained acceptance as first-line or as adjunct therapy to lactulose.²⁰

Other Drugs in Treatment of HE

- Ketoanalogues of branched-chain amino acids (ketoleucine, ketoisocaproate, and ketovaline)²¹
 - Benzoates (act as ammonia scavengers)²²
 - Naloxone (opioid antagonist)
 - Flumazenil (benzodiazepine antagonist)²³

Chronic HE

Chronic HE may be related to increased protein diet or chronic GI bleeding. Etiology is thoroughly evaluated and treated along with the use of lactulose or rifaximin. Neomycin is avoided in chronic HE due to its adverse effects on vestibulocochlear system.

HE due to Acute Liver Failure

Opening intracranial pressure > 10 mm Hg, the hepatic coma may be caused by the cerebral edema. In this situation, the therapy consists primarily of mannitol, mild hypothermia, and barbiturate infusion in refractory cases.²⁴ Treatment is discussed in detail in acute liver failure chapter.

Hepatic Encephalopathy after Surgical Shunts/TIPS

20 to 77% of patients develop HE after TIPS.^{25,26,29} Risk factors for post TIPS encephalopathy are:³⁰

- Age > 60 years
- High MELD score
- Low arterial blood pressure
- Low post-TIPS porto-systemic pressure gradient

Routine treatment with lactulose and/or antibiotics often produces a satisfactory outcome. HE may be temporary, but if recurrent and intractable, then it may require reduction of the shunt's diameter or even its closure. However, this is rarely required. Before closure, eradication of varices by endoscopic methods is advocated.³¹

Artificial Liver Supporting Systems

Artificial liver supporting systems are useful in HE, temporarily to support in an irreversible acute or chronic liver failure till donor is available for liver transplantation. They can sustain the patients with HE while correcting the precipitating factors. Bioartificial liver (BAL) and non-biological systems like MARS are useful.

Liver Transplantation

HE is a clinical sign of liver failure. In many cases, liver transplantation is the only satisfactory long-term treatment and this is true for both patients with FHF and patients with chronic liver disease and chronic encephalopathy. Cirrhotic patients with severe HE have poor survival, even with low MELD score.^{32,33} Some reversibility of cognitive function occurs with transplantation. All patients with encephalopathy should therefore be considered for orthotopic liver transplantation.

REFERENCES

1. Carithers R. Liver transplantation. American Association for the Study of Liver Diseases. Liver Transpl 2000;6:122-35.
2. Leevy C. Economic impact of treatment options for hepatic encephalopathy. Semin Liver Dis 2007;(Suppl 2):26-31.
3. Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore (MD): Williams and Wilkins;1979.
4. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatology 2002;35:716-21.
5. Mullen K. Hepatic encephalopathy. In: Zakim J, Boyer T, editors. Hepatology. A textbook of liver disease. 5th edition. Philadelphia: Saunders-Elsevier 2006:311-31.
6. Cordoba J, Blei A. Hepatic encephalopathy. In: Schiff ER, Sorrell MF, Maddrey WC, editors. Diseases of the liver. 10th edition. Philadelphia: Lippincott Williams and Wilkins 2007:569-99.
7. Butterworth R. Pathogenesis of hepatic encephalopathy: new insights from neuroimaging and molecular studies. J Hepatol 2003;39:278-85.
8. Cadranet JF, Lebietz E, De Martino V, et al. Focal neurological signs in hepatic encephalopathy in cirrhotic patients: underestimated entity? Am J Gastroenterol 2001;96:515-18.
9. Donovan JP, Schafer DF, Shaw BW Jr, et al. Cerebral edema and increased intracranial pressure in chronic liver disease. Lancet 1998;7(351):719-21.
10. Jalan R, Dabos K, Redhead DN, et al. Elevation of intracranial pressure following transjugular intrahepatic portosystemic shunt for variceal haemorrhage. J Hepatol 1997;27:928-33.
11. Córdoba J, Alonso J, Rovira A, et al. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of 1H-magnetic resonance abnormalities after liver transplantation. J Hepatol 2001;35:598-604.
12. Kramer L, Tribl B, Gendo A, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 2000;31:30-4.
13. Mullen K. Hepatic encephalopathy. In: Zakim J, Boyer T, editors. Hepatology. A textbook of liver disease. 5th edition. Philadelphia: Saunders-Elsevier;2006:311-31.
14. Bianchi G, Marchesini G, Fabbri A, et al. Vegetable protein versus animal protein diet in cirrhotic patients with chronic hepatic encephalopathy: a randomized cross-over comparison. J Intern Med 1993;233:385-92.
15. Uribe M, Campollo O, Vargas F, et al. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology 1987;7:639-43.
16. Fritz E, Hammer H, Lipp R, et al. Effects of lactulose and polyethyleneglycol on colonic transit. Aliment Pharmacol Ther 2005;21:259-68.
17. Basilisco G, Marino B, Passerini L, et al. Abdominal distention after colonic lactulose fermentation recorded by a new extensometer. Neurogastroenterol Motil 2003;15:427-33.
18. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy: a controlled, double-blind clinical trial. Am J Dig Dis 1978;23:398-406.
19. Strauss E, Tramote R, Silva EP, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology 1992;39:542-45.
20. Neff G, Kemmer N, Zacharias V, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. Transplant Proc 2006;38:3552-55.

21. Munoz S, Walser M. Utilization of ketoisocaproate for synthesis of hepatic export protein and peripheral proteins in normal and cirrhotic subjects. *Gastroenterology* 1986;90:1834-43.
22. Enns G, Berry S, Berry G, et al. Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. *N Engl J Med* 2007;356:2282-92.
23. Barbaro G, Di Lorenzo G, Soldini M, et al. Flumazenil for hepatic coma in patients with liver cirrhosis: An Italian multicentre double-blind, placebo-controlled, crossover study. *Eur J Emerg Med* 1998;5:213-18.
24. Stravitz R, Kramer A, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. acute liver failure study group. *Crit Care Med* 2007;35:2498-508.
25. Boyer T, Haskal Z. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Hepatology* 2005;41:386-400.
26. Runyon B. Management of adult patients with ascites due to cirrhosis. *Hepatology* 2004;39:841-56.
27. Wong F, Gines P, Watson H, et al. Effects of a selective vasopressin V2 receptor antagonist. Satavaptan. (SR121463B) on recurrence of ascites after large volume paracentesis. *Hepatology* 2006;44(Suppl 1):256A.
28. Gines P, Wong F, Watson H, et al. Effects of a selective vasopressin V2 receptor antagonist satavaptan (SR 121463B) in patients with cirrhosis and ascites without hyponatremia. *Hepatology* 2006;44(Suppl 1):445A.
29. Garcia-Tsao G, Sanyal A, Grace N, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-38.
30. Salerno F, Camma C, Enea M, et al. Transjugular intrahepatic portosystemic shunt for refractory ascites: A meta-analysis of individual patient data. *Gastroenterology* 2007;133:825-34.
31. Madoff D, Wallace M, Ahrar K, et al. TIPS-related hepatic encephalopathy: Management options with novel endovascular techniques. *Radiology* 2004;24:21-36.
32. Thornton J, Mullen K. The role of hepatic encephalopathy in the era of MELD. *Liver Transpl* 2007;13:1364-65.
33. Stewart C, Malinchoc M, Kim W, et al. Hepatic encephalopathy as a predictor of survival in patients with end stage liver disease. *Liver Transpl* 2007;13:1366-71.

(E) HEPATOPULMONARY SYNDROME

It has been reported that 13 to 47% of patients with end-stage liver disease have some form of intrapulmonary vascular abnormalities.¹ The lack of intrinsic cardio-respiratory diseases in a hypoxemic patient with liver disease must prompt one to confirm or exclude the diagnosis of HPS. Mild hypoxemia in patients with liver disease demands follow-up over time, while the detection of severe hypoxemia affects the timing of transplantation and perioperative management. Detection of hypoxemia and the diagnosis of HPS are extremely important for proper management of patients with liver diseases during the perioperative period.⁴³

HPS is defined by the following criteria¹

- Presence of hypoxia
- Existence of liver disease or portal hypertension
- Intrapulmonary vasodilatation
- Widened alveolar-arterial oxygen gradient in room air (DAaO₂ usually >15 mm of Hg)

INCIDENCE

It affects 15 to 20% of patients awaiting LTX.^{4,43} The incidence of HPS has been variously related to the severity of the hepatic dysfunction. Severe HPS not only occurs in patients with advanced liver disease as measured by the Child-Pugh classification,^{5,6} but also in patients with mild liver dysfunction.⁷

PATHOGENESIS

The mechanism of hypoxemia in the early stages of asymptomatic HPS is a pulmonary ventilation-perfusion (VA/Q) imbalance, due to the presence of optimum alveolar ventilation coexistent with high perfusion (areas with low VA/Q ratio). Etiology of liver disease does not seem to affect the development of HPS, as it has been reported in patients with prehepatic portal hypertension in the absence of chronic liver disease, in Budd-Chiari syndrome, and even in patients with acute or chronic inflammatory liver disease without evidence of cirrhosis or portal hypertension.⁸ Pathogenesis of HPS has not been clearly identified. Portal hypertension and the induced vasoactive mediator like nitric oxide, TNF- α and increased expression of endothelial type B endothelin receptors have been implicated in the process.⁴²

Structurally, pulmonary parenchyma is strictly normal but there is a generalized pulmonary vasodilatation at the capillary level. The hallmark of pulmonary vascular

changes in patients with HPS is the presence of dilated vessels at the precapillary and capillary levels and direct A-V communications leading to an intrapulmonary shunt (IPS).^{9,10} These vessels, normally <15 μ m in diameter, may reach 50-80 μ m and, exceptionally, true A-V communications may be present.⁴²

CLINICAL COURSE

Clinical features are progressive onset of dyspnea (aggravated by exercise), platypnea (An increase of symptoms while standing is the result of redistribution of blood to lower lung lobes, i.e. more perfusion, lower oxygenation), orthodeoxia, a worsening of oxygen saturation upon standing that is relieved by recumbent position.⁴² Digital clubbing and cyanosis reflect the impact of chronic hypoxemia and are weakly sensitive but highly specific for the diagnosis of Hepatopulmonary syndrome. Spider nevi are commonly observed.

Recent data suggest that about 50% of patients die 41 months after the diagnosis of HPS.¹¹ Although most patients exhibit the typical stigmata of severe liver dysfunction and portal hypertension, in a few cases, severe gas exchange abnormalities precede and are more clinically relevant than manifestations of liver failure. However, it seems to be that the severity of liver disease does not influence HPS outcome.³⁰

INVESTIGATIONS

Chest X-ray, pulse oximetry, arterial blood gas analysis, spirometry, contrast echo-cardiography, radionuclide lung perfusion scanning and pulmonary angiography:

Chest X-ray

Chest X-ray, a mottled appearance of the chest radiograph. Bilateral interstitial markings, especially in the lower lobes, may reflect the presence of arterial vasodilatation.

Pulse Oximetry

It is a bedside, noninvasive, and inexpensive technique for the initial respiratory screening of patients with liver disease. Only patients selected by abnormal pulse oximetry study should undergo more invasive investigation.³⁵ This approach which is characterized by high sensitivity and moderate specificity¹² may avoid unnecessary arterial blood gas analysis.

The following algorithm has been proposed:¹¹

- SpO₂ of < 97%, identifies patients with mild hypoxemia (pO₂ < 80 mm Hg)
- SpO₂ < 94% identifies subjects with moderate-severe hypoxemia (pO₂ < 60 mm Hg)

A pO₂ value < 80 mm Hg and a DAaO₂ value > 15 mm Hg have been proposed as criteria for further diagnostic evaluation.¹² Abnormal pulmonary gas exchange (alveolar-arterial gradient of oxygen > 15 mm Hg) due to intrapulmonary vasodilatation can be measured by contrast-enhanced echocardiography or technetium 99-labeled macroaggregated albumin (99mTcMMA) lung scanning, in the setting of liver disease.³

Contrast Echocardiography

In this approach, microbubbles derived from agitated saline are injected intravenously. Under normal circumstances, they are not visible in the left atrium because they cannot traverse the pulmonary circulation. Immediate appearance of bubbles within three to five beats indicates pulmonary vasodilatation. Transthoracic approach is preferred over transesophageal echocardiography because of improved sensitivity in cases of early hepatopulmonary syndrome.^{37,38} There is disparity between findings at contrast echocardiography and blood gas exchange. In up to 40% of cirrhotic patients, an abnormal contrast echocardiogram is not accompanied by evidence of hypoxemia.³⁹ Compensatory mechanisms to vasodilatation, including hyperventilation, maintain oxygenation in these circumstances. When other pulmonary abnormalities exist, such as hydrothorax or obstructive disease, contrast echocardiography is not an accurate tool. Contrast echocardiography is a sensitive tool, valuable for screening, but lacking specificity.⁴²

Radionuclide Lung Perfusion Scanning

Injection of Technetium 99-labeled macroaggregated albumin (99mTcMMA) intravenously results in homogenous lung imaging as the macroaggregates lodge in pulmonary arterioles.⁴⁰ When macroaggregates pass through the pulmonary vasculature, they are detected in extrapulmonary tissues. When the brain is scanned, less than 6% of total counts can be detected under normal circumstances. Positive scans (more than 6% brain uptake) had hypoxemia with PaO₂ values below 60 mm Hg, with a positive correlation between the degree of shunting and arterial hypoxemia. The lung perfusion scan provides specificity to the diagnostic workup. It is well suited for patients with intrinsic lung problems where there are difficulties in using contrast echocardiography.⁴²

Pulmonary Angiography

HPS imaging by pulmonary angiography was first reported by Hansoti and Shah.¹² HPS is divided into two types based on pulmonary angiographic images.

Type 1: In this type, the images are initially almost normal or they exhibit a diffuse and fine "spiderlike" pattern with normal reaction (PaO₂ > 500 mm Hg) to the inhalation of pure oxygen. With disease progression, the images exhibit a "spongy" or "blotchy"-like pattern with poor reaction to the inhalation of pure oxygen.

Type 2: In this type HPS, the vasodilatation represents A-V fistula or A-V malformation, for which recovery from hypoxemia cannot be expected.

When inhalation of pure oxygen is not effective for an HPS patient, pulmonary angiography should be performed. If the image exhibits type 2 characteristics, it is difficult to restore pulmonary function by liver transplantation. In patients with severe, advanced HPS, the hypoxemia is mainly due to an increase in intrapulmonary shunt aggravated by a co-existent diffusion-perfusion defect.⁸ To date, OLT is the only proven therapy for HPS.^{13,14}

TREATMENT

The first case report of HPS resolution following OLT appeared in 1989. Since then, a number of case reports and series have reinforced this observation. A review of the literature by the Mayo Clinic showed total resolution or significant improvement in gas exchange following OLT in > 85% of patients.¹³ In 1998, UNOS considered that the presence of hypoxemia due to HPS, once considered a contraindication for OLT, represented, in selected cases, an indication for OLT. Recent evidence that HPS increases morbidity and mortality among waiting list patients supports the UNOS policies that recommend that HPS patients with severe hypoxemia (PaO₂ < 60 mm Hg), independent of the calculated MELD score, receive additional priority on the waiting list.⁴²

Presence of HPS results in an increased morbidity and mortality among patients awaiting or having undergone OLT. Patients with HPS have more pulmonary complications, i.e. respiratory infections and lengthy mechanical ventilation. Determinants of a good prognosis are quantitative radionuclide lung scanning with extrapulmonary uptake > 20% and PaO₂ > 50 mm Hg.¹⁴ Patients with a poor response to 100% oxygen breathing present difficult perioperative management with a high mortality and few possibilities for resolution of HPS.¹⁵

HPS response to medical treatment is very poor. Various modalities of treatment like vasoconstrictors, such as phenylephrine, somatostatin analogues, aspirin, indomethacin, garlic powder, methylene blue, almitrine and Transjugular portosystemic shunt (TIPS) have been tried but none of them are useful while the patient is awaiting a new liver.²⁰⁻²³ Taniai, et al. reported that inhalation of nitric oxide represents a good method to improve hypoxia and to get relief from HPS during the early postoperative period.¹⁶ Inhalation of nitric oxide after pediatric OLT has been reported to improve oxygenation among severely hypoxemic patients.¹⁷⁻¹⁹ Inhalation of nitric oxide reduces the pulmonary-artery pressure and increases arterial oxygenation, without producing systemic vasodilatation.⁵ Hypoxemia associated with the HPS is due to right-to-left anatomic lung shunting resulting from precapillary or capillary vascular dilation. Nitric oxide reaches the alveoli in the portions of the lung that are better ventilated, dilating these local capillary blood vessels, and thereby improving the ventilation to perfusion ratio.⁴²

Oxygen supplementation temporarily improves the quality of life of HPS patients. It is well known that tissue hypoxia produces adverse effects on wound healing and decreases resistance to bacterial wound infection.¹⁶ To reduce the incidence of surgical complications and infections, adequate oxygen supply should be continued for at least 2 weeks or until the patient achieves a stable condition after transplantation.

In most liver transplant centers, the existence of this syndrome, especially among children, is an indication for hepatic transplantation.²⁴⁻²⁶ Today OLT is the only effective treatment option as this condition seems to develop due to underlying liver disease.

LIVER TRANSPLANTATION

HPS is not associated with the severity of hepatic disease. Hypoxemia and hypocapnea are the indications for liver transplantation.²⁷ Rodriguez, et al. suggested that screening for HPS should be performed in all candidates waiting for liver transplantation.²⁸ Patients with HPS in fact show an increased mortality, both among candidates for and recipients after OLT.^{16,17} HPS, once considered a contraindication to the transplant,⁴ but now-a-days has become an indication for it.²⁹

Schenck, et al presented a prospective study on the prognostic significance of HPS in cirrhotic patients awaiting LTX.³⁰ He reported that the patients with HPS had an average survival almost four times less than subjects not affected by this complication (10.6 vs. 40.6 months).

In 1993, Krowka, et al. observed that the mortality in cirrhotic patients at 2.5 years after the diagnosis of HPS

was 41%.³¹ Arguedas, et al. also showed that 1 year after OLT the postoperative mortality was almost two fold greater in patients with HPS than those free of this complication (29% vs. 7%). Furthermore, in comparison with subjects who survived patients who died had significantly lower PaO₂ values, significantly higher alveolar-arteriolar oxygen gradients, and a greater percentage of shunts, as assessed by perfusion scintigraphy.¹⁵ The level of PaO₂ measured on the percentage of intrapulmonary shunts is also indicative of the morbidity.³³

Mortality up to 30% has been reported in the literature with at least 8% of deaths occurring the first 3 months after OLT. This mortality is twice that of all candidates undergoing OLT.¹³ But in a recent report from Kim, et al. reported that the results among LT patients with HPS were not significantly different from the patients without HPS even though the hepatic decompensation was more profound in the former cohort. Liver transplantation is followed by intensive respiratory care is recommend for patients with HPS and he concluded that the presence of HPS may not affect outcomes in patients with decompensated cirrhosis undergoing liver transplantation.³²

This respiratory complication is in fact responsible for an increased mortality and perioperative risk among candidates for liver transplantation.³⁶ Other complications known to occur in patients with HPS undergoing OLT are portal venous thrombosis, Intracranial events and multiorgan failure.³⁷

Time necessary for HPS to recover after transplant vary from few weeks to several months.³⁴ HPS is an independent risk factor for death and it qualifies as major criterion in the prognostic evaluation of patients awaiting liver transplantation. Some transplant centers in USA have recently attributed, in the context of the model of end-stage disease (MELD) system, a higher score to patients with a pO₂ < 60 mm Hg.³⁵

Mazzeo, et al.⁴¹ proposed a simple scoring system to predict risk of mortality in cirrhotic patients with HPS. Score ranges from 1 to 3 for two parameters Child-Pugh score and severity hypoxia. Child-pugh A, B and C are given a score of 1, 2 and 3 respectively. PaO₂ 80-70, 70-60 and 60-50 mm of Hg are given a score of 1, 2 and 3 respectively. Individual score of 2 parameters is summed for a total score, which ranges from 2-6. Risk of mortality is low, moderate and high when the total score is 2-3, 4-5 and 6, respectively.

REFERENCES

1. Fallon M, Abrams G. Pulmonary dysfunction in chronic liver disease. *Hepatology* 2000;32:859.
2. Krowka MJ, Tajik AJ, Dickson ER, et al. Hepatopulmonary syndrome with progressive hypoxia as an indication for liver

- transplantation: Case reports and literature review. *Chest* 1997;116:5:1990.
3. Rodriguez-Roisin R, Agustí AGN, Roca J. The hepatopulmonary syndrome: new name, old complexities. *Thorax* 1992;47:897.
 4. Hansoti RC, Shah NJ. *Circulation* 1996;33:71.
 5. Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol* 2001;34:651.
 6. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042.
 7. Vachiery F, Moreau R, Hadengue A, et al. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. *J Hepatol* 2002;13:233.
 8. Whyte M, Hughes MB, Peters M, et al. Analysis of intrapulmonary right to left shunt in the hepatopulmonary syndrome. *J Hepatol* 1998;29:85.
 9. Hooper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet* 2004;363:1461.
 10. Lange PA, Stoller JK. The hepatopulmonary syndrome. *Ann Intern Med* 1995;122:521.
 11. Abrams G, Sanders M, Fallon MB. Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates. *Liver Transpl* 2002;8:391.
 12. Hansoti RC, Shah NJ. *Circulation* 1996;33:71.
 13. Krowka MJ, Porayko MK, Plevak DJ, et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc* 1997;72:44.
 14. Arguedas MR, Abrams GA, Krowka MJ, et al. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* 2003;37:192.
 15. Krowka MJ, Wiseman GA, Burnett LO, et al. Hepatopulmonary syndrome: a retrospective study of relationships between severity of liver disease, PaO₂ response to 100% oxygen, and brain uptake after 99mTcMAA lung scanning. *Chest* 2000;118:615.
 16. N Tani, M Onda, T Tajiri, et al. Reversal of hypoxemia by inhaled nitric oxide in a child with hepatopulmonary syndrome after living-related liver transplantation. *Transplant Proceed* 2002;34:2791-92.
 17. Egawa H, Kasahara M, Inomata Y, et al. *Transplantation* 1999;67:712.
 18. Alexander J, Greenough A, Baker A, et al. *Liver Transpl Surg* 1997;3:54.
 19. Durand P, Baujard C, Grosse AL, et al. *Transplantation* 1998;65:437.
 20. Vachiery F, Moreau R, Hadengue A, et al. Hypoxemia in patients with cirrhosis: relationship with liver failure and hemodynamic alterations. *J Hepatol* 1997;27:492.
 21. Schenk P, Madl C, Rezaie-Majd S, et al. Methylene blue improves hepatopulmonary syndrome. *Ann Intern Med* 2000;133:701.
 22. Lasch HM, Fried MW, Zacks SL, et al. Use of transjugular intrahepatic portosystemic shunt as a bridge to liver transplantation in a patient with severe hepatopulmonary syndrome. *Liver Transpl* 2001;7:147.
 23. Paramesh AS, Husain SZ, Shneider B, et al. Improvement of hepatopulmonary syndrome after transjugular intrahepatic portosystemic shunting: Case report and review of literature. *Pediatr Transplant* 2003;7:157.
 24. Rabiller A, Nunes H, Lebrec D, et al. Prevention of gram-ve translocation reduces the severity of hepatopulmonary syndrome. *Am J Respir Crit Care Med* 2002;166:514.
 25. Kim HY, Choi MS, Lee SC, et al. Outcomes in patients with hepatopulmonary syndrome undergoing liver transplantation. *Transplant Proc* 2004;36:2762.
 26. Krowka MJ, Mandell SM, Ramsay MAE, et al. Hepatopulmonary syndrome and portopulmonary hypertension: A report of the multicenter liver transplant database. *Liver Transplantation* 2004;10:174.
 27. Tumgor, T Ozkan, Z Ulger, et al. Liver Transplantation of a child with child a cirrhosis and severe hepatopulmonary syndrome. *Transplant Proceed* 2006;38:1432-34.
 28. Rodriguez-Roisin R, Krowka MJ, Hervé P, et al. ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J* 2004;24:861.
 29. Collisson EA, Nourmand H, Fraiman MH, et al. Retrospective analysis of the results of liver transplantation for adults with severe hepatopulmonary syndrome. *Liver Transpl* 2002;8:925.
 30. Schenk P, Schoniger-Hekele M, Fuhrmann V, et al. Prognostic significance of hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042.
 31. Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome. Clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* 1993;104:515.
 32. HY Kim, MS Choi, SC Lee, SW Park, JH Lee, KC Koh, SW Paik, BC Yoo, JC Rhee. Outcomes in Patients With Hepatopulmonary Syndrome Undergoing Liver Transplantation. *Transplant Proceed* 2004;36:2762-63.
 33. Taille C, Cadranet J, Bellocq A, et al. Liver transplantation for hepatopulmonary syndrome: ten years of experience. *Transplantation* 2003;79:1482.
 34. Eriksson LS. Is intrapulmonary arteriovenous shunting and hypoxemia a contraindication for liver transplantation? *Hepatology* 1991;14:575.
 35. Mandell S. Hepatopulmonary syndrome and portopulmonary hypertension in the Model of End Stage Disease (MELD) era. *Liver Transpl* 2004;10:554.
 36. Mazzeo AT, Lucanto T, Santamaria LB. Hepatopulmonary syndrome: a concern for the anesthetist? Preoperative evaluation of hypoxemic patients with liver disease. *Acta Anaesthesiol Scand* 2004;48:178.
 37. Martinez G, Barbera JA, Navasa M, et al. Hepatopulmonary syndrome associated with cardiorespiratory disease. *J Hepatol* 1999;30:882.
 38. Aller R, Moya JL, Moreira V, et al. Diagnosis of hepatopulmonary syndrome with contrast transesophageal echocardiography: advantages over contrast transthoracic echocardiography. *Dig Dis Sci* 1999;44:1243.
 39. Abrams G, Jaffe CC, Hoffer PB, Binder HJ, Fallon MB. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with HPS. *Gastroenterology* 1995;109:1283.
 40. Abrams G, Nanda N, Dubovsky E, Krowka MJ, Fallon MB. Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach. *Gastroenterology* 1999;114:305.
 41. G Bottari, AT Mazzeo, and LB Santamaria. The importance of predicting the prognosis in patients with hepatopulmonary syndrome: A simple scoring system. *Transplantation Proceed* 2006;38:795-97.
 42. M Passarella, MB Fallon, SM Kawut. Portopulmonary Hypertension *Clin Liver Dis* 2006;10:653-63.
 43. AT Mazzeo, G Bottari, C Praticò, et al. Significance of hypoxemia screening in candidates for liver transplantation: Our Experience. *Transplant Proceed* 2006;38:793-94.

(F) SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) defined as the spontaneous infection of the ascitic fluid in a cirrhotic patient, in the absence of any source of intra-abdominal infection. It is the most common bacterial infection in cirrhotic patients with ascites contributing to 25-30% of hospital admissions.¹ SBP is due to decreased antibacterial factors in the ascitic fluid such as complement. Rate of recurrence is about 60-70% of patients after one year of the first episode. The prevalence drops to 3% in asymptomatic outpatients undergoing regular therapeutic paracentesis.² Source of infection in SBP is usually from enteric route, commonly *E. coli*.

RISK FACTORS

Patients with tense ascites undergoing therapeutic paracentesis are not at a higher risk for SBP compared with patients responding to diuretic therapy.³ Risk of developing SBP is approximately 55% in 1 year if:^{4,5}

- Ascites total protein content < 1 g/dL
- Bilirubin > 3.2 mg/dL
- Platelet count < 98,000/mm³

CLINICAL FEATURES

Many patients may be asymptomatic. So suspicion and early diagnoses are essential in improving outcomes in patients with SBP. Some centers follow routine diagnostic tap in all hospitalized patients on admission to rule out SBP.¹⁰ Usually present as fever, nonspecific abdominal pain/discomfort, worsening hepatocellular function and unexplained encephalopathy.¹⁰

CORRELATION WITH HRS

SBP is associated with the development of HRS in about 30% of the patients and carries a high mortality rate of 40-100%.¹ The development of HRS may be prevented by intravenous albumin administration at a dose of 1.5 mg/kg at diagnosis and 1.0 mg/kg after 48 hours.⁶

DIAGNOSIS

A polymorphonuclear leukocyte cell count >250/mm³ confirms the diagnosis.^{1,26} Positive culture of ascites fluid is usually seen 50 to 60% of cases.²⁹ Simultaneous blood cultures are also positive in more than 50% cases. Rapid diagnosis can be made by using a urine reagent dipstick to test ascitic fluid. If leukocyte esterase is strongly positive, the diagnosis of SBP is highly likely. It provides a quick bedside diagnosis of SBP.^{8,9}

TREATMENT

Third-generation cephalosporins are the treatment of choice in these patients. SBP should be treated with intravenous (IV) cefotaxime or another third generation cephalosporin for 5 days, leading to a resolution in 90% cases of SBP.¹⁰ Cefotaxime used every 12 hours or the combination of amoxicillin-clavulanic acid is equally effective.^{1,7,11} ciprofloxacin intravenous, followed by oral ciprofloxacin also compares favorably to IV ceftazidime for treatment of SBP.¹² Plasma volume expansion with albumin in addition to antibiotics has been shown to lessen renal dysfunction and lower the rate of in-hospital and 3-month mortality (22% versus 41%).¹³ The beneficial effects of albumin administration in SBP are related to improvement in cardiac function and a decrease in arterial vasodilatation.¹⁴ These effects cannot be replicated by other volume expanders, such as hydroxyethyl starch.¹⁵ A potential role for branched-chain amino acid supplementation as an adjunct in therapy of SBP is reported in a case study and needs to be evaluated in prospective manner.¹⁶

MORTALITY

The mortality rate ranges from 30 to 50% for each bout of SBP.¹⁷ The early detection and prompt treatment of SBP has led to a decline in mortality in recent years.²⁶

PROPHYLAXIS

Prophylaxis with a quinolone group of antibiotic such as norfloxacin is recommended routinely to prevent the recurrences and improve survival.¹ After a single bout of SBP, there is a 70% 1-year cumulative probability of developing a further episode of SBP and prophylaxis is appropriate.¹⁸ Oral norfloxacin (400 mg/day) or ciprofloxacin (750 mg once every week) can reduce the risk for SBP to 20%.¹⁹ A recent study showed that IV ceftriaxone is better than oral norfloxacin to decrease the incidence of hospital-acquired infections.²⁰

Cirrhotic patients admitted with a gastrointestinal hemorrhage also should be prophylactic antibiotics, as this leads to a decreased infection rate, improved survival, and a decreased rate of further variceal bleeding.¹⁰ Primary prophylaxis against SBP in patients who never had a previous episode but have a low protein ascitic fluid with norfloxacin resulted in a statistically significant decrease in the incidence of SBP compared with placebo.²¹ Trials using rifaximin, a nonabsorbable antibiotic with a low likelihood of causing bacterial resistance for primary prevention of SBP, are being initiated.^{22,23,26}

The addition of cisapride (20 mg BID) to norfloxacin in patients who had recovered from an episode of SBP or had low ascitic fluid protein significantly lowered the probability of SBP and death in the subsequent 18 months.^{24,26} β -Blockers seem to reduce the incidence of bacterial translocation and probability of developing SBP at 1 year in patients receiving them for prophylaxis against variceal bleeding.²⁵

REFERENCES

1. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment, and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 2000;32:142-53.
2. Evans LT, Kim WR, Poterucha JJ, et al. Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. *Hepatology* 2003;37:897-901.
3. Sola R, Andreu M, Coll S, et al. Spontaneous bacterial peritonitis in cirrhotic patients treated using paracentesis or diuretics: results of a randomized study. *Hepatology* 1995;21:340-44.
4. Llach J, Rimola A, Navasa M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. *Hepatology* 1992;16:724-27.
5. Guarner C, Sola R, Soriano G, et al. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. *Gastroenterology* 1999;117:495-99.
6. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495-501.
7. Rimola A, Salmeron JM, Clemente G, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: Results of a prospective, randomized, multicenter study. *Hepatology* 1996;23:941-42.
8. Castellote J, Lopez C, Gornals J, et al. Rapid diagnosis of spontaneous bacterial peritonitis by use of reagent strips. *Hepatology* 2003;37:745-47.
9. Torun S, Dolar E, Yilmaz Y, et al. Evaluation of leukocyte esterase and nitrite strip tests to detect bacterial peritonitis in cirrhotic patients. *World J Gastroenterol* 2007;13(45):6027-30.
10. Priya Grewal, Paul Martin. Pretransplant management of the cirrhotic patient. *Clin Liver Dis* 2007;11:431-49.
11. Ricart E, Soriano G, Novella MT, et al. Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J Hepatol* 2000;32:596-602.
12. Angeli P, Guarda S, Fasolato S, et al. Switch therapy with ciprofloxacin vs. Intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. *Aliment Pharmacol Ther* 2006;23:75-84.
13. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403-09.
14. Fernandez J, Navasa M, Garcia-Pagan JC, et al. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol* 2004;41:384-90.
15. Fernandez J, Monteagudo J, Bargallo X, et al. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatology* 2005;42:533-35.
16. Taniguchi E, Kawaguchi T, Shimada M, et al. Branched-chain amino acid supplementation complements conventional treatment for spontaneous bacterial peritonitis. *Dig Dis Sci* 2006;51:1057-60.
17. Toledo C, Salmeron JM, Rimola A, et al. Spontaneous bacterial peritonitis in cirrhosis: predictive factors of infection resolution and survival in patients treated with cefotaxime. *Hepatology* 1993;17:251-7.
18. Tito L, Rimola A, Gines P, et al. Recurrence of spontaneous bacterial peritonitis in cirrhosis: frequency and predictive factors. *Hepatology* 1988;8:27-31.
19. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: Results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12:716-24.
20. Grange JD, Roulot D, Pelletier G, et al. Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: A double-blind randomized trial. *J Hepatol* 1998;29:490-94.
21. Fernandez J, Ruiz del Arbol L, Gomez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006;131:1049-56.
22. Adachi JA, DuPont HL. Rifaximin: a novel nonabsorbed rifamycin for gastrointestinal disorders. *Clin Infect Dis* 2006;42(4):541-47.
23. DuPont HL, Jiang ZD. Influence of rifaximin treatment on susceptibility of intestinal gramnegative flora and enterococci. *Clin Microbiol Infect* 2004;10:1009-11.
24. Sandhu BS, Gupta R, Sharma J, et al. Norfloxacin and cisapride combination decreases the incidence of spontaneous bacterial peritonitis in cirrhotic ascites. *J Gastroenterol Hepatol* 2005;20:599-605.
25. Gonzalez-Suarez B, Guarner C, Villanueva C, et al. Pharmacologic treatment of portal hypertension in the prevention of community-acquired spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2006;18:49-55.
26. Stefania Angeloni, Cinzia Leboffe, Antonella Parente, et al. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. *World J Gastroenterol* 2008;14(17):2757-62.

(G) HYPONATREMIA

Hyponatremia is a frequent complication of liver cirrhosis, responsible for considerable morbidity.¹ Hyponatremia occurs frequently in liver cirrhosis, where the so-called effective hypovolemia^{2,3} determines hemodynamic and renal alterations leading to a reduced urinary diluting capacity, which in turn, causes solvent retention.

DILUTIONAL HYPONATREMIA

Water in excess with respect to Na^+ retention, the extra-water dilutes the solutes causing hyponatremia. Na^+ **deficit**: When solvent is retained in an attempt to re-expand the volume loss due to solute depletion, as during diuretic treatment, the hyponatremia is due sodium deficit, even though there is still an excess solvent with respect to solutes. These events represent a homeostatic defense of volume, attended by anti-diuretic hormone (ADH) release driven by the volume state even in the face of low plasma osmolality.⁴⁻⁶

PATHOGENESIS OF HYPONATREMIA¹⁸

Hyponatremia can originate from four possible conditions

- Hyponatremia of solute deficit, or depletion: Loss of either Na^+ or K^+ , or both.
- Dilutional hyponatremia: A rise in total body water or water excess. It is a consequence of a higher rate of renal retention of water in relation to sodium, due to a decrease in free-water clearance.⁶
- A combination of the above two mechanisms.
- A shift of water from cells to the extracellular fluid (ECF), where it dilutes Na^+ . This occurs when an osmotically active solute is added to the ECF, driving an osmotic flow of water from cells.

Patients with ascites, particularly when treated with diuretics, experience uncontrollable thirst and are not instructed by their physician against water intake as much as against salt intake. Hence, the patient retains water but not Na^+ , and a relative solvent excess with respect to solutes is generated, leading to hyponatremia.

CLINICAL PRESENTATION

Dilutional Hyponatremia or Pure Na^+ Deficit

Presentation is linked to swelling of the brain, intracranial hypertension, altered membrane potentials⁷ (due to reduced cellular K^+ concentration) and attendant changes in osmolytes and glutamine concentration.⁸

CNS related symptoms: Nausea, vomiting, dizziness, confusion, headache, blurred vision, lethargy, coma and seizures.

GI symptoms: Reduced tone of the bowel musculature with sphincter contraction, leading to a pseudo-paralytic ileus.

Pure Na^+ Depletion

Signs of volume depletion: Tachycardia, orthostatic hypotension, flat jugular veins, cold extremities, oliguria.

If there is K^+ depletion, clinical picture might be unrevealing and K^+ depletion masked by the concomitant treatment with K^+ sparing diuretics, acidosis, rhabdomyolysis and renal failure. Plasma $\text{Na}^+ > 125$ mEq/L: Asymptomatic, while Plasma Na^+ less than 110 mEq/L presents with severe symptoms. It is a medical emergency and can lead to death by central pontine myelinolysis.⁹

Central Pontine Myelinolysis

It is seen as a symmetric area of increased signal in the centre of the pons by nuclear magnetic resonance (NMR). The patient experiences rapid progression to coma, facial diplegia and/or multiple cranial nerve involvement, spastic quadriparesis that may progress to quadriplegia. Although its occurrence is higher in the hyponatremia of cirrhosis and hypoxia, over correction (>25 mEq/48 h) of the alteration represents the main cause. Symptoms and NMR findings may develop in days to weeks following the correction of hyponatremia.¹⁰ The cause of brain swelling is the hypertonicity of the brain with respect to ECF maintained by K^+ and its anions. K^+ concentration inside the cells is initially not affected by the water retained and/or the Na^+ lost, as these initial events occur in the ECF. When water diffuses into the brain cells, volume regulatory mechanisms are triggered, that include K^+ extrusion and loss of non-electrolytic osmolytes.⁸ Later, the diffusion of osmolytes outside brain cells allows the recovery of K^+ . An excessively rapid correction might interfere with the mechanisms of cell volume regulation and produce excessive shrinkage or more rapid swelling, aggravating symptoms and risks.⁹⁻¹²

The most important factor that dictates the clinical response of the patient is the rate of change of serum sodium. Reaching marked low Na^+ levels chronically may be entirely asymptomatic, while apparently less severe falls could be life threatening if occurring in few hours.

DIAGNOSIS OF HYPONATREMIA¹⁸

Diagnosing the hyponatremia and its etiology is important, whether it is water excess or solute deficit, or their combination. This diagnosis is purely clinical, based on a careful history, appraisal of volume status, renal function, cardiac output and central venous pressure. Simple measurements of plasma and urine creatinine, Na⁺ and plasma uric acid are helpful in doubtful cases. Body weight is important, as a sudden gain in few days argues in favour of water surfeit, while solute deficit is more likely if weight is unchanged. Calculating the ratio of urine to plasma Na⁺ concentration over that of creatinine (UNa/PNa×PCr/UCr) requires only 1 ml of urine. It expresses quantitatively the fraction of filtered Na⁺ which is being excreted. Values < 0.01 indicate a Na⁺ retaining state, hence, a hyponatremia due to Na⁺ deficit. Values > 0.02 suggest renal Na⁺ wasting, i.e. solvent excess, unless the patient is receiving diuretics. Values < 0.01 measured in patients taking diuretics strongly suggest diuretic abuse and the triggering of a powerful Na⁺-retaining state, capable of decreasing urine Na⁺ concentration even in the face of diuretic administration.

TREATMENT¹⁸

Goals of treatment according to severity of hyponatremia

- Severe hyponatremia (Plasma Na⁺ <115 mEq/L).
Step 1: Bring plasma Na⁺ to less severe values (>115 mEq/L) in few hours (at a rate not exceeding 1.5 mEq/L/h).
Step 2: Bring to less worrisome values (>120 to 125 mEq/L) in 24 hours.
Step 3: Bring plasma Na⁺ to normal in few days.
- Symptomatic hyponatremia (PNa⁺ > 115, < 125 mEq/L): Step 2 and 3
- Mild hyponatremia/Asymptomatic (Plasma Na⁺ > 125mEq/L): Step 3

Calculation

Sodium deficit (mEq) = (130-Current plasma Na⁺) × Total body water (TBW)

TBW is the same before and during the hyponatremia of solute deficit.

TBW is calculated by multiplying the body weight in kg by 0.6, the fraction of water over weight.

Total body water (liters) in normal individuals: 60% of lean body weight in males and 50% of lean body weight in females.

Potassium deficit = (Normal potassium-current potassium) × TBW

Water Excess

It is exactly equivalent to the change in body weight, if available and correctly recorded.

Correction of Na⁺ Deficit

- Step 3 requires only dietary supplementation of the calculated deficit.
- Steps 1 and 2 require the infusion of the calculated amount of Na⁺ as 3% hypertonic solution, corresponding to 513 mEq/L. Step one should be accomplished in 3-4 h and step two in 12-24 hour. (For calculating Na⁺ deficit, 115 mEq/L is used as desired value for step 1, and 125 mEq/L for step 2)

Aquaretics (VPA-985, a selective vasopressin; V2-receptor antagonists) used in hyponatremia of water excess, they could be useful even in that of solute deficit only if associated to the infusion of normal saline at a rate calculated to replenish Na⁺ stores.¹³⁻¹⁵

Water Excess/Dilutional Hyponatremia

- Step 3 requires only water restriction. Necessary weight loss, corresponding to the solvent excess calculated, must be followed on a scale till desired plasma Na⁺ is achieved slowly over few days.
- Steps 1 and 2 require some ways to remove water from the body: Furosemide

With Furosemide infusion of 40-80 mg/hour, urinary Na⁺ excretion is approximately 70-80 mEq/L.^{16,17} The hourly urine volume excreted is replaced with half the equivalent volume of normal saline containing 155 mEq/L of Na⁺. The sodium loss induced by the diuretic is replaced together with 50% of the water loss. Thus, this method induces a net solvent excretion of 50% of the urine flow. During correction, the rise in Plasma Na⁺ will abstract water from cells, re-expanding the ECF. If the diuresis required takes long-time, the replacement saline infusion should also include KCl. This treatment can't be given in presence of renal failure, where the extra water can be abstracted by ultrafiltration. Paracentesis in hyponatremic patients also removes liters of hypotonic fluid. The amount of fluid replaced, even in part, by normal saline that contains 155 mEq/L of Na⁺, the procedure is identical to that of furosemide-induced diuresis with partial restitution of normal saline, and will slowly correct hyponatremia.

CONDITIONS ASSOCIATED WITH HYPONATREMIA

Hyponatremia and Ascites

A prospective study from Spain showed that the prevalence of hyponatremia (serum Na^+ <130 mEq/L) in patients hospitalized for various complications of cirrhosis was 35%.¹⁹ Survival is significantly reduced in patients with spontaneous development of hyponatremia.¹⁹ Of note, all patients with hyponatremia had ascites. In another study from Italy, hyponatremia (serum Na^+ <130 mEq/L) was found in approximately 30% of patient admissions for complications of cirrhosis, and 96% of the patients with hyponatremia had associated ascites.²⁰

Hyponatremia and encephalopathy

Hyponatremia is common in patients with cirrhosis and is associated with remarkable changes in brain cells, particularly a reduction in myo-inositol and other intracellular organic osmolytes related to the hypo-osmolality of the extracellular fluid. These changes in brain cells may predispose to hepatic encephalopathy. Severe hyponatremia is a major risk factor of hepatic encephalopathy in patients with cirrhosis and refractory ascites and normalizing serum sodium levels in patients with severe hyponatremia could reduce the risk of hepatic encephalopathy.

MELD Score and Hyponatremia

There is need for improvement of the MELD score as some subsets of patients with cirrhosis may have high mortality despite low MELD scores.²¹⁻²⁴ In this regard, several recent studies have shown that serum sodium concentration is a good marker of prognosis in patients awaiting transplantation.²⁵⁻²⁷ As per the results of these studies, the use of serum sodium in the assessment of severity of cirrhosis has been recommended. In patients with cirrhosis awaiting liver transplantation, MELD score and serum sodium concentration are the only independent predictive factors of 3 and 12 months survival in patients with cirrhosis awaiting liver transplantation. Addition of serum sodium to MELD score may improve the prognostic accuracy than MELD score alone.^{28,29}

REFERENCES

1. Borroni G, Maggi A, Sangiovanni A, et al. Clinical relevance of hyponatremia for the hospital outcome of cirrhotic patients. *Dig Liver Dis* 2000;32:605-10.
2. Bichet D, Szatalowicz V, Chaimovitz C, et al. Role of vasopressin in abnormal water excretion in cirrhotic patients. *Ann Intern Med* 1982;96:413-17.
3. Henriksen JH, Bendtsen F, Sorensen TI, et al. Reduced central blood volume in cirrhosis. *Gastroenterology* 1989;97:1506-13.
4. Schrier RW, Berl T, Anderson RJ. Osmotic and non-osmotic control of vasopressin release. *Am J Physiol* 1979;236:F321-32.
5. Hammer M, Olgaard K, Schapira A. Hypovolemic stimuli and vasopressin secretion in man. *Acta Endocrinol* 1988;118:465-73.
6. Bartoli E, Satta A, Melis F, et al. Volume receptors in guinea pig labyrinth: Relevance with respect to ADH and Na control. *Am J Physiol* 1989;257:F341-6.
7. Arieff AI, Guisado R. Effects on the central nervous system of hypernatremic and hyponatremic states. *Kidney Int* 1976;10:104-16.
8. Restuccia T, Gomez-Anson B, Guevara M, et al. Effects of dilutional hyponatremia on brain organic osmolytes and water content in patients with cirrhosis. *Hepatology* 2004;39:1613-22.
9. Sterns RH, Thomas DJ, Herndon RM. Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. *Kidney Int* 1989;35:69-75.
10. Ashraf N, Locksley R, Arieff A. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med* 1981;70:1163-68.
11. Androgúe HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000;342:1581-89.
12. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Engl J Med* 1987;317:1190-95.
13. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: A randomized double-blind multicenter trial. *Gastroenterology* 2003;124:933-39.
14. Wong F, Blei AT, Blendis LM, et al. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: A multicenter, randomized, placebo-controlled trial. *Hepatology* 2003;37:182-91.
15. Ginés P, Jiménez W. Aquaretic agents: A new potential treatment of dilutional hyponatremia in cirrhosis. *J Hepatol* 1996;24:506-12.
16. Bartoli E, Romano G. Measurements of reabsorption by single segments of the human nephron. *J Nephrol* 1999;12:275-87.
17. Fichman MP, Vorherr H, Kleeman CR, et al. Diuretic-induced hyponatremia. *Ann Intern Med* 1971;75:853-63.
18. L. Castello, M. Pirisi, PP Sainaghi, et al. Hyponatremia in liver cirrhosis: Pathophysiological principles of management. *Digestive and Liver Disease* 2005;37:73-81.
19. Porcel A, D F Rendón P, Macías M, et al. Dilutional hyponatremia in patients with cirrhosis and ascites. *Arch Intern Med* 2002;162:323-328.
20. Borroni G, Maggi A, Sangiovanni A, et al. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. *Dig Liver Dis* 2000;32:605-10.
21. Everson GT. MELD: the answer or just more questions? *Gastroenterology* 2003;124:251-54.

22. Freeman RB. MELD: the holy grail of organ allocation? *J Hepatol* 2004;42:16-20.
23. Cholongitas E, Senzolo M, Triantos C, et al. MELD is not enough—enough of MELD? *J Hepatol* 2005;42:475-7.
24. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD *J Hepatol* 2005;42:S100-7.
25. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004;40:802-10.
26. Biggins SW, Rodriguez HJ, Bacchetti P, et al. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology* 2005;41:32-9.
27. Ruf AE, Kremers WK, Chavez LL, et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005;11:336-43.
28. Ruf A, Kremers W, Chavez L, et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl* 2005;11:336-43.
29. MC Londoño, A Cardenas, M Guevara, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. *Gut* 2007;56:1283-90.



Index

A

- ABO-incompatibility 191
- ABO-incompatible LTX 209
- Active alcohol or drug abuse 34
- Acute cellular rejection 215
 - diagnosis 216
 - Doppler ultrasonography 216
 - liver biopsy 216
 - late onset 217
 - pathogenesis 215
 - reactivation of HCV and rejection 217
 - response to treatment of ACR 218
 - risk factors 216
 - signs 216
 - symptoms 216
 - treatment 217
- Acute hepatitis B infection 360
 - prognosis 361
 - symptoms 360
 - treatment 361
- Acute liver failure 314, 388
 - apoptosis 389
 - causes 314
 - in children 314
 - in infants 314
 - epidemiology 388
 - ALF in Asian countries 388
 - ALF in USA and UK 388
 - laboratory investigations 389
 - necrosis 389
 - pathophysiology 389
 - prognostic criteria 390
 - Clichy criteria 390
 - criteria in pediatric age group 390
 - King's college criteria 390
- Acute renal injury after liver transplantation 284
 - drug clearance by dialysis 284
 - treatment 284
- Alagille syndrome 400
 - clinical presentation 400
 - diagnosis 400
 - incidence 400
 - pathogenesis 400
 - treatment 400
- Alanine aminotransferase 360
- Alcoholism 378
 - compliance 380
 - liver transplantation 379
 - other issues 380
 - malignancies 380
 - osteopenia 380
 - recipient selection 378
 - recurrent disease 379
 - social issues 378
 - social issues after transplantation 379
 - recidivism 379
- Alpha 1-antitrypsin deficiency 397
 - clinical presentation 397
 - diagnosis 398
 - liver biopsy 398
 - phenotyping 398
 - treatment 398
 - hepatic symptoms 397
 - pulmonary symptoms 397
- Anastomotic biliary stricture 232, 235
 - in DDLT 232
 - in LDLT 235
- Anatomical relations around the hilum 10
 - bile duct 12
 - blood supply 12
 - hepatic artery 11
 - portal vein 10
- Anatomical variations in intrahepatic biliary tract 13
- Anatomical variations in the portal vein 16
- Anatomical variations of hepatic arterial supply 14
- Anatomy of hepatic veins 18
 - inferior phrenic veins 20
 - left hepatic vein 18
 - left medial hepatic vein 19
 - middle hepatic vein 18
 - MRHV and IRHV 19
 - right hepatic vein 18
- Anatomy of liver 8
 - Bismuth's segmental anatomy 10
 - Couinaud's segmental anatomy 9
 - embryology 8
 - lobar anatomy 9
 - segmental anatomy 9
- Anesthesia for acute liver failure 326
 - preoperative preparation 326
 - role of hepatectomy as a bridge to transplantation 326
 - cerebrovascular stability 327
 - delay in recovery of graft function 327
 - fluid balance 327
- Anesthesia in liver transplantation 320
 - intraoperative management 321
 - anhepatic phase 321
 - dissection phase 321
 - reperfusion phase 321
 - monitoring of patient prior to induction patient's position 321
 - CVS monitoring 321
 - induction 322
 - intracranial pressure 321
 - IV access 321
 - laboratory monitoring 322
 - preoperative immuno-suppression dose 321
 - role of dopamine 321
 - temperature 321
 - total intravenous anesthesia 322
 - volatile anesthetic agent 322
- post-transplant period 324
- preoperative assessment 320
 - albumin 320
 - ammonia 320
 - ascites 321
 - bilirubin 320
 - cardiac functions 320

- hepatic dysfunction 320
 - hepatic synthetic functions 321
 - international normalized ratio 320
 - lung functions 320
 - premedication 321
 - prothrombin time 320
 - role of regional anesthesia 324
 - specific considerations 322
 - acidosis 323
 - CVP monitoring 323
 - electrolyte imbalance 322
 - fibrinolysis 323
 - hyperkalemia 323
 - hypotension 323
 - massive ascites 322
 - post-reperfusion syndrome 323
 - role of cell saver 322
 - Antibody mediated rejection 195
 - Antibody mediated/hyperacute rejection 209
 - Antibody therapy 173
 - muromonab-CD₃ 173
 - side effects 173
 - Anti-interleukin-2 receptor antibodies
 - basiliximab, daclizumab 173
 - autoimmune hepatitis 174
 - fulminant hepatic failure 175
 - pharmacokinetics 174
 - primary biliary cirrhosis 174
 - primary sclerosing cholangitis 174
 - retransplantation 175
 - side effects 174
 - steroid withdrawal 175
 - Antimetabolites 172
 - mycophenolate mofetil 172
 - pharmacokinetics 172
 - pharmacology 172
 - side effects 172
 - Arterial complications 251
 - hepatic artery stenosis 251
 - hepatic artery thrombosis 251
 - diagnosis 252
 - early HAT 251
 - late HAT 251
 - treatment 252
 - Ascites 429
 - etiology 429
 - investigations 430
 - pathophysiology 429
 - signs 429
 - symptoms 429
 - treatment 430
 - aim of treatment 430
 - drugs 431
 - general measures 430
 - Aspartate aminotransferase 360
 - Assessment of hepatic malignancies 50
 - Autoimmune hepatitis 314, 383
 - indication for liver transplantation 384
 - liver transplantation in AIH 384
 - recurrence of disease after transplantation 384
 - treatment 383
 - drugs 383
 - indication of medical treatment 383
 - rescue therapy 384
 - standard therapy 383
 - Autoimmune liver diseases 383
 - Autologous bone marrow stem cells 426
 - contraindications 426
 - procedure 426
 - flow cytometric analysis 426
 - infusion of cells 426
 - Auxiliary partial orthotopic liver transplantation 144
 - advantages 146
 - citrullinemia 145
 - indications 145
 - left APOLT in the recipient 145
 - portal inflow modulation in APOLT 145
 - surgical technique 145
 - technical difficulties 145
 - Azathioprine (AZA) 172
-
- B**
-
- Bacterial infections 317
 - Barrett's esophagitis 293
 - BCLC staging classification and treatment 348
 - advanced stage 348
 - early stage HCC 348
 - end stage 349
 - intermediate stage 348
 - Bench procedure 93
 - Bile duct anastomosis 102
 - Bile leak 228, 231
 - Biliary complication in posterior sector grafts 240
 - Biliary complications 226
 - incidence 226
 - sutures and techniques of anastomosis 227
 - technical issues 226
 - Biliary complications in donors 241
 - bile leak and injury 241
 - treatment 241
 - Biliary reconstruction 110
 - Biliary strictures 229
 - classification 229
 - risk factors 229
 - types 229
 - Bioartificial liver support 332
 - different bioartificial systems 332
 - amsterdam medical center bioartificial liver 333
 - extracorporeal liver assist device 332
 - HepatAssist system 332
 - modular extracorporeal liver support system 332
 - evidence-based medicine 333
 - history of bal devices 332
 - Bleeding 317
 - Body mass index 276
 - Brain dead donor 59
 - Brain dead donor liver 88
 - Bridging therapy 352
 - PEI ablation 354
 - contraindications 354
 - radiofrequency ablation 353
 - complications 354
 - TACE 352
 - complications 353
 - Budd-Chiari syndrome 411
 - diagnostic work-up 411
 - presentation 411
 - treatment 412
 - liver transplantation 413
 - medical treatment 412
 - surgical management 412
-
- C**
-
- Cardiac disease 291
 - Cardiovascular disease 34
 - Care in patients with renal disease 283
 - Care of the donor 59
 - general treatment 59
 - specific treatment 59
 - cardiovascular care 60
 - endocrine 60
 - hematology 59
 - hemodynamic goals 60
 - hypothermia 60
 - infection 60
 - pulmonary care 60
 - renal 60
 - Carrel patch 88
 - Caudate lobe 13
 - Causes of noncompliance in children 318
 - methods to monitor 318
 - objective method 318
 - Cavoportal hemitransposition 122
 - complications 123
 - Cellular basis of rejection 204
 - Celsior solution 91
 - Chimerism 208
 - Cholangiocarcinoma 36
 - Chronic HBV infection 361
 - symptoms 361
 - treatment 361

Chronic rejection 220
 diagnosis 220
 histologic features 220
 pathophysiology 220
 treatment 221
 MMF 221
 retransplantation 221
 sirolimus 221
 tacrolimus 221
 Chronic renal disease after liver transplantation 285
 CINs and renal toxicity 282
 Cockcroft-Gault formula 283
 Combination antiviral therapy after transplant 366
 Common problems in organ donors 59
 Complications in recipient 228
 Confluence patterns of left intrahepatic bile ducts 14
 Congenital hepatic fibrosis and polycystic kidney disease 315
 Contraception after transplantation 298
 Core antibody positive donors 42
 Correlation of HBV and HCC recurrence 352
 Corticosteroids 167, 298
 adverse effects 167
 mechanism 167
 pharmacokinetics 167
 route of administration 167
 Creatinine clearance 283
 Cryopreservation of vascular grafts 91
 CT evaluation of segmental anatomy and fatty liver 46
 Cystic fibrosis 398
 clinical presentation 398
 liver 398
 other systems 398
 defect 398
 diagnosis 398
 gene therapy 399
 role of LTX 398
 role of multi-organ transplantation in CF 399
 Cytokines and chemokines in rejection 208

D

Deceased donor 95
 Deceased donor hepatectomy 84
 Delivery in liver transplant recipient 299
 breastfeeding 299
 Diabetes insipidus 59
 Diabetes mellitus 289
 risk factors 289
 treatment 289

Diagnosis of biliary complications 230
 Difference in *in-situ* and *ex-situ* split 133
 Different psychological complaints 338
 Digital subtraction angiography 252
 Diseases after liver transplantation 301
 alcoholic liver disease 305
 risk factors 305
 autoimmune hepatitis 303
 differential diagnosis 304
 risk factors 304
 Budd-Chiari syndrome 305
 hepatitis B virus 302
 differential diagnosis 303
 risk factors 302
 hepatitis C virus 301
 hepatocellular carcinoma 305
 risk factors 306
 hereditary hemochromatosis 305
 nonalcoholic steatohepatitis 305
 primary biliary cirrhosis 304
 differential diagnosis 304
 risk factors 304
 primary sclerosing cholangitis 304
 differential diagnosis 304
 Disease-specific criteria 26
 primary biliary cirrhosis 26
 primary sclerosing cholangitis 26
 Dissection of splenic vein 87
 Dissection of supra-celiac aorta 86
 Distribution of transplant centers is USA 27
 Domino DDLT 151
 Domino LDLT 151
 Domino transplantation procedure in second recipient 152
 Donor complications 47
 Donor evaluation 43
 Donor hepatectomy 76
 Donor hepatectomy in LDLT 74
 selective inflow occlusion 74
 Donor liver biopsy 275
 Donor nutrition 61
 Donor operation in FAP patient 152
 Donor organ 58
 sources 58
 Donor residual liver 74
 Donor risk index 67
 calculation 68
 survival rates 68
 Donor surgery 70
 Donors with positive serology HBV/HCV 85
 Doppler ultrasonography 181, 187
 hepatic artery 188
 DUS findings for HA stenosis 188
 DUS findings for hepatic artery thrombosis 188
 hepatic veins 189

DUS findings for HV outflow obstruction 189
 DUS findings for HV stenosis 189
 portal vein 188
 DUS criteria for PV stenosis 188
 DUS findings for diagnosis of PV aneurysm 189
 postoperative DUS protocols 187
 Dual grafts 140
 different dual grafts 141
 recipient operation 141
 two left lobe grafts 141
 technical modification 141
 back table procedure 141
 bile duct 142
 dissection phase 141
 first left lobe graft 141
 hepatic artery anastomosis 142
 hepatic venous anastomosis 142
 second left lobe graft 141
 use of right lobe and left lateral segment/left lobe graft 142
 recipient operation 142
 Dyslipidemia 290
 follow-up 290
 risk factors 290
 treatment 290
 drug interactions 290

E

Early cell cycle inhibitors 168
 calcineurin inhibitors 168
 mechanism of action 168
 cyclosporine (Cs A) 168
 tacrolimus 169
 Early detection of brain death 61
 Early graft function in LDLT 56
 Effect of corticosteroids on bones 292
 investigations 292
 treatment 292
 aim 292
 Electrolyte disturbance 197
 hyponatremia 198
 hyponatremia 198
 central pontine myelinosis 198
 sodium 197
 maintenance of sodium lever 198
 Embryonic stem cells 427
 Employment after transplantation 336
 Eosinophils 206
 Epstein-Barr virus 265
 Esophageal varices 437
 pathophysiology 437
 pharmacotherapy 439
 administrative of recombinant activated factor VII 440
 gastric varices 440
 recurrent variceal hemorrhage 439

- role of balloon tamponade 439
- role of EVL 439
- role of TIPS/surgical shunts 439
- role TIPS 439
- prophylactic treatment 437
 - endoscopic variceal ligation 438
 - role of β -blockers 438
 - small EVs 438
- surveillance policy 437
- treatment of bleeding 438
 - definitive treatment 439
 - endoscopic treatment 439
 - general care 438
- Ethical issues 63
- Euro-Collins solution 91
- Evaluation of hepatic veins 43
- Evaluation of recipient at
 - transplantation center 32
- Exceptions to MELD score 29
- Extracorporeal liver supporting
 - systems 329
 - indications 329
 - types of liver support 329
- Extrahepatic bile duct necrosis 241
- Extrahepatic malignancy 34
- Ex-vivo perfusion 394

F

- Familial amyloid polyneuropathy 149
 - liver transplantation 150
 - domino LTX in FAP 150
 - FAP world transplant register 150
 - presentation of FAP 150
 - prevalence 149
- Fatigue after LTX 335
- Fatty change–donor selection 55
- Follow-up of donor 48
- Functional/surgical lobes of liver 9
- Future trends in organ allocation 30

G

- General care and preparation of
 - recipient 97
- General care during post-
 - transplantation period 155
 - antifungal treatment 158
 - prophylaxis 158
 - antiviral treatment 160
 - core antibody positive donors 160
 - HBV positive recipient 160
 - HCV positive recipient 160
 - blood sugar control 158
 - cytomegalovirus prophylaxis 158
 - blood components 159
 - electrolyte correction 159
 - gabexate mesylate 159
 - low molecular weight

- heparin 159
- nutrition 159
- pneumocystis carinii
 - prophylaxis 159
- pre-emptive care 158
- prostaglandin E1 159
- routine CMV prophylaxis 158
- dressing of the wound 158
 - albumin 158
 - analgesics 158
 - antibiotics 158
 - proton pump inhibitors 158
- post-transplant follow-up 161
- respiratory care 155
 - arterial line central line and Swan Ganz catheters 157
 - continuous infusion
 - analgesia 157
 - Foley's catheter 157
 - monitoring of vital signs 155
 - nasogastric tube 157
 - patient controlled analgesia 157
 - postural changes 157
 - volume replacement 157
- surgical drain care 157
 - ascites 157
 - T-tube 157
- Graft function 163
 - postoperative evaluation 163
- Graft preservation 90
- Graft regeneration 165
 - evaluation 165
- Graft volume estimation 54

H

- HA thrombosis 317
- HAART regimen 267
- Harvesting deceased liver 85
 - surgical techniques 85
- HBV and HCV related
 - nephrotoxicity 283
- HBV DNA 359
- HBV genotypes 359
- HBV in Asia 364
- HBV prophylaxis 365
- HBx protein 359
- HCC and liver transplantation 29
- HCC recurrence 351
- HCV and HRQL 336
- HCV and liver transplantation 372
 - post-transplant recurrent HCV 372
 - response to treatment 375
 - ascites in HCV recipients 375
 - genotyping 375
 - HBsAb positive grafts in HCV patients 375
 - HCV +ve recipients, after LTX 375

- HCV antibody positive grafts 375
- histological confirmation 375
- qualitative HCV-RNA by
 - PCR 375
- spontaneous clearance of
 - HCV 375
- treatment 373
- Heart-beating donors 58
- Helicobacter pylori and LTX 270
- Helper T-lymphocytes and
 - rejection 205
- Hepatic arterial anastomosis 101
- Hepatic arterial anatomy 50
- Hepatic artery 73, 188
- Hepatic artery anastomosis 110
- Hepatic artery infusion therapy 193
- Hepatic encephalopathy 449
 - classification 449
 - clinical presentation 449
 - diagnosis 450
 - differential diagnosis 451
 - pathogenesis 449
 - risk factors 449
 - treatment 451
 - antibiotics 451
 - correction of precipitating factors 451
 - dietary protein restriction 451
 - lactulose 451
- Hepatic graft protection 60
- Hepatic hemodynamics 181
 - graft portal flow estimation 182
 - methods of flow measurement 182
 - angiography 183
 - DUS 183
 - finger palpation method 182
 - transit time flow meter probes 183
 - portal flow and portal venous pressure measurement 181
- Hepatic vein complications 247
 - diagnosis 247
 - treatment 247
- Hepatic vein reconstruction 106
- Hepatic veins 189
- Hepatitis B DNA polymerase 359
- Hepatitis B virus 358
 - different HBV mutants 358
 - hepatitis B antigens 359
 - hepatitis B core protein 359
 - structure 358
 - viral replication 358
- Hepatitis C virus 370
 - diagnosis 371
 - abnormal liver function tests 371
 - anti-HCV antibody 371
 - HCV RNA levels 372
 - follow-up 372

- genotypes 370
 - replication 370
 - mode of transmission 370
 - presentation 371
 - acute hepatitis C 371
 - chronic hepatitis C 371
 - prophylaxis 372
 - structure 370
 - treatment 372
 - Hepatocellular carcinoma 347
 - diagnosis 348
 - staging 347
 - Hepatocyte transplantation 394, 415
 - advantages 416
 - clinical studies 416
 - future alternative sources 418
 - indications 415
 - natural course of transplanted hepatocytes 417
 - routes of hepatocyte transplantation 416
 - sources of hepatocytes 417
 - banking of human liver cells 417
 - bone marrow-derived cells 417
 - fetal hepatocytes 417
 - hepatocyte apoptosis during rejection 417
 - immortalized cells 417
 - liver rejected for transplantation 417
 - liver resected for malignancy 417
 - Hepatopulmonary syndrome 454
 - clinical course 454
 - incidence 454
 - investigations 454
 - chest X-ray 454
 - contrast echocardiography 455
 - pulmonary angiography 455
 - pulse oximetry 454
 - radionuclide lung perfusion scanning 455
 - pathogenesis 454
 - treatment 455
 - Hepatorenal syndrome 36, 443
 - clinical features 443
 - diagnostic criteria 444
 - management 445
 - median survival 444
 - outcome and prevention 446
 - role of albumin 446
 - role of pentoxifyllin 446
 - pathogenesis 443
 - treatment 445
 - specific treatment 445
 - supportive treatment 445
 - Hereditary hemochromatosis 399
 - disease recurrence after LTX 399
 - hepatic iron overload 399
 - presentation 399
 - survival rates 399
 - treatment 399
 - Herpes simplex virus 267
 - High risk patients and organ allocation 28
 - Histidine-tryptophan-ketoglutarate solution 91
 - Historical review of
 - immunosuppression 5
 - cyclosporine era 5
 - immunosuppression during earlier times 5
 - tacrolimus era 6
 - HIV infection 35
 - HIV positive recipient 266
 - HLA-C 207
 - HRQL in pediatric transplantation 337
 - Human cord blood stem cells 427
 - Human leucocyte antigen and rejection 206
 - Hyperacute rejection 222
 - clinical presentation 223
 - diagnosis 223
 - differential diagnosis 223
 - mechanism of injury 222
 - pre-transplant conditioning 222
 - survival results 224
 - treatment 223
 - Hyperglycemia 59
 - Hyperkalemia and liver transplantation 285
 - Hypertension 291
 - risk factors 291
 - treatment 291
 - Hyperuricemia 292
 - etiology 292
 - risk factors 292
 - treatment 293
 - Hyponatremia 460
 - clinical presentation 460
 - central pontine myelinosis 460
 - dilutional hyponatremia 460
 - pure Na⁺ depletion 460
 - conditions association with
 - hyponatremia 462
 - hyponatremia and ascites 462
 - hyponatremia and encephalopathy 462
 - MELD score and
 - hyponatremia 462
 - diagnosis 461
 - pathogenesis 460
 - treatment 461
 - calculation 461
 - water excess 461
 - Hyponatremia and MELD score 29
 - Hypothermia 59
-
- I**
- Ideal deceased donor 84
 - Ideal donor 84
 - Immune tolerance 207
 - Immunodeficiency with ESLD 315
 - Immunogenicity 229
 - Immunosuppression and HRQL 336
 - Immunosuppression drugs 166
 - azathioprine 172
 - basiliximab 174
 - corticosteroids 167
 - cyclosporine 168
 - daclizumab 174
 - mycophenolate mofetil 172
 - sirolimus 170
 - tacrolimus 169
 - Immunosuppression in liver transplantation 166
 - induction/initial phase 166
 - maintenance phase 166
 - treatment of rejection 166
 - Immunosuppressive drugs and pregnancy 298
 - Immunosuppressive drugs used in LTX 161
 - advagraf 162
 - azathioprine 163
 - cellcept 162
 - cyclosporine 162
 - mycophenolate mofetil 162
 - myfortic 163
 - prograf 162
 - sirolimus 163
 - tacrolimus/FK-506 162
 - tolerance 163
 - Inferior vena cava and hepatic veins 50
 - Inferior vena cava thrombosis 248
 - Informed consent before transplant 47
 - Inraportal pattern 14
 - Initial poor function 214
 - assessment of graft function 214
 - Injury to the confluence of hepatic ducts 241
 - Intrahepatic biliary anatomy 12
 - left hepatic duct 13
 - right hepatic duct 13
 - Intravenous immunoglobulin 194
 - Issues related to detransplantation 146
 - Issues related to pediatric
 - pretransplant care 312
 - acute on chronic liver failure 312
 - advantages 313
 - donor pool for pediatric transplantation 312
 - infections 312
 - malnutrition 312
 - vascular complications 312

J

Jackson-Pratt drain 76

K

Kupffer cells 207

L

Late cell cycle inhibitors 170
 sirolimus 170
 side effects 171
 Left lateral segment 77
 Left lobes graft 81
 surgical techniques 81
 Ligaments of liver 9
 Live donor 41, 94
 Liver biopsy 146, 275
 complications 275
 different approaches 275
 laparoscopic liver biopsy 275
 open needle biopsy 275
 percutaneous liver biopsy 275
 transjugular biopsy 275
 Liver resection for HCC 352
 Liver resection in post-transplant biliary stricture 237
 Liver transplantation 1, 33
 ABO-incompatible (ABO-1) LDLT 5
 adult-to-adult LDLT 4
 concept of living donor 3
 contraindications 34
 absolute 34
 relative 34
 dominos 5
 dual grafts 54
 indications 33
 trauma 34
 split liver 4
 Liver transplantation and
 coagulopathy 324
 causes of coagulopathy in ESLD 324
 high blood loss during liver
 transplantation surgery 325
 coagulation monitoring 325
 risk factors 325
 intraoperative coagulopathy 325
 management of coagulopathy
 in OLT 325
 indications for blood
 component therapy 325
 thromboelastography 325
 Liver transplantation in ALF 391
 bioartificial liver 393
 liver-supporting devices for
 ALG 393
 medical management of acute
 liver failure 391
 coagulopathy 392

electrolytes 391
 fluid balance 391
 hypercapnia 391
 hypoglycemia 391
 intracranial hypertension 392
 N-acetylcysteine 392
 nutrition 391
 prophylactic antibiotics and
 antifungal drugs 392
 reduction of cerebral edema 392
 role of hypothermia 392
 metabolic and renal problems 393
 role of APOLT 391
 role of LDLT 391
 Liver transplantation in Asian
 countries 341
 Hong Kong 342
 India 342
 Japan 341
 Korea 341
 Taiwan 341
 Liver transplantation in Europe 345
 Liver transplantation in situs
 inversus 21
 Liver transplantation in
 Western countries 343
 Liver transplantation team 39
 anesthesiologist 39
 financial coordinator 40
 hepatologist/transplant
 physician 39
 nurse coordinator/transplant
 coordinator 40
 nutritionist 40
 pathologist 39
 pharmacist 40
 radiologist 39
 social worker 40
 surgeon 39
 Local infusion therapy 193
 Looping of supra-celiac aorta 86
 Lymphatic drainage of bile duct 21
 Lymphatics 20
 Lymphocyte cross match test 224
 procedure 224

M

Major histocompatibility complex 206
 Makuuchi ligament 20
 Malignancy 293
 risk factors 293
 alcohol and tobacco 293
 CINs 293
 cutaneous diseases 293
 survival 293
 Maple syrup urine disease 150
 Marginal donor 67
 characteristics 67

MDCTA (multidetector computed
 tomographic angiography) 252
 MELD score and HRQL 336
 Metabolic liver diseases 144
 Metabolic syndrome 290
 Microangiopathy 229
 Molecular adsorbent recirculation
 system 329
 anticoagulation 330
 complications 330
 contraindications 331
 indications 330
 principle 329
 procedure 330
 prometheus system 331
 Monitoring renal function 283
 MR cholangiography for biliary
 tree evaluation 46
 MSUD 150
 Mycobacterium tuberculosis 260

N

Neonatal hemochromatosis 314
 Neutrophils 206
 Nitric oxide in ACR 208
 Non-alcoholic steatohepatitis 402
 Non-anastomotic biliary
 strictures 234, 237
 in LDLT 237
 in DDLT 234
 Non-disease-specific criteria 24
 Child-Turcotte-Pugh classifica-
 tion 24
 evolution of meld scoring system 25
 MELD equation 25
 MELD score in HCC patients 25
 PELD equation 26
 PELD scoring system 26
 Non-heart-beating donor 62
 Nonhepatic malignancy 36

O

Obesity 36, 288
 etiology 288
 management 288
 Occlusion/stenosis of MHV graft in
 right lobe LDLT 247
 diagnosis 248
 treatment 248
 Organ allocation policy 27
 Organ allocation system in USA
 and liver transplantation 27
 Organ patient index 68
 Osteoporosis 291
 mechanism 292
 presentation 292
 risk factors 292
 Overlap syndrome 386

P

-
- Parasites 269
 Parenchyma transection 73
 Pathophysiological changes after
 brainstem death 58
 cardiovascular changes 58
 cardiovascular collapse phase 59
 hyperdynamic phase 58
 hemodynamic changes 58
 Pediatric immunosuppression 175
 initial immunosuppression 175
 newer immunosuppression
 drugs 175
 CAMPATH 1-H 176
 FK 778 176
 FTY 720 176
 RAD (everolimus) 175
 thymoglobulin 176
 Plasmapheresis/plasma exchange 192
 Pneumocystis carinii/jiroveci 269
 Policy for declaration of brain death 61
 Portal hypertension 436
 causes 436
 hepatic 436
 prehepatic 436
 Portal vein 188
 Portal vein arterialization 123
 arterial complications 124
 pretransplant hepatic artery
 thrombosis 124
 different techniques 123
 technical complications 123
 arterialized hepatic allograft
 study 124
 combined liver-intestine
 transplant 124
 liver allograft injury and right-
 sided heart failure 123
 portal hypertension 123
 post-transplant follow-up 124
 renoportal anastomosis 124
 Portal vein complications 245
 late PV aneurysm after
 transplantation 246
 PV stenosis 245
 PV thrombosis 245
 rethrombosis 246
 signs 245
 symptoms 245
 treatment 246
 Portal vein evaluation 44
 Portal vein in a live donor 17
 Portal venous anatomy 50
 Post-transplant infection 258
 abdominal infections 258
 bilomas 258
 peritonitis 258
 wound related infections 258
 aspergillus infection 268
 diagnosis 268
 risk factors 268
 treatment 268
 bacterial infections 259
 candida infection 267
 diagnosis 267
 source 267
 treatment 267
 CNS infections 259
 cryptococcus 268
 diagnosis 268
 presentation 269
 treatment 268
 cytomegalovirus infection 262
 clinical course 262
 pathogenesis 262
 source 262
 types 262
 early infections 258
 fungal infections 267
 late infectious 258
 legionella pneumophila
 infection 261
 listeria monocytogenes 261
 nocardia 261
 pulmonary infections 258
 viral infections 261
 Post-transplant life in children 318
 compliance 318
 major risk factors 318
 minor risk factors 318
 Potential transplant recipient 50
 Presence of portocaval shunts 51
 Presentation of biliary complication 228
 Preservation injury 119
 Pre-transplant PV thrombosis in
 recipient 120
 diagnosis 120
 grading 121
 pathogenesis 120
 surgical treatment plan 121
 Prevalence of hepatic steatosis 55
 Prevalence of NAFLD 402
 age 402
 clinical outcome 403
 correlation of NAFLD and HCC 404
 diagnosis 403
 gender 402
 liver transplantation 404
 natural history 403
 racial and ethnic differences 402
 risk factors 402
 treatment 404
 Previous abdominal surgery 35
 Primary biliary cirrhosis 384
 treatment 384
 medical management 384
 surgical management 385
 Primary hyperoxaluria 315
 Primary nonfunction 213
 recipient factors 213
 risk factors 213
 Primary sclerosing cholangitis 385
 diagnosis 385
 management 385
 Procedure for harvesting
 DCD donors 63
 donor evaluation 64
 HA thrombosis and survival rates 65
 ischemic cholangiopathy 65
 organ evaluation 64
 organ preservation 64
 PNF rate ranges 65
 recipient operation 64
 Protozoa 269
 Psychological complaints in donors 337
 Psychological factors in rejection 209
 Psychological problems in patients on
 waiting list 337
 Pulmonary conditions 35
 hepatopulmonary syndrome 35
 portopulmonary hypertension 35
 pulmonary hypertension 35
 pulmonary tuberculosis 35
 Pulmonary dysfunction 59
 PV anastomosis 106
-
- R**
 Radionuclide HIDA scans 146
 Recipient evaluation and
 assessment 315
 Recipient liver biopsy 276
 liver biopsy for acute rejection 276
 different types of cells in acute
 cellular rejection 277
 protocol liver biopsy after
 transplantation 277
 liver biopsy in chronic rejection 279
 acute on chronic rejection 280
 other indications of liver biopsy
 in hepatic allograft 280
 perfusion/preservation
 injury 280
 treated rejection 280
 liver biopsy in humoral/antibody
 mediated rejection 278
 C4D immunostaining 278
 interpretation of C4D immuno-
 peroxidase staining 279
 Recipient surgery 97
 Recipient surgery for deceased donor
 liver transplantation 113
 implantation technique 113

piggyback technique 114
 standard technique 113
 role of temporary portocaval shunts
 in liver transplantation 115
 advantages 115
 Reduced-size liver transplantation 313
 Redundant bile duct after LTX 240
 Rejection and HRQL 336
 Remnant donor 75
 Renal failure 36
 Renal USG 283
 Reperfusion injury 61
 Reperfusion syndrome 118
 etiology 118
 prevention 118
 treatment 118
 Response of human body to
 infection 359
 Retransplantation 36, 237, 310
 Retransplantation and organ
 allocation 29
 Reversible fulminant hepatic failure 144
 Right lateral sector graft 80
 Right lobe donor hepatectomy 70
 surgical techniques 70
 Right lobe graft 70
 Right posterior segment 80
 Role of APOLT in present
 transplantation scenario 147
 Role of LDLT in HCC patients 354
 Role of other cells in ACR 206
 Role of regulatory T-cells 205

S

Serum creatinine 283
 Sexual life after liver
 transplantation 337
 Shunt procedures 124
 Single pass albumin dialysis 331
 Small for size syndrome 127
 evaluation of shunt patency 129
 graft selection and criteria 128
 measurement of portal vein
 pressure 129
 medical management 128
 small for size dysfunction 127
 small for size non-function 127
 surgical techniques 129
 Sphincter of ODDI dysfunction 240
 Spiral CT angiography 252
 Splenectomy 193
 Splenic arterial steal syndrome 256
 causes 256
 common sites 256
 diagnosis 257

3-D CT scan 257
 angiography 257
 differential diagnosis 257
 follow-up 257
 mechanisms 256
 presentation 256
 treatment 257
 Splenic vein cannulation 87
 Split liver 55
 Split liver transplantation 131, 313
 indications 313
 drug toxicity 314
 extrahepatic biliary atresia 313
 procedures 131
 selection of graft 313
 small for size syndrome 313
 surgical techniques 133
 donor procedure 133
 recipient surgery for split liver for
 adult and child 135
 surgical procedure 135
 technical difficulties and
 modification in SLT for
 2 adults 135
 types of splitting the donor liver 133
 ex-situ splitting 133
 in-situ splitting 133
 Spontaneous bacterial peritonitis 458
 clinical features 458
 correlation with HRS 458
 diagnosis 458
 mortality 458
 prophylaxis 458
 risk factors 458
 treatment 458
 Stem cell transplantation 426
 route of implantation 426
 Strongyloides stercoralis 269
 Supraportal pattern 14
 Survival after Re-TX 310
 Survival rates after APOLT 146

T

Thrombotic microangiopathy 195
 Time interval between transplantation
 and pregnancy 298
 Toxoplasma gondii 269
 TPN-related cholestasis 315
 Transjugular portosystemic shunt 51
 Transplantation statistics 30
 Treatment in potential heart-beating
 donors 60
 diabetes insipidus 60
 donor hypernatremia 60
 hyperglycemia 60
 hypothyroidism 60

Treatment modalities used for in ABO-
 incompatible transplantation 192
 Treatment strategy according to
 BCLC staging 349
 HCC-role of LTX 349
 Milan criteria 350
 UCSF criteria 350
 university of Pittsburgh
 criteria 350
 Triple immunosuppression therapy 194
 Tyrosinemia 314

U

UNOS (united network for organ
 sharing) 27
 UNOS and its territory 27

V

V5 and V8 division and
 reconstruction 75
 Vaccination 270
 Vanishing graft syndrome in
 dual grafts 143
 Varicella zoster virus 267
 Vascular anatomy 50
 Viral hepatitis 314
 Viral infections 317

W

Wilson's disease 314, 407
 diagnosis 407
 electron microscopy 408
 follow-up 409
 genetic diagnosis 408
 imaging studies 408
 positron emission tomography
 scan (PET scan) 408
 prognosis 409
 radiolabelled copper 408
 signs 407
 symptoms 407
 treatment 408

X

Xenogenic cell transplantation 422
 Xenogenic hepatocytes 422
 Xenoperfusion 422
 Xenotransplantation 420
 advantages 420
 major hurdles for development 420
 ethical issues 421
 immunological barrier 420
 xenoviruses 421