THE PROTOCOL BOOK
for Intensive Care

THE PROTOCOL BOOK
for Intensive Care

Fourth Edition

Editor

Soumitra Kumar MBBS MD DM FCSI FACC FESC FSCAI FICC FICP

Professor, Division of Cardiology
Department of Medicine
Vivekananda Institute of Medical Sciences
Kolkata, West Bengal, India

Forewords

Sukumar Mukherjee
Manotosh Panja
Amal Kumar Banerjee
Pradip Kumar Deb

JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD

New Delhi • London • Philadelphia • Panama

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Offices

J.P. Medical Ltd
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-2031708910
Fax: +02-03-0086180
Email: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +507-301-0496
Fax: +507-301-0499
Email: cservice@jphmedical.com

Jaypee Medical Inc.
The Bourse
111, South Independence Mall East
Suite 835, Philadelphia, PA 19106, USA
Phone: + 267-519-9789
Email: joe.rusko@jaypeebrothers.com

Jaypee Brothers Medical Publishers (P) Ltd
17/1-B Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
Email: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
Shorakhute, Kathmandu
Nepal
Phone: +00977-9841528578
Email: jaypee.nepal@gmail.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Inquiries for bulk sales may be solicited at: jaypee@jaypeebrothers.com

The Protocol Book for Intensive Care

First Edition: 2003 (by Editor)
Second Edition: 2008
Third Edition: 2010
Fourth Edition: **2014**

ISBN 978-93-5090-740-5

Printed at

To
My Family,
Friends
and
Well-wishers

Swami Vivekananda

The secret of religion lies not in theories but in practice.
To be good and to do good — that is the whole of religion.

Contributors

Achyut Sarkar
Associate Professor
Department of Cardiology
Institute of Postgraduate Medical Education and Research
Kolkata, India

Amitava Majumder
Assistant Professor
Department of Medicine
Vivekananda Institute of Medical Sciences, Kolkata, India

Aniket Niyogi
Senior Registrar, ITU
Belle Vue Clinic, Kolkata, India

Arghya Chattopadhyay
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Arup Ratan Datta
Head, Department of Nephrology
Fortis Hospital, Anandapur
Kolkata, India

Basab Bijoy Sarkar
Consultant Physician
Fortis Hospital, Anandapur
Kolkata, India

Bipul Barman
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Debashis Datta
Consultant Gastroenterologist
Fortis Hospital, Anandapur
Kolkata, India

Debashis Sarkar
Consultant Physician
Sri Aurobindo Seva Kendra
Kolkata, India

Dinobandhu Naga
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Dipankar Mondal
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Jayanta Roy
Consultant Neurologist
Apollo Gleneagles Hospital
Kolkata, India

Joydeep Mukherjee
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Kayapanda M Mandana
Chief Cardiac Surgeon
Fortis Hospital, Anandapur
Kolkata, India

Samar Ranjan Pal
Associate Professor
Division of Rheumatology
Department of Medicine
Vivekananda Institute of Medical Sciences, Kolkata, India

Saptarshi Mukhopadhyay
Senior Resident
Department of Medicine
Ramakrishna Mission Seva Pratishthan, Kolkata, India

Shuvanan Ray
Chief of Cardiac Interventions
Fortis Hospital
Anandapur, Kolkata, India

Siddhartha Bandopadhyay
Deputy Visiting Cardiologist
Department of Medicine
Ramakrishna Mission Seva
Pratishthan
Kolkata, India

Soumitra Kumar
Professor
Division of Cardiology
Department of Medicine
Vivekananda Institute of Medical
Sciences, Kolkata, India

Subhasis Chakraborty
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan
Kolkata, India

Sudeshna Majumder
Professor
Division of Cardiology
Department of Medicine
Vivekananda Institute of Medical
Sciences, Kolkata, India

Sudip Mondal
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan
Kolkata, India

Sudipto Chatterjee
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan, Kolkata, India

Sujata Majumder
Assistant Professor
Department of Medicine
Vivekananda Institute of Medical
Sciences, Kolkata, India

Sujoy Ghosh
Assistant Professor
Department of Endocrinology
Institute of Postgraduate Medical
Education and Research
Kolkata, India

Sulagna Banerjee
Medical Officer
Division of Non-invasive Cardiology
Ramakrishna Mission Seva
Pratishthan, Kolkata, India

Sumit Sen Gupta
Consultant Pulmonologist
Fortis Hospital
Anandapur, Kolkata, India

Susanta Chakraborty
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan, Kolkata, India

Sweety Trivedi
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan, Kolkata, India

Uttio Gupta
Senior Resident
Department of Medicine
Ramakrishna Mission Seva
Pratishthan, Kolkata, India

Yashesh Paliwal
Consultant Intensivist
In-charge, ICU, Fortis Hospital
Anandapur, Kolkata, India

Foreword to the Fourth Edition

Medical Sciences have progressed by leaps and bounds—not only in understanding of pathogenesis but also in formulation of evidence-based and cost-effective approach in their management. Parallel to novel diagnostic aids, technological improvement in acute care medicine has supplemented quality of management to a greater extent to achieve precision. The medical practice is ever-changing with the introduction of newer concepts and devices in an algorithmic manner as it is done in this fourth edition of the book *The Protocol Book for Intensive Care* under the able editorship of Professor Soumitra Kumar and his team. This book covers all the major branches of medical emergencies such as cardiology, pulmonary medicine, central nervous system, metabolic medicine, and of course, rheumatology. In this multidisciplinary and multi-author book the presentations are simple, logical and maintain orderly flow of decision-making process.

The compilation of most of the 'acute care medicine' by thoughtful contribution of senior experienced clinicians of Kolkata under the guidance of erudite Professor Kumar has come out like *'Pocket Guidelines Update'*. I am sure this algorithmic approach with holistic vision would be very practical for the clinicians who practice acute emergencies.

I am convinced that timely arrival of this edition will improve level of acute care further in patients with health crisis. And for this laudable effort of educational promotion, Professor Soumitra Kumar and his associates deserve special appreciation and thanks.

Sukumar Mukherjee
MD FRCP(Lond) FRCP(Edinburgh)
FSMF FICP FISE FIMSA
Ex-Professor and HOD of Medicine
Medical College, Kolkata, India
Past President
Association of Physicians of India

Foreword to the Fourth Edition

It is indeed a pleasure for me to write a Foreword for this fourth edition of *The Protocol Book for Intensive Care*. I have known Dr Soumitra Kumar since he started working with me in his postgraduation days and his academic zeal was always very commendable. He has indeed matured a great deal with times and along with his team of acclaimed colleagues and enthusiastic students, he has produced a real praise-worthy publication. I am given to understand that the first 3 editions have been very popular and I am very hopeful that the fourth one too will be equally well-appreciated and read. I wish Dr Kumar and his team all success for the book.

Manotosh Panja
MD DM FCSI FACC FICP
Ex-Director, Professor and HOD
Department of Cardiology
Institute of Postgraduate Medical Education and Research
Kolkata, India
President
Cardiological Society of India (1995-96)
President
Association of Physicians of India (2003-04)
Dean
Indian College of Physicians (2012-13)

Foreword to the Fourth Edition

Medical Sciences, in the past few decades, have progressed at lightning speed. The advent of intensive care has decreased morbidity and mortality in patients with medical emergencies which constitute nearly 30-40% of medical practice today.

Professor Soumitra Kumar first published the *Protocol Book* in 2003. This year, he is going to publish the 4th edition of the book with a focus on intensive care. Truly speaking, we need this sort of protocol book which presents in a brief and practical manner, the approach towards diagnosis and management of medical emergencies. This compilation of treatment approaches on various aspects of intensive care pertaining to the various systems has been well-chosen and written by very experienced faculty.

Professor Soumitra Kumar needs to be complimented for the excellent selection of topics. This book shall be useful to all sections of medical profession. Professor Kumar has set up a healthy trend in publishing the 4th edition of this book. I am sure that this book will find a permanent place on the shelves of all physicians.

Amal Kumar Banerjee
MD DM FACC FESC FACP FAPSC FICC FCSI FICP
Past President
Cardiological Society of India
Association of Physicians of India
SAARC Cardiac Society

Foreword to the Fourth Edition

The Fourth Edition of *The Protocol Book for Intensive Care* is indeed a praiseworthy compendium of contemporary guidelines on the management of acute cardiac emergencies and related common acute medical problems. The guidelines have been supported by relevant scientific evidence and appropriate class of recommendation, as is the current practice. I am sure that it will find its place in the book-shelf of many doctors' clinics and will prove to be very handy to both cardiologists and internists alike in their day-to-day practice. I congratulate Dr Soumitra Kumar and the galaxy of very competent authors for this excellent piece of work.

Pradip Kumar Deb
MD DM FCSI FESC
President
Cardiological Society of India

ALL INDIA HEART FOUNDATION
4874 (First Floor), Ansari Road
24, Daryaganj
New Delhi-110 002

DR. S. PADMAVATI
FRCP (Lond.) FRCPE, FACC, FAMS
PRESIDENT-All India Heart Foundation
DIRECTOR-National Heart Institute

NATIONAL HEART INSTITUTE
(WHO Collaborative Centre in Preventive Cardiology)
49, Community Centre
East of Kailash
New Delhi-110 065
E-mail : padmavat@del2.vsnl.net.in

Foreword to the First Edition

The Protocol Book represents guidelines for the diagnosis and management of common medical emergencies seen in hospitals. It covers mostly cardiac problems but also includes respiratory, gastrointestinal, renal diseases and diabetes. It has the same objectives as the American Heart Association/ American College of Cardiology's *Pocket Guidelines Updates* compiled by the Special Task Forces of these organisations which are proving extremely useful for practicing physicians.

This book has been compiled by the postgraduate students of the Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, Kolkata, under the guidance of senior consultants in these departments at the hospital and under the able Editorship of Dr Soumitra Kumar. The text is written in a typical 'Senior Resident' language that can be easily understood by their colleagues. The latest 'state-of-the-art' information and knowledge has been used in preparing the various sections. It is a very laudable effort on the part of the postgraduate staff.

I am sure **The Protocol Book** will prove very useful for all categories of physicians dealing with acute emergencies in hospitals.

S Padmavati
FRCP (London) FRCPE FACC FAMS
President—All India Heart Foundation
Director—National Heart Institute

Preface

In the Fourth edition, *The Protocol Book* has been renamed as *The Protocol Book for Intensive Care* on the basis of feedback from the publishers that many potential readers have felt confused to figure out what protocol it is all about ! Now, as an editor, I feel relieved that no one will be left flustered even if he/she is judging the book by its cover. However, I will submit with utmost humility that if one judges by the cover alone, he/she will really miss out on the rich content of the book inside.

Indeed, as an editor, I feel that the book is quite rich in information, more sound in its evidence-base and very useful and handy in terms of practical tips in handling cardiac and related medical emergencies. One chapter, namely "Post-operative Care following Cardiac Surgery" has been added to the previous list of chapters (as in second and third editions) making the total number twenty-seven.

Like the previous editions, theme of this edition too is to emphasize on the successful "total management" of the patient. I have been deeply affected to find successful management of cardiac problems becoming futile when the patient succumbed to non-cardiac problems like sepsis or renal failure.

I am personally grateful to all the contributors of this edition for their sincere cooperation and hard work. My junior colleagues, mostly post-graduate students at Vivekananda Institute of Medical Sciences, Kolkata, have really toiled hard to update the chapters to the best of their ability. More senior contributors (many from Fortis Hospital, Anandapur, Kolkata), who are experts in their respective fields, have supplemented this effort with their experienced and deft-finishing touches. I am particularly thankful to Mr B Mukherjee for his unstinting support and cooperation in primary composition of the chapters. I also sincerely acknowledge the continued patronage of M/s Zydus Pharmaceuticals for this title over last one decade. Finally, I am indebted to my family members (my parents, wife and son) for putting-up with my academic pursuits yet again often at the cost of my family commitments.

Soumitra Kumar

Contents

Acute ST-Elevation Myocardial Infarction

chapter 1

Subhasis Chakraborty, Soumitra Kumar

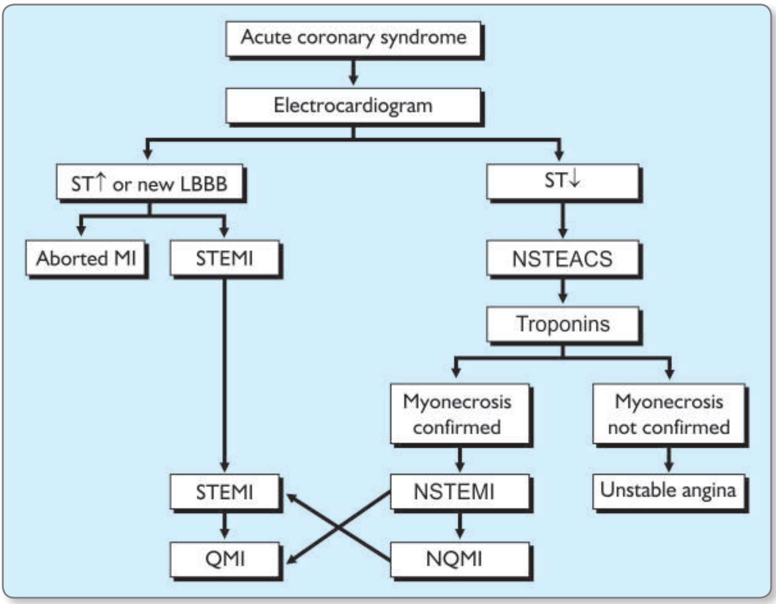
Third Universal Definition of Myocardial Infarction (Joint ESC/ACCF/AHA/WHF Task Force 2012)

Definition of Myocardial Infarction

Criteria for Acute Myocardial Infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

Flow chart 1.1 Classification of acute coronary syndrome



(*Abbreviation:* LBBB: Left bundle branch block; NSTEACS: Non-ST segment elevation acute coronary syndromes; QMI: Q-wave myocardial infarction; NQMI: Non-Q-wave myocardial infarction; MI: Myocardial infarction; STEMI: ST segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction)

- Detection of rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB)
  - Development of pathological Q-waves in the echocardiogram (ECG)
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes, or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (> 5 × 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition either:
  i. Symptoms suggestive of myocardial ischemia, or
  ii. New ischemic ECG changes, or
  iii. Angiographic findings consistent with a procedural complication, or
  iv. Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q-waves or new LBBB, or (ii) antiographically documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for Prior Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q-waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause
- Pathological findings of a prior MI.

Classification of Myocardial Infarction

Type I: Spontaneous Myocardial Infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion nonobstructive or no CAD.

Type 2: Myocardial Infarction Secondary to an Ischemic Imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).

Type 3: Myocardial Infarction Resulting in Death when Biomarker Values are Available

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases, cardiac biomarkers were not collected.

Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention

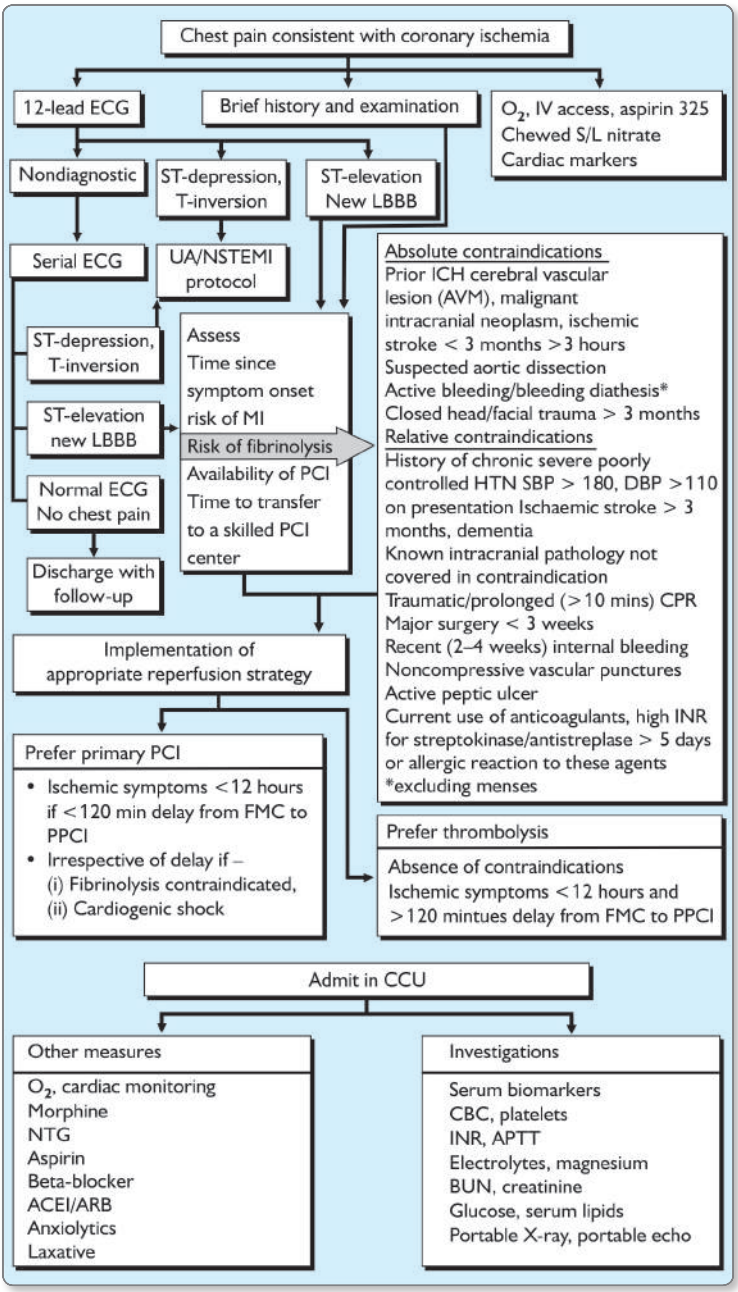
Myocardial infarction associated with percutaneous coronary intervention (PCI) is arbitrarily defined by elevation of cTn values $>5 \times 99$th percentile URL in patients with normal baseline values ($\leq$99th percentile URL) or a rise of cTn values $>20\%$, if the baseline values are elevated and are stable or falling. In addition, either:

i. Symptoms suggestive of myocardial ischemia, or
ii. New ischemic ECG changes or new LBBB, or
iii. Angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or
iv. Imaging demonstration of new loss of viable myocardium or new regional wall motion abormality are required.

Type 4b: Myocardial Infarction Related to Stent Thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Flow chart 1.2 Initial hospital management and selection of reperfusion therapy



Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting

Myocardial infarction associated with coronary artery bypass grafting (CABG) is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL. In addition, either:

i. New pathological Q-waves or new LBBB, or
ii. Angiographic documented new graft or new native coronary artery occlusion, or
iii. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Prehospital Issues

Time from symptom onset to reperfusion with primary percutaneous coronary intervention (PCI) or fibrinolytic drug, is called total ischemic time and is particularly important for patients with ST segment elevation myocardial infarction (STEMI). Longer total ischemic times are associated with more myocardial damage and adverse clinical consequences. Incidentally, prehospital delay comprises about 60 to 70 percent of the total ischemic time. Figure 1.1 depicts a hypothetical construct of the relationship among duration of symptoms of acute MI before reperfusion therapy, mortality reduction and extent of myocardial *salvage*. Reperfusion therapy results in the highest mortality benefit in the first 2 to 3 hours after onset of symptoms of acute MI

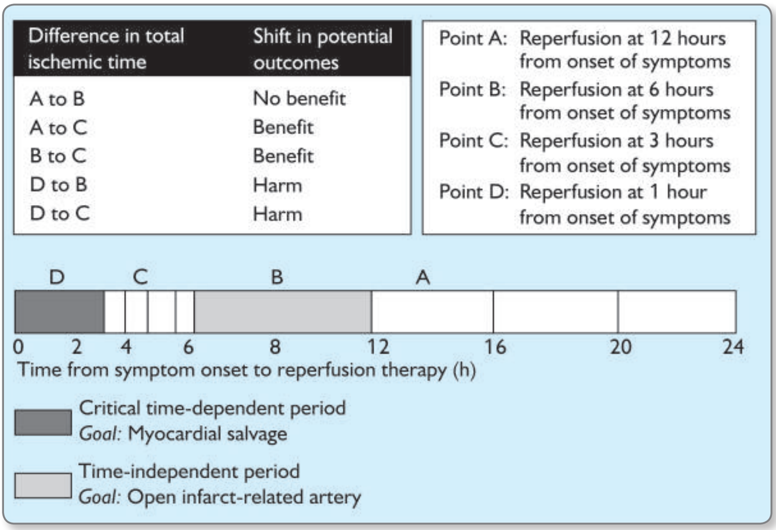


Fig. 1.1 Relationship of outcome and myocardial salvage as a function of total ischemic time

(AMI), most likely a consequence of myocardial salvage. The exact duration of this critical early period may be modified by several factors, including presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands and duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. Between 6 and 12 hours after onset of symptoms, opening the infarct-related artery is the primary goal of reperfusion therapy and myocardial salvage in this period is the secondary and uncertain goal.

The over-reaching goal is to keep total ischemic time with 120 minute (ideally within 60 minutes) from symptom onset to initiation of reperfusion treatment. The following modus operandi should be followed by medical system based on the mode of patient transportation and capabilities of the hospital which receives the patient.

Transportation by emergency medical services (EMS) is recommended and self-transportation should be discouraged. If the EMS has fibrinolytic capability and patient qualifies for therapy, prehospital fibrinolysis should be treated within 30 minutes of arrival of EMS on the scene. If EMS is not capable of administering prehospital fibrinolysis and patient is transported to a non-PCI-capable hospital, door to needle time should be within 30 minutes, if fibrinolysis is indicated. However, if EMS is not capable of administering prehospital fibrinolysis and patient is transported to a PCI-capable hospital, EMS arrival-to-balloon time should be within 90 minutes. Following presentation to a non-PCI-capable hospital, it may be considered appropriate to consider emergency interhospital transfer of the patient to a PCI-capable hospital for mechanical revascularization in following three situations:

1. Fibrinolysis is contraindicated.
2. Percutaneous coronary intervention can be initiated promptly within 90 minutes from EMS arrival-to-balloon time at the PCI-capable hospital or within 60 minutes compared with when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital.
3. Fibrinolysis is administered and unsuccessful, i.e. "rescue PCI" is indicated.

Initial Hospital Management

ST-elevation myocardial infarction patients should be admitted to the quiet and comfortable environment of coronary care unit (CCU) that provides for continuous monitoring of the ECG and pulse oximetry and has ready access to facilities for hemodynamic monitoring and defibrillation. Beside chair or commode is allowed when patient becomes stable. Oxygen by nasal cannula at 2 L/minute is administered for initial 6 hours and continued thereafter only if oxygen saturation is less than 90 percent. Patients initially admitted to CCU who demonstrate 12 to 24 hours of clinical stability may be transferred to the step down unit. Low risk STEMI patients who have undergone successful PCI may be admitted directly to step down unit for post-PCI care rather than to the CCU.

- An intravenous (IV) access is mandatory with a running infusion (NS/D5W) to keep the vein open. A second IV access to be started if IV medication is being given. This may be a saline lock.
- Continuous ECG monitoring for arrhythmias and ST segment deviation is mandatory. Vital signs need to be monitored every 1.5 hours until stable, then every 4 hours and as needed. Continuous oximetry monitoring is also recommended. Nasal cannula at 2 L/minute when stable for 6 hours; thereafter reassess for oxygen need (i.e. oxygen saturation less than 90%) and consider discontinuing oxygen.
- Patient should not be administered oral feeds except sips of water until stable. Thereafter, a therapeutic lifestyle change (TLC) diet comprising 2 g sodium/day, low saturated fat (less than 7% of total calories/day), low cholesterol (less than 200 mg/day) diet is advised.
- Bed rest is recommended during the acute, unstable phase; however, bedside commode and light activity are permitted when stable.
- Blood sample for laboratory tests are to be sent immediately on admission but one should not wait for results before implementing reperfusion strategy. These induced serum biomarkers for cardiac damage, CBC with platelet count, prothrombin time with International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), electrolytes, magnesium, BUN, creatinine, glucose, and serum lipids.
- Antiplatelet and antithrombotic cotherapies (as per ESC guidelines for the mangement of STEMI 2012 and ACCF/AHA guidelines for management of STEMI 2013).

A. **Antiplatelet drugs:**

- *Aspirin: Primary PCI (Class IB recommendation):* Loading dose of 150 to 300 mg orally or 80 to 150 mg IV if oral ingestion is not possible, followed by a maintenance dose of 75 to 100 mg/day to be continued indefinitely. [ACC/AHA 2013 Guidelines 81 mg is the preferred dose].
  With fibrinolytic therapy: Starting dose 150 to 500 mg orally or IV dose of 250 mg if oral ingestion is not possible followed by maintenance dose of 75 to 100 mg/day indefinitely.
  Without reperfusion therapy: Starting dose 150-500 mg orally.
  Chronic kidney disease: No dose adjustment.
- *Clopidogrel: Primary PCI (Class IC recommendation):* Loading dose of 600 mg orally, followed by maintenance dose of 75 mg/day for one year.
  With fibrinolytic therapy: Loading dose of 300 mg orally if aged ≤ 75 years, followed by a maintenance dose of 75 mg/day for one year:
  If patient has not received a loading dose of clopidogrel:
  - *If PCI performed ≤ 24 hours after fibrinolysis:* Clopidogrel 300 mg before or at time of PCI

- *If PCI performed > 24 hours after fibrinolysis:* Clopidogrel 600 mg loading before or at time of PCI

Without reperfusion therapy: 75 mg/day orally for one year.
Chronic kidney disease: No dose adjustment.

- *Prasugrel: Primary PCI (Class IB recommendation):* Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day for one year. In patients with body weight < 60 kg, if used, a maintenance dose of 5 mg is recommended.

  In patients > 75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used, if treatment is deemed necessary.
  If loading dose of clopidogrel not given
  - If PCI is performed > 24 hours after treatment with a fibrin-specific agent or > 48 hours after a nonfibrin specific agent, prasugrel 60 mg at time of PCI.

  Chronic kidney disease: No dose adjustment. No experience with end-stage renal disease/dialysis.
- *Ticagrelor: Primary PCI (Class IB recommendation):* Loading dose of 180 mg orally, followed by 90 mg bid for one year.
  Chronic kidney disease: No dose adjustment. No experience with end-stage renal disease/dialysis.
- *Glycoprotein IIB/IIIa (GP IIb/IIIa) inhibitors:*
  Primary PCI:
  - GPIIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no reflow or a thrombotic complication (Class IIa recommendation).
  - Routine use of a GPIIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications (Class IIbB recommendation).
  - Upstream use of GPIIb/IIIa inhibitor (Vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI (Class IIbB recommendation).

  Dosage:
  Abciximab: Bolus of 0.25 mg/kg IV or 0.125 µg/kg/minute infusion (maximum 10 µg/min) for 12 hours.
  Eptifibatide: Double bolus of 180 µg/kg IV (given at 10 min interval) followed by an infusion of 2.0 µg/kg/minute for 18 hours.
  Tirofiban: 25 µg/kg over 3 minute IV, followed by a maintenance infusion of 0.15 µg/kg/minute for 18 hours.
  All the three agents have class IIa recommendation as per recent ACCF/AHA 2013 Guidelines with abciximab having level A of evidence again B for other two.

B. **Antithrombotic drugs:**

- *Unfractionated heparin: Primary PCI*—70-100 u/kg IV bolus when no GP IIb/IIIa inhibitor is planned. (Class IC recommendation)

50 to 70 u/kg IV bolus with GPIIb/IIIa inhibitors. (Class IC recommendation)

- *With fibrinolytic therapy:* 60 u/kg IV bolus with a maximum of 4000 u followed by an IV infusion of 12 u/kg with a maximum of 1000 u/h for 24 to 48 hours. (Class IC recommendation)
- *Target aPTT:* 50 to 70 sec or 1.5 to 2.0 times that of control to be monitored at 3,6,12 and 24 hours.

  Without reperfusion therapy: Same dose as with fibrinolytic therapy.

  Chronic kidney disease: No adjustment of bolus dose.
- *Enoxaparin:*

  With primacy PCI: 0.5 mg/kg IV bolus. (ESC class IICB recommendation; ACCF/AHA-no recommendation)

  In patients < 75 years of age, 30 mg N bolus followed 15 min later by 1 mg/kg SC every 12 hours until hospital discharge for a maximum of 8 days. The first two doses should not exceed 100 mg.

  With fibrinolytic therapy: In patients > 75 years of age, no IV bolus; start with subcutaneous dose of 0.75 mg/kg with a maximum of 75 mg for the first two subcutaneous doses. (Class IA recommendation)

  In patients with creatinine clearance of < 30 mL/minute, regardless of age, the SC doses are given once every 24 hours.

  Without reperfusion therapy: Same dose as with fibrinolytic therapy.

  Chronic kidney disease: No adjustment of bolus dose. Following thrombolysis, in patients with creatinine clearance < 30 mL/minute, the SC doses are given once every 24 hours.
- *Bivalirudin:*

  With primary PCI: 0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure as clinically warranted (Class IB recommendation)

  After the cessation of the 1.75 mg/kg/hour infusion, a reduced infusion dose of 0.25 mg/hour may be continued for 4 to 12 hours as clinically necessary. Preferred over UFH with GPIIb/IIIa receptor antagonists in patients with high risk of bleeding. (Class IIa B recommendation)

  Chronic kidney disease.
  - In patients with moderate renal insufficiency (GFR 30–59 mL/min) a lower initial infusion rate of 1.4 mg/kg/hour should be given. The bolus dose should not be changed.
  - In patients with severe renal insufficiency (GFR < 30 mL/minute) and in dialysis-dependent patients bivalirudin is contraindicated. (ESC 2012); as per ACCF/AH 2013 guidelines, reduce infusion to 1 mg/kg/hour if GFR < 30 mL/ minute.
- *Fondaparinux:*

  With primary PCI: Not recommended as sole anticoagulant

With fibrinolytic therapy: 2.5 IV bolus followed by a SC dose of 2.5 mg once daily up to 8 days or hospital discharge.
Without reperfusion therapy
Same dose as with fibrinolytic therapy.
Chronic kidney disease
No dose adjustment.
No experience in patients with end-stage renal disease or dialysis patients.

Duration of thienopyridine therapy for patients receiving a stent (BMS or drug-eluting stent [DES]) during PCI for ACS, clopidogrel 75 mg daily [IB] or prasugrel 10 mg daily [IB] should be given for at least 12 months. If the risks of morbidity because of bleeding outweigh the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered [IC]. If coronary artery bypass graft (CABG) is planned and can be delayed, as mentioned earlier, clopidogrel should be withdrawn for at least 5 days and prasugrel for at least 7 days prior to coronary artery bypass (CABG), unless the need for CABG and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding [IC]. Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent (DES) placement (IIbc). In STEMI with a prior history of stroke and transient ischemic at least for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen.

Nitroglycerin (NTG): Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of three doses, after which as assessment should be made about the need for intravenous nitroglycerin [IC].

Analgesia: Morphine sulfate (2–4 mg IV with increment of 2–8 mg IV repeated at 5–15 minutes intervals) is the analgesic of choice for management of pain associated with STEMI [IC]. Patients routinely taking NSAIDs (except for aspirin) both nonselective as well as COX-2 selective agents before STEMI should have those agents discontinued at the time of presentation with STEMI because of the increased risk of mortality, reinfarction, hypertension, heart failure and myocardial rupture associated with their use [IC].

Beta-blockers: Oral beta-blockers therapy should be initiated in the first 24 hours for patients who do not have any of the following:

i. Signs of heart failure.
ii. Evidence of a low cardiac output state.
iii. Increased risk for cardiogenic shock (age >70 years, SBP <120 mm Hg, heart rate >110 bpm or < 60 bpm and increased time since onset of symptoms of STEMI).
iv. Other relative contraindications to *beta-blockade* (PR interval > 0.24 second or third degree heart block, active asthma or reactive

airway disease) [IC]. It is reasonable to administer an intravenous beta-blocker at the time of presentation to STEMI patients who are hypertensive and who do not have the contraindications as mentioned for oral formulations of beta-blockers [IIa-B]. Patients with early contraindications within first 24 hours of STEMI should be re-evaluated for candidacy for beta-blocker therapy as secondary prevention [IC].

Inhibitors of renin-angiotensin-aldosterone system: An angiotensin-converting enzyme (ACE) inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion or left ventricular ejection fraction (LVEF) less than 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications [IA]. For patients presenting within 24 hours of nonanterior wall STEMI but with the pulmonary congestion or LVEF less than 0.40, ACEIs have class IIa recommendation (Level of evidence: B) in absence of contraindications mentioned above.

An angiotensin receptor blocker (ARB) should be administered to STEMI patients who are intolerant of ACEIs and who have either clinical or radiological signs of heart failure or LVEF less than 0.40 [IC]. Valsartan and candesartan have established efficacy for this recommendation.

An intravenous ACEI should not be given to patients within the first 24 hours of STEMI because of risk of hypotension. Refractory hypertension may be one possible exception. Aldosterone blockade is recommended [IA] for post-STEMI patients without significant renal dysfunction (creatinine should be ≤ 2.5 mg/dL in men and ≤ 2.0 mg/dL in women) or hyperkalemia (potassium should be ≤ 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF ≤ 40% and have either symptomatic congestive heart failure (CHF) or diabetes. In the recently presented (ACC 2013) REMINDER trial, 1012 subjects with acute STEMI without diagnosis of heart failure, and with LVEF > 40% were randomized to receive either eplerenone 25 mg or placebo within 24 hours of onset of symptoms on top of standard therapy. The primary composite end-point (which comprised of CV mortality, rehospitalization or hospitalization extended due to HF, sustained VT or VF, EF < 40% after 1 month, natriuretic peptide elevation > 1 month was significantly altered in favor of eplerenone ($p < 0.0001$). However, despite numerical trends (nonsignificant) in favor of VT/VF and HF re-hospitalization, biomarker component of the end-point accounted for most of the overall benefit. Hyperkalemia was not significantly increased.

Metabolic modulation of glucose-insulin axis: An insulin infusion to normalize blood glucose is recommended for patients with STEMI and complicated course [IB]. During the acute phase (first 24-hour after STEMI), it is reasonable to administer an insulin infusion to maintain blood glucose in patients less than 180 mg/dL with an uncomplicated or complicated course while avoiding hypoglycemia [IIB]. Recently reported NICE-SUGAR trial has reported excess deaths, predominantly cardiovascular, in the intensive glycemic control arm of critically ill medical and surgical patients. Whether these results can be extrapolated to management of patients with STEMI is unclear but above-mentioned note of caution about hypoglycemia in 2009 update of ACC/AHA guidelines on STEMI has been made in the light of these findings. After the acute phase of STEMI, it is reasonable to individualize treatment of diabetics, selecting from a combination of insulin, insulin analogs, and oral hypoglycemic agents that achieve moderate glycemic control acutely and are well tolerated.

Lipid management: A fasting lipid profile (or obtaining one from recent past records for all STEMI patients) should be performed within 24 hours of symptom onset and lipid-lowering medication namely statins should be initiated before discharge [IA]. Treatment goals for LDL-C after STEMI should be < 100 mg/dL [IA] and further reduction to < 70 mg/dL appears reasonable [IIa-A]. Dietary advice on discharge should be given to all STEMI patients especially emphasizing on < 7% of total calories from saturated fat and < 200 mg/day of cholesterol [IA]. For patients with non-HDL-C < 130 mg/dL and who also have HDL-C < 40 mg/dL, special emphasis should be given on life-style modification, e.g. exercise, weight loss and smoking cessation [IB]. Drugs like niacin or fibrate to raise HDL-C in this situation have IIa recommendation (Level of evidence : B) after achieving LDL-C < 100 mg/dL with statins. However, if triglycerides are ≥ 500 mg/dL, niacin or fibrates should be initiated before LDL-lowering therapy in order to prevent pancreatitis [IC].

Magnesium: It is reasonable that documented magnesium deficits be corrected, especially in patients receiving diuretics before onset of STEMI [IIa-C]. It is also reasonable that episode of torsade de pointes-type ventricular tachycardia (VT) associated with a prolonged QT interval be treated with 1 to 2 g of magnesium administered as an intravenous bolus over 5 minutes [IIa-C]. However, in absence of documented deficit or torsade de pointes-type VT, routine intravenous magnesium should not be administered to STEMI patients at any level of risk.

Calcium channel blockers: There is no class I recommendation to use of calcium channel blockers (CCBs) after STEMI; however, effect of administration of nondihydropyridine CCBs verapamil and diltiazem initiated later after AMI were studied in the DAVIT-II and MDPIT trials respectively. Based on results of these trials, class IIa recommendation has been accorded to administration of verapamil or diltiazem for relief of ischemia or control of atrial tachyarrhythmias after STEMI to patients in whom beta-blockers are ineffective or contraindicated and in whom there are no signs of CHF, LV dysfunction or AV block (Level of evidence : C). Short-acting dihydropyridine CCB nifedipine is contraindicated in the treatment of STEMI.

Glucose insulin potassium: Despite report of mortality benefit from meta-analysis of early trials with IV infusion of glucose-insulin-potassium (GIK), more recent large-scale studies (including CREATE-ECLA trial with over 20,000 patients) have not supported those conclusions. The more recent IMMEDIATE trial evaluated efficacy of intravenous GIK in patients with CS (including STEMI). There was no significant difference in rate of progression to MI or 30-day-mortality. However, there was a statistically 52% reduction in composite end-point of cardiac arrest or in-hospital mortality and in a select group undergoing imaging, infarct size was seem to be reduced. This has rekindled interest in this therapy but there is no clear-cut recommendation at present. Above-mentioned recommendations for initial management of acute STEMI are based on most recent ACCF/AHA Guidelines 2013 for Management of Patients with STEMI. Recommendations by the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology 2012 for initial management of acute STEMI are similar and are enlisted below.

Table 1.1 Routine medical therapies in acute myocardial infarction [ESC Guidelines 2012]

Agent and indication	Class of Recommendation	Level of evidence
Oral treatment with beta-blockers is indicated in patients with heart failure or LV dysfunction	I	A
Intravenous beta-blockers to be considered at presentation only in patients with high blood pressure, tachycardia and no signs of heart failure	IIa	B
High dose statins to be initiated early after admission in all STEMI patients without contraindication regardless of initial cholesterol values	I	A
Verapamil may be considered for secondary prevention with absolute contraindication to beta-blockers and no heart failure	IIb	B
ACE-inhibitors to be started within first 24-hour of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct	I	A
An ARB, preferably valsartan, is an alternative to ACE-inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE-inhibitors	I	B
Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤ 40% and heart failure or diabetes, provided no renal failure or hyperkalemia	I	B
Oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all STEMI patients without contraindications	IIa	B
ACE-inhibitors should be considered in all patients in the absence of contraindications	IIa	A

Selection of Reperfusion Strategy

In Hospitals with PCI Capability

A total of 23 published randomized controlled trials have compared primary PCI to fibrinolytic therapy in patients with STEMI. A meta-analysis reported

Table 1.2 Primary PCI in STEMI

Subset	Class of recommendation	Level of evidence	Evidence base
• STEMI and ischemic symptoms of less than 12 hours' duration	I	A	Keeley et al Zjilstra et al GUSTO IIB
• STEMI and ischemic symptoms, >12 hours and contraindications to fibrinolytic therapy irrespective of time delay from FMC	I	B	Grzybowski et al MITRA subgroup
• Cardiogenic shock or acute severe HF irrespective of time delay from MI onset	I	B	SHOCK
• Evidence of ongoing ischemia 12 to 24 hours after symptom onset	IIa	B	Schomig et al Gierlocka et al
• PCI of a noninfarct artery at the time of primary PCI in patients without hemodynamic compromise	III	B	Hannan et al
• Manual aspiration thrombectomy is reasonable for patients undergoing primary PCI	IIa	B	TAPAS EXPIRA INFUSE-AMI
• Placement of a stent (bare-metal stent or drug-eluting stent) is useful in primary PCI for patients with STEMI	I	A	Nordann et al Zhu et al
• If performed by an experienced radial operator radial access should be preferred over femoral [ESC 2012]	IIa	B	
• Drug eluting stents should not be used in primary PCI for patients with STEMI who are unable to tolerate or comply with a prolonged course of dual antiplatelet (DAPT) because of increased risk of stent thrombosis with premature discontinuation of one or both agents (BMS should be preferred in this situation-IC)	III	B	Spertus et al Kaluza et al Grines et al Park D et al Jeremias et al

the short- and long-term outcomes of the 7,730 patients (3,872 randomized to primary PCI and 3,867 randomized to fibrinolytic therapy) enrolled in these trials. In this analysis, primary PCI was superior to fibrinolytic therapy in reducing overall short-term death (7% vs 9%, $P = 0.0002$), nonfatal reinfarction (3% vs 7%, $P < 0.0007$), stroke (1.0% vs 2.0%, $P = 0.0004$), and the combined end point of death, nonfatal reinfarction and stroke (8% vs 14%, $P < 0.0001$).

Advantages of primary PCI include achieving complete reperfusion in 90 to 95 percent of patients, having lower risk for reinfarction and stroke, and allowing definitive characterization of coronary anatomy and LV function.

On the basis of these data, patients with STEMI who present to hospitals with PCI capability should have primary PCI as the preferred and routine reperfusion strategy.

Table 1.3 Indications for coronary angiography ± PCI of infarct related artery in patients who were managed with fibrinolytic or who did not receive reperfusion therapy

Subset	Class of recommendation	Level of evidence	Evidence base
• Cardiogenic shock or acute severe HF that develops after initial presentation	I	B	Wu et al Hochman et al Steg et al
• Intermediate or high-risk findings on predischarge noninvasive ischemic testing	I	B	SWISS II DANAMI
• Spontaneous or easily provoked myocardial ischemia	I	C	---
• Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B	Gershlick et al Sutton et al Gibson et al
• Stable patients after successful fibrinolysis, before discharge and ideally between 3 and 24 hours	IIa [ESC 2012 Task Force recommendation: IA]	B	GRACIA SIAM-III WEST CAPITAL-AMI CARESS-in-AMI TRANSFER-AMI STREAM
• PCI for stable patients > 24 hours after successful fibrinolysis	IIb	B	Hochman et al DANAMI ASSENT-2 DECOPI D'Souza et al Gibson et al
• Delayed PCI of a totally occluded infarct artery > 24 hours after STEMI in stable patients	III, No benefit	B	Hochman et al Ioannidis et al

Summary of current recommendations based on ACCF/AHA 2013 Guidelines is as following; most of the recommendations match with ESC 2012 Guidelines except where indicated.

Fibrinolytic Therapy

More than two decades of clinical trial experience have elapsed involving more than 100,000 patients enrolled in clinical trials.

Initial trials of streptokinase (SK) performed in 1980s showed a pronounced mortality benefit, with an 18 percent mortality reduction in the GISSI-1 trial and a 25 percent reduction in the ISIS-2 trial. The benefit extended to 42 percent reduction when aspirin and SK were combined. The GUSTO-1 trial showed a slight mortality benefit (14%) in patients receiving tPA and IV heparin and compared with SK (with either IV or subcutaneous heparin). Risk of hemorrhagic stroke was statistically lower in patients receiving SK compared to those receiving tPA group (6.9% vs 7.8%, $P = 0.006$). Trials of rPA (GUSTO-3) and TNK (ASSENT-2) showed similar rates of mortality and ICH as tPA, with an overall rate of death or nonfatal stroke of approximately 7 percent. TNK was, however, associated with fewer noncerebral bleeding complications and lower rates of transfusion in ASSENT-2 trial.

Thus, newer bolus agents have not surpassed the mortality benefits seen with tPA. However, combined benefits of the ease of administration, diminished potential for dosing errors and lower rates of noncerebral bleeding have led to increasing use of these agents in most centers.

Status of Different Thrombolytic Agents

Streptokinase: Approved for general use

Alteplase: Established standard

Reteplase: Approved for general use

Tenecteplase (TNK-tPA): Approved for general use and likely to replace alteplase because:

i. Bolus injection simplifies administration even in prehospital setting and reduces potential for medication errors.
ii. Increased fibrin specificity provided by TNK-tPA does confer a significant decrease in major systemic bleeding.

A comparison of different thrombolytic agents along with their dosage has been shown in the Table 1.4:

ECG Features Justifying Fibrinolytic Therapy

- New ST-elevation at the J-point greater than 0.1 mV in two contiguous leads other than leads V2-V3, where the following cut points apply
  ≥ 0.2 mV in man ≥ 0.25 mV in men
  < 40 years or ≥ 0.15 mV in women

Table 1.4 Comparison of thrombolytic agents

Property	SK	tPA	r-PA	TNK-tPA
Fibrin specificity	–	++	+	+++
Dose (most frequently used/tested)	1,5 MU/60 minutes	100 mg/ 90 min	2 × 19 u bolus 30 min apart	0.5 mg/kg bolus
Antigenic	+	–	–	– –
Hypotension	+	–	–	– –
Patency at 90 minutes	+	+++	++++	+++
Hemorrhagic stroke	+	++	++	++
Mortality reduction	+	+++	+++	+++
Cost	+	+++	+++	+++
Concomitant heparin	+(LMWH)	+	+	+
Bleeding (noncerebral)	+++	++	++	+

SK: Streptokinase; t-PA: Recombinant tissue–type plasminogen-activator (alteplase); SAK: Recombinant staphylokinase; TNK-tPA: Tenecteplase; rPA: Reteplase

- New or presumable new LBBB (IA)
- 12 lead ECG findings consistent with true posterior MI (IIaC).

Contraindications to Fibrinolysis

Absolute Contraindications

- Any prior ICH
- Known malignant intracranial neoplasm
- Known intracranial cerebrovascular lesion (aneurysm or arteriovenous malformation)
- Ischemic stroke within 3 months
- Known or suspected closed head or facial trauma within 3 months
- Suspected aortic dissection, and
- Active bleeding or known bleeding diathesis.

Relative Contraindications

- Prior ischemic stroke beyond 12 months
- Major surgery within 3 weeks, recent (2–4 weeks) internal bleeding, prolonged or traumatic CPR or noncompressible vascular puncture
- Active peptic ulcer is only a relative contraindication to fibrinolysis unless there is active bleeding. Patients with positive test for occult blood only in stool may be considered for fibrinolytic therapy
- Severe uncontrolled hypertension (>180/110 mm Hg) is a relative contraindication. In view of the linear relationship between severity of

Table 1.5 Indications of fibrinolytic therapy

Subset	Class of recommendation	Level of evidence	Evidence base
• In absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC	I	A	PTT collaborative group AMIS Trial group EMERAS ' ISIS-2 LATE USIM collaborative group ISAM
• Evidence of ongoing ischemia 12 to 24 hours after symptom onset, and a large area of myocardium at risk or hemodynamic instability	II	C	---
• ST-depression except if true posterior (inferobasal) MI suspected or when ST-depression is associated with ST-elevation in lead aVR	III Harm	B	FTT collaborative group deWinter et al TIMI IIIA
• If possible, fibrinolysis should start in the prehospital setting*	IIa	A	
• A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over nonfibrin specific agents)*	I	B	

*ESC 2012 Guideline

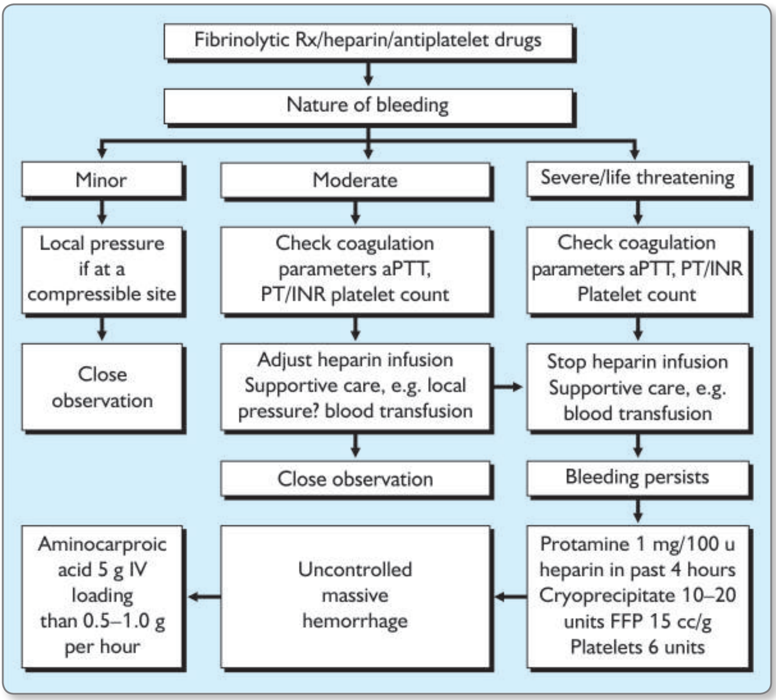
hypertension and ICH, STEMI patients presenting with hypertension should be administered beta-blockers, nitroglycerin and analgesics promptly to lower blood pressure and reduce risk of ICH following fibrinolysis

- Patients on warfarin therapy have higher rates of hemorrhage. Higher the INR, higher is the risk of hemorrhage
- Pregnancy is a relative contraindication to fibrinolysis; however, hemorrhagic diabetic retinopathy is not a contraindication for fibrinolytic therapy.

Management of patients with hemorrhagic complications following fibrinolytic therapy is outlined in Flow chart 1.3.

Occurrence of a change in neurological status after reperfusion therapy, particularly within the first 24 hours after initiating of treatment, is considered to be due to ICH until proven otherwise.

Flow chart 1.3 Management of hemorrhagic complications following fibrinolytic therapy



Assessment of Reperfusion (Noninvasive)

Relief of symptoms and maintenance or restoration of hemodynamic and/or electricity stability are most obvious features of successful reperfusion following fibrinolytic therapy. However, there are objective parameters to assess reperfusion following fibrinolytic therapy. These include:

- ST-segment resolution or persistent elevation on the 12-lead ECG
- Biomarkers
- Noninvasive imaging.

ST-Segment Resolution

A close association with clinical outcomes has been found with ST-segment resolution which is a simple surrogate for both epicardial and myocardial reperfusion.

ST-segment resolution is calculated by taking the sum of ST-elevation (typically measured 20 m/second after the J point) in leads V1–V6, I, and aVL for anterior MI, and adding to the sum of ST-depressions in leads II, III, and aVF; or, for interior MI, taking the sum of ST-elevations in leads II, III, aVF (and I, aVL, V5, V6, if present) and adding the sum of ST-depressions in leads V1–V4. Timing of ECG following reperfusion does not appear to influence the close correlation between ST-resolution and outcomes significantly. However, since failed reperfusion therapy identifies patients at highest risk, early assessment of ST-resolution within 60 to 90 minutes after fibrinolysis is recommended. Percentage of ST-resolution can then be calculated from baseline to some time period after reperfusion which can extend to 180 minutes in some cases after fibrinolysis or immediately after PCI.

Table 1.6 Relation of short- and medium-term mortality to extent of ST-segment resolution following thrombolysis in acute myocardial infarction

Category of resolution	% Resolution	30-d Mortality	180-d Mortality
Complete	≥ 70%	2.9%	4.8%
Partial	30–70	5.8%	8.1%
None	≤ 30%	10.2%	11.1%

Biomarkers

With successful reperfusion, reflow of blood allows faster clearance of necrotic proteins and hence CK-MB and troponin levels peak earlier and decline faster. In contrast, release of these markers of necrosis is slower in absence of successful reperfusion. In the 1990s, attempts have been made to correlate peak CK-MB release with infarct size; however, in contemporary practice, measuring levels of cardiac troponin approximately 3 days after the onset of symptoms may offer the best estimation of total infarct size.

Since troponin remains elevated longer (even weeks after a large MI) than CK-MB and CK-MB returns to normal range within 48–72 hours; it is, therefore, the preferred marker for assessing a recurrent infarction.

Noninvasive Imaging

There is little role for noninvasive (echocardiography, nuclear imaging, CT, and MRI) in the acute diagnosis and treatment of STEMI. Transthoracic echocardiography (TTE) may have a role to play in evaluation of wall motion abnormalities if history and baseline ECG are inconclusive and in the initial assessment of infarct size and ventricular function. Follow-up echocardiography is reasonable only about two or more months later because myocardial stunning may yield misleading results with echocardiography if done earlier. Both nuclear imaging and cardiac magnetic resonance (CMR) imaging are quite precise at quantifying the size of the infarct but have little role in the acute management of STEMI.

Prehospital Thrombolysis

Prehospital fibrinolysis is reasonable in settings in which physicians or fully trained paramedics are present in the ambulance or prehospital transport times are more than 60 minutes.

This has been successfully practiced in European countries. A posthoc analysis of the primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: A randomized study (CAPTIM trial) showed that in patients presenting early (< 2 hours after symptom onset), there was a strong trend for lower mortality with prehospital fibrinolytic therapy versus primary PCI (2.2% vs 5.7%, $P = 0.053$), whereas in patients randomized later (> 2 hours) there was no benefit to early fibrinolytic therapy, suggesting that time delays are very important early after onset of symptoms but are less important later.

Analysis of studies in which > 6000 patients were randomized to prehospital or in-hospital fibrinolysis has shown a significant reduction (17%) in early mortality with prehospital treatment. A much longer mortality reduction was found in patients treated within first 2 hours than in those treated later in a meta-analysis of 22 trials. More recent posthoc analyzes of several randomized trials and data from registries have further confirmed the clinical usefulness of prehospital fibrinolysis. Thus, all these studies have reported outcome data similar to that of primary PCI, provided early angiography and PCI were performed in these patients who needed intervention. A prospective trial, properly sized and randomized, is needed to truly put to the test hypothesis that prehospital fibrinolysis is associated with a similar or better clinical outcome than primary PCI.

When opting for fibrinolytic therapy as the reperfusion strategy in a given patient, prehospital fibrinolysis should be the treatment of choice. This is especially relevant in developing countries like India with few tertiary care centers, predominantly rural population and where people either have to travel long distances to avail of medical facility or have to overcome urban traffic congestion. However, administration of prehospital thrombolysis needs tremendous infrastructure and a co-ordinated program by government or private sector or both.

Requisites for Prehospital Thrombolysis

Requisites for prehospital thrombolysis are as follows:

- Critical care ambulances staffed with physicians ideally or paramedics trained to send prehospital ECG to corresponding hospital's CCUs using telemedicine (appropriate ECG machines are connected to laptop computer with internet connection and the paramedic discusses inclusion and exclusion criteria over phone with physician-on-call).
- Improving public awareness about value of time to treatment after onset of chest pain.
- Emergency dial numbers for hospitals pertaining to a locality.

Rescue PCI

Emergent PCI performed in a patient with evidence of failed reperfusion with fibrinolytic therapy is called rescue PCI. Success of rescue PCI in patients with moderate to large infarctions has been demonstrated in terms of improved LV function and overall clinical outcomes by review of early studies. More data are now available from recent studies like MERLIN and REACT.

In MERLIN trial, despite a significant decrease in rates of subsequent revascularization, rescue PCI did not improve 30-day survival (9.8% for rescue PCI and 11% for conservative therapy, P = 0.7). However, in REACT trial, event-free survival was significantly higher in patients treated with rescue PCI compared to conservative therapy or repeat fibrinolysis (84.6% vs 70.1% vs 68.7%, respectively, overall P value = 0.004).

A recent meta-analysis of eight trials enrolling 1,177 patients demonstrated a significant reduction in risk for heart failure and reinfarction and a trend toward reduction in all-cause mortality when compared with conservative therapy. However, rescue PCI was shown to result in increased risk of stroke and minor bleeding.

Despite impressive results with successfully conducted rescue PCI, prognosis remains poor for those in whom rescue PCI is unsuccessful.

As per ACC/AHA Guidelines (2004)

Class I indications for rescue PCI

- Cardiogenic shock in patients less than 75 years old who are suitable candidates for revascularization (Level of evidence: B)
- Severe congestive heart failure and/or pulmonary edema (Killip Class III) (Level of evidence: B).
- Hemodynamically compromising ventricular arrhythmias (Level of evidence: C).

Class IIa indications for rescue PCI

- Cardiogenic shock in patients 75 years of age or older
- Patients with hemodynamic or electrical instability or persistent ischemic symptoms
- Patients with failed reperfusion and a moderate or large myocardium at risk (anterior).

Facilitated PCI

As the term indicates, 'facilitated' PCI is based on the hypothesis that immediate pharmacologic therapy followed by prompt mechanical reperfusion will result in faster and better restoration of antegrade blood flow in infarct-related artery when compared to primary PCI alone. The pharmacologic therapy may comprise of full-dose lytic therapy or half-dose lytic therapy with GP IIB/IIIa inhibitor or GP IIb/IIIa inhibitor alone and no significant clinical benefit has been achieved with any of these agents.

Despite demonstration of higher TIMI grade 3 flow rates with facilitated PCI compared to primary PCI at the time of initial coronary angiography, a meta-analysis of trials failed to show an improvement in final TIMI 3 flow rates with facilitated PCI. Moreover, facilitated PCI was shown to be associated with significantly increased rates of nonfatal reinfarction, urgent target vessel revascularization, stroke and death compared to PCI. Regimens employing fibrinolytic therapy were in particular associated with higher rates of adverse events. ASSENT-4 PCI trial randomized 1667 patients to PCI with or without full dose tenecteplase (TNK) with a primary end point of 90 days death, cardiogenic shock or congestive heart failure. The TNK plus PCI arm had significantly higher rates of repeat myocardial infarction, repeat target vessel revascularization, stroke and composite of primary end points.

The most recent of facilitated PCI trials has been FINESSE trial. It randomized patients presenting within 6 hours of symptom onset with STEMI into three arms:

i. Primary PCI with use of abciximab as adjunctive in catheterization laboratory
ii. Upfront abciximab administered prior to catheterization laboratory arrival
iii. Combination of half-dose reteplase and abciximab prior to catheterization laboratory arrival.

No difference in the primary outcome (all cause mortality, rehospitalization for congestive heart failure, resuscitated VF occurring > 48 hours after randomization and cardiogenic shock) was found between the three strategies at 90 days. Rather, bleeding was significantly increased in patients who were randomized to facilitated PCI, especially in those receiving half-dose reteplase and abciximab. FINESSE trial thus seems to have finally drawn the curtains down for the concept of facilitated PCI.

Early PCI

Initial trials of PCI within 24 hours of successful fibrinolysis reported increased rates of bleeding, recurrent ischemia, emergency CABG and death. With the advent of stents and GP IIb/IIIa inhibitors, the scenario has changed considerably and recent trials with early PCI after fibrinolytic therapy report more favorable results.

The important trials in this regard are CARESS-in-AMI, CAPITAL-AMI, GRACIA, SIAM-III, WEST, and the more recent TRANSFER-AMI and STREAM. Both CAPITAL-AMI and CARESS-in-AMI included patients < 75 years of age with high-risk features and they underwent PCI within 3 hours of fibrinolytic therapy. Whereas CAPITAL-AMI compared full dose tenecteplase and immediate PCI versus tenecteplase alone and standard care, CARESS-in-AMI compared a strategy of half dose reteplase and abciximab with or without immediate PCI. CAPITAL-AMI reported a significant decrease in the composite end point of death, reinfarction recurrent ischemia and stroke at 6 months and CARESS-in-AMI reported a significant decrease in primary endpoints of death, reinfarction and recurrent ischemia at 30 days. Notably, there was no increase in bleeding rates in either of the trials. Twelve-month follow-up CARESS-in-AMI showed persistent significant benefit in the PCI arm for refractory ischemia and recurrent MI but no difference in terms of death and admission for heart failure.

In comparison to early routine invasive approach in aforesaid two trials, GRACIA-1 and WEST trials performed PCI following successful fibrinolysis relatively late (12–24 hours): GRACIA-1 reported a significant decrease in primary endpoint of death, reinfarction or revascularization at 1 year compared to standard care (9% vs 21%, P = 0.0008). In contrast, the smaller WEST trial showed just nonsignificant trends towards differences in primary endpoints of death, reinfarction, refractory ischemia, cardiogenic shock and major ventricular arrhythmias at 30 days between the PCI and the conservative arms.

Other studies (SIAM III, GRACIA-2) have assessed outcomes of PCI performed in the intermediate period (3–12 hours) after successful fibrinolysis. In these trials, routine PCI was performed after full dose reteplase or tenecteplase and benefit was demonstrated both in terms of epicardial and myocardial reperfusion and composite clinical endpoints at 6 months.

More recent in these series of trials has been TRANSFER-AMI. More than 1000 high-risk patients with STEMI in this study were randomly assigned to interhospital transfer for intended routine early PCI (within 6 hours after fibrinolysis) or an ischemia-guided strategy, in which patients were transferred for angiography only in the case of failed fibrinolysis or recurrent ischemia. The actual median interval from lysis to balloon inflation was 3.9 hours. As in the early trials, rate of recurrent ischemia was significantly reduced with early routine PCI as compared to a selective invasive approach, without any significant increase in rates of bleeding. The latest of the reports has been AMICO Registry. In this Registry, FAST-PCI strategy (reduced-dose fibrinolytic therapy followed by urgent PCI) was shown to reduce the mortality and combined endpoint of death, reinfarction and stroke among STEMI patients, without increasing the risk of stroke or bleeding, compared to PCI. Fibrinolysis before hospital admission also increased the initial infarct-related artery (IRA) patency and decreased the likelihood of shock at presentation.

The latest in this list of trials is STREAM which included 1832 patients with STEMI who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour, patients were randomly assigned to undergo either primary PCI or fibrinolytic therapy with bolus tenecteplase (amended to half-dose in patients > 75 years of age), clopidogrel and enoxaparin before transport to a PCI-capable hospital. Emergency coronary angiography was performed if fibrinolysis failed; otherwise angiography was performed 6 to 24 hours after randomization. Primary endpoint was a composite of death, shock, congestive heart failure or re-infarction up to 30 days. There was no statistically significant difference (p=0.21) between the fibrinolysis and primary PCI group. Thus, this study showed a strategic alignment of prehospital or early fibrinolysis and contemporary antithrombotic cotherapy coupled with timely coronary angiography resulting in effective reperfusion in a specific onset of patients with STEMI (as described above). However, early fibrinolysis was associated with a slightly increased risk of intracranial bleeding.

The average time of interval from fibrinolysis to PCI in the trials mentioned above has been 2 to 17 hours implying that transfer for PCI need not be undertaken on an emergency basis. Such a strategy (often referred to as ***Pharmaco-invasive strategy***) emphasizes on very early fibrinolysis (< 2 hours) for achieving greater rates of successful reperfusion and at the same time allows a transition of care that causes less stress both to the patient and to ambulance crews.

The ESC 2012 has accorded class I (Level of evidence : A) status to PCI after successful lysis within 24 hours of fibrinolysis therapy independent from angina and/or ischemia. In the latest ACCF/AHA 2013 STEMI guidelines, coronary angiography +PCI in stable patients after successful fibrinolysis before discharge and ideally between 3 hr and 24 hr has been accorded class IIa of recommendation (Level of evidence B). Considerations should be given in both groups to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory.

Delayed PCI

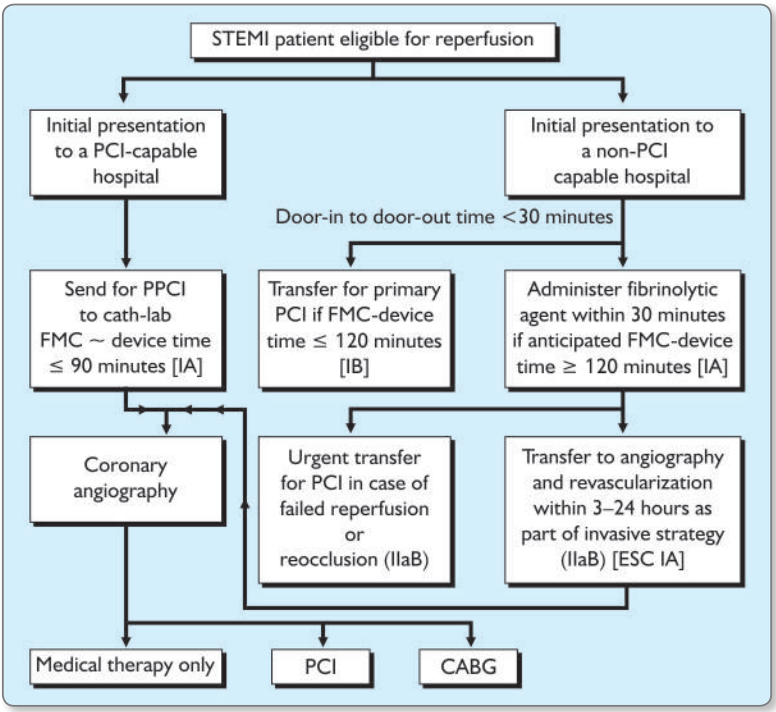
This hypothesis postulates that benefit in terms of improved ventricular function, increased electrical stability and provision of collaterals can be gained by late (12 hours to 3 months) patency of occluded infarct arteries. However, OAT (occluded artery trial) failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI. Despite achieving a high rate of initial procedural success with good 1-year patency (amongst a subset), the expected decline in death, MI and heart failure did not occur. In fact, there was a statistically greater incidence of fatal and nonfatal MI in the intervention vs medical group as ascertained by investigators. Criticism of this trial includes exclusion of high risk patients with New York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three vessel disease) or severe individual ischemia on stress testing. Regardless of these concerns, this study has led to a new class III recommendation against PCI of a totally occluded artery > 24 hours after STEMI in asymptomatic patients without the previously noted high-risk criteria.

However, OAT trial has not closed the chapter of open artery hypothesis. Two years after publication of the OAT trial, a meta-analysis of 10 studies enrolling 3,560 patients that were randomized to either late PCI of the IRA (range 1–26 days after the MI) or optimal medical treatment was published. The primary endpoint of this meta-analysis was all cause mortality. In addition, left cardiac remodelling was also assesed in those studies with echocardiographic analyzes. Late PCI was shown to improve survival as compared with medical treatment [Or 0.49 (95% CI 0.26–0.94), P = 0.030] during a follow-up period of 2.8 years (42 days to 10 years). This beneficial effect in all-cause mortality reduction was associated with favorable effects on cardiac function and remodeling. Late PCI demonstrated significantly greater improvement in LV ejection fraction and LV end-diastolic and end-systolic volume indices. This meta-analysis by virtue of an adequate final sample size and long clinical follow-up fully addressed the open artery hypothesis. This hypothesis postulates that survival after MI depends on the effect of mechanical recanalization of the IRA which serves to improve LV remodeling and healing and enhances electrical stability.

Most of the patients included in the analysis (84%) showed total IRA occlusion. Degree of angiographic success was variable (range 72–100%) as were both the rates of stent implantation (range 0–100%) and the glycoprotein IIb/IIIa inhibitor usage. Thus, the setting in this meta-analysis was poorly representative of the current PCI technology and outcomes, and yet late PCI was still able to significantly reduce the all-cause mortality rate. Patients with subtotal occlusion derived greater benefit than patients with total occlusion. Patients symptomatic for angina or heart failure and those with residual ischemia or documented viability are more likely to benefit from late PCI at a long-term follow-up. Patients with uncomplicated AMI, especially with reduced life expectancy, however, may not benefit from routine PCI. Benefit in terms of remodeling was seen to be more obvious with a median follow-up of 4 years and this lends support to the hypothesis that restoration of antegrade blood flow to the peri-infarct area interrupts progressive apoptosis of the hibernating myocardium and prevents development of cardiomyopathy.

At the extreme end of the spectrum are patients with a chronic total occlusion (CTO), defined as a complete occlusion at least 3 months old. Benefit from recanalization in this setting is independent of time and is based on relieving symptomatic ischemia and angina, enhancing LV function, reducing predisposition to ventricular arrhythmias and improving tolerance of contralateral coronary occlusion. From a clinical standpoint, CTO recanalization is usually rewarding in symptomatic patients, or in patients with evidence of silent ischemia in a large territory at risk and/or with presence of viable myocardium.

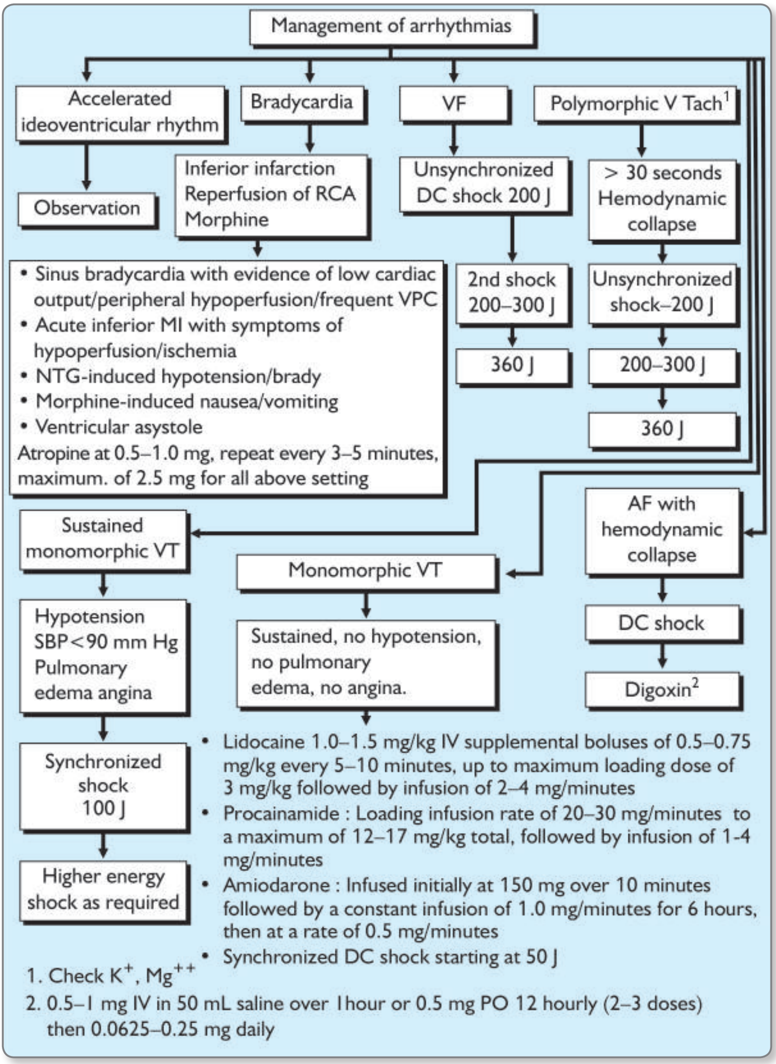
Flow chart 1.4 Approach to reperfusion in STEMI



Indications of CABG in Patients

- Urgent CABG is indicated in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF or other high-risk features : Class of recommendation I (Level of evidence : B).
- CABG is recommended in patients with STEMI at time of operative repair of mechanical defects : Class of recommendation I (Level of evidence : B).
- Aspirin should not be with-held before urgent CABG.
- Clopidogrel or ticatrelor should be discontinued at least 24 hours before urgent on-pump CABG; if possible.
- Eptifibatide and tirofiban should be discontinued at least 2 to 4 hours before urgent CABG; abciximab should be discontinued at least 12 hours before urgent CABG.

Flow chart 1.5 Management of arrhythmias following STEMI



Flow chart 1.6 Indications for pacing following STEMI

Indications for pacing

Temporary transcutaneous pacing

Class I

1. Sinus bradycardia with hypotension unresponsive to atropine
2. Mobitz type II 2° A-V block
3. 3rd degree heart block
4. B/LBBB
5. Newly acquired or age indeterminate fascicular block
6. RBBB or LBBB +1° A-V block

Class IIa

1. Stable bradycardia (SBP > 90 mm Hg. No hemodynamic compromise)
2. Newly acquired or age-indeterminant RBBB

Class IIb

1. Newly acquired or age-indeterminant 1° AV block

Class III

1. Uncomplicated MI without evidence of conduction disease

Temporary transvenous pacing

Class I

1. Asytole
2. Symptomatic bradycardia (sinus bradycardia + hypotension or type I 2° A-V block with hypotension with atropine)
3. Alternating BBB
4. New or age indeterminate bifaascicular block with 1° A-V block
5. Mobitz type II 2° A-V block

Class IIa

1. RBBB and LAHB or LPHB (new or indeterminate)
2. RBBB with 1° AV block
3. LBBB, new or indeterminate
4. Incessant VT, for atrial or ventricular overdrive pacing
5. Recurrent sinus pauses (> 3 seconds) no responsive to atropine

Class IIb

1. Bifascicular block of indeterminate age
2. New or age-indeterminate isolated RBBB

Class III

1. Heart block, type I 2° A-V block, accelerated ideoventricular rhythm, prior BBB/fascicular block

Permanent pacing

Class I

1. Persistent 2° A-V block in the His-Purkinje system with B/L BBB or CHB after MI
2. Persistent symptomatic 2nd, 3rd degree A-V block
3. Advanced (2-3°) A-V block + associated BBB (> 16 days) symptomatic A-V block at any lead

Class IIa

1. None

Class IIb

1. Persistent advanced (second or third degree) block at the level of the AV node

Class III

1. Transient AV conduction disturbances in the absence of in intraventricular conduction defects
2. Transient A-V block in the presence of isolated left anterior fascicular block acquired - left anterior fascicular Block in the absence of AB block Persistent 1° A-U block in the presence of BBB old/persistent

Discharge from CCU

↓

AMI

High risk patients

- Arrhythmia or pump failure (sinus tachy, AF, atrial flutter)
- Arrhythmia or electrical instability (VT/VF)
- Acute intraventricular conduction disturbances
- Circulartory failure (CHF, pulmonary edema, hypotension)
- Large anterior MI

↓

Prolonged monitoring in intermediate care unit

Uncomplicated

- Bed rest for no longer than 24 hours
- Bed side commode from admission
- Transfer to medical unit on 3rd day/nonacute care unit
- Progressive ambulation
- Risk factor modification
- Risk stratification

↓

Discharge by 7 days

Other Complications of Acute Myocardial Infarction

i. **Ventricular septal rupture (VSR):**
Incidence: 1–2 percent in prethrombolytic era, now dramatically reduced.
Time of occurrence: Usually 2–5 days after MI
Therapy: Surgery, percutaneous closure

ii. **Mitral regurgitation (MR):**
Incidence: Mild to moderate MR, 13–45 percent.
Severe MR leading to cardiogenic shock: 1 percent
Time of occurrence: 2–7 days after MI
Therapy: Surgical repair or less commonly replacement of mitral valve PCI has no role.

iii. **Cardiac rupture:**
Incidence: 3 percent of post-MI patients
Time of occurrence: 50 percent occur in first 5 days; 90 percent occur within 2 weeks.
Therapy: Immediate pericardiocentesis in case of subacute rupture; Acute rupture is often immediately fatal.

iv. **Pseudoaneurysm (Contained rupture):** Communicate with body of left ventricle through a narrow neck. May be clinically silent; diagnosed by Echo/CT/MRI.
Therapy: Surgical resection because spontaneous rupture may occur.

v. **Ventricular aneurysm:**
   a. *Acute aneurysm:* Occur with transmural anteroapical infarcts and expand during systole. May result in severe heart failure or even cardiogenic shock.
   b. *Chronic aneurysm:* Are those which persist more than 6 weeks. They are less compliant and rarely expand during systole.

Therapy: Anticoagulation if a mural thrombus is demonstrated surgical therapy (Aneurysmorrhaphy) in patients with refractory heart failure and ventricular arrhythmias.

PCI after 12 hours of MI but before 24 hours of MI in patients not reperfused earlier may be beneficial in those with acute aneurysm.

vi. **Dynamic LVOT obstruction:** Uncommon complication after acute anterior MI resulting from hyperkinesis of basal and mid segments of LV. Resultant venturi effect cause LVOT obstruction and MR. Free wall rupture can occur.
Therapy: Slow addition of beta-blockers, small boluses of IV normal saline may reduce LVOT gradient.

vii. **Pericarditis:**

a. *Early pericarditis:*
Incidence: 10 percent (approx)
Time of occurrence: 24 to 96 hours after MI.
Therapy: Aspirin 650 mg every 4 to 6 hours. Avoid NSAIDs and corticosteroids colchicine for recurrent pericarditis.

b. *Late pericarditis or Dressler's syndrome:*
Incidence: 1–3 percent
Time of occurrence: 1–8 weeks.
Therapy: Aspirin If > 4 weeks have elapsed after MI, NSAIDs and even steroids may be started for severe symptoms.

Secondary Prevention after STEMI

- **Smoking:** Complete cessation and also avoid second hand smoke.
- **Physical activity:** Minimum goal–30 minutes 3 to 4 days per week; optimal daily.
- **Weight management:** Goal—BMI 18.5 to 24.9 kg/m^2
- **Blood pressure:** Goal—less than 140/90 mm Hg or less than 130/80 mm Hg if chronic kidney disease or diabetes.
- **Diabetes management:** Goal—HbA1C < 7 percent
- **Lipid management:** High dose statins for all unless contraindicated; primary goal LDL < 70 mg/dL
  Non-HDL-C < 100 mg/dL.
- **Antiplatelet drugs:** Aspirin 75—162 mg/day if not contraindicated to continue indefinitely clopidogrel 75 mg/day for one year.
  Prasugrel (10 mg/day) or ticagrelor (90 mg twice daily) following PCI up to one year.
- **ACE-inhibitors** in patients post-STEMI with history of heart failure, LV systolic dysfunction, diabetes or anterior infarction (Class IA); for all patients post-STEMI unless contraindicated (Class IIaA); ARBs preferably valsartan to be prescribed in case of ACEI intolerance.
- **Beta-blockers** for post-STEMI patients with history of heart failure or LV systolic dysfunction (IA) beta-blockers for all STEMI patients in absence of contraindications (IIaB).
- **Aldosterone antagonists**, e.g. eplerenone, for post-STEMI patients with LVEF ≤ 40 percent and heart failure or diabetes, provided no renal failure or hyperkalemia.

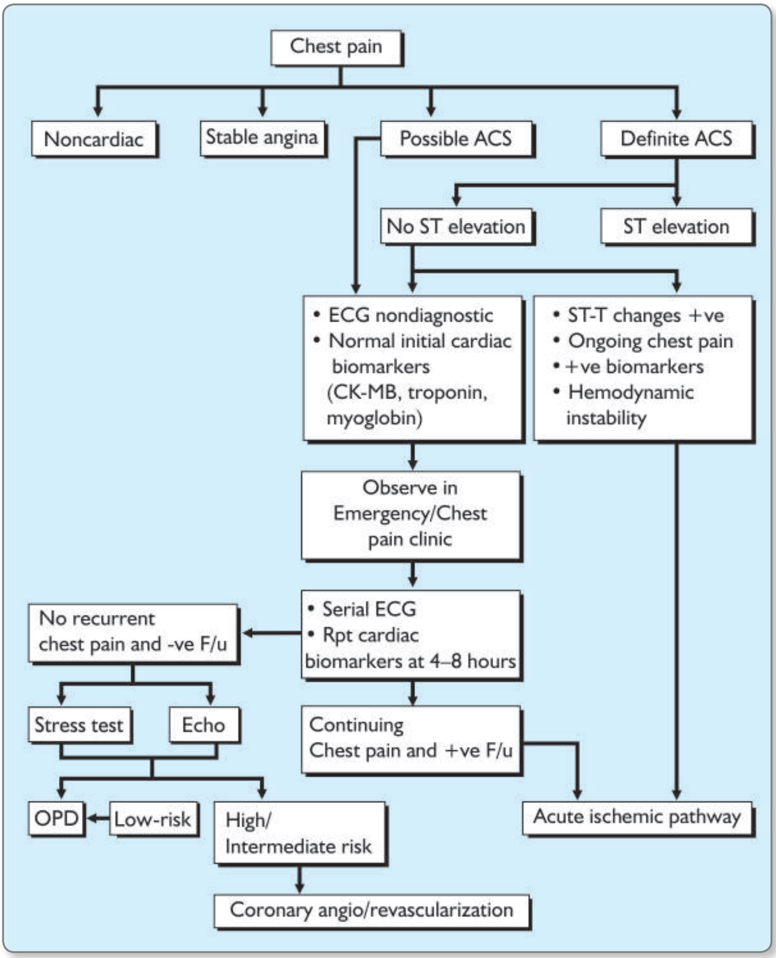
Suggested Reading

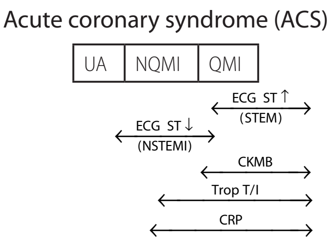
1. Kumar S, Cannon CP. Acute coronary syndrome. M Cmillan's Reference Series. ST-elevation myocardial infarction; 2012:33-70.
2. O'Gara P, Kushner FG, Aschieim DD, et al. ACCF/AHA Guidelines for the management of ST-elevation myocardial infarction: Executive Summary. Circulation 2013;127:00-00.
3. Steg PG, James SK, Atar D, et al. for the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. Eur. Heart J. 2012;33:2569-2619.
4. Thygesan K, Alpert JS, Jaffee AS. Simoons ML, et al. the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Third Universal Definition of Myocardial Infarction. European Heart J. 10.1093/eurheartj/ehs/84.

chapter
2

Management of Unstable Angina and Non-ST Elevation Myocardial Infarction

Bipul Barman, Soumitra Kumar





Cardiac Biomarkers in Acute Coronary Syndrome

Risk Stratification in UA/NSTEMI

Cardiac biomarkers can be currently described under the three following heads:

- Established biomarkers
- Emerging biomarkers
- Developing biomarkers.

Established Biomarkers

Creatinine kinase-MB

Creatinine kinase-MB (CK-MB) is a cystolic carrier protein for high energy phosphates and for a long time, it has been the gold standard for AMI diagnosis. Its elevation occurs 4 to 8 hours after MI and peaking occurs at 18 to 24 hours. Hence, sensitivity of CK-MB for AMI is only 50 percent when measured early at the time of presentation. Its sensitivity and specificity can be increased by serial testing. Serial testing CK-MB also enables the clinician to detect early reinfarction. Cardiac muscle damage is likely if the CK-MB is > 3 to 5 percent of total CK activity. However, since CK-MB does exist in skeletal as well as cardiac muscle, this marker is not strictly cardiac specific. False positive results can be obtained in skeletal muscle injury, postsurgery, renal failure and peripartum period.

Electrophoretic methods were used to detect isoenzymes originally, advent of antibody-associated techniques does now allow determination of cardiac protein concentration or mass rather than enzymatic activities. Peak level of markers of necrosis and area under time-release curve of CK-MB from repetitive serial sampling has been used to estimate infarct size. After the introduction of cardiac troponin assays in clinical practice, CK-MB has had a progressive diminution in its role in diagnosis and prognostication of ACS.

Myoglobin

By virtue of its some molecular mass, myoglobin leaks from necrotic myocardium far more rapidly than AST, CK or LDH. Early rise and high sensitivity are two properties that have led to the adoption of myoglobin as part of multimarker strategies. There is also a greater availability of assays for myoglobin. However, in view of its very poor specificity, myoglobin appears to be acceptable only if the alternative is to admit most or all patients for delayed troponin testing instead. Rapid-release kinetics also make myoglobin useful for noninvasive monitoring of reperfusion in patients with established MI. As it appears now, myoglobin is likely to be eventually superseded by ultrasensitive troponins or a new marker for cardiac ischemia.

Troponin

Troponin is at present the preferred biomarker for diagnosis of AMI. Since it has a higher sensitivity for detecting myocardial injury than CK-MB and it also provides useful information about prognosis. The degree of elevation of cardiac troponin has been shown to correspond with a gradient or mortality risk. According to the universal definition for AMI laid down by ESC-ACC-AHA-WHF in 2012, increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population (URL = upper reference limit). This discriminatory percentile is designated as decision level for diagnosis of MI and one elevated value above decision level is required. However, detection of a rise and/or fall of the measurement is essential to the diagnosis of AMI especially in patients with background elevation of troponin levels (e.g. patients with chronic renal failure). Only those troponin assays are acceptable which have independent validation of optimal precision [coefficient of variation (CV) ≤10%]. Better precision (CV ≤ 10%) allows for more sensitive assays.

Blood samples for measurement of troponin should be drawn on first assessment (often some hours after onset of symptoms) and 6 to 9 hours later. An occasional patient may require an additional sample between 12 and 24 hours if earlier measurements are not found to be elevated and index of suspicion for MI remains high. Troponin values generally remain elevated for 7 to 14 days following onset of infarction. With rising blood concentration of cardiac troponin T (cTnT) and cardiac troponin I (cTn1), risk of death and cardiac events rise progressively.

Although troponin T (single assay type only) and troponin I assays generally provide equivalent clinical information, standardization is a problem with troponin I since large number of commercially available assays are available. Each assay has its specific analytical characteristics and it is important that clinicians should be coversant with the specifications of the particular assay for correct interpretation. Most of the current assays use a cut-off in clinical practice in the range of 0.03 to 0.08.

Sensitive cardiac troponin assays

Very recently, high sensitive or ultrasensitive cardiac troponin assays have become available amidst the controversy prevailing over very low detectable levels of troponin. Fully automated assays have become available which have higher sensitivity than the previous assays and also have improved precision at the lower limit of detection that is below 99th percentile in a normal reference population. These assays have clinical cut-offs in a range of 0.01-0,02 or even below. Such extrasensitive assays may, however, pose new problems. Firstly, there are good number of medical conditions that are associated with raised troponins even at current cut-off levels. Secondly, lower range of detection may lead to further unnecessary negative investigations such as coronary angiogram.

These issues were addressed by Keller et al and Reichlin et al both reporting large multicenter evaluation of diagnostic performance of several sensitive assays for troponin. Interestingly, their principal findings have been highly consistent in the two studies, overall accuracy of troponin for the diagnosis of myocardial infarction has improved with the sensitive assays (94-96%) as compared with older assays (85 to 90%). The improved accuracy was most pronounced in the early period after onset of chest symptoms. This is evident in the study by Reichlin et al. which reported that the diagnostic accuracy of the sensitive assays within 3 hours after onset of chest pain was 92 to 94 percent as compared with 76 percent by standard assay.

Elevations of troponin in the absence of overt ischemic heart disease

Troponin elevations results from myocardial necrosis and it is not synonymous with ischemia. Clinical situations in which cardiac troponins can be raised in the absence of overt ischemic heart disease are large in number. They include:

- Congestive heart failure—acute and chronic
- Cardia contusion or trauma including surgery, ablation, pacing, and more
- Pulmonary embolism, severe pulmonary hypertension
- Aortic dissection
- Renal failure
- Apical ballooning syndrome or Takotsubo cardiomyopathy
- Hypertrophic cardiomyopathy
- Tachy- or bradyarrhythmias or heart block
- Rhabdomyolysis with cardiac injury
- Stroke and subarachnoid hemorrhage
- Infiltrative disease, e.g. amyoloidosis, hemochromatosis, sarcoidosis or scleroderma
- Myopericarditis or myocardial extension of endocarditis
- Drug toxicity or toxins
- Burns, especially with affection of >30 percent of body surface area
- Criticly ill patients especially with respiratory failure or sepsis
- Extreme exertion.

Emerging Biomarkers

Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide

Like atrial natriuretic peptide, brain natriuretic peptide (BNP) is secreted from the heart in response to stimulation of stretch receptors within heart wall following cardiac volume overload states. Hence, BNP and N-terminal pro-brain natriuretic peptide (NT-ProBNP) have become well-established biomarkers for left ventricular dysfunction.

However, they are also now being investigated for acute myocardial ischemia and infarction and they have emerged as prognostic indicators of long-term mortality early after an acute coronary event. This association was observed across the spectrum of ACS, including patients with STEMI, NSTEMI and UA, those with and without elevated cardiac troponin and those with and without clinical evidence of heart failure. The therapeutic benefits that can be derived from BNP and NT-ProBNP assays in ACS are not fully clear at this moment. However, in a sub-study of FRISC II trial, a trend toward better outcomes was observed following an early invasive strategy in patients with NT-ProBNP in the highest tertile.

C-reactive protein

C-reactive protein (CRP) is a biomarker widely in use as a marker of general inflammatory process. It is an acute phase reactant, synthesized in liver after stimulation by cytokines mainly IL-6. Recent studies have compared CRP with established markers of ACS and have shown that it can provide supportive diagnostic and prognostic information in this setting. The cut-point for hs-CRP in ACS setting is much higher than in stable CAD. Measurement of hs-CRP in patients with ACS has been recommended as reasonable (class IIa) for risk stratification when additional prognostic information is desired by the clinician.

Multimarker approach

In a recent analysis made by Sabatine et al in 450 patients of OPUS-TIMI-16 and in 1635 patients of TACTICS-TIMI-18, an approach with multiple markers in ACS without ST-elevation were investigated and BNP. CRP and cTn were all found to be independent predictors of adverse outcome. The incidence of adverse events correlated not only with positivity of each marker but also with number of positive markers.

Developing Biomarkers

Presently available biomarkers have facilitated diagnosis and prognostication of ACS to a great extent but the areas where they have been found to be deficient are:

- Low sensitivity in the first 4 to 6 hours after onset of chest pain (potentially being addressed by ultrasensitive troponins now).
- Poor markers of ischemia in absence of myocardial necrosis.
- Affected by inflammation or injury to other body systems.

A number of novel biomarkers are in developmental stage in recent years and some have shown promise in terms of earlier diagnosis and risk-stratification over and above existing biomarkers. None are yet ready for regular use. A brief account of most promising of these biomarkers is presented below:

Myeloperoxidase

Myeloperoxidease (MPO) is a degranulation product which comes from white cells. MPO may be involved in the development of lipid-laden soft plaque, protease cascade activation (which affects stability and thrombogenicity of the plaque), cytotoxic and prothrombogenic oxidized lipid production, and consumption of nitric oxide consumption (which leads to vasoconstriction). Thus, MPO is an indicator of inflammation as well as plaque instability, but not ischemia.

Recently, a commercial assay has become available. Despite the promise mentioned above, more studies are needed to establish the efficacy of myeloperoxidase in detecting mild ACS and adverse prognosis.

Soluble CD40 ligand

Soluble CD40 ligand (sCD40L) is a signalling protein that reflects both inflammatory and platelet interactions with the plaque. Current studies are encouraging, including one when combined with placental growth factor (PIGF), but more studies need to be performed before strong conclusion can be drawn.

Matrix metalloproteinase-9

Metaloproteinases are a class of 24 endopeptidases that are physiologic regulators of extracellular matrix. Matrix metalloproteinase-9 (MMP-9) is localized in the plaque shoulder, the thinner area prone to rupture. Additional investigations will be necessary for better acceptance of MMP-9 commercialization and clinical application.

Fatty acid binding proteins

Fatty acid binding proteins (FABPs) are the major vehicle for cytosolic transport of long chain unesterified fatty acids. Heart type FABP (H-FABP) appears in the blood soon after onset of infarction (within 2 to 3 hours after MI) and returns to the normal range within 12 to 24 hours in individuals without renal impairment. Nakata et al have shown that H-FABP has greater diagnostic value and sensitivity than cTnT, CK-MB, and myoglobin in patients with suspected ACS within 6 hours from acute chest pain onset. It has also been suggested that FABP is a marker of ischemia in absence of myocardial necrosis and it may prove to be useful in early identification of ACS in patients with chest pain of uncertain origin. It was brought that it could outperform myoglobin in early diagnosis of ACS; however, currently available studies are constrained by lack of specificity.

Free fatty acid unbound to albumin

Free fatty acids unbound to albumin (FFAU) have also been evaluated for early identification of cardiac ischemia. Several investigations have preliminarily evaluated the sensitivity of the marker on admission to emergency room and have shown that FFAU elevation occurs before other, more traditional markers of cardiac necrosis. However, additional studies are needed to fully evaluate the true potential of this biomarker.

Ischemia-modified albumin

Levels of ischemia-modified albumin (IMA) could hold strong negative predictive value for ischemia even prior to necrosis. This is based on the theory that metal binding site of the albumin molecule is damaged during ischemia. Together with cTnT and ECG, IMA has a strong potential to rule out ACS; with IMA outperforming the other two tests individually. However, there has been difficulty assessing IMA due to lack of gold standard of non-necrotic ischemia.

Pregnancy-associated plasma protein A

This is a member of the insulin-like growth factor family of proteins and it is thought to be released when neovascularization occurs. Thus, pregnancy-associated plasma protein (PAPP-A) may be a marker of incipient plaque rupture. In some studies it has appeared to identify patients at risk for subsequent events but there is no available standardized assay at present.

Placental growth factor

It is a member of vascular endothelial growth factor (VEGF) and was shown to be profoundly up-regulated in early and advanced atherosclerotic lesions. Placental growth factor (PIGF) is mainly involved in the inflammatory process of atherosclerosis. PIGF has shown promise to identify not only patients of ACS but also patients with an increased risk of recurrent instability after discharge. However, like PAPP-A, no standard assay is yet possible.

RISK STRATIFICATION IN UA/NSTEMI

The initial medical history, physical examination, ECG, assessment of renal function and cardiac biomarker measurement in patients with symptoms suggestive of ACS can be integrated into an estimation of risk. It is useful in selection of the site of care and selection of initial medical and interventional therapies. The TIMI, GRACE and PURSUIT risk scores have been developed for short and longer-term risk assessment.

TIMI Risk Score tool, composed of 7 (1 point) risk indicators rated on presentation has been developed and validated for UA/NSTEMI patients. It is useful to predict both 30 days and 1 year mortality.

History

- Age ≥ 65 years
- ≥ 3 CAD risk factors
- Known CAD (stenosis ≥ 50%)
- ASA in past 7 days

Presentation

- Recent severe angina (at least 2 episode over last 24 horus)
- ↑ Cardiac markers
- ST deviation ≥ 0.5 mm

TIMI Risk Score 0–2 points: Low risk
TIMI Risk Score 3–4 points: Intermediate risk
TIMI Risk Score 5–7 points: High risk

Grace Risk Score (Tables 2.1 and 2.2) is based on a large unselected population of an international registry with a full spectrum of ACS patients.

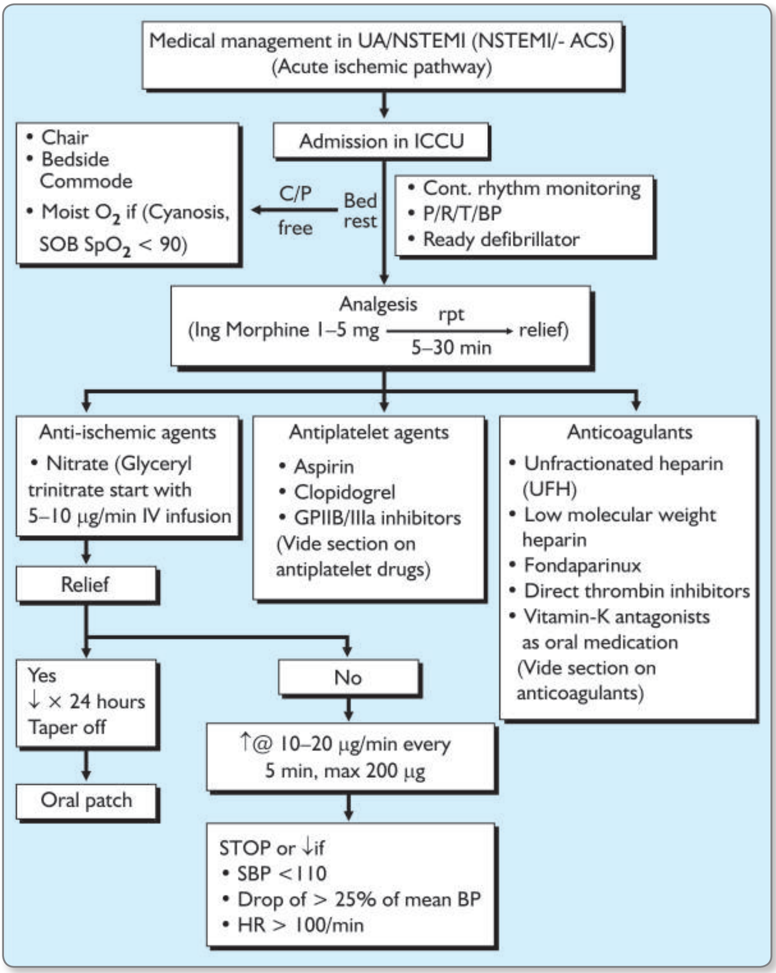
Table 2.1 GRACE prediction score card

Medical history			Findings at initial hospital presentation			Findings during hospitalization		
1.	Age in years	Points	4.	Resting heart points Rate beats/min		7.	Initial serum creatinine	Points mg/dL
	≤ 29	0						
	30-39	0		<49.9 0			0-0.39	1
	40-19	18		50-69.9	3		0.4-0.79	3
	50-59	36		70-89.9	9		0.8-1.19	5
	60-69	55		90-109.9	14		1.2-1.59	7
	70-79	73		110-149.9	23		1.6-1.99	9
	80-89	91		150-199.9	35		2-3.99	15
	≥ 90	100		>200	43		>4	20
2.	History of congestive heart failure		5.	Systolic blood pressure mm Hg		8.	Elevated enzymes	Cardiac
		24		<79.9	24			15
				80-99.9	22			
				100-119.9	18			
				120-139.9	14			
				140-159.9	10			
				160-199.9	4			
				>200	0			
3.	History of myocardial infraction	12	6.	ST-segment depression	11	9.	No in-hospital precutaneous coronary intervention	14

Table 2.2 Total risk score = Sum of points

GRACE Risk Score	In-hospital risk-stratification	GRACE risk-score	Post-discharge to 6 months risk stratification
<108	Low	<108	Low
109–140	Intermediate	89–118	Intermediate
>140	High	>118	High

Initial hospital management of NSRE–AC8



GRACE risk score makes it possible to assess risk of in-hospital and 6 months death. It is applicable to both ST-elevation and non-ST elevation ACS.

The PURSUIT risk model was developed on the basis of the PURSUIT trial and it is another useful tool to predict the 30-day incidence of death and composite of death and MI. The markers included in the risk model (in order of strength) are: (1) age, (2) heart rate, (3) systolic blood pressure, (4) ST-segment depression, (5) signs of heart failure and (6) cardiac biomarkers.

Bleeding is associated with an adverse prognosis in NSTE-ACS and all efforts should be made to reduce bleeding whenever possible. The CRUSADE bleeding score was developed comprising of a few variables (Baseline hematocrit, creatinine clearance, heart rate, sex, sign of CHF at presentation, prior vascular disease, diabetes mellitus, systolic blood pressure) from a large cohort from the CRUSADE registry. The rate of major bleeding increased gradually with rising bleeding risk score. Age is not listed among the predictors, but is contained in the creatinine clearance calculation.

Beta-Blockers

- Beta-blockers are recommended in absence of contraindications particularly in patients with hypertension or tachycardia. Patients on chronic β-blocker therapy admitted with ACS should be continued on β-blocker therapy if not in Killip Class >III (ESC Class IB). Oral β-blocker treatment is indicated in all patients with LV dysfunction without contraindication (ESC Class IB). IV β-blockers may be considered in stable hemodynamic state with hypertension and tachycardia (ESC Class IIaC).
- Intravenous beta-blocker
  Esmolol (50–300 mg/kg/min)
  Metoprolol (5 mg every 5 min)
  Atenolol (5 mg IV)
  (Monitor H/R, BP, ECG, rales, rhonchi).
- Oral β-blocker
  Metoprolol (50 mg BD to 200 mg BD)
  Propranolol (80-320 mg 2–4 dose)
  Atenolol (25–100 mg OD)
  Bisoprolol (5–20 mg OD)

TARGET HEART RATE: 50-60/min

- **Calcium channel blockers (Verapamil, diltiazem)**
  For symptom-relief in patients already on nitrates and β-blockers (ESC Class IB) and in patients with contraindications to β-blockers (ESC Class IIB)
  Vasospastic angina
  Nifedipine or other dihydropyridines, should not be used unless combined with β-blockers.

Other Anti-Ischemic Therapies

Ranolazine: It exerts anti-anginal effect by inhibiting late sodium current. MERLIN-TIMI-36 trial showed ranolazine was safe and reduced recurrent ischemic events but did not reduce composite of death or MI. It is indicated alone or in combination with nitrates, beta blockers or amlodipine for the treatment of chronic refractory angina.

Nicorandil: It is a K-ATP channel opener. A pilot double blind, placebo controlled study of 245 patients with UA/NSTEMI showed that when nicorandil was added to conventional treatment the number of episodes of transient myocardial ischemic and different tachyarrhythymias were significantly reduced. Further trials are underway; for patients with refractory angina nicorandil can be added as IV infusion at the rate of 2 to 6 mg/h. Unlike classical nitrates, hemodynamic tolerance does not develop with prolonged use of nicorandil.

Ivabradine: Ivabradine selectively inhibits the primary pacemaker current in the sinus node and may be used in patients with β-blocker contraindication.

Trimetazidine and perhexiline: Trimetaqzidine and perhexiline exert metabolic effects without hemodynamic changes.

Antiplatelet Treatment in Non-ST Elevation ACS (NSTE-ACS)

Aspirin

It remains the gold standard of antiplatelet therapy. Aspirin irreversibly inhibits TXA_2 production by inhibiting cyclo-oxygenase-1 (Cox-1) enzyme thereby diminishing platelet aggregation. Four clinical trials with differing designs and aspirin doses (75–1300 mg daily) have shown more than 50A percent reduction in risk of death or MI in patients presenting with UA (NSTEMI) treated with aspirin.

A recent meta-analysis by the antiplatelet trialist's collaboration reviewed 287 studies involving 1,35,000 patients in comparison of antiplatelet therapy versus control and 77,000 patients in comparisons of difference antiplatelet regimens. It shows antipatelet therapy reduced 22 percent serious vascular event, 34 percent nonfatal MI, 25 percent nonfatal stroke, and 15 percent vascular mortality. Aspirin was the most widely used antiplatelet. The APT meta-analysis also found the risk reduction did not significantly differ among aspirin doses ranges from 75 to 1500 mg/day. The risk of bleeding was seen to rise when daily dose exceeded 200 mg. Thus, a dose of 75 to 162 mg daily could be the optimal dose for long-term therapy and should be taken indefinitely. However, a loading dose of 150 to 365 mg (nonenteric coated and chewed) is recommended. Absolute contraindications of aspirin therapy are aspirin allergy, active bleeding or a known platelet disorder. Clopidogrel is an alternative to aspirin in case of aspirin intolerance.

Aspirin resistance: Although it is often used to describe failure of aspirin to prevent vascular events in some patients, yet it actually means that there is failure of aspirin to inhibit TXA_2 production. It might result from non-compliance, inadequate dose, poor absorption or rapid metabolism and systemic interference with aspirin access to the active site of COX-1 enzyme.

Clopidogrel

- Based on CURE trial results, 300 mg of Clopidogrel as loading dose followed by 75 mg/day as maintenance dose is indicated in all NSTEACS patients with aspirin.
- Patients undergoing PCI (PCI-CURE trial) also benefited from clopidogrel; although bleeding risk was increased, reduction of ischemic complications overweighed the bleeding risk. Aspirin dose reduction to 75 to 100 mg/day in combination with clopidogrel reduces bleeding risk.
- In ARMYDA-2 study, use of a 600 mg loading dose of clopidogrel 4 to 8 hours prior to planned PCI was associated with a reduction of the composite endpoint (death/MI/target vessel revascularization) within 30 days as compared with the standard loading dose of 300 mg.
- In ALBION study too, higher loading doses of 600 and 900 mg of clopidogrel in NSTEACS induced higher levels of inhibition on platelet aggregation with a faster onset of action; however no reduction of ischemic complications or increase in bleeding risk was noted. Currently, 900 mg loading dose is not recommended for routine clinical use.
- CURE study showed a trend towards increased bleeding rates in patients undergoing bypass grafting in whom clopidogrel was not discontinued 5 days prior to the procedure.

In the more recent CURRENT OASIS-7 trial, 25,086 patients with an ACS who were referred for an invasive strategy were randomized to either double-dose clopidogrel (a 600 mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300 mg loading dose and 75 mg thereafter) and either higher dose aspirin (300–325 mg daily) or lower dose aspirin (75–100 mg daily). The primary outcome was cardiovascular death, myocardial infarction or stroke at 30 days. No significant difference was noted between a 7-days, double-dose clopidogrel regimen and standard regimen, or between higher dose aspirin and lower dose aspirin in terms of the primary outcome. However, in distinction to aspirin, there was a key sub-group of interest; among patients who underwent PCI those who received higher-dose clopidogrel (600 mg loading dose, 150 mg once daily) seemed to benefit. In this population, there was a 15 percent overall reduction in the primary end-point of cardiovascular death, MI or stroke again with a small penalty to be paid with an increased rate of bleeding, but no major excess in the more severe bleeding categories.

Monitoring antiplatelet therapy with platelet function tests may identify poor responders who would benefit from a change in therapy, such as a dosage increase. Gold standard to monitor clopidogrel is the vasodilator-stimulated phosphoprotein (VASP) assay due to its $P2Y_{12}$ selectivity and the fact that it does not require pretreatment measurement. In contrast to the VASP assay, light transmission aggregometry (LTA) requires pretreatment measurement. 'Verify now' was developed as a point of care, whole blood, semi-automated, cartridge-based platelet function test to determine the response to antiplatelet agents (both aspirin and clopidogrel). The platelet function analyzer PFA-100 can be used to identify patients with severe platelet defects or von Willebrand disease. Despite availability of several tests, it is however still unclear whether results of platelet function tests can be used in clinical decision-making.

Clopidogrel involves several cytochrome P(CYP)450 isoenzymes especially CYP 2C19 for conversion to active metabolic R130964. This major genetic polymorphism are associated with loss of function : CYP2C19*1, CYP2C19*2 and CYP2C19*3. The CYP2619*3 accounts for 99 percent of Asians.

Selective and limited approach to platelet genotype assessment and platelet function testing is needed until better clinical evidence exist (Class IIb recommendation).

Newer Thienopyridine Derivatives

Newer Antiplatelet Drugs

Prasugrel: It provides more profound and faster antiplatelet effect than clipidogrel. TRITON-TIMI38 demonstrated reduction in ischemic events with prasugrel, but an increase in major bleeding episodes compared to clopidogrel (0.4% vs. 0.1 percent; p=0.0002). There was overall 13 percent better outcome with prasugrel and 52 percent lesser incidence of stent thrombosis (both early and late). Excess bleeding with prasugrel was not seen in diabetes which can probably be explained by the fact that platelets are known to be more hyperactive in diabetics. IN PRINCIPLE-TIMI 44 and recently presented ACAPULCO studies, prasugrel achieved higher levels of platelet inhibition.

It is reversible inhibitor of P2Y12 receptor with a half-life of approximately 12 hours. A large clinical trial, PLATO (platelet inhibition and patient outcomes), compared ticagrelor with clopidogrel in approximately 18,000 ACS patients, with primary endpoint of cardiovascular death, MI and stroke at 12 months. Results of PLATO trial reported that ticagrelor reduced the primary composite of vascular death, nonfatal MI, or nonfatal stroke compared with clopidogrel, while achieving a similar safety profile. Of note, the use of this agent was shown to be associated with an increase in two adverse events, dyspnea and ventricular pauses.

Although these side effects were of mild-to-moderate intensity and also occurred in patients with clopidogrel.

Cangrelor: A potent, short-acting intravenous P2Y12 receptor inhibitor has rapid onset of action and also has reversibility. Two large randomized clinical trials have tested cangrelor in PCI (CHAMPION PCI and CHAMPION PLATFORM) with a composite primary endpoint of death, MI and urgent target vessel revascularization at 48 hours. However, according to recently published reports both CHAMPION trials were terminated early due to lack of efficacy with cangrelor. In CHAMPION PCI, cangrelor administered intravenously 30 min before PCI and continued for 2 hours after PCI, was not superior to 600 mg of oral loading of clopidogrel in reducing composite endpoint of death from any cause, myocardial infarction or ischemia-driven revascularization at 48 hours. In the most recent CHAMPION PHOENIX trial, cangrelor significantly reduced rate of ishemic events, icluding stent thrombosis during PCI (both urgent and elective) compared to clopidogrel (600 mg or 300 mg). Primary end points of composite of death, MI, ishemia driven revascularization or stent thrombosis were significantly lowered in cangrelor arm by 22% and this was mainly contributed by significant risk reduction in periprocedural MI (20%) and stent-thrombosis (38%). Cangrelor was not associated with an increase in bleeding complications.

Thrombin-Receptor Antagonist (TRAS)

Vorapaxar (Formerly SCH 530348) is a TRA that blocks platelet protease activated receptor-1). A recent trial (TRA 2°P—TIM150) by Morrow et al found no change in all cause mortality while decreasing the risk for cardiovascular death and ischemic events and increasing risk for major bleeding.

Glycoprotein IIb/IIIa Inhibitors (GPIIb/IIIa Inhibitors)

There are three intravenous (IV) platelet GPIIb/IIIa receptor antagonists that have been approved for use in ACS (Table 2.3).

1. **Abciximab:** is the FAB fragment of the chimeric human-murine monoclonal antibody c7E3.
2. **Eptifibatide:** a nonimmunogenic cycle heptapeptide with an active pharmacophore that is derived from the structure of barbourin, a platelet GPII/b/IIIa inhibitor from the venom of the southeastern pigmy rattlesnake.
3. **Tirofiban:** a tyrosine derivative with a molecular weight of 495 kd, is a nonpeptide inhibitor (peptidomimetic) of the platelet GPIIb/IIIa receptor.

Table 2.3 Comparison of GP IIb/IIIa receptor inhibitors

Characteristic	Abciximab	Eptifibatide	Tirofiban
Type	Antibody	Peptide	Nonpeptide
Molecular weight	~50,000	~800	~500
Plasma half-life	Short (min)	Extended (2 h)	Extended (2 h)
Platelet bound half-life	Long (h) 1.5-2.0	Short (S) 250-2500	Short (S) >250
Drug to GF IIb/IIIa receptor ratio 50% return of platelet function (without transfusion)			
Use for medical treatment for ACS	12 hrs	-4 hrs	-4 hrs
Use for PCI			
	++*	+++	+++
	+++	+++	++
Dosage	0.25 meg/kg as IV bolus (over 1 min) 0.125 mcg/kg/min as continuous infusion Maximum dose: 10 mcg/min *For stabilization of UA* Start the bolus dose, followed by IV infusion up to 24 hrs prior to possible intervention and then stop 12 hrs after intervention *For the prevention of ischemic cardiac complication related to PCI* Start the bolus dose 10–60 min prior to the intervention followed by the infusion for 12 hrs.	UA/NSTEMI 180 mcg/kg/IV bolus over 1-2 min Followed by 2 mcg/kg/min continuous IV × 72-96 hrs. If PCI is performed during therapy, continue for 18–24 hrs post PCI. PCI without prior Rx for UA/NSTEMI 180 mcg/kg IV bolus × 2 doses 10 min apart then, 2 mcg/kg/min IV × 18–24 hrs.	UA/NSTEMI 0.4 mcg/kg /min IV for 30 min followed by 0.1 mcg/kg/min IV infusion × at least 48 hrs. Maximum duration: 108 hrs. If PCI performed, continue infusion through angiography and continued × 12–24 hrs postangioplasty/atherectomy. PCI w/o prior treatment for UA/UNSTEMI 10 mcg/kg/kg IV administered over 3 min immediately prior to procedure followed by 0.15 mcg/kg/min IV infusion × 26 hrs.

Contd...

Contd…

Characteristic	Abciximab	Eptifibatide	Tirofiban
Dosage in chronic kidney disease	No specific recommendations for use or for dose adjustment in case of renal failure.	Since 50% cleared through kidney, infusion dose should be reduced to 1 mcg/kg/min in such patients. Dose of bolus remains unchanged at 180 mcg/kg. Eptifibatide is contraindicated in patients with a.cr.a <30 mL/min.	Dosage adaptation is required in renal failure. Fifty percent of the dose only if CrCl< 30 mL/min.
Adverse reactions	Bleeding	Bleeding	Bleeding
	Thrombocytopenia**	Hypotension	Thrombocytopenia**
	Nausea, vomiting	Hypersensitivity	Nausea
	Hypotension	(Anaphylaxis, rash, urticaria)	Rash
	Bradycardia		Headache
	Pain in extremities		Fever and chills
	Peripheral edema		
	Hypersensitivity		

+++ Marked benefit; ++ Moderate benefit; *Refractory angina if PCI performed within 12 hrs
**Monitor platelet counts prior to therapy, 2–4 hrs after bolus and at 24 hrs
***Monitor platelet count, Hb, Hct prior to therapy, 6 hrs after bolus and then daily.

GP IIb/IIIa Inhibitors in a Consecutive Strategy

All three GP IIb/IIIa inhibitors were tested in trials where an invasive strategy was not encouraged. A meta-analysis including 31,402 NSTE-ACS patients treated in clinical trials using GP IIb/IIIa inhibitors showed a 9 percent significant risk reduction for death and MI at 30 days with GP IIb/IIIa inhibitors (11.8% vs 10.8%). The risk reduction was more conspicuous particularly in high-risk patients. GP IIb/IIIa inhibitors had no effect in troponin-negative patient and in women; however, most of them were actually troponin negative and women with troponin release derived the same benefit as men. In GUSTO-4-ACS trial, 7,000 patients on aspirin and UFH were randomized to one of the three drug regimens; placebo, abciximab bolus plus 24 hours infusion, abciximab bolus plus 48 hours infusion. No significant benefit was demonstrated for the two groups treated with abciximab and an increased bleeding risk was observed.

In PURSUIT trial comparison involved high dose eptifibatide regimen versus placebo., Although significant benefit was observed in eptifibatide arm, bleeding risk was more.

Tirofiban has been tested in two separate trials. In PRISM trial tirofiban showed significant reduction in the composite endpoint of death. MI or refractory ischemia than UFH up to 30 days but not beyond that.

In PRISM-Plus trial which considered higher risk patient than PRISM trial were randomized to three different arms: tirofiban alone, tirofiban plus UFH, or UFH alone. The tirofiban alone arm was stopped soon after the start of trial because of an excess adverse event but tirofiban + UFH group showed significant reduction of the risk of death, MI and refractory ischemia compared to UFH alone.

GP IIb/IIIa Inhibitors in an Invasive Strategy

Consistent results have been obtained in three different meta-analysis exploring the impact of the use of GP IIb/IIIa inhibitors in the setting of PCI. The meta-analyses showed that a significant risk reduction for death and MI at 30 days could be achieved when GP IIb/IIIa inhibitors were administered before taking patients to the catheterization laboratory and maintained during PCI. In CAPTURE, in patients with UA/NSTEMI and planned PCI were pretreated with abciximab for 24 hours and maintained for 12 hours. Trial results showed without routine use of stents and clopidogrel, abciximab significantly reduced rate of death, MI and need for urgent intervention for recurrent ischemia when compared with placebo at 30 days (11.3% vs 15.9%, P = 0.012). The benefit was restricted to patients with elevated TnT levels. In ISAR-REACT-2 high-risk NSTE-ACS patients were randomized following pre-treatment with aspirin and 600 mg clopidogrel to either abciximab or placecbo. Abciximab-treated patients showed significanty lower target vessel revascularization, death or MI compared to placebo (8.9% vs 11.9%, P =- 0.03) and the effect was more pronounced in troponin-positive patients. ESPRIT trial showed that when eptifibatide was used as a bolus of 180 µg/kg followed by an infusion of 2.0 µg/kg/min for 18 to 24 hours, it caused significant reduction of death, MI, urgent TVR than placebo in patients undergoing PCI. In RESTORE trial, patients presenting with ACS who underwent PCI within 72 hours of presentation were treated with heparin and aspirin with the addition of tirofiban or placebo. Treatment with tirofiban showed reduction in the short-term rate of death, MI or revascularization for failed PTCA or recurrent ischemia without an increase in major bleeding.

Glycoprotein (GP) IIb/IIIa Inhibitors and Coronary Artery Bypass Graft

Inhibition of platelet aggregation may result in bleeding complications, either spontaneously or at the time of cardiac surgery. GP IIb/IIIa inhibitors should be discontinued at the time of cardiac surgery. Eptifibatide and tirofiban have a short half-life and hence platelet function should be expected to recover by the end of CABG. Abciximab has a longer effective half-life and earlier discontinuation may be needed.

Adjunctive Therapy

Several trials in the field of NSTE-ACS, as well as observational studies in PCI, have shown that LMWH, predominantly enoxaparin, can be safely used with GP IIb/IIIa inhibitors without compromising efficacy. In OASIS-5, GP IIb/IIIa inhibitors were used with aspirin, clopidogrel and fondaparinux in 1308 patients or enoxaparin in 1273 patients. Overall bleeding complications were lower with fonxaparinux than with enoxaparin.

The ISAR-REACT-2 STUDY showed that better outcome can be obtained with abciximab added to pretreatment with aspirin and a 600 mg loading dose of clopidogrel when compared to only aspirin plus clopidogrel in the students of high-risk PCI patients with UA/NSTEMI.

ACUITY trial showed bivalirudin with combination of GP IIb/IIIa inhibitor has higher bleeding risk than bivalirudin alone.

What is the best time to initiate therapy? (Upstream or in the catheterization laboratory)

Two randomized trials have explored alternative dosing regimens with eptifibatide. In the BRIEF-PCI trial, a short infusion of <2 hours was compared to the longer standard infusion of 18 hours. No differences were found between the two groups in terms of periprocedural myonecrosis or ischemic events at the end of 30 days; however, bleeding rates were higher in the standard infusion group (4.2% vs. 1.0%, P = 0.02).

In the ACUITY timing trial, 9207 patients in the 2GPI (GP IIb/IIIa inhibitors) arms (heparin with GPI and bivalirudin with GPI) underwent a second randomization to either early (at randomization) GPI or deferred selective

GPI (at time of PCI). At 30 days, deferred GPI was associated with a non-significant greater rate of composite ischemia and major bleeding events were significantly reduced in this group.

In the EARLY-ACS trial, in 9492 patients with high-risk NSTE-ACS undergoing angiography at 12 to 96 hours, the strategy of early, routine double-bolus eptifibatide followed by an infusion was compared to a strategy of initial placebo followed by provisional eptifibatide (at the operator's discretion). Routine early eptifibatide was not superior to delayed provisional used and increased the risk of major bleeding and red-cell transfusions by 42 percent (P = 0.015) and 31% (P <0.001), respectively. Thus, these trials do not support routine upstream use of GP IIb/IIIa inhibitors; however, additional analyzes are ongoing to determine whether specific high-risk groups of patients with NSTE-ACS stand to benefit from such a strategy.

Is Addition of GPIIb/IIIa Inhibitors Necessary during PCI in Patients Pretreated with High-Dose Clopidogrel?

This question cropped up when the results of ISAR-REACT study became available showing that low and moderate-risk patients undergoing planned PCI pretreated with a 600 mg loading dose of clopidogrel at least 2 hours prior to the procedure may not benefit from administration of a GPIIb/IIIa inhibitor (death, MI, urgent TVR; placebo vs abciximab 4.0 vs 4.2%, P=NS).

The ISAR-REACT-2 study had a design similar to ISAR-REACT but involved patients with ACS. Addition of abciximab to aspirin 500 mg and clopidogrel (600 mg at least 2 hours prior to PCI) was associated with a significant reduction in the primary endpoint (abciximab vs placebo, 8.9 vs 11.9%, RR=0.75, P=0.03), with the most pronounced difference in patients with a positive troponin test at baseline (for troponin (+), abciximab vs placebo, 13.1 vs 18.3%, RR=0.71, P=0.98). There were no differences in the rate of major and minor bleeding events or urgent blood transfusions.

Can Direct Thrombin Inhibitors be used as an Alternative to GpIIb/IIIa Inhibitors?

This concept will be discussed in details in the section on direct thrombin inhibitors. In low-risk patients with NSTEACS, direct thrombin inhibitors offer an alternative to combination of UFH and GPIIb/IIIa inhibitors. The value of combined therapy with aspirin, clopidogrel and bivalirudin as an alternative to aspirin, clopidogrel, UFH and GPIIb/IIIa inhibitor in high-risk patients (NSTEMI) requires further randomized studies.

Antithrombin Treatment in Patients with NSTE-ACS

Better anticoagulation regimens have been developed given the limitations of unfractionated heparin (UFH) which include its sometimes difficult to manage effects on coagulation, the need for repeated monitoring of coagulation, narrow therapeutic window, potential induction of platelet activation and risk of thrombocytopenia. The three new anticoagulants, enoxaparin, fondaparinux and bivalirudin have demonstrated improvements against UFH and represent new alternative therapies (Table 2.4).

Unfractionated Heparin (UFH)

UFH has long been the only thrombin inhibitor used in unstable angina patients, despite the lack of definitive proven benefit over placebo in ACS patients treated with aspirin. One of the many recognized challenges of UFH therapy is achieving and maintaining a target level of anticoagulation. For this, frequent monitoring of the activated partial thromboplastin time (aPTT) is recommended (Table 2.5).

Duration of treatment of UFH: It is determined by the patient's overall clinical status; however, in most instances a period of 48 to 72 hours is adequate. Weaning is recommended to minimize "rebound" thrombin generation.

Heparin-induced thrombocytopenia (HIT): HIT is a devastating complication that occurs in up to 5 percent of patients who receive IV UFH with a lower incidence when LMWH is utilized, ranging from 0.5 percent to 1.0 percent. HIT is due to formation of antibodies against a complex of heparin and platelet factor 4 and it results in disseminated thrombotic vascular occlusion (DVT, PE, MI, stroke etc).

Treatment

- Stop heparin including LMWH
- **Lepirudin:** IV bolus of 0.4 mg/kg; continuous infusion 0.15 mg/kg/hour
- **Argatroban:** Continuous IV infusion 2 mcg/kg/min.

Low Molecular Weight Heparin (LMWH)

Necessity of close monitoring of anticoagulant activity, as well as a high incidence of HIT encouraged the development of alternative antithrombin strategies, namely LMWH. Several randomized clinical trials have compared the efficacy and safety of LMWH (Enoxaparin, Dalteparin, Fraxiparine) and UFH among initially medically managed patients presenting with ACS. Among those, enoxaparin was the only LMWH to demonstrate a significant and sustained benefit over UFH; in the meta-analysis of TIMI 11B and ESSENCE trials, enoxaparin was associated with a significant reduction of death and MI at 8,14 and 43 days.

Dosage in NSTE-ACS:	Enoxaparin: 1mg/kg SCq12 hours Dalteparin: 120 iu/kg SCq12 hours
Chronic kidney disease:	GFR 10–50 mL/min—usual dosage GFR < 10 mL/min—50% of usual dosage or avoid.

Table 2.4 Major characteristics of the different anticoagulants

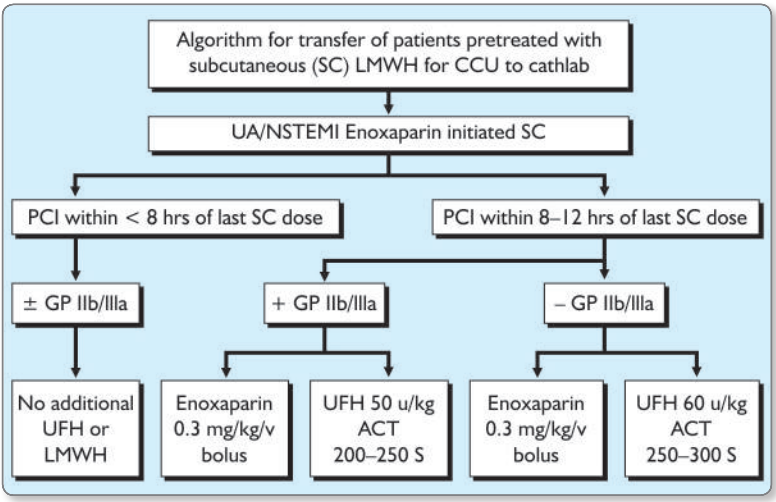
	UFH	**Enoxaparin**	**Fondaparinux**	**Bivalirudin**
Chemistry	Animal origin	Animal origin	Synthetic peptide	Synthetic peptide
Thrombin binding	Yes	Yes	No	Bivalent reversible
Action independent of antithrombin	No	No	No	Yes
Inhibition of fibrin-bound thrombin	No	+/-	+/-	Yes
Inhibition of thrombin mediated platelet activation	No	+/-	+/-	Yes
PF4 complexing and risk of heparin induced thrombo-cytopenia	Yes	Reduced	No	No
Clearance	Endothelial and renal	Renal	Renal	Proteolytic 20% renal
Elimination t1/2	60–90 min	270 min	1020 min	25 min
Anticoagulation monitoring	Yes	No	No	No
Indication	PCI, ACS	ACS	ACS	PCI
Dosage	70 u/kg IV bolus (max 5000 u), then 12–15u/kg/hr (max 1000 u/hr)	1 mg/kg q12 h subcut	2.5 mg/day subcut	0.75 mg/kg IV bolus followed by 1.75 mg/kg/hr IV infusion (REPLACE 2) or 1 mg/kg IV bolus followed by 2.5 mg/kg/hr IV infusion (ACUITY)
Antidote	Protamine	None	None	None

Table 2.5 Patient-specific heparin-dosing nomogram*

aPTT	Repeat Bolus**	Rate change	Repeat aPTT
< 35 second	60 u/kg	↑ 4 u/kg/hour	4 hour
35–49 second	30 u/kg	↑ 3 u/kg/hour	6 hour
50–70 second***	0	No change	6 hour
71–90 second	0	↓ 2 u/kg/hour	6 hour
> 90 second	0	↓ 3 u/kg/hour	4 hour

aPTT — activated partial thromboplastin time.
* Initial dose: 60 u/kg bolus (not to exceed 5000 u); maintenance infusion : 15-18 u/kg/hour. Begin infusion at < 1200 u/hour
** Patients > 65 years of age and those receiving fibrinolytics and/or GPIIb/IIIa antagonists have reduced heparin requirements (bolus and infusion)
*** Target range (for acute coronary syndrome).

Monitoring: No routine laboratory monitoring is required except platelet count at baseline and periodically thereafter. However, in certain clinical settings (e.g. renal insufficiency, severe obesity), an antiXa level can be measured. commonly accepted therapeutic range is 0.5 to 1.0 antiXa units/mL.



Direct AntiXa Inhibitor: Fondaparinux

Fondaparinux is a synthetic pentasaccharide and is a specific inhibitor of factor Xa activity. Its pharmacokinetic properties allow for a simple, fixed dose, once daily regimen of subcutaneous injections, without the need for monitoring.

In OASIS 5 trial, a total of 20, 078 patients with NSTE-ACS received either fondaparinux (2.5 mg given SC once daily) or enoxaparin (1 mg/kg given SC twice daily) for a mean of 6 days. The number of patients experiencing death, MI or refractory ischemia at 9 days was similar between groups; however, the rate of major bleeding was reduced by 50 percent with fondaparinux and a composite of the primary outcome and major bleeding favored fondaparinux at 9 days. Fondaparinux was associated with a significantly reduced number of deaths at 30 days and 180 days. A subgroup analysis for both primary efficacy end point and major bleeding suggests that fondaparinux may be particularly beneficial among patients with impaired renal performence.

In 6207, patients of OASIS 5 undergoing PCI, a significant increase in rate of catheter thrombus was reported in fondaparinux treated patients compared with enoxaparin treated patients, although acute coronary complications remained similar. This serious drawback for PCI was also found in ASPIRE and OASIS 6 studies. The adjunct of a full dose of UFH has been recommended on top of the fondaparinux treatment to perform PCI to avoid this excess of risk in catheter thrombosis. Recent OASIS-8 trial has supported the use of a standard dose of UFH prior to PCI in the patients pretreated with fondaparinux in preference to low-dose UFH.

Dosage of Fondaparinux in ACS: 2.5 mg Once Daily

Dosage in patients with chronic kidney disease: Contraindicated in severe renal failure (Cr Cl < 30 mL/min). However, as much lower risk of bleeding complications was observed in OASIS-5 with fondaparinux as compared with enoxaparin, even in patients with severe renal failure, this drug might be the anticoagulant of choice in this situation.

Direct Thrombin Inhibitors

The direct thrombin inhibitors (DTI) hirudin has shown some promise in preventing early ischemic/thrombotic events in patiens with ACS in GUSTOIIb and OASIS-2 studies. However, these efficacy results were however balanced by an excess of major bleeding requiring transfusion with hirudin. The safety concerns were then raised against the use of hirudin and probably caused the interruption of further development of this agent.

Bivalirudin (or hirulog) has been investigated more than 10 years ago as an adjunctive therapy for high-risk PCI and is now the only DTI labeled for PCI. After the dose-ranging studies, the recent REPLACE-1 and REPLACE-2 trials have shown that bivalirudin provided similar protection from ischemic events as UFH/enoxaparin plus GPIIb/IIIa inhibitors, with markedly reduced bleeding. On the basis of these preliminary studies, it appeared that bivalirudin has the safety and efficacy potential to replace UFH in treatment of ACS. Additional information in the contemporary setting of ACS was brought by the results of ACUITY trial. The study was designed to test the hypotheses that in moderate-to-high risk patients with ACS undergoing an invasive strategy, compared with UFH or LMWH + GPIIb/IIIa inhibitors, (i) bivalirudin + GPIIb/IIIa inhibitors will result in less adverse ischemic events and less bleeding and (ii) bivalirudin alone will result in similar rates of ischemic events and markedly reduced bleeding. Triple ischemic endpoint (death/MI/Urgent revascularization) occurred similarly among three treatment arms, satisfying the criteria of noninferiority of bivalirudin alone or with GPI compared with UFH/enoxaparin + GPI. Bivalirudin alone was found superior to heparin + GPI in reducing the incidence of major bleedings and in terms of net clinical outcome, bivalirudin was superior to heparin + GPI.

Dosage of bivalirudin: Intravenous bolus of 0.1 mg/kg and infusion of 0.25 mg/kg/hour. Additional intravenous bolus 0.5 mg/kg and infusion increased to 1.75 mg/kg/hour before PCI.

Dosage in NSTE-ACS patients with chronic kidney disease: If the Cr Cl < 30 mL/min, reduction of the infusion rate to 1.0 mg/kg/hour should be considered. If a patient is on hemodialysis, the infusion should be reduced to 0.25 mg/kg/hour. No reduction in the bolus dose is needed.

Newer Antithrombotics

Factor Xa inhibitors: Currently, a number of intravenous and oral direct factor Xa inhibitors are in the process of clinical development. Some information on initial clinical results are already available with one parenteral (otamixaban) and several oral inhibitors of factor Xa: endoxaban apixaban, rivaroxaban, waroxaban and YM150. Results of a phase-2 study with otamixaban in the context of PCI have been published recently. In the recent ATLAS-ACS 2 trial, rivaroxaban reduced the risk of composite end point of death from CV causes, myocardial infarction or stroke. It increased the risk of major bleeding and intracranial hemorrhage but not risk of fatal bleeding. In contrast in APRAISE-2 trial apixaban at a dose of 5 mg twice daily when added to high-risk patients after an ACS, increased the number of major bleeding events without a significant reduction in recurrent ischemic events.

Direct Thrombin Inhibitors

The future may bring expanded use of DTIs. Despite many favorable features, ximelagatran was withdrawn because of evidence of hepatoxicity. Currently, at least 7 DTIs are being evaluated in clinical trials involving deep venous thrombosis, ischemic heart disease and atrial fibrillation. The oral DTI dabigatran is clearly the leader in the path of development with major trials in all three arenas.

Anticoagulants

Apart from DTIs, other oral and parenteral anticoagulants are also under development. These agents can be divided into two groups based on their primary target in the coagulation cascade : (i) inhibitors of initiation of coagulation that target tissue factor, tissue factor VII a complex and active site-blocked FVIIa. A parenteral recombinant protein (γ NAAAP c2) has been successfully tested in phase-2 trial of patiens of NSTE-ACS, (ii) inhibitors of the propagation of coagulation which target factor IXa, Xa or their respective cofactors (factor VIIIa, Va). These drugs are based on aptamer technology, single-stranded nuclei acids that can be tailored for specific targets with a high affinity.

Other Therapies

Inhibitors of the Renin-Angiotensin-Aldosterone System

In AMI patients GISS-3, ISIS-4, and trial found a 0.5 percent reduction in absolute mortality with ACE inhibitors initiated within 24 hours. The angiotensin receptor blocker, valsartan has been found to be as effective as captopril in patients at high-risk of CV events after MI. However, a combination of the two was found to be harmful. In patients with UA/NSTEMI it is recommended that in the absence of hypotension or other known contraindications, an ACE inhibitor (or angiotensin-receptor blocker in patients intolerant of ACE inhibitors) should be administered orally within the first 24 hours in to patiens with pulmonary congestion or LVEF ≤0.04 (class I) and state that these can also be useful in patients without these features (class IIa).

The selective aldosterone receptor blocker eplerenone, used in patients with MI complicated by LV dysfunction and either heart failure or diabetes, reduced morbidity and mortality in the EPHESUS trial and is indicated long term for patients without significant renal dysfunction or hyperkalemia.

Lipid-lowering Therapy

A fasting lipid profile should be obtained within first 24 hours of admission for ACS. In the absence of contraindications, regardless of baseline LDL-C levels, statins should be given to post-UA/NSTEMI patients, including postrevascularization patients. The benefit was first observed in LIPID trial in which pravastatin led to 26 percent reduction immortality (P = 0.004).

In the PROVE-It TIMI-22 trial, a 16 percent reduction in the hazard ratio for primary composite endpoint of all causes death, MI and stroke was seen with high dose atorvastatin 80 mg compared with standard dose pravastatin 40 mg in patients within 10 days of an ACS.

Recommendations about antithrombotic agents (Based on 2011 ESC guidelines on NSTE-ACS and ACCF/AHA 2011 focused update of 2007 guidelines on UA/NSTEMI)

Recommendations for Oral Antiplatelet Agents

	Class[a]	Level[b]
Aspirin should be given to all patients without contraindications at an initial loading dose of 150 to 300 mg, and at a maintenance dose of 75 to 100 mg daily long-term regardless of treatment strategy	I	A
A $P2Y_{12}$-inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as exercise risk of bleeding	I	A
A **proton pump inhibitor** (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal hemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*H. elicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids)	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated	I	C
Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced)	I	B
Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for $P2Y_{12}$-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high-risk of life-threatening bleeding or other contraindications	I	B
Clopidogrel (300 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel	I	A
A 600 mg loading dose of clopidogrel (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option	I	B
A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases	IIb	B

	Class[a]	Level[b]
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used	IIb	B
In patients pretreated with $P2Y_{12}$ inhibitors who need to undergo nonemergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high-risk of ischemic events should be considered	IIa	C
Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and nonselective NSAID) is not recommended	III	C

a = class of recommendation; b=level of evidence; COX = cyclo-oxygenase; CABG = coronary artery bypass graft; DAPT = dual (oral) antiplatelet therap; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention.

Recommendations for GP IIb/IIIa Receptor Inhibitors

	Class[a]	Level[b]
The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischemic and bleeding events	I	C
Among patients who are already treated with DAPT, the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low	I	B
Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with $P2Y_{12}$ inhibitors	IIa	C
In high-risk patients eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischemia and the risk of bleeding is low	IIb	C
GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy	III	A
GP IIb/IIIa receptor inhihitors are not recommended for patients on DAPT who are treated conservatively	III	A

a = class of recommendation; b=level of evidence; GP = glycoprotein; DAPT = dual (oral) antiplatelet therapy, LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Recommendations for Anticoagulants

	Class[a]	Level[b]
Anticoagulation is recommended for all patients in addition to antiplatelet therapy	I	A
The anticoagulation should be selected according to both ischemic and bleeding risk, and accordingly to the efficacy-safety profile of the chosen agent	I	C
Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favorable efficacy – safety profile with respect to anticoagulation	I	A
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of contomitant use of GP IIb/IIIa receptor inhibitors) should be added at the time of PCI	I	B
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available	I	B
If fondaparinux or enoxaparin are not available, **UFH** with a target aPTT of 50 to 70s or other LMWHs at the specific recommended doses are indicated	I	C
Bivalirudin plus provisional GP IIb/IIIa receptor inhibitors are recommended as an alternative to UFH plus GP IIb/IIIa receptor inhibitors in patients with an intended urgent or early invasive strategy, partucularly with a high-risk of bleeding	I	B
In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge. Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated	IIa	C
Crossover of heparins (UFH and LMWH) is not recommended	III	B

a = class of recommendations; b=level of evidence; GP = glycoprotein; DAPT = dual A (oral) antiplatelet therapy; ACT = activated clotting time; aPTT = activated partial thromboplastin time; GP = glycoprotein; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Difference between ESC (2011) and ACCF (2011)

NSTE-ACS Guidelines

1. Ticagrelor is recommended only by ESC Guidelines.
2. Prasugrel is given **Class IIb** recommendations by ACCF/AHA for administration at 60 mg dosage promptly upon presentation in patients with UA/NSTEMI for whom PCI is planned before definition of coronary anatomy, if both the risk for bleeding is low and need for CABG is considered unlikely (Level of Evidence : C).

3. For UA/NSTEMI patients in whom an initial conservative (i.e. noninvasive) strategy is selected, ACCF/AHA has given Class IIb recommendation (Level of Evidence : B) to addition of tirofibran/eptifibatide to anticoagulant and oral antiplatelet therapy; however ESC has labeled this as Class III.

Coronary Revascularization Procedures

A number of randomized trials have been conducted in the content of increasing procedural experience, technological improvements in revascularization procedures and the development of new antiplatelet and anticoagulant regimen. Two general approaches have emerged from reviews of these studies:

i. *Early invasive management:* It involves routine cardiac catheterization and revascularization with PCI or CABG, depending on the coronary anatomy. It may be (a) urgent or (as quickly as possible after hospital presentation) (b) early (within a few hours).
ii. *Early conservative management:* It is the initial medical management with catheterization and revascularization carried out only if the patient demonstrates recurrent ischemia either at rest or on a noninvasive stress test. It is also termed as 'Ischemia guided' or 'selective invasive strategy'.

Comparison of Early Invasive and Conservative Strategies

Nine randomized trials have assessed two general strategies, with first three trials demonstrating no significant difference, whereas the remaining six trials have shown a significant benefit of an early invasive strategy. A few selected trials are discussed below:

TIMI-3B: A total of 1473 patients were randomized to early invasive versus early conservative therapy. There was no difference in the rate of primary endpoint, death, MI or strongly positive exercise test at 6 weeks (16.2% in early invasive group vs 18.1% in conservative group, P=NS). Similarly, there was no difference in the incidence of death or MI at 6 weeks or 1 year (10.8% vs 12.2%, P=NS).

VANQUISH: A total of 920 patients were randomized on the basis of CK-MB elevation within 72 hours of admission. More patients in the early invasive group experience in-hospital death (21% vs 6%, P = 0.007) or a composite death or MI (36% vs 15%, P = 0.004); statistically differences persistent as 1 year and a trend towards higher mortality was still observed at 2 years.

FRISC-II study: A total of 2457 patients were enrolled with chest pain within the previous 48 hours plus either: (a) ST or T wave changes, (b) elevated troponin T or CK-MB. They received subcutaneous dalteparin in-hospital and then were randomized to an invasive versus conservative strategy. There was also a second randomization to prolonged (3 months) versus only in-hospital LMWH.

The primary endpoint, death or MI at 6 months was significantly lower in the invasive versus conservative group (9.4% vs. 12.1%, P = 0.031).

Additional analysis showed greater benefit of the invasive strategy in higher risk group (ST-depression, Troponin-T positive). Five-year follow-up data are now available, and overall death or MI was lower with an invasive strategy (PR = 0.81, P = 0.009) but there was no significant difference in 5-year mortality.

TACTICS-TIMI-18: This study used GP IIb/IIIa inhibitor tirofiban in all patients. Here, 2220 patients were randomized to invasive therapy or conservative therapy. The primary outcome of death, nonfatal MI or rehospitalization for ACS at 6 months was 15.9 percent in invasive group and 19.4 percent in conservative group (P = 0.025). Using the TIMI risk score, there was significant benefit of the early invasive strategy in intermediate (score 3-4) and high-risk (5–7) patients, where low risk (0–2) patients had similar outcomes when managed with either strategy.

RITA-3: Enrolled 1810 patients and randomized to early intervention and medical management group. At 4 months, the primary endpoint of death, MI, or refractory angina was significantly lower in earlier intervention group (9.6% vs. 14.5%, P=0.001). At 5 years follow-up, there was still significantly reduced death and MI in early invasive arm (P=0.044).

A meta-analysis of these five and two smaller trials found that the incidence of death or nonfatal MI in the invasive group was 1.2 percent versus 14.4 percent in the conservative group (P≤0.001).

VINO: This small study comprising 131 patients who showed significant reduction in death and MI in early intervention group compared with ischemia-guided strategy (6.2% vs. 22.3%; P < 0.001).

ISAR-COOL: This study was designed to determine whether prolonged antithrombotic pretreatment might improve the outcomes of patients undergoing routine invasive management. Total 410 patients were enrolled. All patients received UFH, aspirin, clopidogrel and tirofiban and were randomized to early (< 6 hours) or delayed (3–5 days) angiography or revascularization. The primary outcome of nonfatal MI or death occurred in 5.19 percent of the early invasive group compared to 11.6 percent of the delayed invasive group by 30 days (PR = 0.51, P = 0.04).

ICTUS: A total of 1200 ACS patients with elevated troponin T level were enrolled. All patients were treated with optimal medical therapy that included aspirin, clopidogrel, LMWH, and lipid-lowering therapy; abciximab was given to those undergoing revascularization. At 1 year, there was no significant difference in the rate of primary endpoint, death MI, or rehospitalization for angina in the invasive versus conservative strategy (22.7% vs. 21.2%, P = 0.33). Three-year follow-up results of the ICTUS trial showed that an early invasive strategy was no better than a selective invasive strategy in reducing the rate of the primary endpoint (P = 0.09).

TIMACS: This trial randomly assigned 3031 non-ST elevation ACS patients to routine early intervention (coronary angiography within 24 hours) or to delayed intervention (coronary angiography at 36 hours or more). Overall difference between two groups in terms of the primary endpoint (composite of death, MI or stroke) was not statistically different. However, early intervention reduced the composite of death, MI or refractory ischemia (secondary endpoint) and in high-risk patients, was superior to a delayed invasive strategy.

On analysis of the clinical settings in which the trials were performed, it is conspicuous that the first three trials, TIMI IIIB, VANQWISH, and MATE had no or negligible stent use, no clopidogrel before or after PCI and no GP IIb/IIIa receptor antagonists. In this respect, they differ from the modern trials with substantial stent use and modern antiplatelet therapy. If only the trials of modern era are analyzed, the fixed effects model demonstrated a significant benefit with respect to death and myocardial infarction at 6 to12 months with the invasive strategy when compared with the conservative strategy. Nevertheless, there is still substantial heterogeneity, which can be largely attributed to ICTUS. In the random effects model, the point estimate for the odds ratio for death and myocardial infarction at 6 to 12 months is more in favor of the invasive strategy.

Among the markers of risk in NSTE-ACS, troponin-T is considered the most robust; however, ICTUS trial tells us that apparently not all patients with elevated troponins gain from revascularization. There appear to be some groups in which the initial hazard is not rewarded by a long-term benefit. There are two potential consequences from this conclusion. First, any effort should be made to reduce the early hazard of the intervention, e.g. pretreatment with clopidogrel 600 mg. The second consequence would be to lay down criteria that identify patients who may not benefit from revascularization in ACS. Until there criteria are validated in appropriately sized clinical studies, it appears prudent to pursue the invasive strategy in most patients with high-risk NSTE-ACS, given the evidence from all previous trials. In addition, the results of the ISAR-COOL trial suggest that when pursuing the invasive strategy, intervention should be performed as early as possible because most cardiac complications occur within the first day after hospital admission. TIMACS suggests that early invasive strategy within 12 to 24 hours (medium 14 hours) is preferred in high-risk patients, whereas a more delayed approach may be beneficial in low-to-intermediate risk patients.

Michelangelo: OASIS-5 women's substudy presented in 2007, worse outcome was reported with invasive strategy among women with NSTE-ACS. Women did not benefit from a routine invasive strategy (within 7 days). Similar trends have been reported by subgroup analysis of FRISC-II and RITA-3 in the past. This issue too needs to be addressed specifically in a separate large trial.

Indications of Urgent Invasive Strategy

Urgent coronary angiography and revascularization should be undertaken within 2 hours in the following patients:

- Refractory angina (e.g. evolving MI without ST abnormalities)
- Recurrent angina despite antianginal treatment associated with ST depression (≥ 2 mm) or deep negative T waves
- Clinical symptoms of heart failure or hemodynamic instability ('shock')
- Life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia)

In addition to aspirin, clopidogrel, anticoagulants (UFH/LMWH/fondaparinux), a GP IIb/IIIa inhibitor (tirofiban, eptifibatide) should be added in symptomatic patients bridging the time to catheterization.

Indications of Early Invasive Strategy

Early coronary angiography and revascularization should be performed within 72 hours in moderate-to-high risk patients, i.e. patients with following features:

- Elevated troponin levels
- Dynamic ST-or T-wave changes (symptomatic or silent) (≥ 0.5 min)
- Diabetes mellitus
- Reduced renal function (GFR < 60 mL/min/1.73 m^2)
- Depressed LVEF < 40 percent
- Prior MI
- Early post-MI angina
- PCI within 6 months
- Prior CABG.

Conservative (No PCI/Elective PCI) Strategy

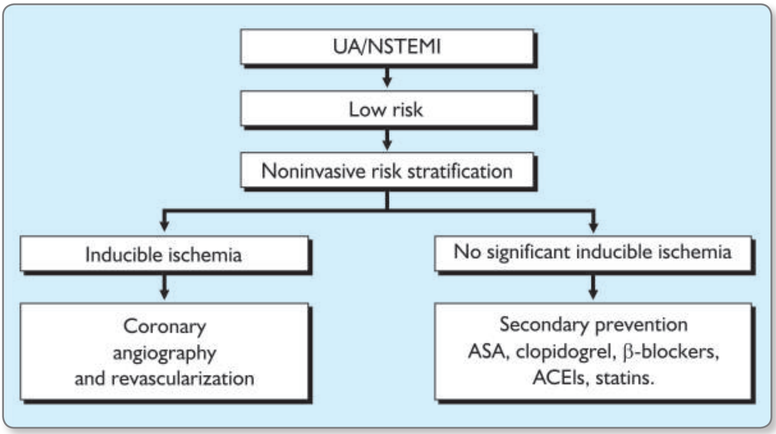
This is recommended in patients, who have following features:

- No recurrence of chest pain
- No signs of heart failure
- No abnormalities in the initial ECG or a second ECG (6–12 hours)
- No elevation of troponins (on arrival and at 6–12 hours)

The further management in these patients is similar to the evaluation of stable CAD. Before discharge, a stress test for inducible ischemia is useful for further decision making.

Table 2.6 Risk stratification of patients with UA/NSTEMI

High-risk (Annual mortality > 3%)	**Intermediate risk (Annual mortality 1–3%)**	**Low-risk (Annual mortality < 1%)**
Severe resting LV dysfunction (LVEF<35%) High-risk treadmill score (score -11 or less) Severe-exercise LV dys function (Exercise LVEF 35%) Stress induced large perfusion defect (particularly if anterior) Stress induced multiple perfusion defects of moderate size Large, fixed perfusion defect with LV dilation or increased lung uptake (Thallium-201) Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (Thallium 201) Echocardiographic wall-motion abnormality (>2 segments) developing at low dose dobutamine (10 mcg/kg/min or less or at low heart rate (<120/min) Stress echocardiographic evidence of extensive ischemia	Mild/moderate resting LV dysfunction (LVEF 35-49%) Intermediate risk treadmill score (–11 to 5) Stress induced moderate perfusion defect without LV dilation or increased lung intake (Thallium 201) Limited stress echocardiographic ischemia with a wall-motion abnormality only at higher doses of dobutamine involving ≤ 2 segments	Low-risk treadmill score (5 or greater) Normal or small myocardial perfusion defect at rest or with stress. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress.



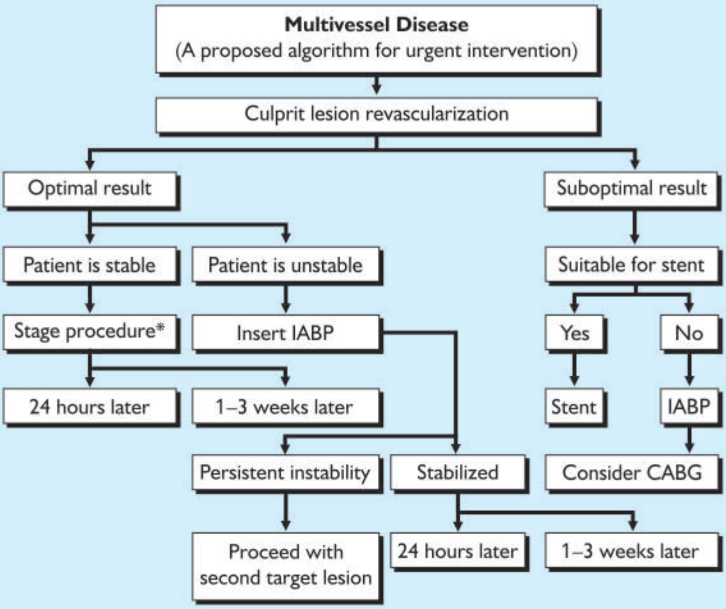
Emerging Role of CT-coronary Angiography

Recently published ROMICAT II trial on 1370 subjects with possible acute coronary syndrome, a coronary CT angiography based strategy for low-to-intermediate risk patients appeared to allow safe, expedited discharge from the emergency department of many patients, who would otherwise be admitted. A higher rate of detection of coronary disease was also observed.

Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting

Patients with NSTE-ACS are not a homogenous population. Left ventricular function is very important prognostically. Coronary pathology varies from single-vessel disease involving small territory to severe multivessel disease. Several trials have compared PTCA and CABG in patients with ischemic heart disease, many of whom had UA, with both revascularization strategies

An algorithm for intervention in UA/NSTEMI with multivessel CAD



** Indications for staging*

- *Thrombus immediately after PTCA*
- *Severe dissection or impaired flow after intervention*
- *Procedure duration > 3 hours*
- *Contrast media volume > 400 cc*
- *Borderline lesions (50–70% stenosis) without objective evidence for ischemia*

resulting in similar rates of death or MI, but a greater need for additional procedures in those initially treated with PTCA (RITA trial, ERACI trial). But in the BARI trial, diabetics with triple-vessel disease had a significantly lower mortality with CABG compared to PTCA at 5 years (80.6% vs 65.5%), P=0.003). SYNTAX trial compared PCI using drug-eluting stents to CABG in triple vessel or left main CAD. Rates of primary endpoint were significantly higher in the PCI group vs CABG (17.8% vs 12.4$, P=0.002) in large part because of an increased rate of repeat revascularization (13.5% vs 5.9%, P <0.001). Patients with left ventricular dysfunction in particular often have severe multivessel disease which may not be amenable to PCI and these patients may have to be referred for CABG.

The 2007 ACC/AHA UA/NSTEMI guidelines recommend CABG as the preferred revascularization strategy for patients with significant left main disease (> 50% stenosis) (Class I), patients with three-or two-vessel disease, who have significant proximal LAD stenosis and either treated diabetes mellitus (Class IIa) or LV dysfunction (Class I). Special aspects of management of UA/NSTEMI in patients with chronic kidney disease have recently been addressed by ESC 2011 NSTE-ACS Guidelines.

Important variations in coronary artery pathology are as follows:

- Number of arteries involved
- Location of stenosis within the artery (e.g. proximal LAD lesion is much more ominous than a distal circumflex lesion)
- Length and morphology of stenosis.

Recommendations for Patients with CKD (ESC 2011 NSTE—ACS Guidelines)

	Class[a]	Level[b]
Kidney function should be assessed by CrCl or eGFR in patients with NSTE-ACS, with special attention to elderly people, women, and patients with low body weight, as near normal serum creatinine levels may be associated with lower than expected CrCl and eGFr levels.	I	C
Patients with NSTE-ACS and CKD should receive the same first-line antithrombotic treatment as patients devoid of CKD, with appropriate dose adjustments according to the severity of renal dysfunction.	I	B
Depending on the degree of renal dysfunction, dose adjustment or switch to UFH with fondaparinux, enoxaparin, bivalirudin, as well as dose adjustment with small molecule GP IIb/IIIa receptor inhibitors are indicated	I	B
UFH infusion adjusted to aPTT is recommended when CrCl is <30 mL/min or eGFR is < 30 mL/min/1.73 m^2 with most anticoagulants (fondaparinux <20 mL/min).	I	C

	Class[a]	Level[b]
In patients with NSTE-ACS and CKD considered for invasive strategy, hydration and low-or iso-osmolar contrast medium at low volume (<4 mL/kg) are recommended	I	B
CABG or PCI is recommended in patients with CKD amenable to revascularization after careful assessment of the risk-benefit ratio in relation to the severity of renal dysfunction.	I	B

a = class of recommendation; b = level of evidence; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CABG = coronary artery bypass graft; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Medical Regimen on Discharge

1. For UA/NSTEMI patients treated medically without stenting, aspirin should be prescribed indefinitely; clopidogrel (75 mg per day) or ticagrelor (90 mg twice daily) should be prescribed for up to 12 months. Recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily. For aspirin allergic patients, use either clopidogrel or ticagrelor alone (indefinitely) or try aspirin desensitization. There are no data for therapy with two concurrent $P2Y_{12}$ receptor inhibitors and this is not recommended in case of aspirin allergy.
2. For UA/NSTEMI patients treated with a stent (BMS or DES), aspirin should be continued indefinitely. Clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months in patients receiving DES and up to 12 months for patients receiving BMS continuation of a $P2Y_{12}$ receptor inhibitor beyond 12 months may be considered following DES placement (Class IIb recommendation).
3. Beta-blockers especially in patients with reduced LV function on long term (IA)
4. ACE inhibitors indicated long-term in all patients with LVEF < 40% and in patients with diabetes, hypertension or chronic kidney unless contraindicated (IA). ACE inhibitors should be considered for all other patients to prevent recurrence of ischemic events (IIa-B). Agents and doses of proven efficacy are recommended.
5. Angiotensin-receptor blockers should be considered in patients who are intolerant to ACE inhibitors and/or who have heart failure or MI with LVEF < 40 percent (I-B).
6. Aldosterone receptor antagonists (blockade) should be considered in patients after MI who are already treated with ACE inhibitors and beta-

blockers and who have a LVEF < 35 percent and either diabetes or heart failure, without significant renal dysfunction (Serum creatinine > 2.5 mg/dl for mean and > 2.0 mg/dL for women) or hyperkalemia (I-B).

7. Statins are recommended in all NSTE-ACS patients (in absence of contraindications) irrespective of cholesterol levels initiated early (within 1–4 days) after admission. Intensive lipid lowering therapy (e.g. atorvastatin 80 mg as in PROVE-IT TIMI-22 trial) with target LDL-C < 70 mg percent is advised.
8. Calcium channel blockers are indicated especially in hypertensive patients, either alone or in combination with beta-blockers.
9. Long-term nitrates are indicated in patiens with angina.

Risk Factor Modification

1. Stop smoking
2. Weight reduction
3. Control of diabetes HbA_1C < 7 percent
4. Control of hypertension BP < 130/85
5. LDL < 100 mg percent or preferably < 70 mg percent
   HDL > 40 mg percent (men) or > 50 mg percent (women)

Suggested Reading

1. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart et al. 2007;28:1598-1660.
2. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341-81.
3. Hamm CW, Bassand JP, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal 2011, doi 10.1093/euheartj/ehr236.
4. Hamm CW, Mollmann H, Bassand JP, et al. The ESC Textbook of Cardiovascular Medicine; 2nd edn, Oxford University Press, 2009.
5. Thygesen K, Mair J, Katus H, Plebani M. et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010,31:2917-2204.
6. Van de Werf F, Bax J, Betrju A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation : the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909-45.
7. Wijns W, Kolh P, Danchin N, Di Mario et al. Guidelines on Myocardial Revascularization. The Task Force on Myocardial Revascularization Society of Cardiology (ESC)

and the European Association for Cardio-Thoracic Surgery (EACTS), Eur Heart J 2010;31:250-255.

8. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA Focussed Update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines J Am Coll Cardiol 2011,57:1920-59.

chapter 3

Cardiogenic Shock

Sweety Trivedi, Soumitra Kumar, Sudeshna Majumder

Definition

Clinical evidence of systemic hypoperfusion with:

i. SBP < 90 mm Hg for at least 30 minutes or MABP 30 mm Hg lower than baseline or need for supportive measure to maintain SBP > 90 mm Hg
ii. Severe reduction in cardiac index (< 1.8 L/min/ m^2 without support or < 2.2 L//min/m^2 with support)
iii. Pulmonary capillary wedge pressure > 15mm Hg

Etiology

1. **Acute myocardial infarction:**

Pump failure (65-80%)
- Large infarct size
- Small infarct with pre-existing severe LV dysfunction

Mechanical (12%)
- Acute MR
- Ventricular septal rupture
- Free wall rupture
- Pericardial tamponade
- RVMI

2. **Other conditions:**

a. Fulminant myocarditis or end stage cardiomyopathy
b. Severe myocardial contusion
c. Prolonged hypotension with pre-existing severe CAD and severe LV dysfunction
d. Prolonged cardiopulmonary bypass
e. Septic shock with severe myocardial depression
f. LV outflow tract obstruction → Aortic stenosis; → HOCM
g. LV filling obstruction → Mitral stenosis; → Left atrial myxoma
h. Acute mitral regurgitation
i. Acute aortic insufficiency
j. Iatrogenic

Cardiogenic shock complicates 5 to 8 percent of cases of ST-elevation myocardial infarction (STEMI) and 2.5 percent of cases of non-ST-elevation myocardial infarction (NSTEMI) patients. Cardiogenic shock has a higher mortality rate (71.7%) than those without CS (12%, P < 0.001). Mortality with CS from NSTEMI is higher than that with STEMI (7.25% vs 6.3%, P = 0.05). With more aggressive triaging and increasing use of primary PCI for STEMI and early invasive strategy for NSTEMI, incidence of CS with AMI in declining. In patients who develop CS, it occurs within 24 to 48 hours in 59 to 74 percent of patients, within 3 to 4 days in 11 percent of patients and later than 4 days after the infarction in 30 percent of patients. Cardiogenic shock occurs earlier when it is due to left main CAD or right CAD rather than left anterior descending CAD. A slight majority of pump failure cases have three-vessel CAD (56%) or left main stem disease (16%). Left anterior descending coronary artery disease is responsible for 42 percent of CS cases, right coronary artery (RCA) disease for 30 percent, and left circumflex disease for only 14 percent.

There are differences in the populations of patients with STEMI and NSTEMI that develop CS. Non-ST-elevation myocardial infarction patients are older and more commonly diabetic, and generally have underlying multi-vessel disease and develop shock progressively while in the hospital rather than at admission.

Risk Factors

In Patients with Ischemic Cause of Cardiogenic Shock

Identification of high-risk patients is important as cardiogenic shock has a poor prognosis (70–90% mortality); therefore prevention by treating this high-risk group promptly before onset of cardiogenic shock definitely decreases the mortality.

Risk factors are:

- Age
- Systolic blood pressure at presentation
- Killip class at entry
- Heart rate
- Anterior infarction
- Height
- Weight
- Time to treatment
- Diabetes mellitus
- History of cigarette smoking
- Current smoking
- Previous coronary artery bypass grafting
- Hypertension
- Stroke
- Recurrent infarctions.

Of these, the following have a 90 percent sensitivity to predict outcome:

- Age
- Systolic blood pressure at entry
- Killip class at entry
- Heart rate
- Location of infarction.

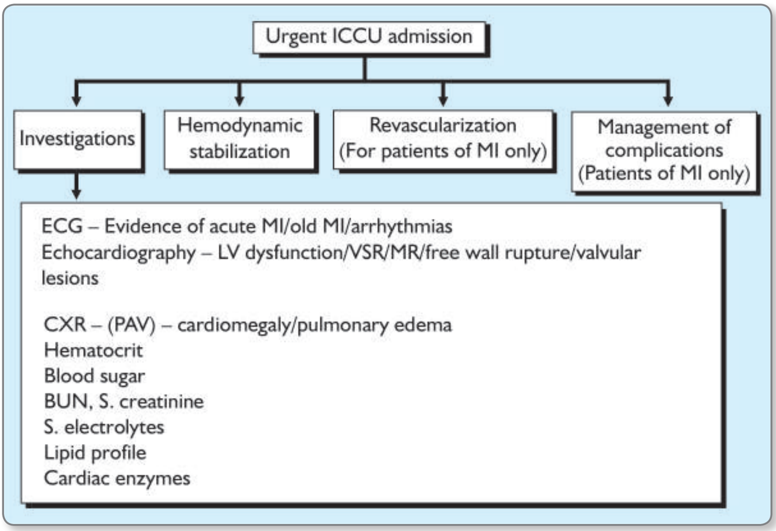
Diagnosis

A. History of acute myocardial infarction/cardiac disease with accompanying symptoms

B. Physical findings:
   - Hemodynamic instability
     – Hypotension, tachycardia, tachypnea
   - Peripheral vasoconstriction
     – Cool extremities with cyanosis
   - Pulmonary congestion
     – Diffuse rales in the chest
   - Systemic congestion
     – Prominent neck veins, edema, gallop rhythm, murmur of VSD or MR, electromechanical dissociation in free wall rupture
   - Findings specific to the underlying cause.

Management

Clinical diagnosis of shock established.



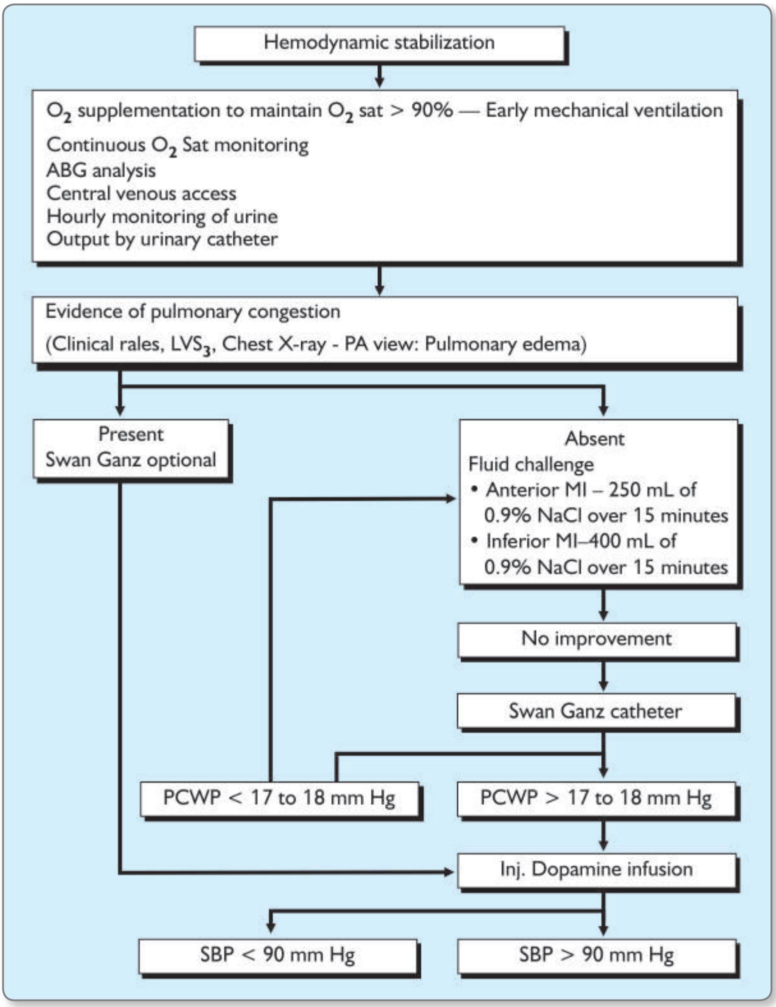
ACC/AHA indications for pulmonary artery catheterization in acute infarction.

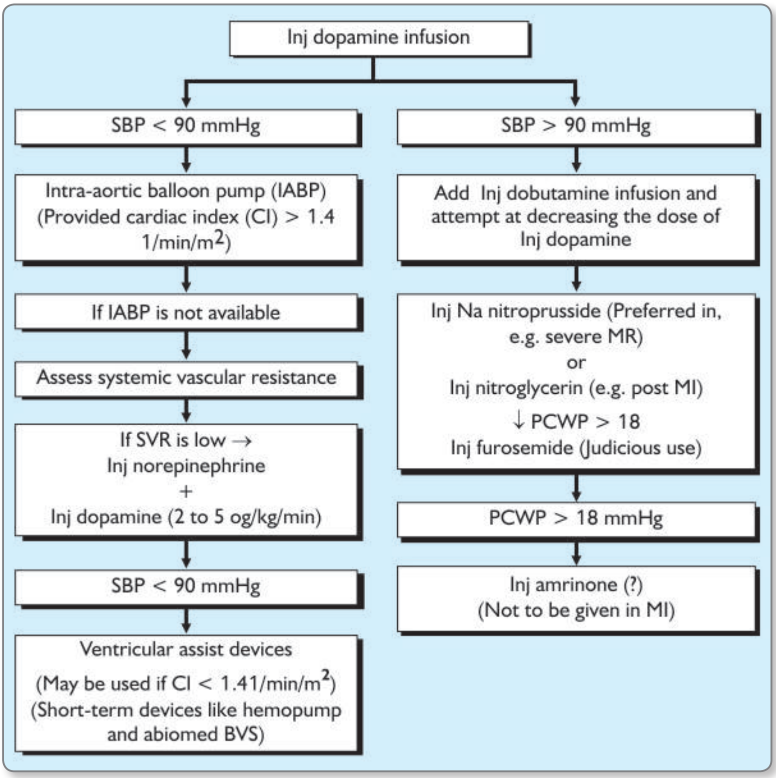
Class I

- Severe or progressive CHF or pulmonary edema
- Cardiogenic shock or progressive hypotension
- Suspected mechanical complications of acute infarction.

Class II

Hypotension which does not respond promptly to fluid administration in a patient without pulmonary congestion.



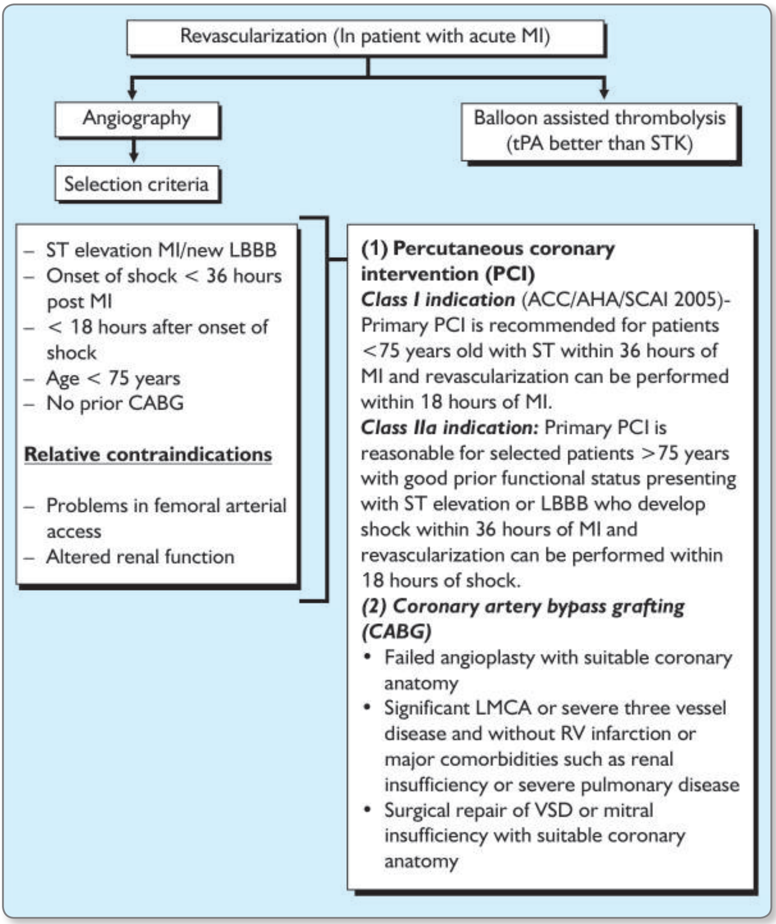


Mechanical Support Devices

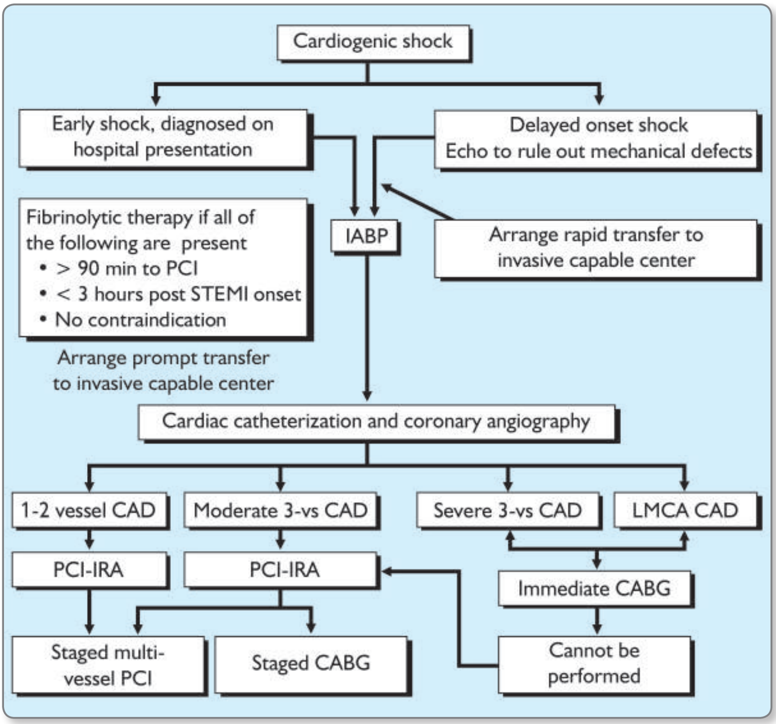
1. IABP
2. Percutaneous cardiopulmonary support
3. Left ventricular assist devices
4. Extracorporeal life support.

IABP

- Intra-aortic balloon counter pulsation has long been the mainstay of mechanical therapy for CS
- Inserted through common femoral artery with proximal end placed just distal to distal left subclavian artery
- The 30 to 50 cc helium filled balloon is inflated in diastole (Improved coronary and peripheral perfusion) and deflates in systole (Decrease afterload)
- Hemodynamic effects:
  - ↓ peak systolic arterial pressure
  - ↓ heart rate



  - cardiac output and ↑↑end-diastolic aortic pressure
  - ↔ LVEDP/PCWP
  - ↑↑↑↑ diastolic aortic pressure
  - ↑↑↑↑ mean aortic pressure
- Indications:
  - AMI ± CS
  - Refractory unstable angina
  - Stabilization of left main disease
  - Complications of AMI
  - Weaning from cardiopulmonary bypass



*PCI in noninfarcted artery is indicated in hemodynamically compromised patients if the stenotic artery perfuses a large area of myocardium and the procedure can be performed efficiently.

- High-risk cardiac percutaneous revascularization
- Bridge to cardiac transplantation
- High-risk noncardiac surgery in coronary patients
- Refractory arrhythmias
- Myocardial contusion
- Right ventricular failure.

Contraindications

- Severe peripheral vascular disease
- Severe aortic incompetence
- Active bleeding
- Patients with contraindications to anticoagulation
- Thrombocytopenia (< 50,000)
- Acute stroke.

Complications

- Limb ischemia
- Cholesterol embolization
- Infection.

Does IABP Extend Life in CS?

Previous studies have been inconclusive; however, the recently published IABP SHOCK II trial in which IABP was compared to optimal medical therapy (OMT) on top of PCI in STEMI patients with CS, IABP was not shown to have any edge over OMT in terms of the primary end-point of 30-day-mortality. Lack of benefit in terms of primary end-point benefit is supported by lack of benefit in terms of secondary end-points of serum lactate, hemodynamic parameters, SAPS-2 socre, serial creatinine, CRP etc.

Percutaneous Cardiopulmonary Support

- Provides complete circulatory support during PCI independent of the underlying cardiac rhythm and cardiac function
- Can be used in–
  a. High risk PCI
  b. Myocardial jeopardy score > 3
  c. Vessel in question is the last remaining vessel
- Standby CPS is preferred than prophylactic CPS except in patients with extremely depressed LV function (EF < 20%)
- It involves insertion of large bore cannula in femoral artery and vein. Blood is drawn via cannula placed at right atrium level and circulated through a membrane oxygenator and heat exchanger and reintroduced through femoral artery

Left Ventricular Assist Devices

Currently, two percutaneous left ventricular assist devices [p(VAD)] are being used:

1. Tandem Heart pVAD
2. Impella 2.5 system

1. **Tandem Heart pVAD:** It is a left atrial to femoral arterial pVAD driver by a low speed centrifugal continuous flow pump. It removes blood from the left atrium by using cannula that is inserted through the femoral vein and into the left atrium via transseptal puncture. Blood is then returned to a systemic artery usually femoral with retrograde perfusion of abdominal and thoracic aorta.
2. **Impella 2.5 system:** It is a miniature 12F rotatory pump placed across the aortic valve that directly aspirates blood from LV cavity and expels into ascending aorta. It is distally connected to a portable mobile console that

displays actual revolution/minute. At its maximum speed of 51,000 rpm it provides output of 2.5 L/min. Impella 5 is also available.

PROTEFT I trial has demonstrated that Impella 2.5 system provides excellent hemodynamic support during high-risk PCI.

Advantage over IABP

IABP requires certain residual level of left ventricular function whereas LVADs provide active circulatory support and better hemodynamic profile even in high-risk cases or cases with poor LVEF.

Disadvantages over IABP

LVAD are not currently recommended as first line treatment in CS because although they have better hemodynamic profile, there is no improvement in the 30-day survival.

Extracorporeal Life-support

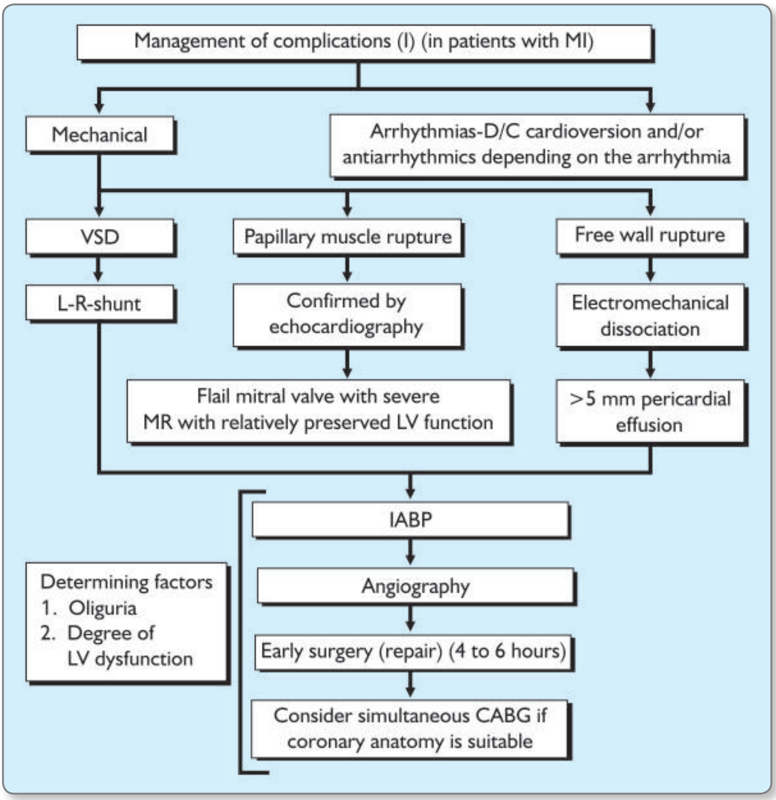
- It involves extracorporeal circulation of blood through an extracorporeal membrane oxygenator (ECMO) which relieves both the right and left heart and the lungs of the part of their workload.
- Anticoagulation is required.
- It might be considered as destination therapy or bridge to transplant but there is a limited experience with these devices, and observational studies have had conflicting results with no systematic direct comparison.

Treatment recommendations for CS as per ESC guidelines are as follows:

Treatment modality	Class of recommendation	Level of evidence
Oxygen	I	C
Mechanical ventilatory support according to blood gases	I	C
Hemodynamic assessment with balloon floatation catheter	IIb	C
Inotropic agents: Dopamine	IIb	B
Dobutamine	IIa	C
Intra-aortic balloon pump	I	C
LV assist devices	IIa	C
Early revascularization	I	B

SHOCK Trial Registry

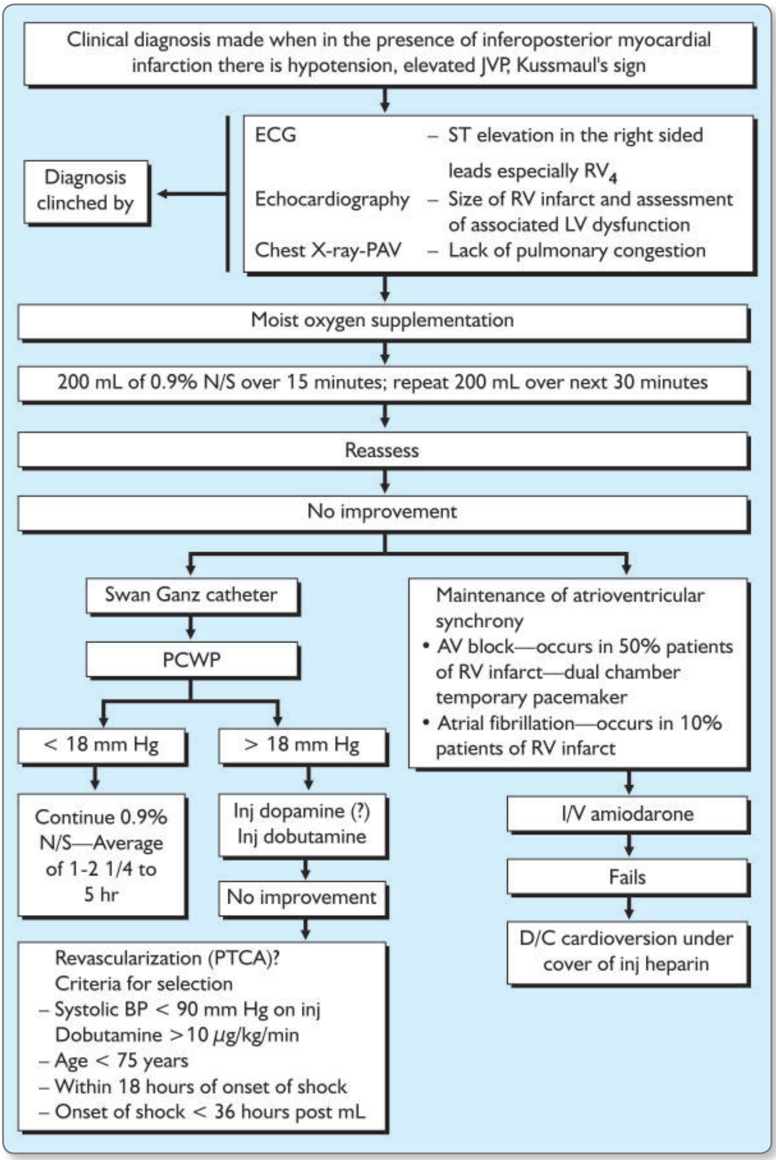
The randomized SHOCK trial registry compared a direct invasive strategy of emergency early revascularization to initial medical stabilization including thrombolysis and IABP, followed by delayed revascularization as clinically determined. At 6 and 12 months, 13 lives were saved for every 100 patients treated with early revascularization compared with the second group.

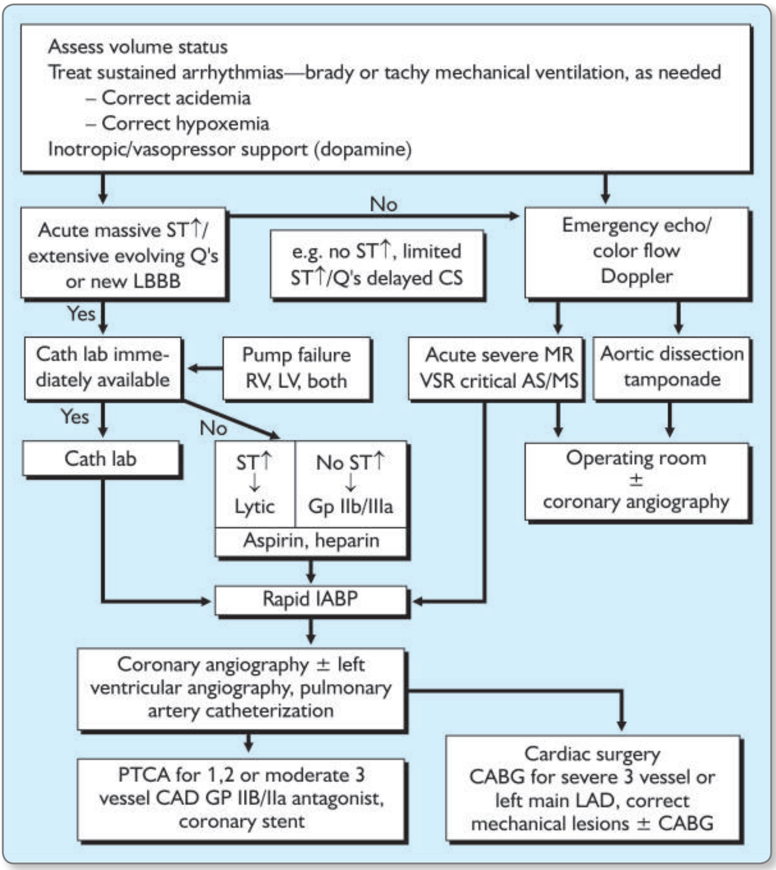


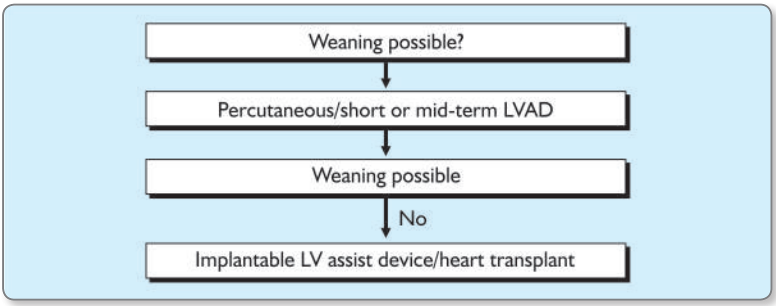
The improved survival was seen for patients with early and late shock and regardless of infarct location or the presence of comorbidities (e.g. diabetes, prior hypertension or MI). Although the small subgroup of those older than 75 years did not appear to benefit, there were imbalances between the groups and larger registries demonstrate a markedly lower in-hospital mortality for early patients, who were clinically selected for early revascularization, even after adjustment for their lower risk profile. More than 80 percent of trial survivors were NYHA CHF Class I and Class II at 1 year postinfarct.

Use of stents and GPIIb/IIIa antagonists are independently associated with improved survival. PCI should be performed with IABP support and low osmolality ionic contrast dye should be used. Outcome of patients, who underwent rescue PCI after thrombolysis was similar to those, who underwent direct PCI in the SHOCK trial. Low PCI success rates and no reflow remain challanges.

Management of right ventricular infarction




Assess volume status
Treat sustained arrhythmias—brady or tachy mechanical ventilation, as needed
– Correct acidemia
– Correct hypoxemia
Inotropic/vasopressor support (dopamine)
Acute massive ST↑/ extensive evolving Q's or new LBBB
No
e.g. no ST↑, limited ST↑/Q's delayed CS
Emergency echo/ color flow Doppler
Yes
Cath lab immediately available
Pump failure RV, LV, both
Acute severe MR VSR critical AS/MS
Aortic dissection tamponade
Yes
No
Cath lab
ST↑ ↓ Lytic
No ST↑ ↓ Gp IIb/IIIa
Aspirin, heparin
Operating room ± coronary angiography
Rapid IABP
Coronary angiography ± left ventricular angiography, pulmonary artery catheterization
PTCA for 1,2 or moderate 3 vessel CAD GP IIB/IIa antagonist, coronary stent
Cardiac surgery CABG for severe 3 vessel or left main LAD, correct mechanical lesions ± CABG


Weaning possible?
Percutaneous/short or mid-term LVAD
Weaning possible
No
Implantable LV assist device/heart transplant

Approximately, one-third of patients improve rapidly and dramatically after PCI, whereas most show no immediate hemodynamic improvement. Patients may deteriorate hemodynamically after reperfusion is established, particularly if they are reperfused late. Patients with cardiogenic shock and non-ST segment elevation MI have a higher-risk profile than shock patients with ST segment elevation but similar in-hospital mortality.

Dosage

Ionotropes

1. Inj dopamine—Infusion rate of 2 to 5 mcg/kg/min and increased every 2 to 5 min to a maximum of 50 mcg/kg/min. Route of administration—Central.
2. Inj dobutamine—Infusion rate of 2.5 to 10 mcg/kg/min. Route of administration—Central/peripheral.
3. Inj norepinephrine—Infusion rate of 2 to 4 mcg/min till a maximum of 15 mcg/min. To be combined with Inj dopamine (2 to 5 mcg/min) for renal protection. Route of administration—Central.
4. Inj amrinone—Bolus of 0.75 mg/kg over 2 to 3 min. If effective then 5 to 10 mcg/kg/min. If required, doses may be increased to 15 mcg/kg/min for short periods.

Vasodilators

1. Inj sodium nitroprusside—Infusion at 20 mcg/min with increments till a maximum of 200 to 300 mcg/min.
2. Inj nitroglycerin—Infusion at 5 to 10 mcg/min to a maximum of 100 to 150 mcg/min.

Newer Agents

Levosimendan is a relatively new calcium sensitization and K-ATP channel opener, which improves myocardial contractility without increasing oxygen requirements. It also induces peripheral and coronary vasodilation. Although levosimendan is well studied in acute heart failure, yet in view of its vasodilatory effects with subsequent blood pressure lowering, it is unlikely to become the drug of first choice in CS. However, it can improve hemodynamics in CS when combined with catecholamines to maintain adequate perfusion pressures. Its current role in CS needs to be defined in further studies.

Nitric oxide synthase inhibitors are another group of agents that are being tried in CS in view of hyperactivity of eNOS and iNOS. Following the dose-ranging SHOCK-2 study, the TRIUMPH trial (Tilarginine acetate injection in a Randomized International Study on Unstable MI patients with CS), the largest study in CS, investigated if the use of tilarginine improved survival in CS. Despite showing an immediate increase in blood pressure, NO synthase inhibition failed to demonstrate a survival benefit, which led to discontinuation of the trial after inclusion of 398 patients based on a prespecified interim analysis.

Some Formulae

1. Systemic vascular resistance $= \dfrac{80 \times (\text{MAP} - \text{CVP})}{10}$

   $= 1000$ to 1500 dynes/sec/cm^{-5}

2. Cardiac index $= \dfrac{\text{CO}}{\text{Body surface area}} = 2.5$ to 4.5 l/min/m^2

3. Cardiac output (Echocardiography): of any valve $\rightarrow$

   $\pi r^2 \times$ velocity time integral $\times$ heart rate

   (Where 'r' is the radius at the level of the valve)

Suggested Reading

1. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2008;51:210-47.
2. ESC guidelines on the management of acute myocardial infarction in patients of acute persistent ST-segment elevation. Eur Heart J. 2008;29:2909-45.
3. Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute mycardial infarction—etiologies management and outcome: a report from the SHOCK Trial Registry. Should we emergently revascularize occluded coronaries for cardiogenic shock ? J AM Coll Cardiol. 2000;36(suppl A):1063-70.
4. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295:2511-5.
5. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117:686-97.
6. The TRIUMPH Investigators. Effect of tilarginine acetate in patients with acute myocardial infarction and cardiogenic shock the TRIUMPH randomized controlled trial. JAMA. 2007;297:1657-66.
7. Thiele H, Allam B, Chateller G, et al. Shock in acute myocardial infarction: the Cape Horn for trials. Eur Heart J. 2010;31:1828-35.
8. Webb JG, Lowe AM, Sanboen TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol. 2003;42:1380-6.

chapter 4

Acute Heart Failure

Arghya Chattopadhyay, Soumitra Kumar

Etiology

a. Left ventricular causes: Acute myocardial infarction
Exacerbation of chronic heart failure*
Valvular regurgitation
Severe myocardial Ischemia
Others: Endocarditis
Myocarditis
Arrhythmias
Cardiomyopathy
Hypertensive crisis

b. Unrelated to left ventricle: Mitral stenosis
Thrombosed prosthetic mitral valve
Left atrial myxoma (rare)
Pulmonary venous obstruction (very rare)

Mechanisms Underlying Decompensation of Chronic Heart Failure*

- Noncompliance with treatment: 42%
- Inadequate preadmission treatment: 12%

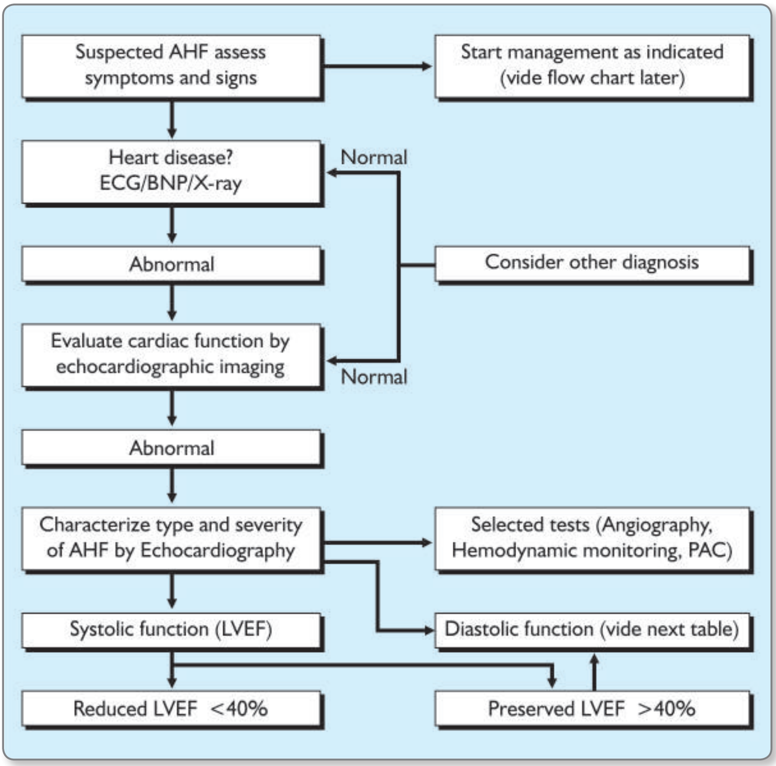
Classification of acute heart failure (Based on clinical and hemodynamic study by Forrester 1977)

		Mortality
Class I (Warm and dry)	Cardiac index 2.2–3.5 l/m/m^2 PCWP <18 mm Hg Normal tissue perfusion	2.2%
Class II (Warm and wet)	Cardiac index 2.2–3.5 l/m/m^2 PCWP >18 mm Hg Normal tissue perfusion	10.1%
Class III (Cold and dry)	Cardiac index < 2.2 l/m/m^2 PCWP < 18 mm Hg Severe tissue hypoperfusion	22.4%
Class IV (Cold and wet) Cardiogenic shock	Cardiac index < 2.2 l/m/m^2 PCWP > 18 mm Hg Severe tissue hypoperfusion	55.5%

- Ischemia: 14%
- Arrhythmias: 6%
- Poor BP control: 6%
- No precipitating cause: 20%

Diagnosis of Acute Heart Failure (AHF)

Arterial blood gas: Decreased PaO_2
(Indicated in severe HF or diabetics) Lowered pH



Decompensation of Pre-existing Chronic HF

- Lack of adherence
- Volume overload
- Pulmonary embolism
- Infections, e.g. pneumonia
- Cerebrovascular accident
- Surgery

Grading of congestion

Variables	1	0	1	2	3
A. **Bedside assessment**					
1. Orthopnea*	—	None	Mild	Moderate	Severe/worst
2. JVP (cm)	< 8 and no hepato-jugular reflex (HJR)	—	8–10/hepato-jugular reflex	11-15	> 16
3. Hepatomegaly	Absent in the setting of normal JVP	Absent	Liver edge	Moderate pulsatile enlargement	Massive tender enlargement is extending to midline
4. Edema	—	None	1+	2+	3+/4+
B. **Laboratory**					
Natriuretic peptides (One)					
BNP	—	< 100	100–299	300-500	>500
NT-proBNP	—	< 400	400–1500	1500-3000	>3000
C. **Dynamic Maneuvers**					
1. Orthostatic testing	Significant ↓ in SBP/↑ HR	No change in SBP/HR	—	—	—
2. 6 min. walk test	—	No difficulty	Mild	Moderate	Severe/worst
3. 6 min. walk test/ (distance in metres)	> 400	300-400	200–300	100-200	< 100
4. Valsalva maneuver	Normal response	—	Absent/over-shoot pattern	Square wave pattern	—

Congestion grade: <1 = none; 1-7 = mild; 8-14 = moderate; 5-20 = severe.
*Orthopnea: = absent, 1 = mild (use of one pillow); 2 = moderate (> 1 pillow); 3 = Severe (Sleeps in armchair on a setting position).
Modified from Gheorghiade M, Follath F, Ponikowski, et al. Eur J Heart Fail. 2010;12:423.

- Renal dysfunction
- Asthma/COPD
- Drug abuse
- Alcohol abuse
- Inadequate preadmission treatment
- Poor BP control.

Investigations

ACC/AHA guidelines for initial evaluation of patients with heart failure (2009 Focused Update of ACC/AHA 2005 Guidelines).

Class-I Indications

1. Thorough history and physical examination to identify cardiac and non-cardiac disorders/behaviours that might cause HF/accelerate its development/progress (Level of evidence: C).
2. Obtain careful history of current and past use of alcohol, drugs, current or past standard or alternative medicines (Level of evidence: C).
3. Initial assessment of the patients ability to perform routine and desired activities of daily life (Level of evidence: C).
4. Assess volume status; orthostatic blood pressure changes, measure height, weight, body mass index (Level of evidence: C).
5. Initial Lab.: Complete blood count, urine routine examination, serum electrolytes (including calcium and magnesium), blood urea nitrogen, creatinine, fasting blood sugar, HbA1C, lipid profile, liver function test and thyroid-stimulating hormone (Level of evidence: C).
6. 12-lead ECG and chest radiography (posteroanterior) (Level of evidence: C).
7. Two-dimensional echocardiography with Doppler; radionuclide ventriculography to assess LVEF and volumes (Level of evidence: C).
8. Coronary arteriography in patients with angina, significant Ischemia except those, who are not eligible for revascularization (Level of evidence: C).

Clinical clues to the presence of noncardiogenic pulmonary edema

	Cardiogenic	Noncardiogenic
History	Cardiac event, e.g. orthopnea	Severe noncardiac illness
Examination	Cool peripheries, S3, JVP↑, "Moist" crackles	Usually warm peripheries, JVP↓, no S3, "dry" and more extensive crackles
ECG	Usually abnormal	Usually normal
CXR	Perihilar distribution	Peripheral distribution
PCWP	> 20 mm Hg	< 20 mm Hg
Echo	Almost always abnormal	Usually normal

	Systolic failure	Diastolic failure
History	Coronary disease	Hypertension
Examination	S3	S4
Chest X-ray	Cardiomegaly-present	Generally absent
ECG	Q waves, low R wave voltage, ST elevation	Electrical LVH

Stage	Chest X-ray	Approximate left atrial pressure (mm Hg)
Pre-edema ↑ flow in vessels Distended lymphatics	Upper lobe diversion Kerley lines	12-15
Interstitial edema Fluid in perialveolar spaces	Fluid in fissures Peribronchial cuffing Micronodule Hilar blurring	15-20 19-24
Alveolar edema Alveolar flooding	Fluffy hilar shadowing "Bat's wing"/"butterfly" shadowing. Pleural effusions, loss of lung volume	> 25

Electrocardiogram

A normal electrocardiogram (ECG) is uncommon in heart failure; helps to identify (a) rhythm; (b) etiology in AHF and (c) loading conditions of the heart.

Biomarkers:

1. Inflammation [Elucidating the pathogenesis of HF; provide prognostic information and risk stratification; identify subjects at risk for HF].
   a. CRP
   b. TNF
   c. Fas (APO-1)
   d. IL-1,6,18
2. Oxidative stress [elucidating pathogenes B; provide prognostic information and risk stratification and potential targets of therapy].
   a. Oxidized low density lipoproteins
   b. Myeloperoxidase
   c. Urinary biopyrrins
   d. Urinary and plasma isoprostane
   e. Plasma malondialdehyde
3. Extracellular matrix remodeling [pathogenesis and targets of therapy].
   a. Matrix metalloproteinases (MMP)
   b. Tissue inhibitors of metalloproteinase
   c. Collagen propeptides

   d. Propeptide; procollagen type I
   e. Plasma procollagen type III
4. Neurohormones [Pathogenesis; risk stratification and target of therapy):
   a. Norepinephrine
   b. Renin
   c. Angiotensin-II
   d. Aldosterone
   e. Arginine vasopressin
   f. Endothelin
5. Myocyte injury [Pathogenesis, risk stratification and target therapy]
   a. Cardiac specific troponin I and T
   b. Myosin light chain kinase-I
   c. Heart type fatty acid protein
   d. CKMB
6. Myocyte stress [Risk stratification; subjects at risk; target of therapy and diagnosis and monitoring of therapy].
   a. BNP
   b. N-terminal pro-BNP
   c. Mid-regional fragment of proadrenomedullin
   d. ST2
7. New Biomarkers [Prognostic information and risk stratification]
   a. Chromogranin
   b. Galectin 3
   c. Osteoprotegerin
   d. Adiponectin
   e. Growth differentiation factor 15

Clinical relevance of promising novel biomarkers

Biomarker	Diagnosis	Prognosis	Value as a therapeutic guide	Cardiac specificity
NT-proBNP and BNP	++++	++++	++	Specific
MR-proANP	++++	++++	Properly similar to NT-proBNP/BNP	Specific
sST2	+	++++	?	Relatively nonspecific
GDF-15	-	+++	?	Relatively nonspecific
Highly sensitive troponins	+	++++	?	Specific
CRP	-	++	?	Nonspecific
TNF-α	-	++	?	Nonspecific
IL-6	-	++	?	Nonspecific
PTX3	-	++	?	Unknown
MPO	-	++	?	Relatively nonspecific
Gal-3	-	+++	?	Relatively nonspecific
ET-1	-	++	?	Relatively nonspecific
UCN-1	-	++	?	Relatively nonspecific
Copeptin	-	++	?	Nonspecific
MR proADM	-	++++	?	Nonspecific
RDW	-	++++	?	Nonspecific
Cystatin C	-	++++	?	Nonspecific
NGAL	-	++++	?	Nonspecific
β-Trace protein	-	+++	?	Nonspecific

Brain Natriuretic Peptide

1. Levels increase progressively with worsening NYHA class.
2. Levels are higher in HF with low EF than HF with preserved EF.
3. Levels $\uparrow$ with age and worsening renal function.
4. Levels are more in female than male.
5. Inverse relationship with BMI.
6. Level does not necessarily indicate that decompensation is present/ even imminent because stable HF patients have high value.
7. Increased in acute coronary syndrome and various hyperdynamic circulatory states like sepsis, hyperthyroidism and cirrhosis.
8. Patient with RV dysfunction as a result of pulmonary embolism, pulmonary hypertension or severe lung disease may have increased BNP.
9. Patient with flash pulmonary edema may not have elevated levels because they are often evaluated before NP are released from LV.
10. Patient with pericardial restriction do not have $\uparrow$BNP as LV wall stress is only minimally elevated.

Suggested Cut-off values for BNP and NT-proBNP use in specific situations

	Cut-off value Pg/mL	Sensitivity (%)	Specificity (%)
To rule-out			
BNP	< 30–50	97	62
NT-proBNP	< 300	99	68
To diagnose ADHF			
Single test screening strategy			
BNP	< 100	90	76
NT-proBNP	< 900	90	85
Multiple test screening strategy			
BNP	< 100 to exclude	90	73
	100-400 gray zone	–	–
	>400 include in	63	91
NT-proBNP, age-stratified Approach	<450 for age <50 years	90	84
	<900 for age 50-75 years		
	<1800 for age >75 years		
Special situations			
Renal dysfunction (GFR <60 mL-Min – 1.73 m-2)			
BNP	< 200	88	63
NT-proBNP	(1) <1200 all ages Or (2) age-stratified approach Above	89	72

Contd...

Contd...

	Cut-off value Pg/mL	Sensitivity (%)	Specificity (%)
Obesity			
BNP	170 for BMI < 25 kg/m^2	90	77
	110 for BMI 25-35 kg/m^2	90	77
	54 for BMI ≥ 35 kg/m^2	91	70
NT-proBNP	< 900, no adjustment for BMI	87	76
	Age-stratified out points, No adjustment for BMI	86	90

PPV indicates positive predictive value; NPV negative predictive value; DHF acutely decompensated heart failure; BNP brain natriuretic peptide; NT pro-BNP amino-terminal pro-B type natriuretic peptide, GFR glomerular filtration rate; and BMI body mass index.
*Indicates not applicable.

Bedside Echocardiography

Presence of updated portable machines has made bedside assessment convenient and extremely useful in emergency cardiac management. Decrease in size (Hand carried devices) and technical upgradation (e.g. CW doppler, color flow imaging, tissue harmonic imaging, tissue doppler imaging, etc.) have made this tool almost mandatory in routine management of cardiac emergencies. Such devices are also useful in outpatient department as an adjunct to physical examination and for medical student teaching.

Echocardiography in AHF

Role in etiological diagnosis and formulation of treatment guidelines.

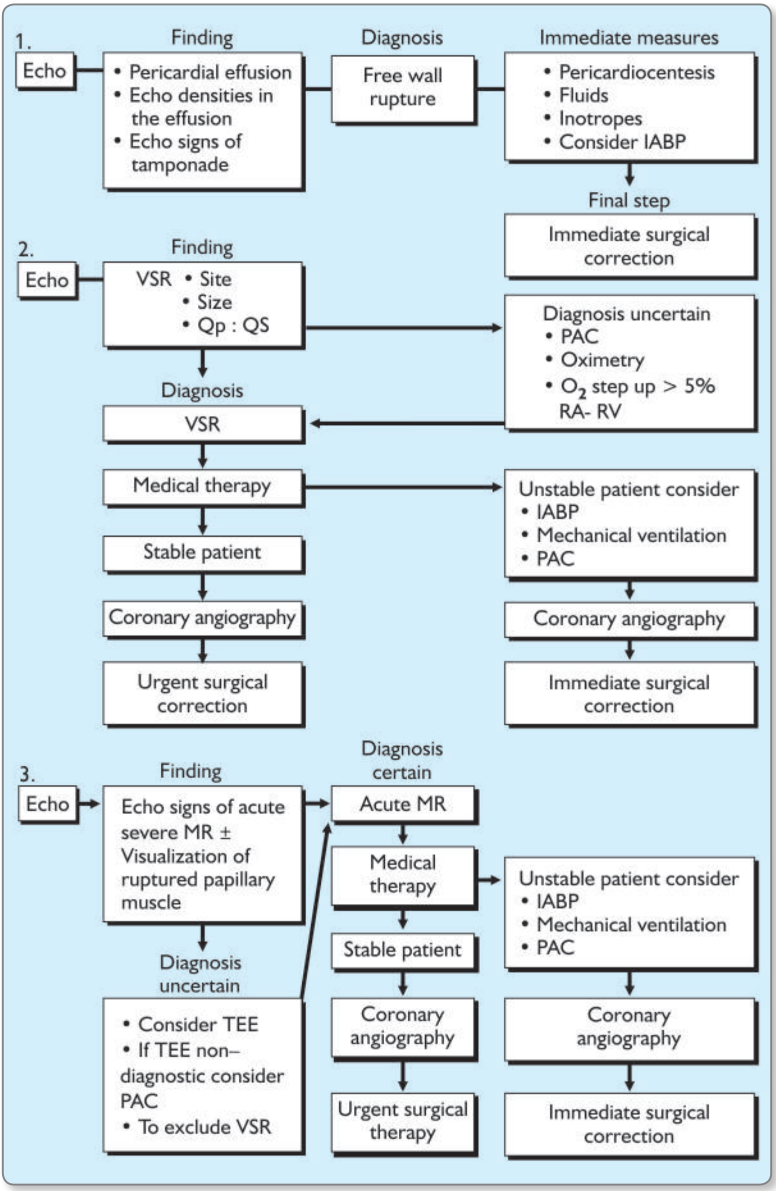
Hemodynamic Assessment by Echocardiography

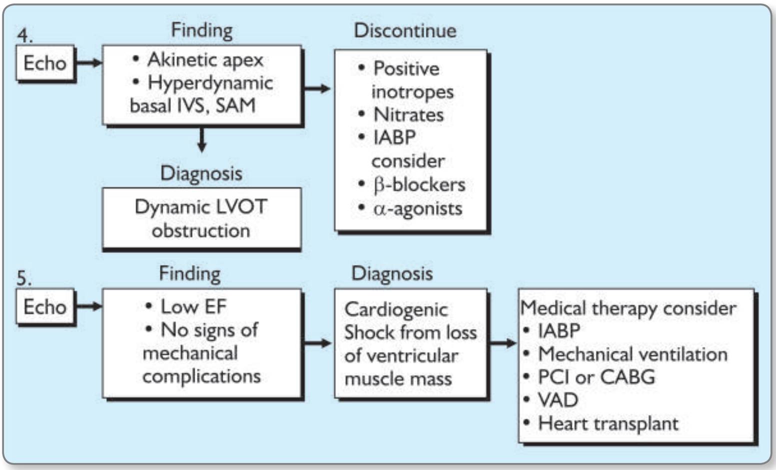
Assessment of Ventricular Function

Load Dependent Variable

i. Stroke volume = $(\text{diameter}_{LVOT})^2 \times 0.785 \times \text{VTI}_{LVOT}$
   (VTI = Velocity time integral)
ii. Cardiac output = (Heart rate x Stroke volume)/Body surface area
iii. Ejection fraction (LVEF) from volume data obtained by Simpson's method
   EF = (LVEDV – LVESV)/LVEDV × 100%
iv. dp/dt: Rate of pressure increase during isovolumic contraction and can be estimated from continuous wave Doppler mitral regurgitation jet.

$$\frac{dp}{dt} = \frac{\text{Pressure change between 1 m/s and 3 m/s}}{\text{Time difference between 1 m/s and 3 m/s}}$$


1.
Echo
Finding
• Pericardial effusion
• Echo densities in the effusion
• Echo signs of tamponade
Diagnosis
Free wall rupture
Immediate measures
• Pericardiocentesis
• Fluids
• Inotropes
• Consider IABP
Final step
Immediate surgical correction
2.
Echo
Finding
VSR • Site
• Size
• Qp : QS
Diagnosis uncertain
• PAC
• Oximetry
• O_2 step up > 5% RA- RV
Diagnosis
VSR
Medical therapy
Unstable patient consider
• IABP
• Mechanical ventilation
• PAC
Stable patient
Coronary angiography
Urgent surgical correction
Coronary angiography
Immediate surgical correction
3.
Echo
Finding
Echo signs of acute severe MR ± Visualization of ruptured papillary muscle
Diagnosis certain
Acute MR
Medical therapy
Unstable patient consider
• IABP
• Mechanical ventilation
• PAC
Diagnosis uncertain
• Consider TEE
• If TEE non–diagnostic consider PAC
• To exclude VSR
Stable patient
Coronary angiography
Coronary angiography
Urgent surgical therapy
Immediate surgical correction



v. Myocardial performance index (Tei index) = ICT + IRT/ET
(ICT = Isovolumic contraction time, IRT = Isovolumic relaxation time, ET = Relaxation time)

Normal value is 0.39±0.05. This index is altered in both systolic and diastolic myocardial dysfunctions and may also play an important role in assessing RV function.

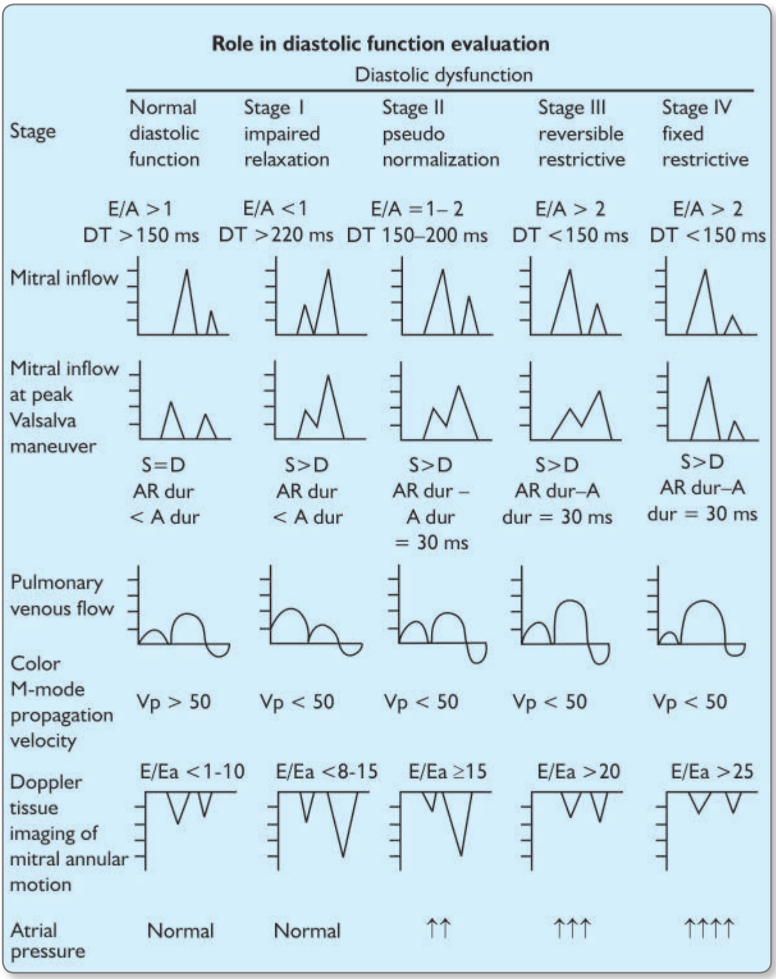
Load Independent Variables

i. Velocity of circumferential fiber shortening
ii. Maximal elastance Emax
iii. Preload recruitable stroke work [dp/dt max /EDV]
iv. Preload-adjusted maximal power and preload adjusted peak power.

Estimation of LV Filling Pressure

LV filling pressure is the most important hemodynamic data to obtain in the ICU.

i. Features in echocardiographic assessment which suggest elevated LV filling pressure.
   - Enlarged LA size, decreased function
   - Transmitral E/A ratio > 2
   - Deceleration time (DT) < 150 ms
   - Pulmonary venous flow: S/D < 40%
     AR amplitude > 25 cm/sec
     AR - A duration = 30 ms



A—Peak late diastolic transmitral flow velocity; A dur—Duration of a wave; AR dur—Peak pulmonary venous atrial reversal flow velocity duration; D—Peak diastolic PV flow velocity; DT—Deceleration time; E—Peak early diastolic transmitral flow velocity; Ea—Peak early diastolic myocardial velocity; LV—Left ventricular; S—Peak systolic PV flow velocity; Vp—Flow propagation velocity.

- $E/E_a > 15$
- Color M-mode flow propagation velocity PV < 45 cm/sec
- E/Vp > 2.0

ii. Estimation of LV filling pressure
Sinus rhythm : 1.24 [E/Ea] + 1.9
Sinus tachycardia: 1.47 (E/Ea) + 1.55
Atrial fibrillation: 0.82 (E/Ea) + 6.49

E = Mitral E wave velocity; Ea = Mitral annular tissue dopper velocity; Vp = Propagation velocity of LV inflow on color M mode; SF = Systolic fraction of pulmonary venous flow.

Pulmonary Artery Systolic Pressure

This can be estimated from tricuspid regurgitation (TR) peak velocity

$$RVSP = PASP = 4 \times (\text{peak TR velocity})^2 + \text{estimated RA pressure}$$

RVSP = Right ventricular systolic pressure

Estimation of right atrial (RA) pressure is done from size of inferior vena cava and its response to changes in respiration or a sniff.

IVC	Change with respiration/ sniff	Estimated RA pressure
Normal	Collapse or decrease > 50%	5 mm Hg
Normal (<2 cm)	Decrease < 50%	10 mm Hg
Dilated (>2 cm)	Decrease < 50%	15 mm Hg
Dilated with dilated hepatic veins	No change	20 mm Hg

Pulmonary Vascular Resistance

PVR (Wood units) = $10 \times TRV/TVI_{RVOT}$

[TRV = Tricuspid regurgitant velocity

TVI_{RVOT} = Right ventricular outflow tract time velocity integral]

In patients with increase PASP on Doppler echocardiography, an elevated PVR is suggested by TRV/TVI_{RVOT} ratio of > 0.2.

RV Function Assessment

Tricuspid annular plane systolic excursion (TAPSE) is a simple echocardiographic measure of RV ejection fraction but may be affected by co-existing COPD. A cut-off of 14 mm of TAPSE is independently associated with mortality in an unselected population of patients admitted for HF, even after adjusting for other known risk factors including LV ejection fraction or presence of valvular disease. Maximum velocity of systolic displacement wave of tricuspid annular plane can also be studied using Doppler tissue imaging to assess systolic dysfunction of RV (Normal value 14 cm/sec).

Hemodynamic Monitoring in AHF

i. **Central venous pressure (CVP):** Useful for delivery of fluids and drugs and can also be used to monitor CVP and venous oxygen saturation

(SVO_2). In patients with AHF, CVP rarely correlates with left atrial pressures and therefore, left ventricular (LV) filling pressures. CVP measurements are also influenced by presence of significant tricuspid regurgitation (TR) and positive end-expiratory pressure (PEEP) ventilation.

ii. **Pulmonary artery catheter (PAC):** PAC is a balloon floatation catheter that measures pressures in the superior vena cava (SVC), right atrium RA), right ventricle (RV) and pulmonary artery (PA) as well as cardiac output (by thermodilution) (**Figure 4.1**). Modern catheters can measure the cardiac output semicontinuously as well as mixed venous oxygen saturation and RV end-diastolic pressure and ejection fraction.
   - Insertion of a PAC for diagnosis of AHF is usually unnecessary except in complex patients with concurrent cardiac and pulmonary disease.
   - Pulmonary capillary wedge pressure (PCWP) is not an accurate reflection of LVEDP in patients with mitral stenosis, aortic regurgitation, ventricular interdependence, high airway pressure or stiff LV.
   - Several retrospective studies assessing the use of PAC in acute myocardial infarction demonstrated increased mortality with the PAC. mostly because of inapproapriate use of information derived from the catheter.
   - Use of a PAC is recommended in hemodynamically unstable patients, who are not responding in a predictable fashion to traditional treatments and in patients with a combination of congestion and hypoperfusion.
   - In cardiogenic shock and prolonged severe low output syndrome, it is recommended that the mixed venous oxygen saturation (SVO_2) from the pulmonary artery be measured as an estimation of oxygen extraction. The aim should be to maintain SVO_2 above 65% in patients with AHF.

iii. **Additional methods of hemodynamic assessment:**
   a. *Bedside echocardiography:* Already discussed in this chapter
   b. Noninvasive methods that are used to determine cardiac output include Doppler probes positioned in the suprasternal notch, the esophagus or the aorta. Currently, this technology does not compare reliably with thermodilution techniques and is not routinely used.
   c. *Bioimpedance:* Methodology quantitates flow through the thoracic aorta by assessing changes in impedance when current is applied across the thorax. Topical electrodes are placed on the chest and neck. The technique has been shown to correlate favourably with thermodilution methods in a wide spectrum of critically ill patients but is less reliable in conditions which significantly change the fluid content of the thorax, e.g. severe pulmonary edema, pleural effusions, hemothorax, etc.

Normal Range of Right Heart Pressures

Site	Pressure/mm Hg
Right atrium (RA)	0-5
Right ventricle (RV)	
Systolic	15-30
Diastolic	0-6
Pulmonary artery (PA)	
Systolic	15-30
Diastolic	5-13
Pulmonary wedge (PCWP)	2-12

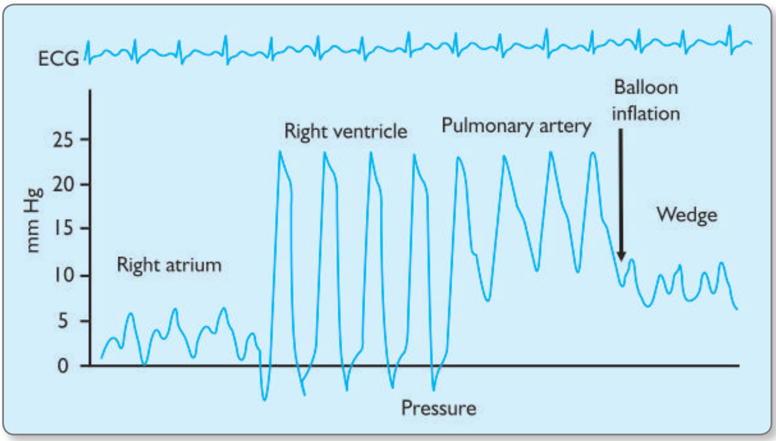


Fig. 4.1 Pressure tracing seen during advancement of a pulmonary artery catheter.

Some Calculations

Systemic vascular resistance (SVR) $= \dfrac{80\ (\text{MAP} - \text{CVP})}{\text{CO}}$

$= 1000 - 1500$ dynes/s/cm^{-5}

Pulmonary vascular resistance (PVR) $= \dfrac{80\ (\text{MPAP} - \text{PCWP})}{\text{CO}}$

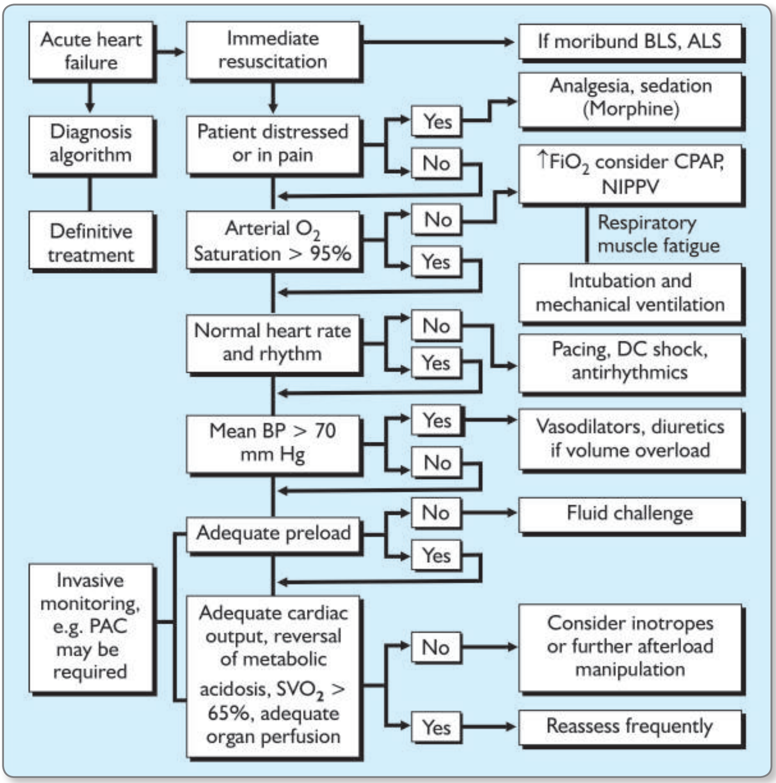
$= 120 - 250$ dynes/s/cm^{-5}

Cardiac index $= \dfrac{\text{CO}}{\text{Body surface area}} = 2.5 - 4.5\ l/\text{min/m}^2$

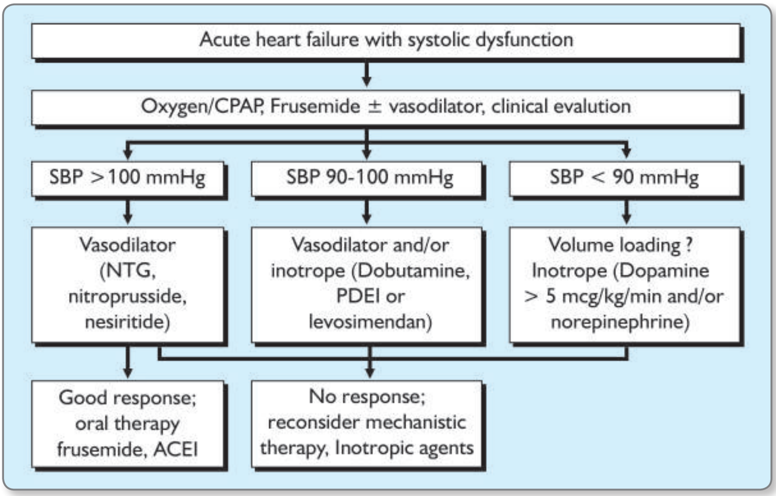
Hemodynamic Parameters in Different Conditions

Conditions	RA	PA	PCWP	CI	PVR	SVR
LV infarction	↔ or ↑	↔	↑↑	↓	↓	↑
RV infarction	↑	↓	↓	↓	↓	↑
VSD	↔ or ↑	↑	↑	↑	↑	↑
Papillary muscle rupture	↔ or ↑	↑	↑↑	↓	↑	↑
Massive pulmonary embolism	↑	↑	↓	↓	↑↑	↑
Tamponade	↑↑	↓	– to RA	↓	↔	↑
Early septicemia	↓	↓	↓	↑	↓	↓
Late septicemia	↔ or ↑	↔ or ↑	↑		↑	↑
Hypovolemia	↓	↓	↓	↓	↔	↑

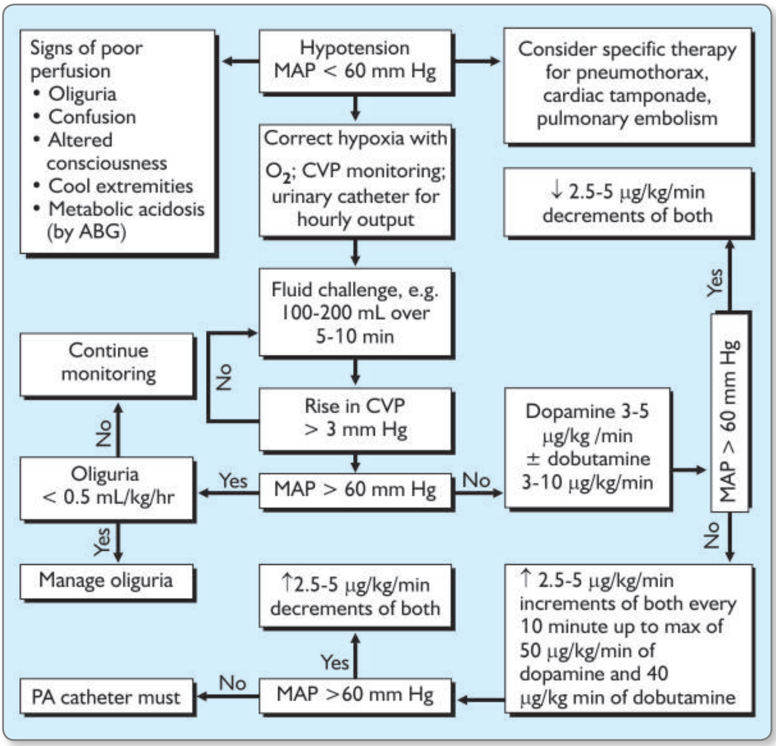
Approach to the Patient with Acute Heart Failure



Approach to AHF with Systolic Dysfunction



Approach to AHF with Hypotension



Further Management of Hypotension Depending on Hemodynamic Subsets

$SVO_2 > 60\%$, $CI > 2.2$ *l*/min/m^2, SVR < 1300 dyne.sec.cm^{-5}

- Reassure frequently
- Management of hypotension, hypoxia, oliguria, metabolic acidosis

$SVO_2 > 60\%$, $CI > 2.2$ *l*/min/m^2, SVR > 1300 dyne.sec.cm^{-5}

- IV nitrates (Nitroglycerin or isosorbide dinitrates) ± fluids
- Consider inodilators (Amrinone, milrinone)

$SVO_2 < 60\%$, $CI < 2.2$ *l*/min/m^2, PCWP < 18-20 mm Hg

- Fluid challenge → MAP > 60 mm Hg → IV nitrates ± Consider inodilators

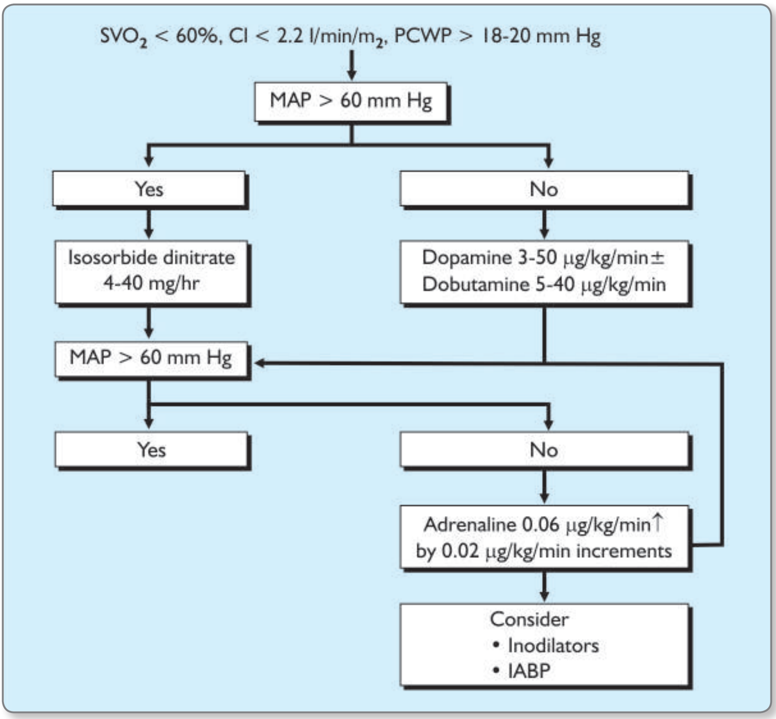
$CI > 2.2$ *l*/min/m^2, $SVO_2 < 60\%$, MAP > 60 mm Hg

- ↑ Dobutamine
- Consider inodilators (Milrinone/amrinone)

$CI > 2.2$ *l*/min/m^2, $SVO_2 > 60\%$, MAP < 60 mm Hg

- Noradrenaline 0.05 µg/kg/min, increase by 0.05 µg/kg/min increments
- Consider sepsis syndrome and manage accordingly.

$SVO_2 < 60\%$, $CI < 2.2$ *l*/min/m^2, PCWP < 18-20 mm Hg



Recommendation for Hospitalization Patients with Acute Docompensated Heart Failure (ADHF)

Hospitalization Recommended

i. Evidence of severe ADHF including hypotension, worsening renal function, mental status.
ii. Dyspnea at rest: Typically reflected by resting tachycardia, less commonly reflected by SpO_2<90%
iii. Hemodynamically significant arrhythmia including new onset rapid atrial fibrillation
iv. Acute coronary syndrome

Hospitalization should be Considered

i. Worsened congestion even without dyspnea
ii. Signs and symptoms of pulmonary or systemic congestion even in absence of weight gain
iii. Major electrolyte disturbances
iv. Associated comorbid conditions: Pneumonia, pulmonary embolism, dialectic ketoacidosis, symptoms suggestive of TIA/stroke
v. Repeated firing by implantable cardioverter-defibrillator
vi. Previously undiagnosed HF with signs and symptoms of systemic and pulmonary congestion

Treatment Goals for Patients Admitted for ADHF

i. Improve symptoms, especially congestion and low-output systems
ii. Restore normal oxygenation
iii. Optimize volume status
iv. Identify etiology
v. Indentify and address precipitating factors
vi. Optimize chronic oral therapy
vii. Minimize side effects
viii. Identify patients who might benefit from revascularization
ix. Identify patients who might benefit from device
x. Identify risk of thromboembolism and need for anticoagulation therapy
xi. Educate patients concerning medications and self-management of HF
xii. Consider and when possible, initiate a disease management program

Monitoring Recommendations for Patients Hospitalized with ADHF

Frequency	Value	Specifics
At least daily	Weight	Determine after voiding in the morning Account for possible increased food intake due to improved appetite

Contd...

Contd...

Frequency	Value	Specifics
At least daily	Fluid intake and output	
More than daily	Vital signs	Orthostatic blood pressure if indicated Oxygen saturation daily until stable
At least daily	Signs	Edema, ascites, pulmonary rales, hepatomegaly, Increased JVP, hepatojugular reflux, Liver tenderness,
At least daily	Symptoms	Orthopnea, paroxysmal nocturnal dyspnea (PND) or cough, nocturnal cough, dyspnea, fatigue lightheadednsss,
At least daily	Electrolytes	Potassium. sodium
At least daily	Renal function	BUN, serum creatinine

PHASE OF MANAGEMENT

Phase I : Management in ED

Dyspnea is the most common complain in ADHF patients the initial management of uncomplicated ADHF is management of respiratory issue.

O_2 and I/V Morphine

i. O_2 should be delivered by nasal cannula/mask as early as possible.
ii. For more severe hypoxia $SaO_2 < 90\%$ with cardiogenic pulmonary edema NIV with PEEP should be started.
iii. Morphine may be helpful in early stage of disease specially who are anxious and have chest discomfort.

However, morphine use has been associated with likelihood of mechanical ventilation, ICU admission, prolong hospital stay. Should be avoided in hypotension, bradycardia, advanced AV block or CO_2 retention.

Noninvasive Ventilation (NIV)

Reduce respiratory distress and to improve LV function by reducing afterload. ESC guideline recommends use of CPAP with initial PEEP of 5 to 7.5 cm H_2O with uptitration to 10 cm H_2O if needed. FIO_2 should be ≥ 0.40 for cardiogenic pulmonary edema.

Diuretics

i. Most important drug in a patient with ADHF.
ii. ESC guideline: Furosemide should be initially given in an I/V bolus dose of 20-40 mg/0.5 to 1 mg bumetamide/10-20 mg torasemide.
iii. Furosemide dose should not exceed 100 mg in the first 6 hours and 240 mg during first 24 hours.

iv. DOSE trial: Optimal dose and means of administration. Initial result from DOSE study have demonstrated bolus every 12 hours and continuous infusion appear to be equivalent in terms of symptom relief, changes of renal function and measure of congestion.

Although high dose therapy (2.4 × oral dose given IV) was not superior to low dose (1 × oral dose) on the basis of the primary efficacy end-point of global symptom relief during 72 hours; high dose was associated with improvement in dyspnea, resolution of signs, symptoms of congestion, net fluid loss and greater decrease in NTProBNP.

Indication	Diuretics	Doses	Comments
Moderate volume overload	Furosemide or Bumelanide or Torsemide	20-40 mg 0.5-1 mg 10-20 mg	Titrate dose accordingly monitor Na^+, K^+, Mg^2, Cr. and BP
Severe volume overload	Furosemide (oral) Furosemide (I/V infusion) Bumetanide Torsemide	40-100 mg 5-40 mg/hr 1-4 mg (Oral/IV) 20-100 mg (Oral/IV)	
Refractory to diuresis	Add: Hydrochlorthiazide or metolazone or spironolactone	50-100 mg 2.5-10 mg 25-50 mg	Combination better than very high dose F More potent of Cr.Ct. < 30 mL/min Best if no renal failure Normal/low K^+
With Alkalosis	Acetazolamide	0.5 mg	I/V
Refractory to loop and thiazide diuretics	Add: Dopamine (Renal vasodilatation) or dobutamine		Consider UF/HD if underlying CRF

Vasodilators

Glyceryl Trinitrate (GTN)

Indication: AHF with adequate BP

Indication	Vasodilator	Dosing	Comments
Pulmonary congestion or edema and SBP should be ≥ 90mm Hg	Nitroglycerin Isosorbide dinitrate Nitroprusside (Hypertensive HF) Nesiritide	Start 10-20 µg/min ↑ up to 200 µg/min Start 1 mg/hr ↑ up to 10 mg/hr Start 3.0 µg/kg/min and ↑ up to 5 µg/kg/min Bolus 2 µg/kg + Infusion 0.015-0.03 µg/kg/min.	Hypotension headache, tolerance Hypotension headache, tolerance Hypotension light sensitive Isocyanate cyanate toxicity Hypotension

Nesiritide

Recombinant form of human BNP available as I/V drug; currently approved by FDA. It is a balanced vasodilator with ↑ CO independent of changes in cardiac contractility and heart rate and less consistently natriuresis and diuresis.

The effect of nesitride was prospectively studied in ASCEND-HF study. It did not reduce the rate of heart failure, recurrent hospitalization or death but also it did not ↑ mortality or worsen renal function as shown by previous meta-analysis (VMAC; NSGET, PROACTION).

Inotropes with vasodialatory properties: Significantly ↓ PCWP and ↑ CO. Retrospective data shows I/V use of inotropes in AHF (except digoxin) ↑ long-term mortality rate. Despite having side effects in North American (ADHERE and OPTIMIZE-HF) and European registries approximately 15 and 25% of patients were treated with inotropes. The use of these drugs should be limited to patients with dilated ventricles and reduced ejection fraction who present with low SBP (< 90 mm Hg) or low measured cardiac output in the presence of signs of congestion and organ hypoperfusion such as altered mentation and urine output and should be stopped as soon as adequate organ perfusion is restored/congestion reduced.

Inotropic agent	Bolus	Infusion rate
Dobutamine	No	(p+) 2-20 μg/kg/min
Dopamine	No	(δ+) < 3 μg/kg/min = Renal inflow (β+) 3-5 μ/kg/min = Inotropic (β+)(α+) > 5 μg/kg/min = Vasopressor
Milrinone	2.5 – 7.5 μg/kg down 10-20 min (Optimal)	0.375 – 0.75 μg/kg/min
Enoximone	0.25 – 0.75 μg/kg	1.25 – 7.5 μg/kg/min
Levosimendan	12 μg/kg during 10 min (optional)	0.1 μg/kg/min whom can be ↓ to 0.05/↑ to 0.2 μg/kg
Norepinephrine	No	0.2 – 1 μg/kg/min
Epinephrine	Bolus 1 mg can be given I/V during resuscitation Repeat every 3 – 5 min.	0.05 – 0.5 μg/kg/min

Milrinone: PDE3 inhibitor approved for short-term circulatory support for advanced HF. In a prospective study OPTIME-HF it did not improve hospital mortality rate; 60-days mortality rate or composite incidence of death/readmission, however, more patients developed severe hypotension and atrial/ventricular arrythmias especially those who have coronary artery disease.

Levosimendan: Calcium sensitization and ATP dependent K^+ channel opener that has positive inotrope and vasodilatory effect.

In REVIVE-II study an improvement in patient self-assessment, a decreased level of BNP and a shorter hospital stay was noted in response to levosimendan when added to standard therapy. However, compared to placebo, it was associated with more hypotension (50% vs. 30%) ventricular tachycardia (25% vs. 17%) and atrial fibrillation 9% vs. 2%).

In SURVIVE study, 6 months of follow-up mortality was 26% in levosimendan group and 28% in dobutamine group. Levosimendan should be considered for patients with low cardiac output states despite the use of oral therapies.

A meta-analysis updated 2008 including 3650 patients (collected on 19 randomized controlled trials) with acute severe heart failure concluded that levosimendan improved hemodynamic parameters when compared with placebo and levosimendan improved both hemodynamic and survival when compared with dobutamine. A more recent meta-analysis updated January, 2009 in 440 patients undergoing cardiac surgery suggested improved survival in levosimendan group versus control group. Levosimendan has also been reported to improve right ventricular contractility and reduce RV afterload. However, in patients with cardiac insufficiency, it has been shown to increase the incidencec of arrhythmias like atrial fibrillation and ventricular tachycardia. Ongoing studies are looking at combinations of levosimendan with thrombocytic therapy and beta-blockers. A multicenter randomized trial powered to clinically relevant end-points such as mortality are needed to confirm the advantages of levosimendan in acute intensive care settings.

Vasopressor agents:

1. Phenylephrine
2. Norepinephrine
3. Digoxin
4. Arginine vasopressin agents known as the antidiuretic hormone.

The main regulator of plasma osmolarity. It acts by binding to three receptors:

i. V_{1a}: Most wide spread; present in smooth muscle, mediates vasoconstriction.
ii. V_{1b}: Anterior pituitary and brain, regulates neural pathway.
iii. V_2 : Renal collecting duct; main regulator of antidiuretic action.

Currently, available antagonists are tolvaptan (oral; selective V_2 receptor antagonist); conivaptan (I/V; V_1 and V_2). In EVEREST trial with tolvaptan, the composite end-point of CV death/hospitalization for heart failure was not significantly different than placebo. However, in the short-term studies, when added to standard therapy modestly improve signs and symptoms during hospitalization and decrease bodyweight without affecting heart failure status. In patients with acute heart failure (AHF) addition of Conivaptan to standard therapy increases urine output without improvement of symptoms or decreasing bodyweight. Currently, conivaptan (intravenous) and Tolvaptan (oral) are approved for treatment of euvolemic hyponatremia in hospital patients with heart failure. However, there was no long-term benefit on mortality or morbidity in heart failure. Side-effects include infusion site phlebitis (for conivaptan), hypokalemia, headache and neurologic deficits (from over-rapid correction of hyponatremia. Recently, FDA has announced a warning in view of the risk of potentially fatal liver injury with tolvaptan. These agents are also known as "Aquaretics".

I/V β-blockers: As general rule *de novo* therapy with β-blocker should not be started during initial phase of AHFS as it acutely decrease cardiac contractility. However, short-acting I/V blocker such as esmolol may be considered when AHF is precipitated by AF and atrial flutter with rapid ventricular rate. These agents should be continued during hospitalization in patients already receiving β-blocker unless shock or severe hypotension or bradycardia is present. On the basis of results of B-CONVINCED trial.

Phase-II management

This is the continuation phase of management after emergency department management. This include optimization of medical therapy and diagnostic work-up.

i. **Treatment of clinical and hemodynamic congestion:** In patients a with congestion diuretics usually continued and switched from I/V to an oral form. Oral diuretics (loop diuretics) should be given twice daily to achieve maximum euvolemia without worsening renal function for those who not respond to loop diuretics, drugs like thiazide and metolazone should be considered. Also spironolactone/eplerenone may be added in patient with hypokalemia. Daily laboratory investigation include Na^+,K^+,Mg^{2+}, BUN, creatinine and intake output. Body-weight should be measured to monitor optimal diuretic therapy without undue complication.
ii. **Implementation of evidence based interventions known to improve outcome in HF:** Both ACC/AHA and ESC guidelines support continuation of ACEIs/ARBs, β-blockers, aldosterone antagonist during hospitalization for ADHF unless hemodynamic instability or other contraindication present.

Aldosterone blocking agents are contraindicated for patients with K+ > 5 mEq/L or Cr > 2.2 mg/dL.

- The DIG trial showed addition of digoxin to ACE inhibitors and diuretics reduces rehospitalization and in retrospect mortality in patients with serum concentration of drug < 1 ng/mL. These benefits were observed particularly in patients with very low EF.
- Combination of hydralazine and nitrates has been shown beneficial in those having low EF along with standard therapy in African-Americans. Less effective in other ethnic group.

- **CRT:** Approximately 40% of ADFS patients with reduced EF have wide QRS, CRT shoud be considered after discharge if patient remains symptomatic after an appropriate trial of evidence based therapies of HF.
- **ICD:** Retrospective data suggest that the ICD status did not decrease event rate after discharge.

Revascularization

Patient with obstructive CAD may benefit from revascularization procedures particularly when there is significant documented Ischemia or hibernating myocardium.

Recommendation Prior to Discharge

a. Check exercise capacity
b. Educate patient and family member regarding disease process and outcomes
c. Life style modification
d. Address potential for micro and macronutrient

Phase-III management (after discharge and during vulnerable phase)

a. Schedule the follow-up according to disease severity (1 wk. to 1 month).
b. Ensure early follow-up with monitoring of BP, bodyweight, Renal function, Electrolytes and possibly BNP.

Potential New Therapies

1. **Soluble guanylate cyclase activators (SGC):** Cinaciguat is a novel nitric oxide (NO) independent activator of SGC and activates soluble form of guanylate cyclase in smooth muscle cell. Thus, leading to the synthesis of cGMP and subsequent vasodilation. During periods of increased oxidative stress as ADHF a significant proportion of heme bound may become Fe oxidized, potentially blunting the effect of NO donors but it is him independent guanyl cyclase activator that is now under investigation in COMPOSE trial.
2. **Chimeric natriuretic peptides (CD-NP):** Combines the beneficial aspects of C type NP with 15-amino acid C-terminal tail of dendroaspis NP (DNP)/N (DNP). CNP lacks the natriuretic effect of ANP/BNP but has benefit of less hypotension because of primary venodilatation as opposed to BNP which is both arteriovenous dilator. DNP has got significant natriuretic effects but also cause hypotension. CD-NP ideally combines the lack of unwanted atrial vasodilation of CNP with positive natriuretic effect.
3. **Direct renin inhibitors:** Inhibition of the 1st enzymatic step in the RAAS cascade, leading to profound suppression of this neurohormonal system. Aliskiren is an example. It has been tested in the ASTRONAUT trial which was presented in ACC 2013 (discussed in chapter in "Chronic Heart Failure").

Sympathomimetic inotropes for acute cardiac failure therapy

Drugs and mediating receptors	Dobutamine ($\beta_1 > \beta_2 > \alpha$)	Dopamine (Dopaminergic > β; High-dose α)	Norepinephrine ($\beta_1 > \alpha > \beta_2$)	Epinephrine ($\beta_1 = \beta_2 > \alpha$)	Isoproterenol ($\beta_1 > \beta_2$)	Milrinone (PDE Inhibitor)	Phenylephrine (α-agonist)
Dose infusion (µg/kg/min)	2-15	2-5 renal effect 5-10 inotropic 10-20 SVR ↑	0.01-0.03 max. 0.1	0.01-0.03 max. 0.1-0.3	0.01-0.1	Bolus: 50-75 (10 min) Drip: 0.375-0.75	0.2-0.3
Elim $t_{1/2}$ (min)	2.4	2.0	3.0	2.0	2.0	150	20
Inotropic effect	↑↑	↑↑	↑	↑↑	↑↑↑	↑	0
Anteriolar vasodilation	↑	↑↑	0	↑	↑	↑↑	↓
Vasoconstriction	HD ↑	HD ↑↑	↑↑	HD ↑	0	0	↑↑↑
Chronotropic effect	↑	0, ↑	↑	↑↑	↑↑↑	0	0
Blood pressure effect	↑	HD ↑	↑	0, ↑	↑	↓	↑↑↑
Diuretic effect (direct)	0	↑↑	↑	0	0	0	↓
Arrhythmia risk	↑↑	HD ↑	↑	↑↑↑	↑↑↑	↑	0

↑ = increase; 0 = no change; ↓ = decrease; Elim $t_{1/2}$, elimination half-life; HD, high dose; PDE, phosphodiesterase; SVR, systemic vascular resistance.aa

4. **Adenosine antagonist rolofylline:** Which is a highly selective adenosine A1-receptor has been studied in PROTECT pilot study. The phase III PROTECT II trial showed only mild benefit of symptom but no effect on the renal protection and had CNS side effects.
5. **Ularitide:** Synthetic analog of urodilatin, a natriuretic and diuretic hormone of the family of A type NP produced by renal tubular cells. It has been investigated in SIRUS trial which showed improved clinical status, hemodynamics and neurohormonal profile, however, it was associated with significant hypotension.
6. **Endothelin antagonist:** Endothelin is most potent endogenous vasoconstrictor and is produced by vascular smooth muscle cell. Tazosentan a nonselective ET A-B antagonist has been shown to improve hemodynamics in HF. In VERITAS study addition of I/V tazosentan to standard therapy did not improve symptions or survival at 7 days.
7. **Cardiac myosin activators:** Omecamtiv mecarbit is under trial, shows marked dose dependent ↑ of EF with reflex bradycardia.
8. **Istaroxime:** New class of drug has dual action on myocyte. By inhibition of membrane bound Na^+K^+ATPase and by enhancing the activity of the sarcoendoplasmic reticulum Ca^{2+} ATPase type 2a (SERCA2a). It is under evaluation in HORIZON-HF Study.
9. **Stresscopin:** The peptide human urocortin 2 (h-UCN2) is now in phase II trial.
10. **Relaxin:** Phase II study Pre-RELAX-AHF study is now going on.

Future prospect: At present outer management consist of treating manufacturers rather than pathophysiology process. Thus a better understanding of cardiac metabolism of dysfunctional but viable myocardium will allow development of specific therapy and because we deal with heterogenous population of patients, it is unlikely that a "One Therapy will fit All".

Discharge Criteria for Patients with AHF

Recommemded for all AHF Patients

i. Exacerbating factor addressed.
ii. Near optimal volume status observed.
iii. Transition from I/V to oral diuretic successfully completed; salt and fluid intake regime laid down.
iv. Patients and family education completed including clear discharge instructions.
v. LVEF documented.
vi. Smoking cessation counseling initiated.
vii. Near optimal pharmacotherapy achieved including ACE I, β-blockers for patients with ↓LVEF or intolerance documented.
viii. Follow-up clinic visit scheduled usually 7 to 10 days.

Should be Considered for Patients with Advanced HF/ recurrent admission for HF

- Oral indication regimen stable for 24 hours
- No I/V vasodilator/inotropes for 24 hours
- Ambulation before discharge to assess the functional capacity after therapy
- Plan for postdischarge management
- Referral for disease management if available.

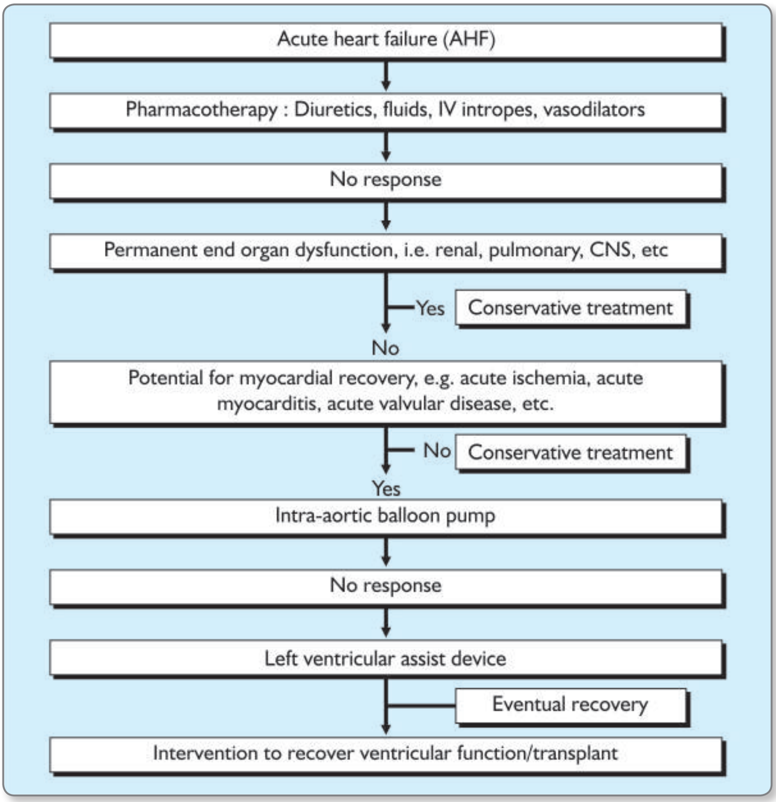
Cardiac Disease and AHF Requiring Surgical Treatment

- Cardiogenic shock after AMI in patients with mutlivessel ischemic heart disease
- Postinfarction ventricular septal defect
- Free wall rupture
- Acute decompensation of pre-existing heart valve disease
- Prosthetic valve failure or thrombosis
- Aortic aneurysm or aortic dissection rupture into the pericardial sac
- Acute mitral regurgitation from:
  - Ischemic papillary muscle rupture
  - Ischemic papillary muscle dysfunction
  - Myxomatous chordal rupture
  - Endocarditis
  - Trauma
- Acute aortic regurgitation from:
  - Endocarditis
  - Aortic dissection
  - Closed chest trauma
- Ruptured aneurysm of the sinus of valsalva
- Acute decompensation of chronic cardiomyopathy requiring support by mechanical assist devices.

Scope of LV Assist Devices in AHF

Type of mechanical assist devices

Extracorporeal (short-term)	Intracorporeal (long-term possible)
• Continuous flow pumps (cheapest) • Centrifugal pumps (may include extracorporeal membrane oxygenators) • Pulsalite (Thoratic, Abiomed) (Especially postcardiotomy)	• Implantable, pulsatile (Heart mate, Novacor) (Bridge to transplant/recovery) • Total artificial heart (If no recovery expected or no transplant candidate; but still experimental)



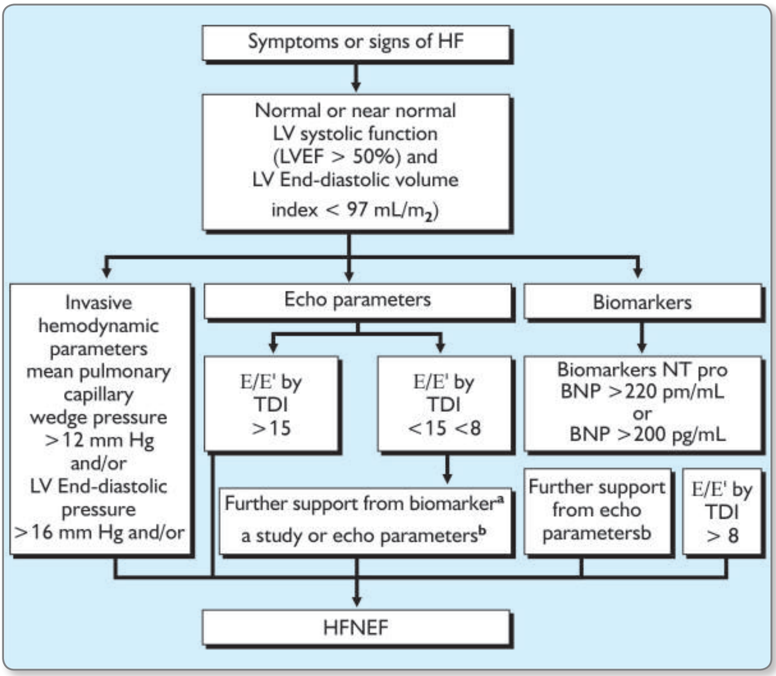
Acute Heart Failure and Normal Left Ventricular Ejection Fraction (HFNEF)

HFNEF is suggested if:

a. Biomarkers: NT proBNP > 220 pm/mL
BNP > 200 pg/mL

b. E/A ratio (Mitral valve inflow velocities by Doppler) < 0.5 (Age > 50 years)
and
Deceleration Time (Mitral valve flow) > 280 ms (Age > 50 years)
or
Ard (Duration of reverse pulmonary vein atrial systole flow) – Ad (duration of mitral valve atrial wave flow) > 30 ms
or
LVMI (LV mass index) > 122 g/m^2 (females)
or
Atrial fibrillation

Primary Diagnosis of HFNEF

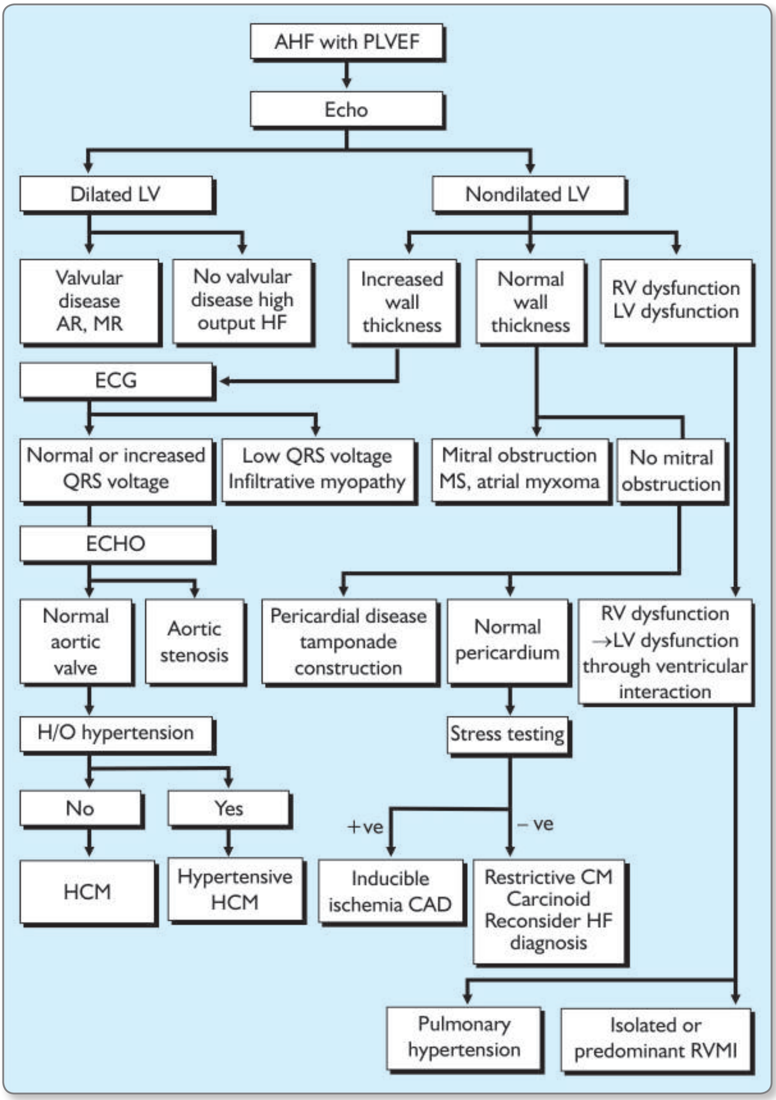


TDI—Tissue Doppler imaging

Evidence Base of Treatment of AHF with NEF

Studies till date (CHARM-Preserved, I-PRESERVE, PEP-CHF) have failed to show improvement in mortality with the use of RAAS antagonists for HFNEF. With respect to morbidity, evidence is conflicting, whereas, perindopril showed improvement in functional capacity in PEP-CHF trial, candesartan was shown to decrease hospitalization for heart failure in CHARM-Preserved and irbesartan failed to show improvement either in terms of functional capacity or repeat hospspitalization. These discrepancies may have resulted owing to faulty conduction of trials, namely enrolment of HF patients with eccentric LV remodeling and coronary artery disease. However, based on evidence, it is reasonable to conclude that there is no compeling evidence to recommend Renin angiotensin system (RAS) blockers as first-line therapy for HFNEF without a specific comorbidity such as hypertension, diabetes mellitus or coronary artery disease. Results of trials with aldosterone antagonists (Spironolactone-TOPCAT and Aldo-DHF) are eagerly awaited. Since aldosterone has been implicated in both vascular and myocardial fibrosis, it is currenty a focus of

Diagnostic (etiologic) flow-chart in AHF with normal LVEF



interest in treatment of HFNEF. In a small study of 30 patients with HFNEF, Mottram et al showed increases in strain with spironolactone independent of change in blood pressure.

In SENIORS trial, effect of nebivolol, a β1-selective blocker with vasodilating properties related to nitric oxide modulation, was studied in elderly patients (>70 years) with clinical HF regardless of LVEF. When patients with an EF greater than 40% were examined, primary outcome for all-cause mortality or hospital admission for cardiovascular disease was not statistically significant. In the COHERE trial, in patients with LVEF > 40%, carvedilol showed improvement in functional status and lower rates of hospitalization. However, magnitude of improvement with carvedilol therapy was lower than that seen in patients with systolic dysfunction.

More large-scale clinical trials are evaluating role of β-blockers in HFNEF like β-PRESERVE (with Metoprolol) and J-DHF (with Carvedilol). Although results of these trials are pending, current clinical trial evidence does not support a primary role for β-blockers in the treatment of HFNEF.

In a small trial of 20 patients with HFNEF, Setaro et al showed that verapamil had a clinicoradiographic score improvement on a HF scale. However, calcium channel blockers have not been studied in large-scale outcome trials for treatment of HFNEF. In the DIG trial, in the subgroup of 988 patients with LVEF > 45%, treatment with digoxin had no effect on hospitalization for HF, mortality due to HF or all-cause mortality. In an observational single-center study of 137 consecutive patients by Fakula et al, statins were associated with significant reduction in mortality. However, such survival benefits have not been observed in other HF studies or statin trials in other populations, raising important question about confounding factors in this observational study.

Small studies have suggested that exercise training may improve diastolic dysfunction. Large-scale trials have not evaluated the effect of exercise on outcomes in patients with HFNEF; however, aerobic exercise could be beneficial in this population in terms of improved functional capacity, weightloss and benefits through risk reduction in diabetes and hypertension.

Some novel strategies are being tried out in HFNEF. These include sildenafil in RELAX trial, pacing in RESET trial and vagal stimulation in HOPE trial.

Treatment Guidelines in AHF with PLVEF

1. Low sodium diet; fluid restriction, initally strict with progressive measured relaxation monitoring renal function.
2. Diuretics: They are recommended in AHF with PLVEF as in other types of HF. thiazide diuretics in mild AHF, loop diuretics (± thiazide diuretics) in moderate to severe AHF with PLVEF. Excessive diuresis, which may worsen renal function or cause orthostatic hypotension, should be avoided (strength of evidence = C)
3. ARBs or ACE inhibitors should be considered in patients with HFNEF in the presence of comorbidities like hypertension, diabetes mellitus or coronary artery disease

- ARBs (Strength of evidence = C)
- ACE inhibitors (Strength of evidence = C)
  However, ACE inhibitors are the first choice over ARBs in patients, who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor (Strength of Evidence = C)

4. β-blocker treatment is recommended in patients with HF and PLVEF who have;
   - Prior MI (Strength of evidence = A)
   - Hypertension (Strength of evidence = B)
   - Atrial fibrillation requiring control of ventricular rate (Strength of evidence = B)
5. Calcium channel blockers should be considered in patients with:
   - Control of ventricular rate in atrial fibrillation if β-blockers are not tolerated or prove to be inadequate alone. (Diltiazem or verapamil are the choice) [Strength of evidence = C]
   - Symptom-limiting angina [Strength of evidence = A]
   - Hypertension (Amlodipine is the choice) [Strength of evidence = C]
6. Measures to restore and maintain sinus rhythm should be considered in patients who have symptomatic atrial flutter-fibrillation but this decision should be individualized [Strength of evidence = C] A meta-analysis by Kong et al did not show any difference in mortality and morbidity with rate or rhythm control in diastolic heart failure.
7. Coronary angiography and revascularization (as indicated) in those with evidence of ischemia (spontaneous or inducible)

Risk-scoring in AHF

The Euro Heart Failure Survey II in 2007 presented a "Risk-scoring" system to assess short-term (in-hospital) mortality (all-cause) in patients presenting with acute heart failure.

Risk contribution		Risk contribution	
Age < 65 years	0	Serum creatinine < 1.4 mg/dl	0
65-80 years	3	1.4 - 2 mg/dl	2
> 80 years	6	> 2 mg/dl	6
SBP > 130 mm Hg	0	Acute STEMI	5
110-130 mm Hg	3	Cold periphery	4
< 110 mm Hg	6	Somnolent or confused	4
		Pulmonary edema	2

In both situations (*de novo* or worsening HF), the markers mentioned above were the strongest predictors of short-term mortality.

All cause in-hospital mortality are stratified as following based on the "Risk-score".

Risk-score	0-3	4-6	7-9	10-12	13-15	>15
Mortality (%)	0.5	2.8	3.0	5.9	10.5	21.5

The Kidney in Heart Failure

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) refers to interaction between cardiac and renal dysfunction which is critical for disease progression and prognosis. Cardiac and renal dysfunction may worsen each other through multiple mechanisms illustrated below:

Mechanism involved in cardiorenal interactions	Impact on renal injury in HF	Impact on cardiac damage in CKD
1. Hemodynamic abnormalities: Low renal blood flow and increased renal venous pressure	+++	+
2. Neurohormonal activation: Sympathetic nervous system and Renin-angiotensin-aldosterone system	+++	+++
3. Coagulation abnormalities or fibrinolytic problems	O	+++
4. Inflammatory and oxidative stress	+++	+++
5. Anemia	+	+++
6. Diuretic treatment of HF	+++/+	O

Five types of cardiorenal syndrome have been described by Ronco et al.

1. Type-1 (acute CRS): Acute decompensated heart failure leads to acute kidney injury.
2. Type-2 (chronic CRS): Chronic HF leads to chronic kidney disease.
3. *T*ype-3 (acute renocardio syndrome): Acute kidney injury that leads to acute cardiac dysfunction such as arrhythmia/HF.
4. Type-4 (chronic renocardiac syndrome): Primary chronic kidney disease that contribute to cardiac dysfunction.
5. Type-5 (secondary CRS): Combined heart and kidney disease dysfunction due to systemic disorder such as sepsis and SLE.

Change in serum creatinine related to treatment with diuretics or ACEIs are not necessarily associated with worse outcomes. New biomarkers (Serum cystatin-C, Neutrophil gelatinase associated lipocalin i.e., NGAL, kidney injury molecule 1, i.e. KIM-1 etc.) might be of additional value to detect early deterioration in renal function but they need further validation. Some new agents are in offing to prevent renal dysfunction but strong evidence is still lacking. Till such time, it is not possible to give one set of hard and fast rules to treat CRS and it is left to the astute physician to make the correct decision.

Suggested Reading

1. Albert LJ, Boehmeer JP, Collins SP et al. Executive Summary: HFSA 2012 Comprehensive Heart Failure Practice Guidelines. J Card Fail 2010;16:475-539.
2. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal Doi:10.1093/eurheart/ehs 104.
3. Kim Han-NA, Januzzi JL. Natriuretic Peptide Testing in Heart Failure, Circulation 2011;123:2015-9.
4. Ronco C, McCulbough P, Anker SD et al. Acute Dialysis Quality Initiative (ADQI) consensus group. Cardiorenal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010;31:703-11.
5. Saraf M, Schrier RW. Cardiorenal Syndrome in Acute Heart Failure Syndromes International Journal of Nephrology 2011. pp. 1-10.
6. Van Kimmenade RRJ, Januzzi JL. Emerging Biomarkers in Heart Failure. Clinical Chemistry 2013;58:1.

chapter 5

Management of Chronic Heart Failure

Arghya Chattopadhyay, Soumitra Kumar

Chronic HF

Definition

A syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery at rest or during stress, caused by cardiac dysfunction.

In congestive heart failure, right atrial pressure (RAP): pulmonary capillary wedge pressure (PCWP) ratio is important. RAP is often but not always correlated with PCWP. There are situations where RAP matches or exceeds PCWP; but there are also situations where right ventricular function is relatively preserved and RAP is less than PCWP.

For practical purposes, the task force for the diagnosis and treatment of CHF of European Society of Cardiology considers the essential components of heart failure to be a syndrome in which patients should have the following features:

- (i) symptoms of heart failure (typically breathlessness or fatigue) either at rest or during exertion and (ii) objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) at rest and (iii) a response to treatment directed towards heart failure (e.g. diuretic administration).
- Criteria I and II should be fulfilled in all cases.

Principles of Treatment

Based on:

- History
- Clinical Examination
- Investigation

1. Identification of Primary Cause
2. Evolution of Stages of Heart Failure
3. Removal of Precipitating Cause

History

- Dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND)
- Fatigue and weakness

- Abdominal symptoms e.g. anorexia, nausea, pain, fullness of abdomen.
- Cerebral symptoms e.g. (in severe HF) headache, insomnia, anxiety, confusion, impairment of memory.

Clinical Examination

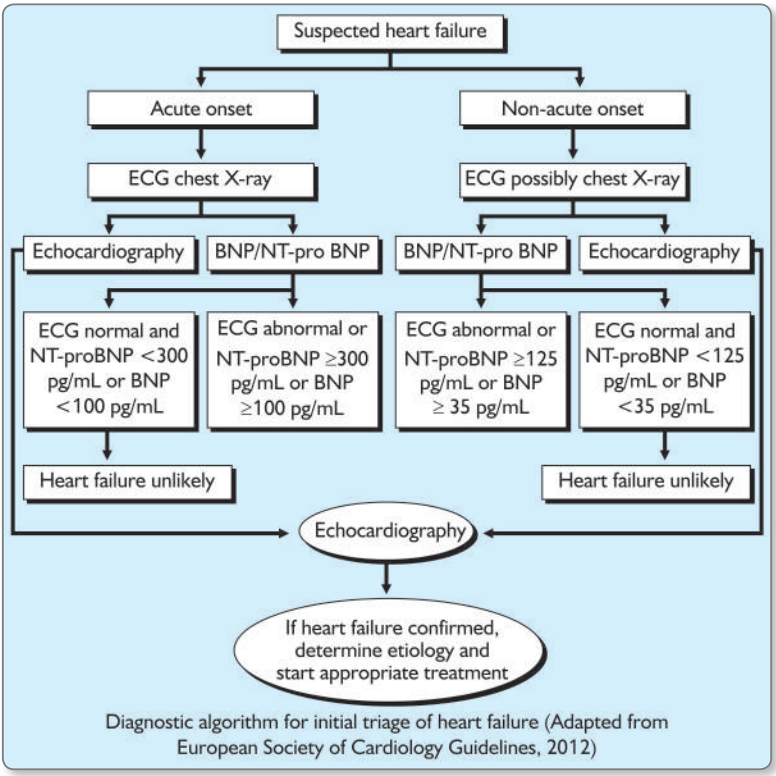
Look for:
Cyanosis, icterus, malar flush, cachexia, edema, coldness of extremities, raised JVP, tachycardia, pulsus alternans

Hypotension
Bilateral pulmonary rales, wheeze
Pleural effusion
Hepatomegaly, ascites,
Cardiomegaly, gallop sound, S_3, S_4.

Investigation

- CBC, Hb%, electrolytes, renal function, LFT, T_3, T_4, TSH
- B-type natriuretic peptide—Bedside assay can be useful in establishing or excluding the diagnosis of congestive heart failure in patients with acute dyspnea. In a recent study, diagnostic accuracy of B-type natriuretic peptide at a cutoff of 100 pg per millilitre was 83.4 percent. The negative predictive value of B-type natriuretic peptide at levels of less than 50 pg per milliliter was 96 percent.
- Chest X-ray, ECG, ABG
- Echocardiography (Bedside)
- Stress test
- Radionuclide ventriculography
- Coronary angiography
- Cardiac Magnetic Resonance (CMR) Imaging.

Flow chart 5.1 Initial triage for heart failure



- Identification of primary cause of heart failure and treatment accordingly.
- Removal and correction of precipitating cause: for example.
  - Anemia, infection, thyrotoxicosis, hypertension
  - Arrhythmia, thromboembolism, obesity, pulmonary embolism
  - Volume overload (e.g. pregnancy), dietary excess
  - Physical and mental stress
  - Drugs: Salt and water retaining drugs, cardiac depressant.

Biomarkers in Heart Failure

Established Biomarkers

BNP and NT-ProBNP: Diagnostic value of these biomarkers in congestive heart failure (CHF) has been discussed in the chapter on "Acute Heart Failure". Is there a role of BNP guided therapy in heart failure? STARS-BNP trial showed that CHF-related death or hospital stay for CHF was significantly lower in BNP guided group (24% vs. 52%, $p < 0.001$) suggesting that therapy directed by BNP level is superior to clinical based therapy.

Predischarge BNP level is an independent prognostic marker of outcome after discharge in patients admitted for heart failure. A study by Logeart et al reported that patients with heart failure whose BNP level does not decline to below 600 pg/mL should receive intensified treatment before discharge.

Which one is better to evaluate heart failure: BNP or NT-proBNP? Longer half-life of NT-ProBNP makes it a better reflector of ventricular stress and hence also a better prognostic marker.

Table 5.1 Promising Biomarkers in chronic heart failure

Biomarker	Proposed pathophysiology	Potential role in patients with chronic HF
Copeptin	Stable plasma surrogate for vasopressin, which is released from the hypothalamus in response to changes in plasma osmolarity and reduced cardiac output	Independent role as a prognostic marker in patients with chronic HF. Probable role as molecular marker for tailored therapies with vasopressin antagonism
Galectin-3	β-galactoside-binding lectin produced by several tissues promotes cardiac fibroblast proliferation and collagen synthesis (maladaptive remodelling)	Predicts mortality independent of natriuretic peptides in patients with chronic HF. Does not appear to be modified by currently available treatment. Potential role as a target for therapy.
GDF-15	Member of the TGF-β cytokine family expressed in most tissues including myocytes	Predictive of mortality in patients with chronic HF beyond established bio-markers Serial changes are prognostically important Could lead to the development of specific treatments for patients with chronic HF
Mid-regional Pro-adreno-medullin (MR-pro-ADM)	Produced by various tissues within the cardiovascular system in response to hemodynamic stress Promotes positive inotropy and vasodilation	Likely to add prognostic value to predictive models for patients with chronic HF beyond that provided by natriuretic peptides and conventional clinical risk factors
Neuregulin 1	Represents a family of growth factors with an important role in cardiac development and the pathogenesis of chronic HF Has a significant role in promoting cardiomyocyte growth and function, and regulation of the stress response	Initial studies show independent associations with disease severity and risk of adverse outcomes in patients with chronic HF Trials with recombinant neuregulin are ongoing, with a phase II trial showing improvement in cardiac structure and function
sST2	Member of the IL-1 receptor family that is secreted from myocytes induced by biomechanical strain Possibly mediates myocardial hypertrophy and fibrosis by compromising the favorable effects of IL-33/ST2 signalling	Independent predictor of morbidity and mortality in patients with chronic HF. Potential role as a novel therapeutic target

Stages of Heart Failure

Stage A: Patients at high-risk for developing heart failure with no structural heart disease, e.g. Patients with hypertension, atherosclerotic disease, diabetes, obesity, metabolic syndrome or patients using cardiotoxins or with family history of cardiomyopathy.

Stage B: Patients with structural heart disease who have not yet developed symptoms of heart failure, e.g. Patients with previous MI, LV remodeling including LV hypertrophy and low ejection fraction, asymptomatic valvular disease.

Stage C: Patients with past or current symptoms of heart failure associated with underlying structural heart disease.

Stage D: Patients with refractory (end-stage) heart failure who require specialized intervention, e.g. patients who have marked symptoms at rest despite maximal medical therapy.

Outline of Treatment of CHF

Stage A:
- Life-style modification:
  Regular exercise
  Smoking cessation
  Discourage alcohol intake and illicit drug use
- Treat hypertension, lipid disorders, metabolic syndrome
- ACEI or ARB in appropriate patients, e.g. for vascular disease or diabetes.

Stage B:
- All measures under stage A
- ACEI or ARB in appropriate patients (vide latter sections)
- Beta-blockers in appropariate patients (vide latter sections)
- Implantable defibrillators in selected patients.

Stage C:
- All measures under stages A and B
- Dietary salt restriction
- Routine use of diuretics for fluid retention, ACEI, Beta-blockers.
- Use in selected patients of:
  - Aldosterone antagonist
  - ARBS
  - Digitalis
  - Hydralazine/nitrates
- Devices in selected patients
  - Biventricular pacing
  - Implantable defibrillators

Stage D:

- Appropriate measures under stage A,B,C.
- Decision re: appropriate level of care.
  Options:
  a. Compassionate end-of-life care/hospice
  b. Extraordinary measures
     – Heart transplant
     – Chronic inotropes
     – Permanent mechanical support
     – Experimental surgery or drugs

Pharmacotherapy of Congestive Heart Failure

Diuretics

Proven Indication of Diuretics (Always Acceptable)

- Symptomatic improvement in case of congestion (NYHA II-IV)

Acceptable Indication but of Uncertain Efficacy and may be Controversial

- Long-term treatment in conjunction with other drugs for heart failure such as ACEIs, vasodilator, beta blockers. **Withdrawal** of diuretics in stable compensated patients with congestive HF has been shown in several studies to result in symptoms of congestion. A history of hypertension, baseline frusemide dose > 40 mg/day, and a low LV ejection fraction (<27%) were independent predictors of diuretic re-initiation.

Not Proven: Potentially Harmful or Contraindicated

- Heart failure without congestion or edema
- Severe decompensated hypokalemia or hyperuricemia.

Guidelines for Use of Diuretics

Initial Diuretic Treatment

- Loop diuretics or thiazides always combined with an ACEI if tolerated (on the assumption that ACEI would suppress the adverse neurohormonal effect of diuretics, although this effect is not uniform)
- If GFR < 30 mL/min, do not use thiazides, except as therapy prescribed synergistically with loop diuretics.

Insufficient Response

- Increase dose of diuretic
- Administer loop diuretics twice daily
- Combine loop diuretics twice daily
- In severe CHF, add metolazone with frequent measurements of serum creatinine and electrolytes.

Potassium Sparing Diuretics (Other than Spironolactone or Eplerenone)

- Use only if hypokalemia persists despite ACE-inhibition or in severe heart failure, despite the combination of ACE-inhibition and low doses of an aldosterone antagonist.
- Start with a one week low dose administration, check serum potassium and creatinine after 5 to 7 days and titrate accordingly. Recheck after 5 to 7 days until potassium values are stable.
- Potassium supplements are generally ineffective in cases of persistent hypokalemia.

Are All Loop Diuretics Equal in Terms of Prognosis?

The answer is yet unclear but in TORIC study, oral torasemide group showed significantly less total and cardiac mortality compared to oral frusemide group. Whether benefits were due to greater biovailability of torasemide and its antialdosteronergic effects remain to be explained.

ACE-Inhibitors

Proven Indications of ACEIs in HF: Always Acceptable

- Symptomatic CHF and documented systolic myocardial dysfunction: improved survival, reduced morbidity, symptomatic improvement and enhanced exercise capacity have all been demonstrated.
- Following acute myocardial infarction with clinical signs of HF or significant systolic dysfunction (Ejection fraction < 40%). Improved survival and reduced morbidity demonstrated.
- Prevention of cardiovascular events, including heart failure in patients with atherosclerotic disease or in patients with diabetes mellitus and additional risk factors.

Acceptable Indication but Uncertain Efficacy and may be Controversial

Heart failure from diastolic dysfunction.

Not Proven: Potentially Harmful or Contraindicated

- Treatment of patients with significant aortic or mitral stenosis
- Treatment of patients with hypotension (SBP < 80 mm Hg)
- Treatment of patients with pronounced renal failure (Serum creatinine > 3.0 mg/dL and/or potassium > 5.5 mg/dL).

Evidence-base of ACEIs

Consensus, V-HeFT II, SAVE, SOLVD, AIRE, ATLAS, TRACE trials.

Angiotensin-Receptor Blockers

Proven Indications of ARBs in HF: Always Acceptable

Symptomatic treatment of patients with HF who do not tolerate ACEIs.

Acceptable Indications but of Uncertain Efficacy and may be Controversial

- Symptomatic treatment in patients who do not tolerate beta-blockers (in patients on ACEIs, diuretics)
- Treatment of patients with a background therapy of both an ACEI and a beta-blocker.

Evidence Base of ARBs

RESOLVD, ELITE I and II, Val HeFT, CHARM, VALIANT, OPTIMAAL trials.

Guidelines for Use of ACEIs and ARBs

- Review the need and dose of diuretics and other vasodilators.
- Avoid excessive diuresis before initiation of treatment. Consider reducing or withholding diuretics, if being used for 24 hours.
- It may be advisable to start treatment in the evening, when the patient is supine, to minimize the potential negative effects on blood pressure.
- Start with a low dose and build up to maintenance doses shown to be effective in large trials.
- If renal function deteriorates substantially (>25% increase in serum creatinine from baseline), or hyperkalemia ensues ($K^+ > 5.5$ mEq/l), stop treatment.
- Avoid NSAIDs and Coxibs.
- Check blood pressure, renal function and electrolytes 1 to 2 weeks after each dose increment, at 3 months and subsequently at 6 months intervals.
- Addition of ARB with combination of ACEI and aldosterone antagonist i.e. triple drug combination increases risk of hypotension, renal dysfunction and hyperkalemia. Until trial results prove favorable, such combinations are not recommended.

Beta-blockers

Proven Indications of Beta-blockers in Heart Failure

- To improve long-term survival in patients with mild to severe HF.
- To improve cardiac function and symptoms in patients with symptomatic chronic HF, already on conventional treatment with ACEIs (or an ARB), diuretics or digitalis.
- To improve outcome in patients with acute myocardial infarction and left ventricular dysfunction with or without symptomatic HF.
- Symptomatic treatment of patients who do not tolerate ACEIs.

Acceptable Indication but of Uncertain Efficacy and may be Controversial

Symptomatic heart failure from diastolic dysfunction.

Not Proven: Potentially Harmful or Contraindicated

- Acute decompensated heart failure
- Congestive HF with pronounced hypotension and/or bradycardia.

Guidelines for Use of β-blocker

- The patient should be on a background therapy with ACEI-inhibition, if not contraindicated. (However, CIBIS III trial has recently demonstrated in 1010 patients with mild to moderate CHF and LVEF ≤ 35 percent that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril).
- The patient should be in a relatively stable condition, without the need of intravenous inotropic therapy and without signs of marked fluid retention. Start with low dose, double dose every 1 to 2 weeks till the dosage evidenced in large trials is reached. Most patients can be managed as out-patients.
- If worsening of HF occurs, first increase dose of diuretics or ACEIs, then temporarily reduce dose of β-blocker, if necessary.
- If hypotension, first reduce dose of vasodilators and then reduce the dose of beta-blocker, if necessary.
- If bradycardia, reduce or discontinue drugs that may lower heart rate; reduce dose of beta-blocker, if necessary; but discontinue only if clearly necessary.
- Always consider reintroduction and/or uptitration of the beta-blocker when the patient becomes stable.
- If a patient develops decompensation of HF while on β-blocker, reduce dose of β-blockers by 25 to 50 percent, rather than withdraw β-blockers unless HF is severe and refractory.
- If inotropic support is needed to treat a decompensated patient on β-blocker, phosphodiesterase inhibitors or levosimendan should be preferred because their hemodynamic effects are not antagonized by β-blocker agents.

Evidence Base of Beta-blockers in CHF

ANZ, BEST, CIBIS I-III, COMET, COPERNICUS, MERIT HF, SENIORS, US CARVEDILOL, PRECISE, MOCHA, CAPRICORN trials. Trial data favor use of carvedilol, metoprolol, bisoprolol and more recently, nebivolol (On the basis of SENIORS trial).

Digitalis

Proven Indications of Digitalis in Heart Failure

Atrial fibrillation and any degree of symptomatic heart failure whether or not left ventricular dysfunction is the cause.

Acceptable Indications but Somewhat Controversial

- Combination of digoxin and beta-blockade appears superior to either agent alone in patients with AF.
- Digoxin has no effect on mortality but may reduce hospitalizations for worsening of CHF in patients with CHF caused by LV systolic dysfunction in sinus rhythm and treated already with ACE inhibitors, beta-blockers and diuretics. Studies have shown that withdrawal of digoxin is often associated with worsening clinical status.

Evidence-base of Digitalis in CHF: PROVED, RADIANCE, DIG Trials

Dosage of Digoxin: It is recommended that dose of digoxin based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and serum digoxin level should be < 1.0 mg/mL. High dose of digoxin (maintenance dose > 0.25 mg daily) for the purpose of rate control in atrial fibrillation is not recommended.

Aldosterone Antagonist

Recommendations for Use in Systolic Heart Failure

Proven indications

Class I: Administration of aldosterone antagonist is recommended for patients with NYHA classes II-IV from reduced LVEF of <35 percent while receiving standard therapy, including ACEI (or ARB) and β-blocker (Level of evidence: A).

Class IIa: Administration of an aldosterone antagonist would be considered in patients following an acute MI with clinical heart failure or history of diabetes mellitus and LVEF of < 40 percent. Patients should be on standard therapy, including ACEI (or ARB) and a β-blocker (Level of evidence: A).

Potentially harmful or contraindicated

Class III: Aldosterone antagonists are not recommended when creatinine is > 2.5 mg/dL or creatinine clearance is < 30 mL/min or serum creatinine is > 5 mmol/L or in conjunction with other potassium-sparing diuretics (Level of evidence: A).

Administration and Dosing Consideration with Aldosterone Antagonists (Spironolactone, Eplerenone)

- Consider whether a patient is in severe HF (NYHA II-IV) despite ACE-inhibition/diuretics.

- Check serum potassium (< 5.0 mmol/L) and creatinine (< 2.5 mg/dL)
- Add a low dose (spironolactone 12.5 to 25 mg, eplerenone 25 mg) daily.
- Check serum potassium and creatinine after 4 to 6 days.
- If at any time serum potassium 5 to 5.5 mmol/L, reduce dose by 50 percent. Stop if serum potassium > 5.50 mmol/L.
- If after 1 month, symptoms persist and normokalemia exists, increase to 50 mg daily. Check serum potassium, creatinine after 1 week.

Evidence Base of Aldosterone Antagonists

RALES (Spironolactone), EPHESUS (Eplerenone), EMPHASIS-HF (Eplerenone), AREA-IN-CHF (Canrenone-an active metabolite of spironolactone).

Vasodilators in CHF

a. **Hydralazine-isosorbide dinitrate:** It may be used as adjunctive therapy in the management of CHF. In case of intolerance of ACE-inhibitors and ARBs, the combination of hydralazine/nitrates can be tried. In the African-American Heart Failure Trial (A-HeFT) Investigators, addition of a fixed dose of isosorbide dinitrate (20 mg) and hydralazine (37.5 mg) (1-2 tablets tid) in blacks including neurohormonal blockers (ACEIs, ARBs, beta-blockers, digoxin, diuretics) was shown to be efficacious and increased survival among black patients with advanced HF. This combination is recommended in African Americans who have been symptomatic despite optimal therapy. In others, if patients are intolerant of ACEIs, the combination may be considered an option despite lack of symptomatic data. However, the combination has poor compliance because of high incidence of side effects.
b. **Nitrates alone:** No evidence to support use in CHF.
c. **Alpha-adrenergic blocking drugs:** No evidence to support use in CHF.
d. **Calcium Channel blockers (CCBs):** Diltiazem and verapamil are not recommended in CHF secondary to systolic dysfunction. Newer CCBs (Felodipine and amlodipine) may be considered as additional therapy for concomitant arterial hypertension or angina not controlled by ACE-inhibitors, beta-blockers and nitrates but they do not provide a better effect on survival when compared with placebo.

Other Options in Medical Management

a. **Ivabradine:** It is inhibitor of I_f channel in sinus node. It slows down the heart rate in sinus rhythm but ineffective in slowing down ventricular rate in atrial fibrillation. SHIFT as well as BEAUTIFUL trials, showed reduction in hospitalization from heart failure (relative risk reduction 26%) but not in cardiovascular death or all-cause mortality.

Administration and dosing consideration: Usual starting dose is 2.5 to 5.0 mg bid in heart failure associated with tachycardia (not controlled with beta-blockers) and increase to 7.5 mg bid. It is usually well-tolerated except for rare side-effects like symptomatic bradycardia and visual effects secondary to phosphenes.

b. **Direct Renin Inhibitors:** Loss of negative feedback inhibition of renin release during chronic treatment with an ACE inhibitor leads to a compensatory rise in renin secretion and downstream components of RAAS cascade. This may overcome ACE inhibition but should be blocked by a direct renin inhibitor. In the ALOFT trial, addition of aliskiren to an ACE inhibitor (or angiotensin receptor blocker) and β-blocker had favorable neurohormonal effects in heart failure and appeared to be well-tolerated. However, in the recently presented ASTRONAUT trial, Aliskiren had no benefit over placebo in terms of CV-related death or HF –related hospitalization. What was troubling was that despite the fact that these patients were very well-treated with background medications, these patients had high mortality in both the groups i.e. Aliskiren and placebo.

c. **Statins:** The CORONA and GISSI-HF trials with rosuvastatin vs placebo did not show any favorable effect in terms of the primary end-point. However, meta-analysis has reported that effects of statins on HF are not a class effect and a significant benefit was noted using lipophilic atorvstatin but not hydrophilic rosuvastatin. Therefore, there is a possibility that lipophilic statins are more useful than hydrophilic statins for the treatment of CHF. Recently, PEARL study involving Pitavastatin, a lipophilic statin has been reported. In the overall Japanese study population, Pitavastatin did not reduce cardiac death or hospitalization for worsening heart failure. However, in patients with LVEF ≥ 30 percent a significant reduction in the primary outcome of composite of cardiac death or hospitalization for worsening HF was observed. Interestingly, only 27.4 percent of patients had ischemic HF in PEARL study compared to 40 percent in GISSI-HF and 100 percent in CORONA study. Further, randomized clinical trials are indicated.

d. **Vasopressin Receptor Antagonists:** These have been discussed in the chapter on "Acute Heart Failure". Their place in chronic heart failure remains uncertain at this point.

e. **Sildenafil:** In rat models, sildenafil has bee demonstrated to have beneficial, afterload independent effects on pressure-loaded right ventricle, but not on the volume-overloaded right ventricle. Since left heart failure may be associated with pulmonary hypertension "out of proportion" of left heart disease, sildenafil may have beneficial effect in such patients. However, in the recently presented RELAX trial with Sildenafil in diastolic heart failure, no improvement was noted compared to placebo in terms of exercise capacity.

Positive Inotropic Therapy in CHF

- Repeated or prolonged treatment with oral inotropic agents (Enoximone, vesanarinone, etc.) increases mortality (generally secondary to arrhythmias) and is not recommended in CHF.
- Intravenous administration of inotropic agents is commonly used in patients with severe episodes of worsening HF with signs of both pulmonary congestion and peripheral hypoperfusion. However, treatment-related complications may occur and their effect on prognosis is uncertain.

Antithrombotics in CHF

- Anticoagulants (Warfarin) is indicated in:
  - CHF with atrial fibrillation, previous thromboembotic event or a mobile left ventricular thrombus (Class of recommendation I Level of evidence A)
  - Warfarin anticoagulation may be considered in patients with dilated cardiomyopathy and LVEF < 35%.
- Antiplatelets agents are indicated in:
  - CHF who have underlying coronary artery disease for prevention of myocardial infarction and death. (Class of recommendation IIa, Level of evidence B).

  Aspirin should be avoided in patients with recurrent hospitalization with worsening HF. There is little evidence to support concomitant treatment with an ACE-inhibitor and aspirin in heart failure.

Antiarrhythmics in CHF

- Beta-blockers reduce sudden death in HF (Class of recommendation I, level of evidence A)
- Beta-blockers may also be indicated alone or in combination with amiodarone or nonpharmacological therapy in the management of sustained or nonsustained ventricular tachyarrhythmias (Class of recommendation IIa, level of evidence C)
- Amiodarone is effective agent for most supraventricular and ventricular arrhythmias (Class of recommendation I, Level of evidence A) It is the preferred treatment in atrial fibrillation and CHF.
- Amiodarone is not recommended for primary prevention of sudden death in patients with HF (Class of recommendation III, Level of evidence A)
- Large trials have shown that prophylactic use of amiodarone in patients with nonsustained asymptomatic ventricular arrhythmias and HF does not affect total mortality.
- Class I anti-arrhythmics reduce survival in HF and should be avoided.

Table 5.2 Summary of pharmacological therapy of eymptomatic CHF secondary to LV systolic dysfunction

	For survival/morbidity	For symptoms alone
NYHA I	ACEIs (ARBs if ACEI intolerant) If post MI, add Beta-blocker and aldosterone antagonist	Reduce/stop duretic
NYHA II	ACEIs (ARBs if ACEI intolerant) [or Beta-blockers (?) as first option (CIBIS III)] If post MI, add Beta-blocker and aldosterone antagonist	± diuretic depending on fluid retention
NYHA III	• ACEI plus ARB or ARB alone if ACEI intolerant • Beta-blocker • Add aldosterone antagonist	+ diuretics + digitalis if still symptomatic
NYHA IV	Continue all of above	+ diuretics + digitalis + consider temporary inotropic support

Worsening Heart Failure

Generally the most frequent cause of worsening HF are:

A. **CARDIAC**
   1. Dysrrhythmias
      a. Bradycardia: (i) Sinus, (ii) Atrioventricular blocks, (iii) Bundle branch blocks
      b. Tachycardias: (i) Atrial fibrillation, (ii) Other supraventricular tachycardias, (iii) Ventricular tachyarrhythmias
   2. Decompensation of valvular heart disease:
      a. Mitral regurgitation
      b. Tricuspid regurgitation
   3. Coronary artery disease (Symptomatic)
      a. Ischemia
      b. Infarction
   4. Over-reduction of pre-load (duireties + ACE inhibitors)

B. **EXTRA-CARDIAC**
   1. Non-complaince with prescribed regimen
   2. Recently added adjunct drugs (β-blockers, NSAIDs, verapamil diltiazem, etc.)
   3. Ethanol abuse
   4. Renal derangement (overuse of diuretics)
   5. Infection
   6. Pulmonary embolism
   7. Thyroid dysfunction (e.g. Amiodarone induced)
   8. Anemia (e.g. Internal bleeding)

Management of End-Stage Heart Failure (NYHA CLASS IV)

The first step is to look for any potentially treatable precipitating cause mentioned above, which if taken care of, results in marked improvement.

Options of maximizing medical management including meticulous identification of fluid retention. Surgical options especially revascularization in ischemic cardiomyopathy and cardiac resynchronization therapy (± implantable cardiverter defibrillator) should be considered before accepting the heart failure as refractory. If indeed HF is refractory, following guidelines are to be followed:

- Refer potentially eligible patient for cardiac transplantation ACC/AHA Guidelines Class I recommendation (Level of Evidence: B).
- Refer patient to a heart failure program with expertise in the management of refractory heart failure ACCF/AHA Guideline Class I recommendation (Level of Evidence: A).
- Discuss option for end-of-life care with patient and family when severe symptoms persist despite application of all recommended therapies ACCF/AHA Guidelines Class I recommendation (Level of Evidence: C).
- Offer patients with implantable cardioverter defibrillators and end-stage disease, the option to inactivate defibrillation ACCF/AHA Guideline Class I recommendation (Level of Evidence: C).
- Consider a LV assist device as permanent or destination therapy in highly selected patients with refractory end-stage HF and an estimated one year mortality more than 50 percent than with medical therapy. ACCF/AHA Class IIa recommendation (Level of Evidence: B).

Cardiac Resynchronization Therapy

The clinical effects of long-term cardiac resynchronization therapy (CRT) have been evaluated in a large number of randomized multicenter trials with crossover or parallel treatment assignment. In NYHA Class III/IV patients, MUSTIC-SR, MUSTIC, MIRACLE, PATH-CHF, MIRACE ICD, PATH-CHF II, COMPANION, CARE HF trials have confirmed a significant alleviation of symptoms and increase in exercise capacity conferred by CRT. Functional benefits and quality of life improvement including reduction in unplanned hospitalization has been sustained. CARE-HF and COMPANION were trials powered to examine the effects of CRT on combined primary end-points of mortality. In COMPANION, CRT-D was associated with a significant decrease in all-cause mortality (relative reduction: 36%, $p=0.003$). In CARE-HF, where only CRT-P was assessed, a 36 percent relative reduction in risk of death ($p < 0.002$) was observed after a mean follow-up time of 29 months. Based on these RCTs, ESC recommendation in patients with heart failure in NYHA class III/IV are:

CRT-P/CRT-D is recommended to reduce morbidity and mortality in following population:

NYHA function was class III/IV
LVEF ≤ 35%, QRS ≥ 120 ms, Sinus rhythm
Optimal medical therapy
Class IV patients should be ambulatory
[Class I Recommendation, Level of Evidence: A]

LV dilatation is no longer required in the recommendation and patients should have reasonable expectation of survival with good functional status for > 1 year for CRT-D. Evidence is strongest for patients with typical LBBB.

Two recent, randomized, prospective, multicenter trials, MADIT-CRT and REVERSE demonstrated reduced morbidity in NYHA Class I and II patients on optimal medical therapy. Only 18 percent of patients in REVERSE and 15 percent of patients with MADIT-CRT were in NYHA I class at baseline although most of these patients had been previously symptomatic. Improvement was primarily seen in patients with QRS ≥ 150 ms and/or typical LBBB. In MADIT-CRT, women with LBBB demonstrated a particularly favorable response. Survival advantage is not established. Consistent with the echocardiographic studies from CARE-HF and REVERSE trials, in MADIT-CRT trial, substantial improvements in LV size and function, LVEF, RV function, left atrial size and mitral regurgitation were observed in patients treated with CRT compared with ICD only.

ESC Recommendations in Patients with Heart Failure in NYHA Class II

CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression in following patient population:

NYHA function class II
LVEF ≤ 35%, QRS ≥ 150 ms, Sinus Rhythm
Optimal medical therapy
[Class I Recommendation (Level of Evidence: A)].

Following are the recommendations in patients with heart failure and permanent atrial fibrillation:

Table 5.3 Recommendations for CRT and ICD

Recommendations	Patient population	Level of evidence
CRT-P/CRT-D should be considered to reduce morbidity	NYHA function Class III/IV LVEF ≤ 35%, QRS ≥ 130 ms Pacemaker dependency induced by AV nodal ablation	IIa (B)
CRT-P/CRT-D should be considered to reduce morbidity	NYHA function Class III/IV LVEF ≤ 35%, QRS ≥ 130 ms slow ventricular rate and frequent pacing	IIa (C)

In patients with a conventional bradyarrhythmic indication for pacing, NYHA III/IV symptoms, an LVEF of ≤ 35 percent and a QRS ≥ 120 ms, a CRT-P/CRT-D is indicated. Chronic RV pacing in patients with LV dysfunction should be avoided. CRT may permit adequate uptitration of β-blocker treatment.

RBBB and CRT: The patient subgroup with RBBB, in CONTAK CD trial for unknown reasons, did not demonstrate a significant improvement in symptom status and LVEF. Tissue doppler imaging is clearly indicated in patients with RBBB. Pacing from alternative stimulation sites e.g. RVOT might lead to better response in such patients.

Echocardiography and CRT: CRT has been shown to benefit HF patients with medically refractory NYHA Class II-IV, LVEF $\leq$ 35 percent and QRS $\geq$ 120 ms (especially with left bundle branch block). However, up to a third of patients with significant LV dyssynchrony on imaging have normal duration QRS, and a significant proportion of HF patients with wide QRS have LV synchrony. This problem is compounded by the fact that 30 to 50 percent patients who meet eligibility criteria for CRT fail to show improvement with this therapy. Hence careful selection of patients for CRT is essential, and imaging based methods to characterize inter and intraventricular dyssynchrony are needed to identify who will benefit from CRT implantation.

Tissue Doppler imaging: TDI has been used in the past to determine candidacy for CRT and to follow-up response to therapy. Although TDI-based measurements yielded interesting data showing asynchrony in different cardiac segments, in the PROSPECT study, no single echocardiographic measure of mechanical asynchrony was identified as being useful for identifying patients more or less likely to respond to CRT. It should be noted that the inter-core laboratory variability was relatively high at 6.5 to 7.2 percent in this study, indicating a need for refinement of methodology. Moreover, asynchrony may be a dynamic problem whose severity and characteristics may vary under different physiologic conditions. Work using echocardiography to better guide selection of patients for CRT is underway. What is definitely established is that presence of extensive posterolateral scarring (on cardiac MRI, nuclear imaging or echocardiography) is a significant predictor of non-response to CRT. Severe valvular heart disease is commonly seen in advanced HF as a cause and effect (especially mitral regurgitation).

Important limitations of TDI include Doppler angle dependency and problem in assessing regional LV torsional dynamics. The rotational component of cardiac contraction plays a significant role in LV ejection and relaxation, and is not well imaged by most TDI techniques. Newer techniques such as “speckle tracking” algorithms using 2D echocardiography involve identification of multiple unique patterns of tissue pixel imaged that are automatically tracked throughout the cardiac cycle. The angular displacement of these pixels can be plotted over time for all visualized segments. This is a sensitive marker of cardiac ischemia, and may prove beneficial as a refined measure of LV dysfunction in HF and dyssynchrony.

Follow-up of CRT

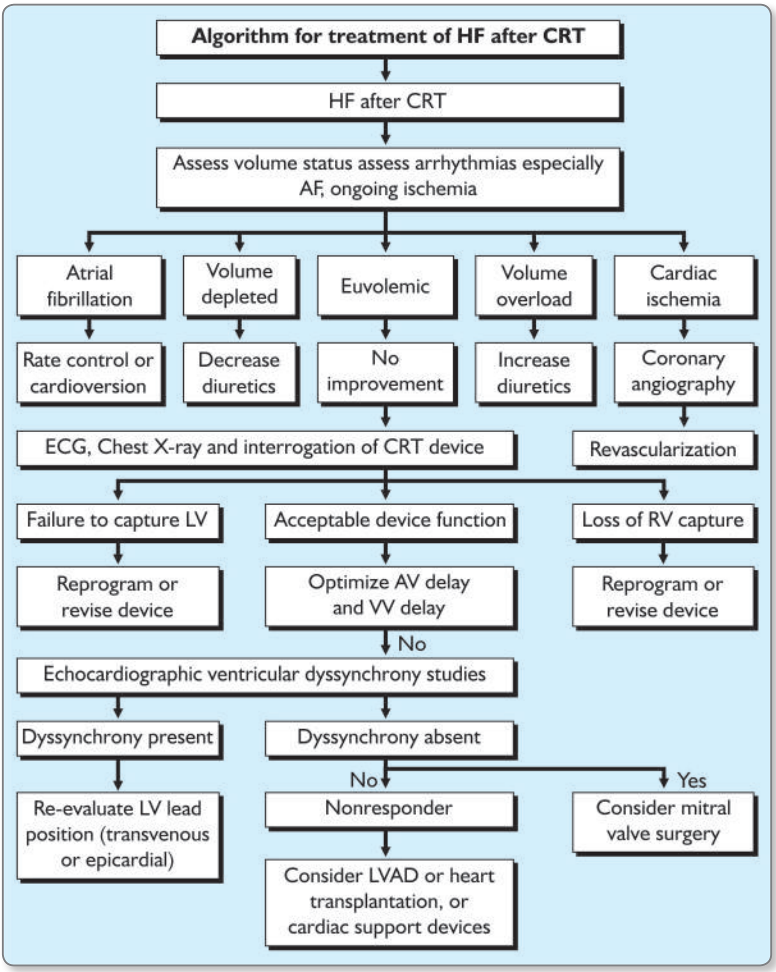
Clinical Parameters

- NYHA functional class
- 6-min walk distance
- Heart failure hospitalizations
- Quality-of-life score
- Exercise capacity (peak VO_2)
- Cardiac mortality

Echocardiographic Parameters

- LV ejection fraction
- Mitral regurgitation
- Dyssynchrony index
- LV dimensions volumes
- dp/dt max

Flow chart 5.2 Treatment of heart failure after CRT



Implantable Cardioverter Defibrillator

In primary prevention trials (SCD-HeFT, CABG-PATCH, DINAMIT, MUSTT, MADIT-I, MADIT-II, DEFINITE) in patients with non-ischemic and ischemic heart failure with EF < 35% in NYHA II-III, ICD showed marked reduction in sudden death (relative risk reduction 23-31%). Of the trials mentioned above, SCD-HeFT trial reported similar reduction in all-cause ischemic cardiomyopathy. The largest study of exclusively non-ischemic cardiomyopathy (DEFINITE) demonstrated a significant 80 percent reduction in arrhythmic death with an ICD.

Indications of ICD

Implantable cardioverter defibrillator (ICD)

- ICD therapy for secondary prevention is recommended for survivors of VF or VT with syncope, an LVEF ≤ 40 percent, on optimal medical therapy and with an expectation of survival with good functional status for more than 1 year.
- ICD therapy for primary prevention is recommended to reduce mortality in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 35 percent, in NYHA functional class II or III, receiving optimal medical therapy and who have a reasonable expectation of survival with good functional status for more than 1 year.
- ICD therapy for primary prevention is recommended to reduce mortality in patients with nonischemic cardiomyopathy with a LVEF ≤ 35 percent, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for more than 1 year.

Surgical Options in Heart Failure

Surgical options in heart failure can be considered under two broad groups.

A. **Traditional surgical approaches**
   - Coronary artery bypass surgery
   - Aortic valve replacement
   - Mitral valve repair
   - LV aneurysmorrhaphy.

B. **Management of End-stage heart disease**
   - Ventricular assist devices
   - Cardiac transplant
   - LV restraining devices
   - Cellular therapies.

Coronary Artery Bypass Grafting

Major RCTs evaluating coronary revascularization in heart failure patients have been:

i. **PARR-2 trial:** Whether PET imaging should be considered in patients with severe LV dysfunction before revascularization.
ii. **HEART trial:** Whether coronary revascularization and optimal medical therapy improves survival of patients of HF who have evidence of dysfunctional but viable myocardium and who are receiving optimal medical therapy.
iii. **STICH trial:** 3 objectives were studied – (a) whether coronary artery bypass grafting (CABG) plus intensive medical therapy (IMT) in patients with HF improves 3-year all-cause mortality compared to IMT alone, (b) to evaluate whether presence of substantial myocardial viability influenced the survival benefit of CABG revascularization and IMT compared to IMT alone, (c) To explore whether surgical ventricular reconstruction (SVR) added to CABG would decrease the rate of death or hospitalization for a cardiac event compared to CABG alone.

Overall conclusion from the above-mentioned trials are as following: evidence suggests that coronary revascularization improves survival compared to medical therapy in patients with CAD and significant LV systolic dysfunction and for those in whom treatable targets are identified. Decisions to perform revascularization in these patients should not be overly influenced by imaging-defined myocardial viability status, as an association with clinical outcomes was not shown. The routine use of SVR as an adjunct to CABG coronary revascularization is not supported by evidence.

Decision-making in Ischemic Cardiomyopathy

1. Assessment of dominant symptoms:
   a. Angina—likely to benefit from revascularization if procedural risk is low to intermediate
   b. Dyspnea—should be subjected to revascularization after viability ± ischemia testing and assessment of procedural risk; otherwise OMT ± CRT are preferred options.
2. Assessment of viability and ischemia:
   a. Echocardiography (Dobutamine stress echocardiography)
      ↓
      Assessment of contractile reserve (CR); if no CR seen in segment >6 mm thickness, can use myocardial contract echo (MCE) to further delineate viability.
      ≥5/17 segments with CR → Hibernating myocardium present
      <5/17 segments with CR → Hibernating myocardium absent
      >3 segments affected → Ischemia present
   b. Nuclear imaging (SPECT)
      >50% peak tracer uptake → viable
      <50% peak tracer uptake → nonviable
      ≥5/17 viable segments → Hibernating myocardium present

<5/17 viable segments → Hibernating myocardium absent
>10% myocardium affected → Ischemia present

c. Magnetic Resonance—CMR
>75% TEI → Nonviable
50-75% TEI → Dobutamine
≥5/17 viable segments → Hibernating myocardium present
<5/17 viable segments → Hibernating myocardium absent
>10% myocardium affected → Ischemia present

3. Scope of revascularization
   - Angina-predominant subjects with low to intermediate procedural risk
   - Dyspnea-predominant subjects with presence of both viability and ishemia even if CAD is only mild to moderate
   - Dyspnea-predominant subjects with severe CAD if singificant viability is demonstrated.

Ventricular Remodeling Surgeries

After transmural myocardial infarction, the ventricule undergoes remodeling pathologically from its normal elliptical shape to a spherical shape and the resultant change in geometry accounts for production of symptoms associated with CHF and increased mortality. Fortunately, success of early lytic therapy and primary angioplasty for acute myocardial infarction has decreased the incidence of true LV aneurysms. Although, the initial enthusiasm of ventricular resection in nonischemic dilated cardiomyopathies ("the Batista procedure") has faded, it has long been established that resection of dyskinetic segments associated with LV aneurysm can increase functional status and prolong life. Various techniques of LV aneurysm repair have been described like Cooley's technique, Jatene's technique, DOR procedure, Fontan procedur. The RESTORE trial involving the DOR (modified left ventricular reconstructive surgery) technique showed that there was increase in LVEF from 29.6 to 39.5 percent, a decrease in end-systolic volume index and considerable improvement in NYHA function class. Most studies outside of the RESTORE trial are single-institution, retrospective analyses. The major study of ventricular reconstruction has been the STITCH trial . One thousand patients with LVEF < 35 percent, coronary artery disease amenable to CABG and dominantly anterior LV dysfunction that was amenable to surgical ventricular reconstruction (SVR) were randomly assigned to undergo either CABG alone or CABG with surgical ventricular reconstruction (SVR). No significant difference was observed at the end of 48 months between the two groups in terms of exercise tolerance, death from any cause or hospitalization from cardiac causes. On the basis of these results, SVR cannot be recommended for routine use in patients with ischemic cardiomyopathy and dominant anterior LV dysfunction.

Ventricular Assist Devices

The devices have evolved over the years and are still rapidly evolving. They can broadly be divided into first-second-, and third generation devices according to their principle of operation.

i. First-generation devices are pulsatile positive displacement pumps, main ones being the Heartmate I, Thoratec PVAD and Novacor. Since they need extensive surgical dissection, presence of a large-diameter lead, audible pump etc., they are being used less now.
ii. Second-generation devices are axial flow pump devices that are being increasingly used now. They are smaller devices and are continuous-flow rotary pumps that have only one moving part, the rotor, unlike the first generation devices (and hence are more durable).
iii. Third-generation devices: Heartware and Duraheart are magnetic third-generation pumps that are now being tested in clincal use.

Left Ventricular Assist Devices (LVADs) are being increasingly inserted into patients with advanced HF. Initially, this was mainly as a bridge to transplant, but now it also a bridge to recovery and increasingly is likely to be used as destination therapy. The results of the REMATCH trial lead to FDA approval of the Heart VE for destination therapy in USA in 2002 and in 2009, FDA approved the Heartmate II for its use as destination therapy. It appears that as device design, patient selection and management, and promptness of referral continues to improve, the outcome for many patients with advanced HF will improve further.

Mitral Valve Surgery in Heart Failure

Functional MR occurs commonly as part of the remodeling process resulting from left-ventricular failure. Surgical correction of the regurgitation either by repair or replacement can be effective, although there are no randomized clinical trial results to substantiate the claim and little evidence to guide timing of mitral surgery for functional regurgitation. Reduction annuloplasty is the most favored means of surgical correction, although mitral valve replacement with preservation of all the subvalvular structure should not be discounted, especially if restrictive motion of anterior mitral leaflet is present preoperatively. Percutaneously, Mitraclip is an interesting advancement in management of MR in heart failure.

Ventricular Restraining Devices

Dilating, remodeling, enlarging heart leads to furthering of heart failure progression. Cardiac restraining procedures and devices have attempted to arrest this process. These include dynamic cardiomyoplasty, ACORN Cor Cap, Paracor Heartnet. The most studied product in the CorCap device which is a mesh-like support that is sewn circumferentially around the ventricle. More data is required to demonstrate its efficacy. Also there is a widespread concern regarding the worsening of diastolic functions of the left ventricle due to these restraining devices.

Cardiac Transplantation

According to ACCF/AHA (2009) Guidelines for Heart Failure in adults, absolute indications for heart transplantation in heart failure include the following:

- Refractory cardiogenic shock
- Dependence on IV inotropic support for adequacy of organ perfusion
- Peak oxygen consumption per unit time (VO2) less than 10 mL/kg/min
- Severe ischemic symptoms with consistent limitations of routine activity that are not amenable to revascularization procedures (CABG, percutaneous coronary intervention)
- Recurrent symptomatic ventricular arrhythmias despite all therapeutic interventions

Major issues with cardiac transplantation are social, infrastructural and operational. Organ procurement is the major problem globally and situation is indeed dismal in India. Otherwise, compared to medical therapy alone, transplant recipients have fewer rehospitalizations, marked functional improvements and longer livers, with 50 percent surviving to 10 years.

Stem Cell Therapy

The possibility of using pluripotent stem cells to replace damaged organs is attractive and has been tried for a range of conditions including chronic HF. The unresolved issues with regard to effective stem cell therapy are:

i. **Which stem cells to use?**
   - Embryonic stem cells are probably the purest form of stem cells and are capable for forming lineages leading to cardiovascular cells. Potential problems with their use include lack of availability, chance of teratoma formation and immunological intolerance, including graft versus host disease.
   - Mesenchymal stem cells can be derived from many tissues, including bone marrow. They can be induced to differentiate into cardiac myocytes but more often mature into osteoblasts and chondrocytes and hence may lead to heterotopic calcification.
   - Myoblasts from skeletal muscles differentiate into mature skeletal muscle cells and fail to couple with adjoining cardiac myocytes. This may be associated with increased arrhythmogenicity.
   - Bone marrow-derived stem cells can be transformed into cardiac myocytes. Their use has been reported to result in a small increase in LV ejection fraction.
   - Stem cells induced from a patient's somatic cells can be induced to form myocyte lineage, but risk of teratoma or neoplasm development persist, as for embryonic stem cells.

ii. **What should be the route of stem cell delivery?**
   - Delivery directly into damaged myocardium by injection, generally at the time of coronary artery surgery, has been tried.
   - Intracoronary injection is the other major technique tried so far.

iii. **What is the appropriate timing of stem cell delivery?**
   - Is it immediately peri-infarct or later when healing (and potentially scar formation) is taking place ? Best option is not yet clear.

Clinical trial results have not yet provided for use of stem cells. The most promising concept that emerges from meta-analysis of 18 randomized and nonrandomized trials is that intracoronary injection of mesenchymal stem cells in patients with HF due to coronary artery disease can improve LVEF by 3.7 percent with small decrease in scar size and LV volume. Whether such a small benefit in LV function translates into clinical benefit is not at all clear. One possible source of appropriate cells is cardiac progenitor cells isolated from endomyocardial biopsies. A trial, CADUCEUS, is underway to assess whether there cells help in clinical practice.

Monitoring in Heart Failure

It has become increasingly apparent that interventions geared toward identifying and monitoring subclinical congestion would be of value in home management of chronic HF. Earlier identification and treatment of congestion together with improved care co-ordination may help to prevent hospitalizations in patients with chronic HF. Such home-monitoring extends from promotion of self-care and home visitations to telemedicine and remote monitoring of external or implantable devices.

Potential Measurements for Heart Failure Monitoring

i. **Patient related data:**
   - *Symptoms:* Breathlessness on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, abdominal fullness, anorexia, nausea, vomiting
   - *Signs:* Jugular venous distension, peripheral edema, pulmonary congestion/rales/pleural effusion, S3 gallop
   - Daily weights
   - Sodium intake
   - Medication compliance/changes.

ii. **Laboratory data:** Serum urea, creatinine, electrolytes.
   Natriurtic peptides (BNP/NT-proBNP)

iii. **Directly recorded data:** Heart rate, blood pressure, ECG (arrhythmias), percentage pacing, pressure sensor data (RV outflow, left atrial, pulmonary artery)

iv. **Calculated data:** Heart rate variability

Activity level
Intrathoracic impedance

Telemonitoring (i.e. transfer of physiological data e.g. BP, Weight, ECG, SaO_2 through technology) trials e.g. TELE-HF, TIM-HF failed to demonstrate any benefit over usual care in terms of all-cause re-hospitalization rates or death.

When permanent pacemakers, ICDs, CRTs are implanted in patients with HF for usual indications, their potential capabilities in terms of detection of arrhythmias, heart rate variability, patient activity level and in selected devices, intrathoracic impedance can be of use. An increase in pulmonary vascular congestion is reflected by decreased impedance, which can be recorded and reported by the device prior to symptom development. Given these potential advantages, remote monitoring of implantable devices has been endorsed by HRS/EHRA expert consensus.

Implantable dedicated hemodynamic monitors have been developed too. These include:

- RV pressure sensor system (Chronicle, Medtronic) – tested in COMPASS-HF trial
- Left atrial pressure sensor (Heart POD, St Jude) – tested in HOMEOSTASIS trial
- Pulmonary artery sensor (wireless, without an implanted battery – heart sensor, cardio-MEMS) – tested in CHAMPION trial

These trials, especially the CHAMPION trials showed that HF related hospitalizations were significantly less frequent in the treatment group (31 vs. 44 percent) with a 1.5 percent rate of device or system-related complications. Notably benefits of sensor guided treatment were similar in patients with preserved LVEF as those with reduced LVEF. Whether home monitoring approaches for HF will live up to their full potential of improving quality of life, functional status and HF outcomes while reducing healthcare costs in the larger population of patients with HF remains to be seen.

Ultrafiltration in End-stage Heart Failure

A recent study by Patarroyo et al reported role of slow continuous ultrafiltration in patients with decompensated, recalcitrant heart failure. Despite effective decongestion in these patients refractory to conventional therapy, in-hospital mortality was high (30% dying before discharge) and 6 out of 63 patients discharged to terminal care in hospital. Thus, this study presents a counterpoint to recent studies highlighting potential short-term benefits of ultrafiltration in acute decompensated heart failure, ultrafiltration in chronic end-stage heart failure does not have a major influence on clinical outcomes and may have actually accelerated deterioration in renal function in a substantial subset of patients.

Metabolic Therapy

Failing heart is an *engine running out of fuel*. Hence, one possible approach is to modulate the substrates for energy production. Fatty acids are the dominant fuel for myocytes (at least in some circumstances) and whereas, weight for weight, oxidation of fatty acids produces more ATP than oxidation of glucose, it takes more oxygen per mole of ATP produced to oxidize lipid.

Perhexiline and etomoxir both inhibit carnitine palmitoyl transferases (CPT) 1, the enzyme responsible for transporting fatty acids into mitochondria. Trimetazidine inhibits fatty acid oxidation. Use of such agents results in a shift towards predominant glucose metabolism and small-scale clinical studies have suggested that they may have a role in HF-therpay. Other approaches include modifying insulin and glucose metabolism with metformin.

Gene Therapy

Pentraxins are cytokine-inducible genes, expressed in specific tissues, which reduce early myocardial damage after myocardial infarction. Gene therapy with MCP-1 blocker also attenuates the development of cardiac remodeling after myocardial infarction. Pharmacogenetics is likely to have a future role in selection of appropriate drugs in a patient with HF.

Immunomodulation

Intravenous immunomodulation (IVIG) has been shown in some studies to improve LVEF, hemodynamics and exercise capacity in patients with chronic HF, independent of etiology. Others have found no impact of IVIG on recent onset idiopathic dilated cardiomyopathy (DCM). Interferon-1β for treatment of virus-related DCM is being tried in a large phase III trial after initial demonstration of symptomatic benefit.

Celacade is an immunomodulatory therapy after initial reports of symptomatic benefit has been tried in ACCLAIM (phase III) trial. Except in a subgroup with NYHA class II HF without previous MI, there was no outcome benefit. Azathioprine with prednisolone has shown improvement in LVEF and LV volumes in patients with biopsy-proven myocarditis (without presence of viral genomes) in comparison to conventional therapy for HF. Other promising therapeutic options include inhibition of Nuclear factor-κB (NF-κB) activation, mannose-binding lectin, IL-18 and IL-6 antagonists, T cell and caspase inhibitors.

Table 5.4 Current status of drugs and devices in HF with regard to morbidity and mortality

Class	Drug	NYHA I	Class II	III	IV
Antiarrhythmics β-blockers	Amiodarone	NA		+/-	+/c
	Metoprolol (long-acting)	NA	+++	+++	+
	Bisoprolol	NA	+++	+++	+++
	Carvedilol	+++	+++	+++	+++
	Bucindolol	NA	NA		
Calcium channel antagonists		NA			
Digitalis		+	+	+	+
Aldosterone antagonist (Spironolactone/Eplerenone)		NA	++	+++/++	+++/++
Inotropic therapy		NA	-	-	-
ACE inhibitors		+++/+	+++/++	+++/++	+++/++
Hydralazine-isosorbide dinitrate		++	++	+	
ARBs		+++	+++	++	
ICDs		NA	+	+	+
Resynchronization therapy		NA	++	+++/++	+++/++

Suggested Reading

1. Heart Failure Society of America, Non-pharmacological management and health care maintenance in patients with chronic heart failure. J. Card Fail 2010;16:e61.
2. Jessup M, Abraham WT, Gasey DE, et al. 2009 focused update incorporated into the ACC/AHA 2005. Guidelines for diagnosis and management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;15(53):1343-82.
3. McMurray J JV, et al for the Task Force for the diagnosis and treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2012;33:1787-1847.
4. Pron G. Coronary Revasculatization in Ischemic Heart Failure Patients. A Rapid Review, 2013. pp. 1-28.
5. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet 2011;378:704-12.

chapter 6

Syncope

Saptarshi Mukhopadhyay, Sulagna Banerjee, Soumitra Kumar

DEF: Syncope refers to the specific pathophysiology involving a transient loss of consciousness and postural tone as a result of cerebral hypoperfusion, with spontaneous and complete recovery and no neurologic sequelae.
D/d: Sleep disorders, coma, shock, delirium, drop attacks, vertigo, presyncope and if seizures.

Incidence: 3 to 37% of general population; accounts for 3% of emergency department visits and 1% of hospital admissions.

Causes of Syncope

	Prevalence
A. Neurally Mediated Syncope:	21-66%
i. Vasovagal faint	
ii. Carotid sinus hypersensitivity	
iii. Situational faints (cough/micturition/defecation/swallow)	
B. Cardiac Arrhythmias:	10-11%
i. Sinus node dysfunction	
ii. Paroxysmal supraventricular and ventricular tachycardia	
iii. Implanted device malfunction	
C. Orthostatic Syncope:	9-10%
i. Secondary autonomic failure (Diabetic and amyloid neuropathy)	
ii. Volume depletion (e.g. Hemorrhage)	
iii. Primary autonomic failure (Multisystem atrophy/Parkinson disease with autonomic failure)	
iv. Drugs and alcohol	
v. Others, e.g. Addison's disease, pheochromocytoma	
D. Other Cardiac Causes:	5-10%
E. Others: Cerebrovascular (Migraine, vascular steal syndrome, vertebrobasilar transient ischemic attack, nonsyncopal causes unindentified etc.	8-37%

Psychogenic pseudosyncope is a group of psychiatric disorders such as conversion and factitious disorders or malingering. Usually the state of pseudo-unconsciousness lasts longer than true syncope and upon physical examination there is no gross neurological abnormality. Instead, cataplexy refers to the loss of muscle tone due to emotions, particularly laughter. The attacks look like syncope in which patients cannot respond at all, although they are completely aware of the surroundings.

Cardiac Syncope

A. Structural cardiovascular or cardiopulmonary disease
   - Aortic stenosis, hypertrophic obstructive cardiomyopathy
   - Pulmonary embolism, pulmonary hypertension
   - Atrial myxoma, myocardial infarction, cardiac tamponade
   - Coronary spasm, aortic dissection.

B. Arrhythmias
   a. Bradyarrhythmias
      - Sinus node disease
      - Second or third degree heart block
      - Pacemaker malfunction
      - Drug induced
   b. Tachyarrhythmias
      - Ventricular tachycardia
      - Torsade de pointes
      - Supraventricular tachycardia.

Diagnostic studies in the evaluation of syncope

Study	Indications
• History and physical examination	All patients
• ECG	Virtually all patients
• Basic laboratory testing	Only if abnormality suspected
• Echocardiography	Patients with known or suspected heart disease
• Exercise stress testing	Suspected coronary disease or exertional syncope (AS, PS, HCM, PAH, Accessory pathways)
• Holter monitoring	Patients with organic heart disease, abnormal ECG or high suspicion for arrhythmia
• External loop recorder	Patients with frequent syncope, suspicion for arrhythmia, abnormal ECG with negative cardiac workup
• Implantable loop recorder	Negative cardiac workup, infrequent syncope, negative tilt and psychiatric examinations
• Transtelephonic electrocardiogram monitoring	Compliant patients with frequent syncope and either no suspected cardiac disease or negative workup

Contd...

Contd…

Study	Indications
• Electrophysiology studies	Organic heart disease and high suspicion for arrhythmia; clinically normal heart but high risk for bradyarrhythmia, especially if frail
• Tilt-table testing	Recurrent unexplained syncope without evidence of organic heart disease or with negative cardiac workup
• Carotid sinus massage	Elderly patients with unexplained syncope or history compatible with carotid sinus syncope, no bruits and no history of CVA
• Adenosine triphosphate (ATP) testing	Identifies a group of patients with otherwise unexplained syncope with definite clinical features and benign prognosis but possibly heterogeneous mechanisms of syncope

Diagnostic clues on electrocardiogram

	Finding	Possible cause of syncope
1.	Short PR interval Delta wave (WPW syndrome)	Supraventricular tachycardia/AF
2.	Bundle branch block Prolonged PR interval	Advanced AV block or complete AV block
3.	Sinus bradycardia Sinus pause Brady-tachy syndrome	
4.	Intraventricular conduction delay Myocardial infarction/ischemia LV or RV enlargement Complex VPCs Long QTc TU abnorlmality	Ventricular tachycardia
5.	a. RBBB with ST-elevation in V1, V2 (Brugada syndrome) b. T wave inversion in V1-V3 sharp wide deflection (epsilon wave) following S in VI (Arrhythmogenic RV dysplasia) c. T wave alternans	Ventricular fibrillation Ventricular tachycardia (LBBB with Lt-axis deviation) Ventricular fibrillation

Echocardiogram

- Evidence shows that echocardiogram adds no additional diagnostic benefit when initial evaluation does not support possible cardiac disease.
- For patients with suspected cardiac disease, echocardiogram is very useful in screening for valvular disenses, pulmonary hypertension, right or left ventricular hypertrophy or cardiomyopathy.

- Echocardiogram can guide the selection of further diagnostic tests like CT or MRI Scans.

Noninvasive ECG Monitoring

- The type and duration of monitoring are determined by the frequency of events (Holter monitoring is carried out for 24 to 72 hours and can record major abnormalities in 27% of patients).
- Holter monitoring is indicated in patients who have clinical or ECG features suggesting an arrhythmic after inconclusive initial evaluation but when the mechanism of syncope remains unclear after full evaluation a loop recorder is indicated; external loop recorders are being increasingly used and can be carried out for about seven days.
- Implantable loop are recorders can monitor ECG for 14 months and can yield diagnostic information in 90% of patients.

Electrophysiological Study

- Electrophysiological testing is useful in identifying the presence of ventricular tachyarrythmia and evaluating the risk of sudden death in patients with CAD.
- An electrophysiological procedure is indicated when the initial evaluation suggests an arrhythmic cause of syncope or the presence of CAD.
- Normal electrophysiological findings cannot completely exclude an arrhythmic causes of syncope, and further evaluations (e.g. ECG, continuous monitoring) are then warranted.

Key Points in History Taking

Situation

- Sudden standing or sitting (Orthostatic syncope)
- Severe pain, fear, instrumentation (Vasovagal syncope)
- Micturition, defecation, severe coughing (Situational syncope) (especially in patients with COPD)
- During or immediately after exertion (CAD, obstructive cardiomyopathy, LQTS, etc.)

Prodrome

- Diaphoresis, nausea, warmth, light headedness
- Diplopia, dysarthria; focal neurologic symptoms, headache
- Chest pain, shortness of breath
- Duration of prodrome.

Witnessed Appearance

Tonic/clonic movements, cyanosis, urinary incontinence, tongue biting.

Postevent Residua

Confusion.

Differentiation of Seizures from True Syncope

i. Seizures tend to be positionally independent whereas syncope is most commonly associated with upright posture.
ii. Seizures are often preceded by an aura whereas syncope is not.
iii. Seizures are often immediately accompanied by convulsive activity and incontinence whereas in true syncope any abnormal motor activity is less severe and incontinence is unusual.
iv. Seizures are typically followed by a confusional period whereas true syncope is typically followed by prompt restoration of mental state (Although fatigue may persist, especially in the case of vasovagal syncope).

Syncope in the Athletic Patients

Syncope in an athletic patients is a common symptom but should always raise the possibility of cardiac pathology. Although most cases of syncope in athletic are reflex syncope and considered benign. Even neurally mediated syncope, if it occurs when an athlete is in a physically dangerous circumstance (Such as driving, motor sports, road cycling), may still be life threatening. Syncope during exertion is often caused by underlying heart disease. (such as hypertrophic cardiomyopathy, right ventricular outflow tract tachaycardia, ion channel defects, arrhythmogenic right ventricular cardiomyopathy, coronary anomalies etc.) and may be a harbinger of sudden cardiac death.

Syncope in an athlete requires a thorough evaluation including a detailed and focussed history and physical examination with the addition of case-dependent diagnostic tests. Ultimately, the purpose of this evaluation is to distinguish between life threatening and nonlife threatening causes of syncope.

Risk Stratification

- Because of the increased risk of mortality among patients of cardiac cause of syncope, risk stratification of patients presenting with transient loss of consciousness at ED is important.

  The European Society of Cardiology recommend admitting patients with real syncope for further evaluation or management as follows :
- Patients with significant heart disease, ECG abnormalities that suggest arrhythmia, or family history of SCD need to be admitted for further evaluation.
- Patients with cardiac arrhythmia, ischemia, structural heart disease or cardiopulmonary disease need to be admitted for initial management.
- Patient with minimal or no heart disease or who suffered recurrent episode of syncope in supine position occasionally need to be admitted.

Many attempts have been made to stratify those at increased risk for mortality. San Francisco Rule Study (SFRS) predicts those at increased risk for serious outcomes with 98% sensitivity and 58% specificity using a simple mnemonic: CHESS: At least one of the following exist:

- **C**ongestive cardiac failure
- **H**ematocrit < 30%
- **E**CG that it abnormal
- **S**hortness of breath
- **S**ystolic hypotension <90 mmHg

The OESIL Risk Score was developed as a prognostic tool to be used in the ED for patients with syncope. It can predict 12 month, all cause mortality using four predictors in a simple mimonic (SAHA):

S Syncope without prodrome
A Age > 65 years
H History of heart disease
A Abnormal ECG

A more comprehensive risk stratification approach was done in the "Syncope Evaluation in the Emergency Department" [SEED] Study.

The SEED study classified patients into three groups:

High Risk Group: Chest pain, CHF, valvular disease, arrhythmia, ischemia, sinus pauses, third degree heart blocks.

QT_C > 500 msec, sinus bradycardia, atrial fibrillation or malfunction of pacemaker/ICD.

Intermediate risk group: Age > 50 years, history of CAD, presence of BBB, family history of SCD or pacemaker /ICD in place.

Low risk > age < 50 years, normal cardiovascular examination and normal ECG findings.

The ROSE[12] (Risk stratification of syncope in the emergency department) study also needs to be mentioned in this context.

Object: The aim of this study was to develop and validate a clinical decision rule (CDR) to predict one month serious out-come and all-cause death in patients presenting with syncope to the emergency department.

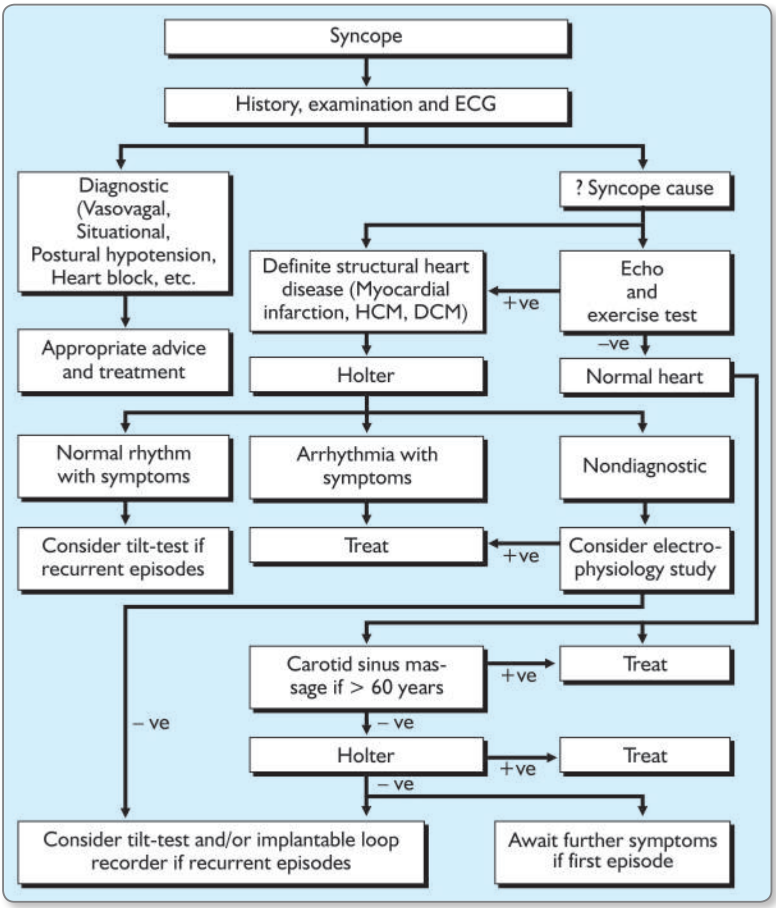
Conclusion: The ROSE rule has excellent sensitivity and negative predictive value in the identification of high-risk patients with syncope. As a component BNP seems to be a major predictor of serious cardiovascular outcomes and all cause death. The ROSE rule and BNP measurement might be valuable risk stratification tools in patients with emergency presentations of syncope and should now be subjected to external validation.

The ROSE rule

B BNP level ≥ 300 pg/ml
Bradycardia ≤ 50 in ED or prehospital

R Rectal examination showing fecal occult blood
A Anemia – hemoglobin ≤ 90 g/L
C Chest pain associated with syncope
D ECG showing Q wave (not in lead-III)
S Saturation ≤ 94% on room air.

Approach to a patient presenting with syncope



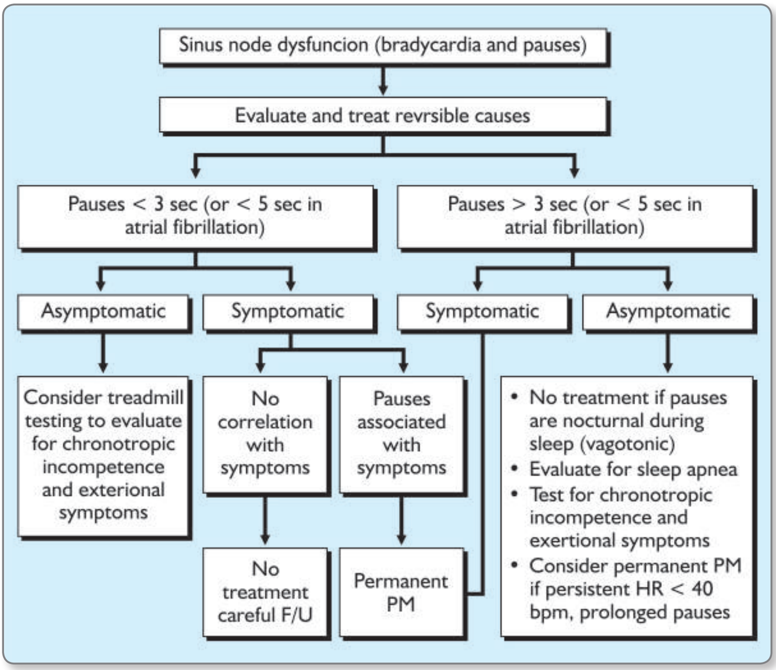
Treatment of Syncope

1. **Neurally mediated syncope**
   - Recognize premonitory symptoms and perform maneuvers to abort the episode (e.g. supine posture, isometric hand grip)

- Suppress trigger factors if possible (e.g. cough)
- *Vasovagal syncope*
  i. Volume expanders (electrolyte containing drinks, fludrocortisone salt tablets)
  ii. Drugs: β-blockers, midodrine (favourable trial result), disopyramide, serotonin uptake inhibitors
  iii. Cardiac pacing may play an useful role in severe cases with recurring periods of symptomatic cardioinhibition (bradycardia on HUTT) [North American Vasovagal Pacemaker study, VASIS, VPS2 studies, etc.]
- *Carotid sinus hypersensitivity:* Only other neurally mediated reflex syncope in addition to vasovagal syncope where cardiac pacing has a definite role.

2. **Orthostatic syncope**
   - Use of antigravitational hose
   - Prescribed periods of upright posture
   - Elevation of bed head at night
   - Increased salt in diet

Approach to a patient with sinus node dysfunction



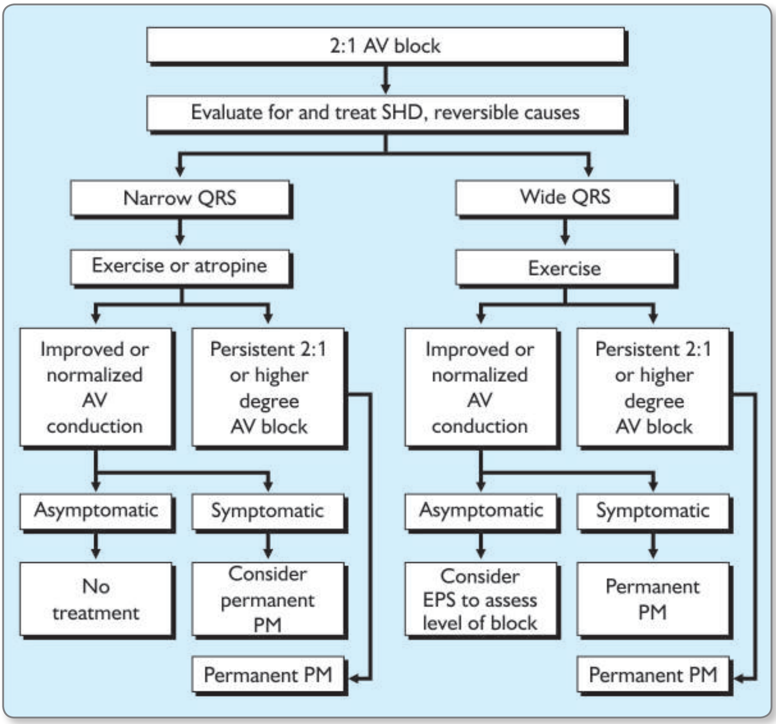


Fig. 6.1 Approach to a patient with 2:1 AV block

- Salt retaining steroids (Fludrocortisone 0.1-0.3 mg/day)
- Erythropoietin to increase circulating blood volume
- Greatest current interest is midodrine (10 mg PO three times daily at approximately 3 to 4 hours intervals; no dose after dinner).

3. **Bradyarrythmias:** A detailed discussion regarding various bradyarrhythmic problems is beyond the scope of this chapter; however some common problem situations are being discussed in form of algorithms to provide some tips in decision making (Figs 6.1 to 6.3).
   For indications of pacing in sinus node dysfunction and AV conduction disturbances, vide ACCF/AHA/HRS 2008 Guidelines and its focussed 2012 update.
4. **Tachyarrythmias**
   - Vide chapter on "Tachycardias".
5. **Other conditions**
   - Septal mycetomy or Alcohol septal ablation in HOCM
   - Surgery for curable lesions (e.g. valvular aortic stenosis or atrial myxoma).

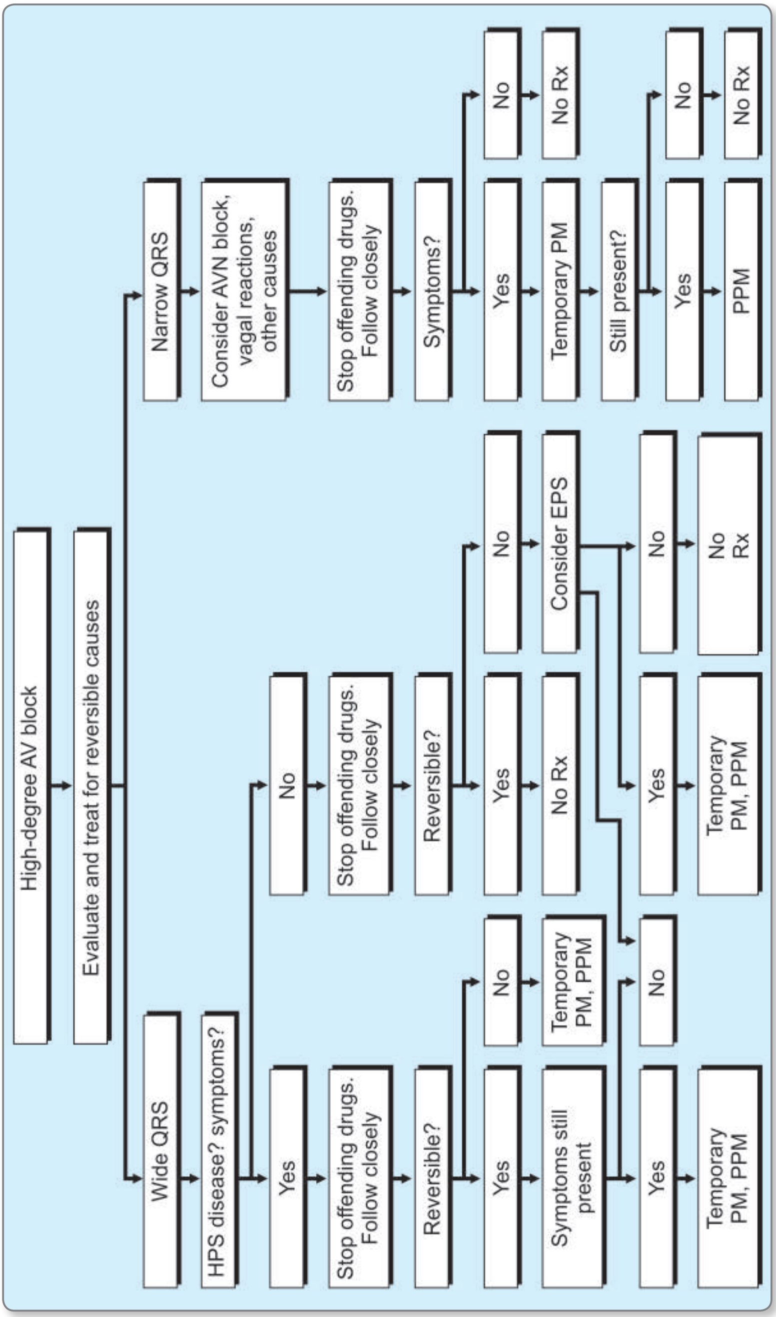


Fig. 6.2 Approach to a patient with high-degree AV block

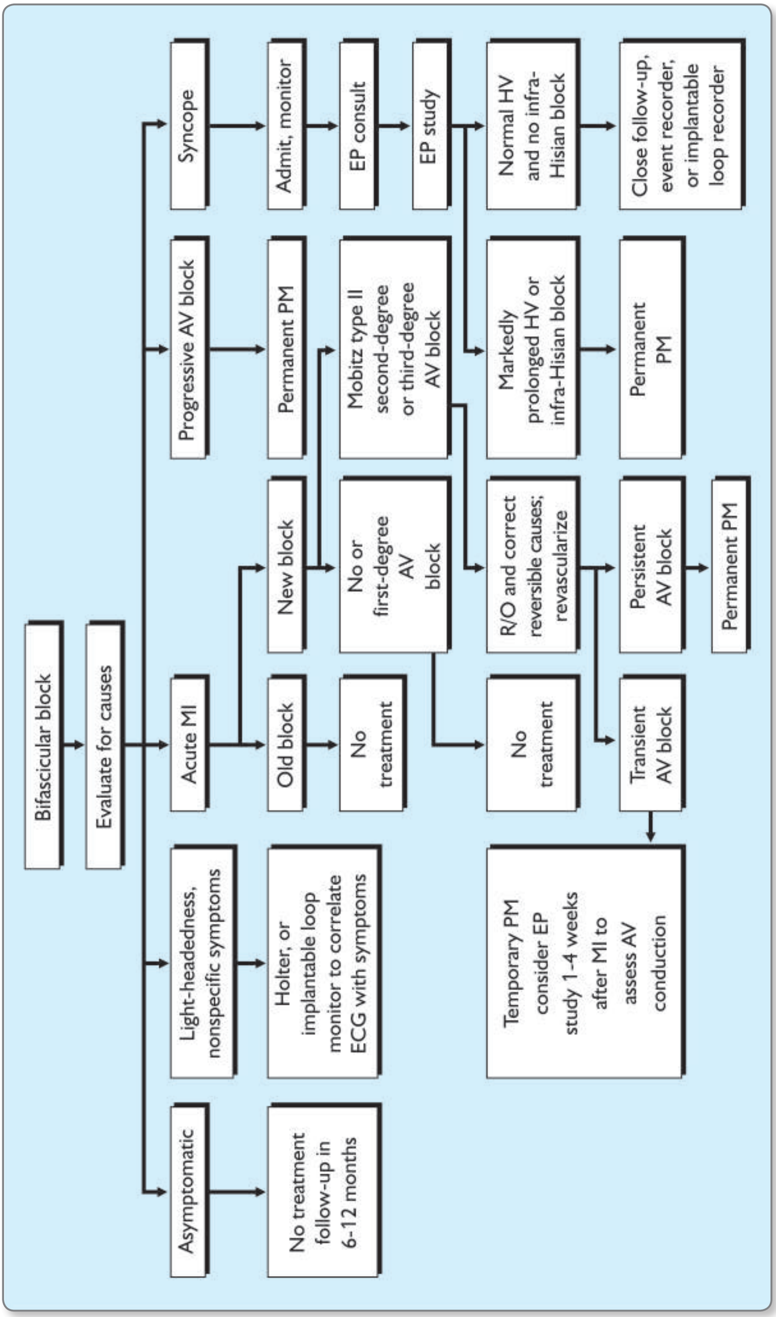


Fig. 6.3 Approach to a patient with bifascicular block

Suggested Reading

1. Ammirati F, Colivichi F, Santini M, et al. Permanent Cardiac Pacing versus medical treatment for the prevention of recurrent vasovagal syncope. Circulation. 2001;104:1261-7.
2. Benditt DG, Can I. Initial Evaluation of "Syncope and Collapse". The need for a Risk Stratification Consensus. J Am Coll Cardiol. 2010; 55:722-4.
3. Hastings JL, Levine BD. Syncope in the Athletic Patients. Prog. Cardiovasc. Dis. 2012; 54:438-44.
4. Kapoor WN. Syncope. N Engl J Med 2000;343:1856.
5. Linzer M, Yang EH, Estes NA 3rd, et al. Diagnosing syncope: Part 2. Unexplained syncope. Clinical Efficacy Assessment Project of the American College of Physicians. Ann Intern Med. 1997;127:76-86.
6. Linzer M, Yang EH, Estes NA 3rd, et al. Diagnosing syncope— Part 1. Value of history, physical examination and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. Ann Intern Med. 1997;126:989-96.
7. Marrison VK, Fletcher A, Parry SW. The older patient with syncope : Practicalities and controversies. International Journal of Cardiology. 2012;155:9-13.
8. Martin TP, et al. Risk stratification of patients with syncope. Ann Emergency Med. 1997;29:459.
9. Mosquede-Garcia R, et al. The elusive pathophysiology of neurally mediated syncope. Circulation. 2000;102:2898.
10. Reed MJ, Newby DE, Coull AJ, et al. The ROSE (Risk Stratification of Syncope in the Emergency Department) Study. J Am Coll Cardiol. 2010; 55:713-21.
11. Samniah N, Sakaguchi S, Lurie KG, et al. Efficacy and safety of midodrine in patients with refractory vasovagal syncope. Am J Cardiol. 2001;88:80-3.
12. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines in device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol. 2012;60:14.

chapter 7

Atrial Fibrillation

Uttio Gupta, Siddhartha Bandopadhyay, Soumitra Kumar

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia affecting 1 to 2 percent of the general population increasing with age.

Definition

AF is defined as cardiac arrhythmia with the following characteristics:

i. Irregular R – R interval
ii. No distinct P wave
iii. Atrial cycle length (if visible) variable and <200 ms (>300 bpm).

Patterns of Atrial Fibrillation

- *First diagnosed AF:* First presentation of AF, irrespective of duration of AF and severity of symptoms
- *Paroxysmal AF:* Episodes self terminating, usually within 48 hours, may be up to 7 days
- *Persistent AF:* Episodes persist > 7 days or requires termination (DC cardioversion/pharmacological)
- *Long standing persistent AF:* Episode lasted for ≥ 1 year when adaptation of rhythm control strategy is decided
- *Permanent AF:* Presence of arrhythmia is accepted by patient and physician.

Clinical Evaluation of AF Patient

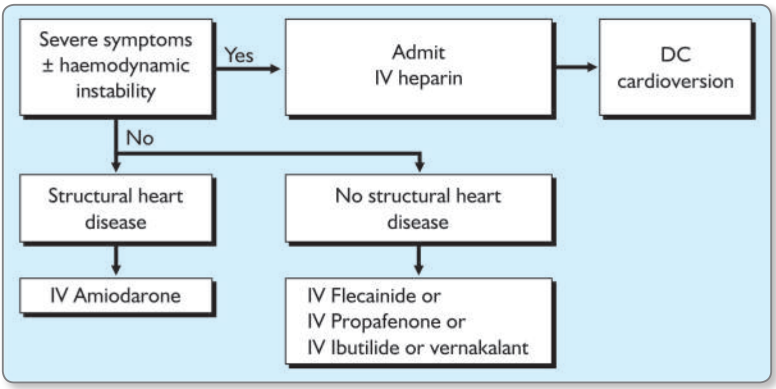
Minimum evaluation:

- History and physical examination
- Electrocardiogram
- Chest radiography
- Echocardiogram
- Blood tests of thyroid function.

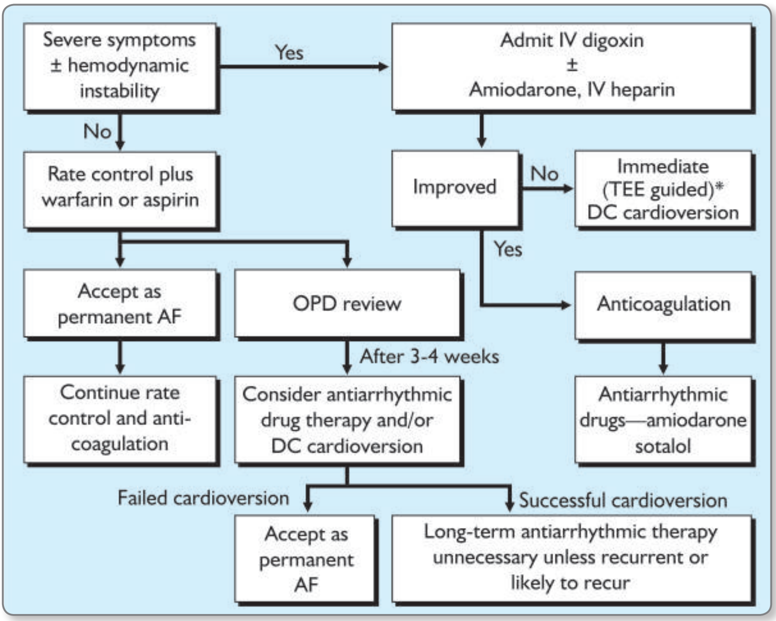
Additional Testing (As Indicated)

- **Exercise testing:**
  - To test adequacy of rate-control
  - To reproduce exercise-induced AF
  - To exclude ischemia prior to treatment with Type 1C antiarrhythmic drug
- **Holter monitoring or event recording:**
  - If diagnosis of type of arrhythmia is in question
  - As a means of evaluating rate control
- **Transesophageal echocardiography:**
  - To identify LA thrombus (in the LA appendage)
  - To guide cardioversion
- **Electrophysiological study:**
  - To clarify the mechanism of wide-QRS complex tachycardia
  - To identify a predisposing arrhythmia, e.g. atrial flutter or PSVT
  - Seeking sites for curative ablation or AV conduction block/modification:

Management of Newly Discovered AF (Duration Known to be ≤ 48 hours)

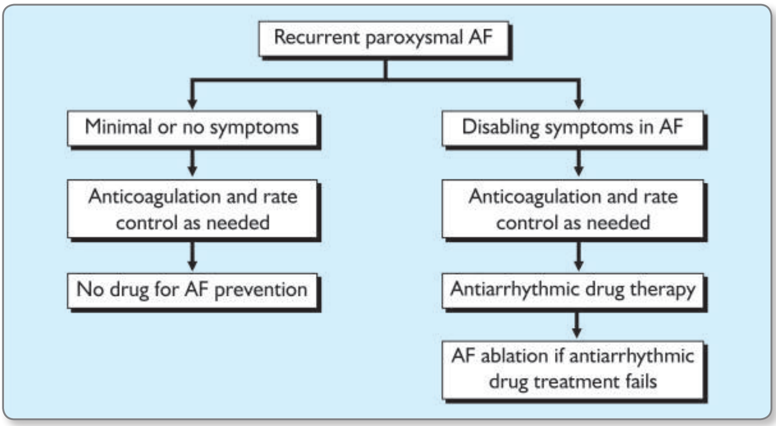


Management of Newly Discovered AF (Duration Known to be ≥ 48 hours or of Uncertain Duration)

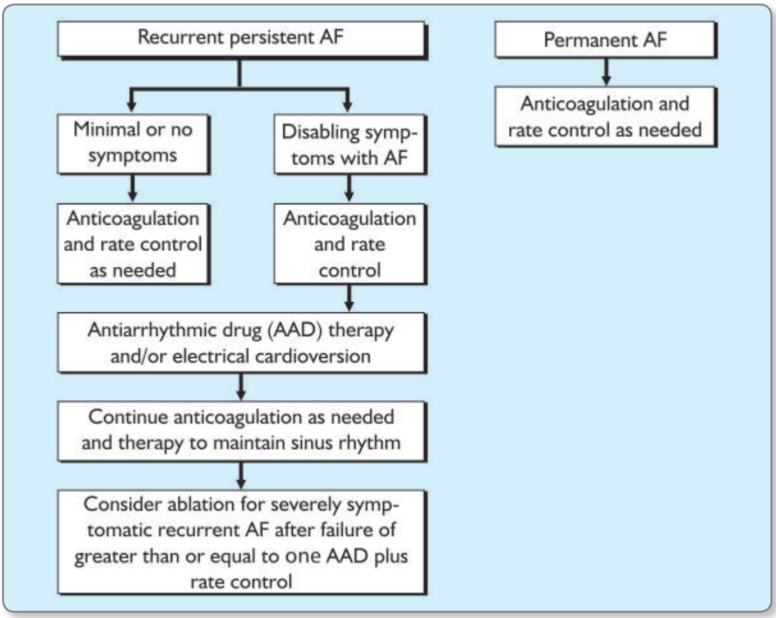


*In a multicenter study (Klein et al 2001), 1222 patients with either AF persisting longer than 48 hours or atrial flutter and previous AF were randomized to a TEE-guided or conventional strategy. Both approaches were associated with comparably low risk of stroke (0.81% with the TEE approach and 0.50% with the conventional approach) after 8 weeks. There were no differnece in the proportion of patients achieving successful cardioversion and the risk of major bleeding did not differ significantly. the clinical benefit of the TEE-guided appraoch was limited to saving time before cardioversion. Patients with AF or atrial flutter in whom LAA thrombus is identified by TEE are at high risk of thromboembolism and should be anticoagulated for at least 3 weeks prior and and 4 weeks after pharmacological or DC cardioversion

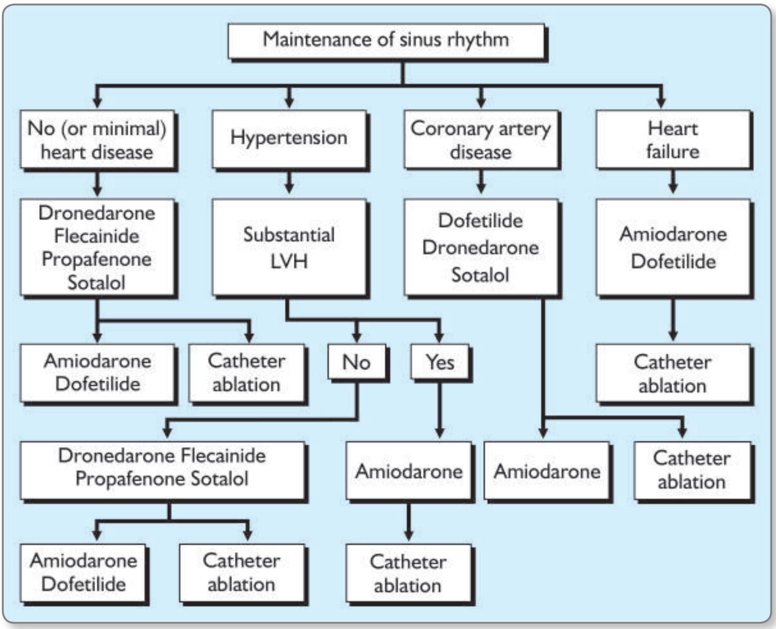
Pharmacological Management of Patients with Recurrent Paroxysmal AF



Pharmacological Management of Patients with Recurrent Persistent AF or Permanent AF



Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm in Patients with Recurrent Paroxysmal or Persistent AF



Electrical Cardioversion

Premedication (Midazolam 1 mg IV)
↓ Anterolateral (Success rate : 76%)
Position of electrodes
↓ Anteroposterior (Success rate 97%)
(in Pacemakers,* COPD, Obesity)
Synchronized DC shock (start with 200 J → 360 J)
↓
Failed defibrillation with initial attempts

i. Anteroposterior position of electrodes + IV Ibutilide (1 mg over 10 min → rpt if necessary)
ii. Dual defibrillation approach: Anterolateral and anteroposterior placement of paddles and deliver 360 J each.
iii. External defibrillator using a new biphasic waveform → converts AF with energy as low as 70 J.

iv. Transvenous electrical cardioversion 1 High energy 200-300 Joules DC shock internally using RA catheter and a back plate.

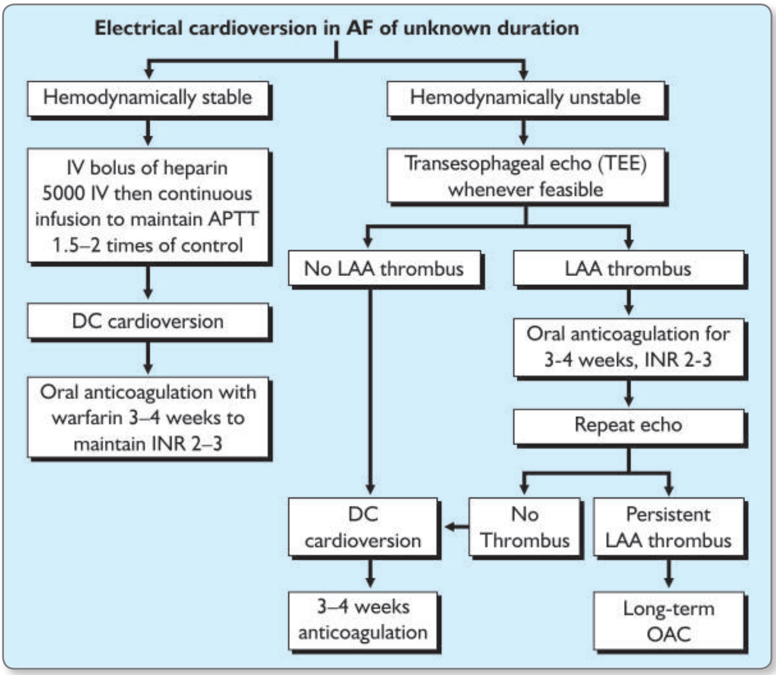
**Cardioversion of AF is safe in patients with implanted pacemaker or defibrillator devices. They have circuits designed for protection against sudden external electrical discharges but programmed data may be altered by current surges. Electricity conducted along an implanted electrode may cause endocardial injury and lead to a temporary or permanent increase in stimulation threshold resulting in loss of ventricular capture.*

Drugs for Pharmacological Cardioversion (Recent Onset AF)

Drugs		Dose	Risks
•	Amiodarone	5 mg/kg IV over 1 hr. Then 50 mg/h.	Hypotension, bradycardia, phlebitis
•	Flecainide	2 mg/kg IV over 10 mins or 200-300 mg PO stat	Prolonged QRS, QT prolongation, atrial flutter with increased ventricular rate
•	Ibutilide	1 mg IV over 10 mins. may be repeated after 10 mins	Torsades de pointes
•	Propafenone	2 mg/kg IV 10 mins or 450-600 mg PO stat	Prolonged QRS ↓/↑ ventricular rate
•	Vernakalant	3 mg/kg IV over 10 mins 2 mg/Kg IV may be repeated after 15 minutes	Under evaluation [C/I in SBP <100 mm Hg, NYHA Class-III/IV HF, Recent(<1 m) ACS, severe AS]

Lists of Commonly Used Antiarrhythmic Drugs

Drugs		Dose	Contraindication
•	Disopyramide	100-250 mg TID	Systolic HF, prolonged QT (<500 ms)
•	Flecainide	100-200 mg BID	CrCl <50 mg/ml, LV systolic dysfunction CAD, Conduction defect
•	Propafenone	150-300 mg TID	Renal impairment, LV systolic dysfunction, CAD, conduction defect
•	Sotalol	80-160 mg BID	LVH, systolic HF, CrCl <50 mg/ml Prolonged QT (>500 ms), hypokalemia
•	Amiodarone	600 mg OD × 1 month then 400 mg OD × 1 month then 200 mg OD	QT prolongation, HF, concomitant digoxin use
•	Dronedarone	400 mg BID	HF (NYHA III/IV) Prolonged QT CrCl <30 mg/ml with drug causing CYP3A4 inhibition



Stroke Risk in Patients by CHA_2DS_2 VASc Score

Risk Factors	**Score**
Congestive HF/LV dysfunction (≤40%)	1
Hypertension	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Stroke/TIA/TE	2
Vascular disease	1
Age 65 – 74	1
Sex (Female)	1
Max. Score	9

Note: Vascular disease – Prior MI, PAD, aortic plaque

Thromboprophylaxis in AF

CHA_2DS_2VASc Score	Treatment options
≥ 2	OAC (VKA)
1	OAC/Aspirin 75-325 mg daily (OAC-preferred)
0	No antithrombotic therapy (preferred)/ Aspirin 75 – 325 mg daily

OAC = Oral anticoagulation; VKA = Vitamin K antagonist.

Clinical Characteristics of HAS-BLED Bleeding Risk Score

Clinical characters	Points
H – Hypertension (SBP > 160)	1
A – Abnormal Renal function and Liver function	1 or 2 (1 point each)
S – Stroke	1
B – Bleeding	1
L – Labile INR	1
E – Elderly (age > 65)	1
D – Drugs or alcohol	1 or 2 (1 point each)
Max.	9 points

Note: Abnormal renal function – Chronic dialysis or renal transplantation or Cr ≥ 200 µmol/L

- Abnormal liver function – Chronic hepatitis disease (cirrhosis) or Hepatic derangement (BNil > × 2 upper limit of normal, AST/ALT/ALP > 3 × upper limit of normal)
- Bleeding – Previous bleeding diathesis or predisposing factor (e.g. Anemia)
- Labile INR – Unstable/high INR or poor time in therapeutic range (<60%)
- Drugs – Antiplatelet, NSAIDs, etc.
- Score ≥ 3 indicates high risk and caution regarding antithrombotic therapy; however, a high HAS-BLED score per se should not be used to exclude patients from OAC therapy.

Special Issues in Anticoagulation

Antiplatelet drugs for patients with AF: Several trials (AFASAK, EAPT, BATAF, SPAF II, etc.) have revealed that VKA was superior to aspirin in reducing stroke, embolism and ICH.

In atrial fibrillation clopidogrel trial with Irbesartan for prevention of Vascular Events – Warfarin arm (ACTIVE W): Oral anticoagulation (Warfarin) was shown to be superior to combined aspirin and clopidogrel with no difference in bleeding events. So, aspirin + clopidogrel is not alternative to VKA; it only can be considered where VKA is unsuitable as interim measure.

Antithrombotic Strategies following PCI (Stenting) in AF

Hemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or Intermediate	Elective	Bare Metal	1 month: Triple therapy of VKA + Aspirin + Clopidogrel
(HAS-BLED Score 0 – 2)			Life-long : VKA (INR 2.0 – 3)
	Elective	Drug eluting	3 months (Olimus gr.) to 6 months (Paclitaxal) Triple tx of VKA + Aspirin + Clopidogrel Up to 12 months = VKA + Clopidogrel Life-long – VKA alone
	ACS	BMS/ Drug eluting	6 months – VKA + Aspirin + Clopidogrel Up to 12 months – VKA + Clopidogrel Life-long – VKA alone
High (HAS-BLED Score ≥ 3)	Elective	Bare metal	2-4 weeks – Triple therapy of VKA + Aspirin + Clopidogrel Life-long – VKA alone
	ACS	Bare metal	4 weeks – Triple therapy of VKA + Aspirin + Clopidogrel Up to 12 months – VKA + Clopidogrel Life-long – VKA alone
		Drug eluting	Not recommended

Low-molecular weight heparins (LMWHs): Use of LMWHs instead of unfractionated heparin (UFH) in patients with AF is based largely on extrapolation from venous thromboembolic disease states and from limited observational studies. Favorable properties of LMWHs (Longer half-life, more predictable bioavailability, predictable antithrombotic response, etc.) may simplify the treatment of AF in acute situations and shorten or eliminate the need for hospitalization to initiate anticoagulation, self-administration of LMWHs out of hospital by patients with AF undergoing elective cardioversion is a promising approach that may result in cost savings.

Periprocedural (Diagnostic/Therapeutic) Management of antithrombotic Therapy: See annexure to this chapter.

Management of antithrombotic therapy in acute stroke: See annexure to this chapter.

Alternatives to Warfarin

Acenocoumarol, another Vitamin K anticoagulant (VKA) has a shorter half-life (10 to 24 hours), a more rapid effect on the prothrombin time, and a shorter duration of action (2 days). It was also discovered in late 1950s. Depending on the individual, the maintenance dose generally lies between 1 to 8 mg daily. Anticoagulant stability has been claimed to be superior with acenocoumarol compared to warfarin (Orv. Hetil et al. 2004).

Pharmacological Characteristics of Newer Oral Anticoagulants

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct Flla inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa Inhibitor
Oral bio availability, %	6.5	80-100	50	62
Half-life, h	12-17	5-13	8-15	6-11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50§
Time to maximum inhibition, h	0.5-2	1-4	1-4	1-2
Potential metabolic drug interactions	Inhibitors of P-gp:verapamll, reduce dose; dronedarone: avoid	Potent Inhibitors of CYP3A4 and P-gp*: avoid	Potent Inhibitors of CYP3A4 and P-gp*: avoid	Potent Inhibitors of P-gp*: reduce dose
	Potent Inducers of P-gp†: avoid	Potent Inducers of CYP3A4‡ and P-gp: use with caution	Potent Inducers of CYP3A4‡ and P-gp† use with caution	Potent Inducers of P-gp†: avoid

*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole. Itraconazole. voriconazole. posaconazole). chloramphenicol. clarithromycin, and protease inhibitors (eg., ritonavir. atanazavir). P-gp inhibitors include verapamll. amiodarone. quinidlne. and clarithromycin. †P-gp inducers Include rifamplcln. St. John's wort (*Hypericum perforatum*). carbamazepine. and phenytoin. ‡ Potent CYP3A4 inducers include phenytoin. carbamazepine. phenobarbital. and St. John's wort. § Of the absorbed drug.
CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoproteln.

Overview of Design of the Pivotal Phase III Trials of New Oral Anticoagulants Compared with Warfarin in Non-valvular Atrial Fibrillation

	RELY	ROCKET	ARISTOTLE	ENGAGE AF
Sample size	18.113	14,264	18,201	21,107
New treatment and dose	Dabigatran 110 mg BID	Rivaroxaban 20 mg	Apixaban 5 mg	Edoxaban 30 mg QD
	Dabigatran 150 mg BID	QD	BID	Edoxaban 60 mg QD

Contd…

Contd...

	RELY	ROCKET	ARISTOTLE	ENGAGE AF
Dose adjustment	No	At randomization	At randomization	During trial
Design	Noninferiority	Noninferiority	Noninferiority	Noninferiority
	PROBE	Double blind	Double blind	Double blind
Patients	$CHADS_2$ score ≥ l	$CHADS_2$ score ≥ 2	$CHADS_2$ score ≥ l	$CHADS_2$ score ≥ 2
Primary outcome	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding
$CHADS_2$ score: = A score to evaluate thromboembolic risk taking into account congestive heart failure (C), hypertension (H), age ≥78 years (A), diabetes (D) (with each such factors scoring 1) and previous stroke/systemic embolism (S), the latter scoring 2 (S_2); PROBE = prospective, randomized, open-label with blinded event adjudication. Major bleeding definition included critical bleed or hemoglobin drop ≥ 2g/dl or ≥ 2 U of packed red cell transfusion (In ROCKET AF and ARISTOTLE, the latter 2 items had to be associated with clinically overt bleeding); BID = twice daily; QD = once daily				

Primary Outcome and Safety Data in Phase III trials with Newer Oral Anticoagulants vs. Warfarin

	RELY	ROCKET-AF	ARISTOTLE
Primary Outcome (Stroke or systemic Embolism)	1.71% per year in Warfarin group vs. 1.54% per year in Dabi 110 group & 1.11% Dabi 150 mg group (p<0.001 for superiority in 150 group and inferiority in 110 group)	2.12% in Rivo group vs. 2.42% per year in Warfarin group but no reduction in ischemic stroke (p<0.0001 for noninferiority) and 0.117 for superiority)	1.60% per year in Warfarin group vs 1.2% per year in Api group (p=0.01 for superiority)
Safety Data (Bleeding or Mortality)	Hemorrhagic stroke and intracranial bleed-ing 0.1% with Dabi 110 & 150 vs. 0.4% with Warfarin GI bleeding – 1.5% with Dabi 150 vs. 1.0% with Warfarin Myo. Infarction → higher trend with both doses of Dabi Total mortality 4.13% per year with Warfarin vs. 3.75% per year with Dabi 150.	Overall, major bleeding 3.60% in Rivo group & 3.45% in Warfarin group (Lower intracranial bleeding with higher GI bleeding in Rivo group Total mortality was 4.5% in Rivo group vs. 4.9% in Warfarin group. Numerically, a non-significantly lower rate of myo. Infarction in Rivo group.	Major bleeding was 3.09% per year in Warfarin group vs 2.13% per year in Api group (p<0.001) Hemorrhagic stroke and intracranial bleeding lower in Api group with similar rates of GI bleeding. Total mortality was 3.94% per year for Warfarin vs 3.52% per year for Api group. Numerically non-significantly lower rate of Myo.infarction with Api.

Availability of these three new treatment alternatives for stroke prevention in non-valvular AF is definitely a significant step forward. Advantages of these agents over Warfarin include absence of need for frequent laboratory monitoring and dose adjustments, lower risk of intracranial bleeding, no clear interactions with food, fewer drug-interactions, etc. However, adherence might be a larger issue in real-life setting than in clinical trials and need for monitoring anticoagulant may be relevant in specific situations. Since, treatment with these agents are generally lifelong, there is also a need for assessing long-term efficacy and safety over decades in real-life setting. Cost is another obstacle and cost-effectiveness of these new agents needs to further established. Management of patients who suffer from bleeding secondary to those agents is another issue since there are no specific antidotes for any of the new agents. More precise information is also needed with regard to following situations:

- Interruption for procedures and/or surgery
- Anticoagulation during cardioversion and ablation procedures
- Dose-adjustment in renal failure
- Utility of these agents in combination with antiplatelet treatments after myocardial infarction and percutaneous coronary intervention
- Anticoagulation in mitral stenosis, mechanical prosthetic valves, stroke without AF and cancer.

  Some information is available for transition between different agents'

Recommendations for Transition between Anticoagulants

Conversion from injectable anti-coagulation to dabigatran or rivaroxaban:

Heparin – Administer first dose at the time when heparin is discontinued
LMWH – Administer first dose at the time when next dose is due

Conversion to injectable anticoagulation from:

- Dabigatran
  - If CrCl $\geq$ 30 mL/min wait 12 hours after last dose of dabigatran
  - If CrCl <30 mL/min, wait 24 hours after last dose of dabigatran
- Rivaroxaban
  - At time of next scheduled rivaroxaban dose.

Conversion from warfarin to:

- Dabigatran – Start dabigatran when INR <2.0
- Rivaroxaban – Start rivaroxaban when INR <3.0.

Conversion from dabigatran to warfarin:

- For CrCl $\geq$ 50 mL/min – Start warfarin 3 days before discontinuing dabigatran
- For CrCl 30-50 mL/min – Start warfarin 2 days before discontinuing dabigatran
- For CrCl 15-30 mL/min – Start warfarin 1 day before discontinuing dabigatran

Conversion from rivaroxaban to warfarin:

- Injectable anticoagulation bridge to be used

Choice of Anticoagulants

When an oral anticoagulation (OAC) is recommended for non-valvular AF, one of the newer OACs (NOACs), e.g. dabigatran, rivaroxaban, apixaban may be considered for most patients on the basis of their net clinical benefit. Such choices are especially indicated when there are difficulties in keeping anticoagulation within therapeutic range or inability to attend or undertake INR monitoring. When dabigatran is prescribed, a dose of 150 mg BID should be considered for most patients in preference to 110 mg BID; however, the latter dose is preferred in:

- Elderly patients, age ≥ 80
- Concomitant use of interacting drugs (e.g. verapamil)
- High bleeding risk (HAS-BLED score ≥ 3)
- Moderate renal impairment (CrCl 30-49 mL/min.)

When rivaroxaban is being considered, a dose of 20 mg OD should be considered for most patients in preference to 15 mg OD, with the latter dose recommended in:

- High bleeding risk (HAS-BLED score ≥ 3)
- Moderate renal impairment (CrCl 30 – 49 mL/min):

Management of Atrial Fibrillation (AF) in Specific Situations : Level of Recommendation

	Class – I	Class – II	Class – III
Heart failure	In hemodynamically stable patient : rate control with β-blockers (IA) &/or Digoxin (IB) in HF-REF Amiodarone (IB) In hemodynamically unstable patient: Rhythm control DC Cardioversion (IC)	In hemodynamically stable patient: rate control with Non-DHAP CCB in HF-PEF (II bC) Amiodarone alone for rhythm control in AF or to facilitate electrical cardioversion of AF (II aB)	In hemodynamically stable patient: rate control. Non-DHP CCB Non-DHP CCB in HF-REF (IIIC)
Acute coronary syndrome	DC cardioversion in severe hemodynamic compromise or intractable ischemia (IC) IV β-blocker to slow ventricular rate (IC)	IV non-DHF CCB (Verapamil, diltiazem) to slow ventricular rate in AF with ACS with HF (II bC)	Flecainide or Propafenone are not recommended in AF with ACS (III B)

Contd…

Contd…

	Class – I	Class – II	Class – III
Pregnancy	DC Cardioversion in hemodynamically unstable patients with AF is safe at all stages of pregnancy (IC)	β-blockers or non-DHP CCB for rate control (IIaC) Use of β-blockers in first trimester to be weighed against potential fetal effects For acute rhythm conversion in pregnant patients with structurally normal hearts, flecainide or ibutilide to be considered if DC cardio-version is consider inappropri-ate (IIbC) Digoxin for rate control if β-blockers or non-DHP CCB are contraindicated (IIbC)	
Hyperthyroidism	β-blockers are recommended for rate control(IC) Non-DHP CCBs are recommended if β-blockers cannot be used (IC)		
Post-operative AF	Oral β-blockers for pre-vention (IA) Ventricular rate control without hemodynamic stability (IB) DC cardioversion in hemodynamically unstable patient (IC) Amiodarone for pre-vention in patients at high risk for postoperative AF (IIaA)	Sotalol for prevention of AF after cardiac surgery (IIbA) → high risk of proarrhythmia IV Vernakalant for cardioversion of postoperative AF ≤ 3 days after cardiac surgery (IIb B) Biatrial pacing for AF prevention after cardiac surgery (IIb A) Corticosteroids for AF prevention after cardiac surgery (IIb B)	
Wolff-Parkinson-White (WPW) syndrome	Catheter ablation of an overt accessory pathway (AF) is recommended to prevent SCD (IA) Catheter ablation also indicated in patients with overt AF but asymptomatic if they are in high risk profession or at high risk of developing AF		

Contd…

Contd…

	Class – I	Class – II	Class – III
Hypertrophic cardiomyopathy	DC cardioversion or pharmacological cardioversion if AF is of recent onset (IB)	Amiodarone (or alternatively disopyramide plus β-blockers to achieve rhythm control in patients with HCM (IIa C) Catheter ablation in symptomatic patients with AF refractory to pharmacological control (IIa A) Ablation procedures (with concomitant septal myectomy if indicated) is indicated in HCM patients with refractory AF (IIb C)	
Pulmonary disease	Correction of hypoxemia and acidosis during acute pulmonary illness or exacerbation of chronic pulmonary disease (IC)	A non-DHP CCB (verapamil or diltiazem) to control ventricular rate (IIa C) β-1 selective blocker (e.g. bisoprolol for ventricular rate control (IIa C)	Theophylline and β-adrenergic agonist agents are not recommended (IIIC) Non-selective β-blockers, sotalol, propafenone and adenosine are not recommended (III C)

Rate versus Rhythm Control

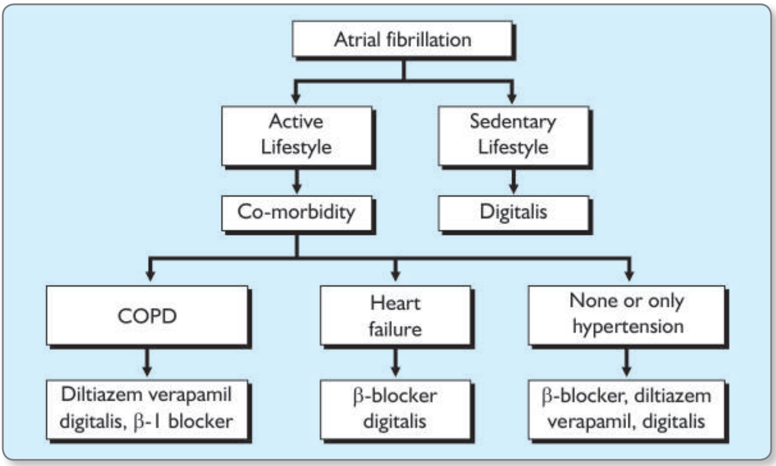
Several trials (AFFIRM, RACE, PIAF, STAF, HOT CAFÉ, AF-CHF) have addressed this issue and they have failed to establish clear superiority of any one strategy over the other. Overall, rate control is needed for most patients with AF unless heart rate is naturally slow. Patients with permanent AF are managed by rate control. Such patients without severe symptoms due to fast ventricular rate may be treated with lenient rate control (resting heart rate <110 bpm.) as demonstrated by the RACE II trial: Strict rate control (resting heart rate < 90 bpm. and controlled increase in heart rate upon moderate exertion) is essential only in patients who remain symptomatic.

Rhythm control may be added to rate control in following situations:

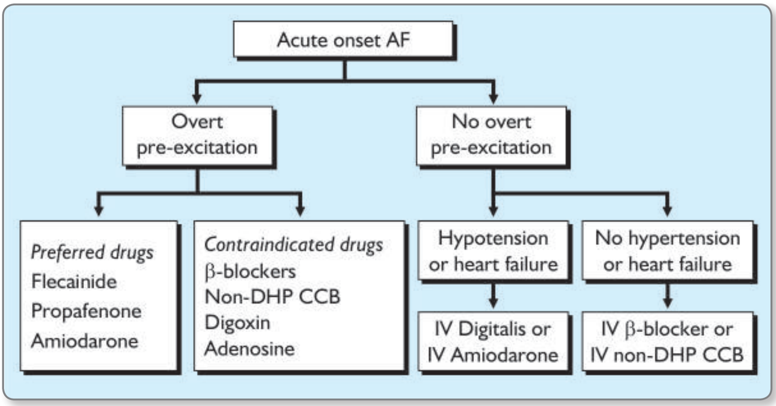
i. If patients remains symptomatic (EHRA score ≥ 2) despite adequate rate control
ii. Younger age or higher activity levels
iii. Paroxysmal AF, especially if it is symptomatic and there is little or no associated heart disease

{EHRA (European Heart Rhythm Association) score of AF-related symptoms: EHRA I – No symptoms, EHRA II – mild symptoms, normal daily activity not affected.
EHRA III – severe symptoms, normal daily activity affected
EHRA IV – disabling symptoms; normal daily activity discontinued

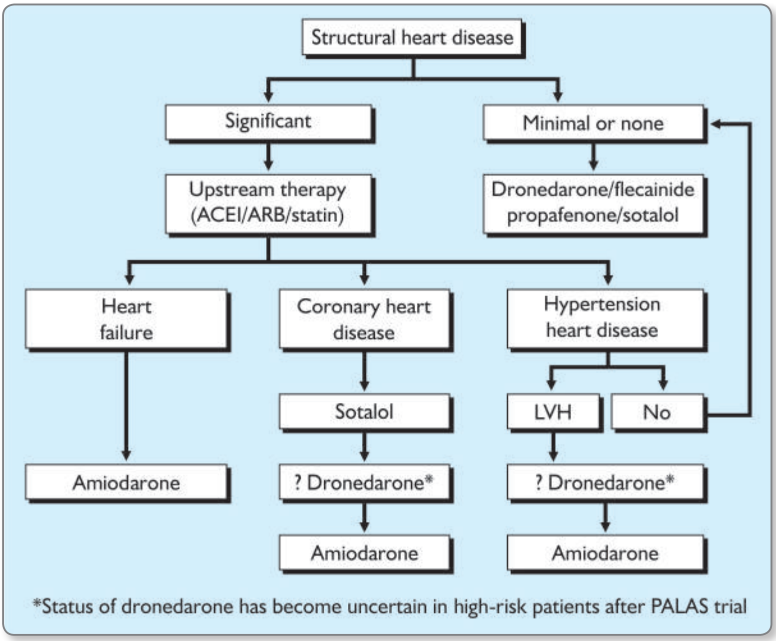
Guidelines for Rate Control



Acute Rate Control in Atrial Fibrillation



Rhythm Control in Atrial Fibrillation



Newer Antiarrhythmic Drugs

Currently available antiarrhythmic drugs, particularly those used to control AF, are not optimal with respect to either long-term efficacy or safety. Amiodarone, the most widely used antiarrhythmic drug, has a particularly variegated spectrum of adverse reactions like altered thyroid function, pulmonary toxicity (which can even be fatal) and peripheral neuropathy. Hence, there is a need for more effective and safer antiarrhythmic regimens for the control of cardiac arrhythmias.

Currently, three categories of antiarrhythmic drugs are under investigation:

i. Atrial-selective agents with simple ion-channel-blocking properties
ii. De-iodinated amiodarone congeners with multichannel blocking properties
iii. Other agents with nonselective ion-channel blocking properties.

New Antiarrhythmic Drugs

Category	Drug	Target
Atrial-selective drugs	Vernakalant (RSD-1235)	Atrial selective K inhibitor—I_{kur}, I_{to}, I_{Na}, I_{KACh}
	AVE0118	Atrial selective K inhibitor—I_{kur}, I_{to}
	AZD 7009	Atrial selective—I_{Kr}, I_{Kur}, I_{Na}
Amiodarone congeners[a]	Dronedarone	I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}, $I_{K(Ach)}$, α, β
	SSR149744C	I_{Kr}, I_{Ks}, I_{KaCh}, $I_{Kv1.5}$, I_{Ca}, I_{to}, α, β
	ATI-2042	Atrial selective—I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}
Others	Azimilide	I_{Kr}, I_{Ks}
	Tedisamil	I_{Kr}, I_{to}, $I_{K\text{-}ATP}$, I_{Kur}, I_{Na}
	Rotigaptide	Gap-junction-modifying drug
	Serotonin 5-HT_4 receptor antagonists	Serotonin 5-HT_4 receptor
	Muscarinic M_2-receptor blocker	Muscarinic M_2-receptor

[a]Amiodarone—I_{Kr}, I_{Ks}, I_{Ca}, I_{to}, I_{Na}, α, β.

Atrial-selective Antiarrhythmic Drugs

These drugs have been developed recently to overcome the consequences of proarrhythmic reactions of ventricular origin. These agents are devoid of QT-prolongation side-effect of most current drugs and consequent risk of VT/VF and torsade de pointes in particular. The recent understanding that ultra-rapid delayed rectifier (I_{kur}) current exists in the atria, but not in ventricular tissues, has set the stage of developing atrial-selective drugs devoid of ventricular proarrhythmic toxicity for the treatment of patients with AF. Apart from I_{kur} blockers, atrial selective sodium channel blockers, muscarinic M_2-receptor blockers and 5-HT_4 receptor antagonists are being developed. Intravenous vernakalant is one of such agents and CRAFT and ACT-1 trials have shown it to be both effective and safe for acute conversion in patients with AF. However, its effectiveness in patients with atrial flutter is uncertain. Its oral formulation is under development for long-term maintenance of normal sinus rhythm following cardioversion. However, their efficacy in this regard remains to be explored and even if found effective, since vernakalant does not impede atrioventricular conduction, addition of a rate-controlling agent during AF recurrences become imperative.

Dronedarone

Chemically, dronedarone is a benzofuran derivative related to amiodarone, and also displays Class III antiarrhythmic activity. However, it also exhibits activity in each of the 4 Vaughan-Williams antiarrhythmic classes. Unlike amiodarone, iodine moieties are not present, reducing toxic effects on the thyroid and other organs. A methyl-sulfonamide group is added to reduce solubility in fats (lipophilicity) and thus reduce neurotoxic effects.

In EURIDIS and ADONIS trials in AF in 2007, dronedarone was significantly more effective than placebo in maintaining sinus rhythm. However, in ANDROMEDA study also published in 2007, dronedarone doubled the death rate compared to placebo in patients with moderate-to-severe congestive heart failure. In the more recent ATHENA trial in non-permanent AF in hemodynamically stable patients ≥ 75 years old or ≥ 70 years if they had at least one CV risk factor, or enlarged LA or LVEF < 40 percent, dronedarone was significantly more effective than placebo in reducing the composite end point of first hospitalization due to cardiovascular events or death. Later, post-hoc analysis of the ATHENA-results showed a significant reduction in rate of stroke.

In the last PALAS trial, 3236 patients who were at least 65 years of age with ≥ 6 months of permanent AF along with a high risk factors for major vascular events were randomized to receive either dronedarone or placebo. The study was prematurely discontinued since dronedarone was found to increase rate of heart failure, stroke and death from cardiovascular causes. This led the FDA to release a Black Box warning that risk of death, stroke and hospitalization for congestive heart failure may be doubled with dronedarone in patients with permanent AF. However, FDA believes that based on ATHENA trial results, dronedarone provides a benefit for patients with non-permanent AF.

Non-pharmacological Treatment of AF

Pacemakers

- In patients with depressed LV function (LVEF ≤ 45%) and mild heart failure symptoms with any type of AF, implantation of a CRT pacemaker may be considered after AV node ablation (ESC Recommendation: IIb C)
- In patients with paroxysmal AF and normal LV function, implantation of a dual-chamber (DDD) pacemaker with mode-switch function may be considered after AV node ablation (ESC Recommendation: IIb C).
- Implantation of a single chamber (VVIR) pacemaker may be consider after AV node ablation in patients with persistent AF or permanent AF and normal LV function (ESC Recommendation IIb C).

Left Atrial Catheter Ablation

Last few years have progressively established catheter ablation strategies targeting either the substrate and/or triggers for AF. Catheter ablation has been shown to be atleast as effective and probably better, than antiarrhythmic drugs. Hence, in experienced centers, it is increasingly being used as a first-line strategy for rhythm control management of paroxysmal AF. However, it should not be considered for asymptomatic patients at this point in time.

Consideration of catheter ablation in patients with symptomatic recurrences of paroxysmal AF on antiarrhythmic drug therapy is a ESC Class IA indication. Catheter ablation as an alternative to antiarrhythmic drugs as first-line therapy or persistent symptomatic AF that is refractory to antiarrhythmic therapy are ESC class IIaB indications. Ablation of common atrial flutter is recommended as part of an AF ablation procedure if documented prior to the ablation procedure or occurring during the AF ablation (ESC Class I B recommendation).

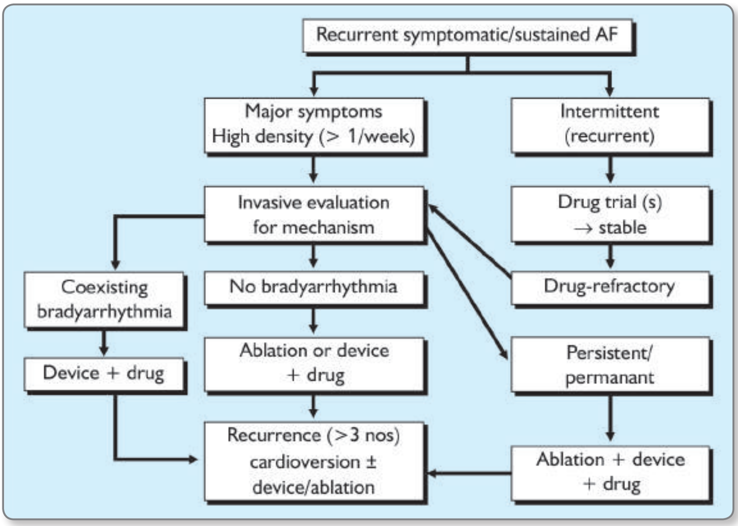
Catheter ablation of AF targets isolation of the pulmonary veins; if already on oral anticoagulation (OAC) for AF, it should be continued during the ablation procedure with a target INR around 2.0. Post-ablation, low molecular heparin or IV heparin should be considered as 'bridging therapy' prior to resumption of OAC therapy which should be considered for minimum of 3 months. Continuation of OAC beyond 3 months should be considered on the basis of standard indications

Surgical Ablation

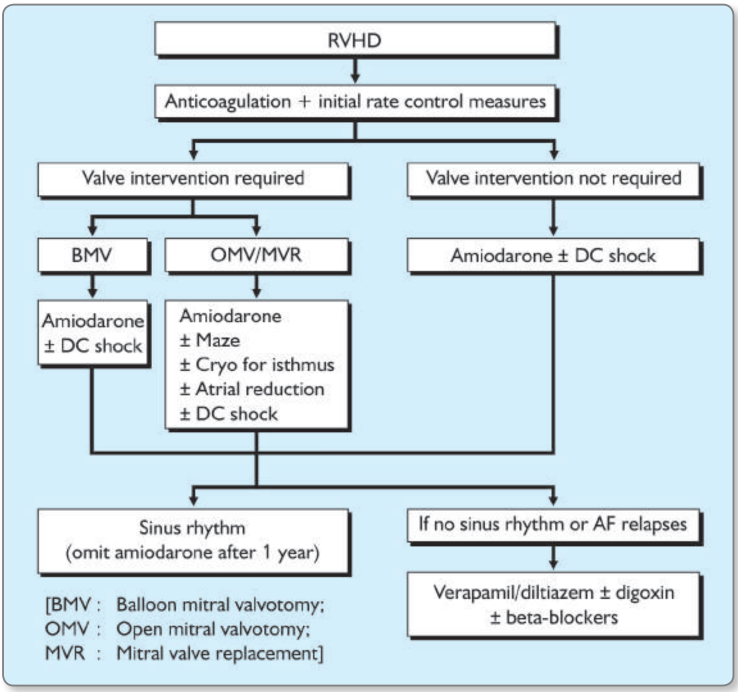
- Assuming that re-entry is the predominant mechanism responsible for development and maintenance of AF, atrial incisions at critical locations would create barriers to conduction and prevent sustained AF ('Maze' procedure is used to describe this type of cardiac surgery based on the concept of a geographical maze).
- Since its introduction, the procedure has gone through 3 iterations (Maze I, II and III) using cut and sew techniques. Success rates of around 95 percent over 15 years of follow-up have been reported in patients undergoing mitral valve surgery.
- Despite its high success rate, the Maze operation has not been widely adopted other than for patients undergoing cardiac surgery for other reasons because of the need for cardiopulmonary bypass.
- Surgical ablation of AF in symptomatic patients undergoing cardiac surgery is a Class IIa A indication (ESC); however, surgical ablation for asymptomatic AF patients if feasible with minimal risk or minimally invasive surgical ablation of AF after failed catheter ablation for symptomatic AF are Class IIb C indications (ESC).

Hybrid Therapy of Atrial Fibrillation

Newer approaches to rhythm control in the post-AFFIRM era employ 'hybrid' therapies combining pharmacologic and non-pharmacologic interventions (Devices or ablation therapy) Figure below shows a AF management algorithm to achieve rhythm control employing 'Hybrid therapy' for drug-refractory AF. Cost-effectiveness of this approach will need to be assessed.



Management Strategy for Patients with Rheumatic Valvular Heart Disease (RVHD) and AF



Upstream Therapy

The above-mentioned caption refers to treatment options that prevent or delay myocardial remodelling associated with hypertension, heart failure or inflammation (e.g. after cardiac surgery) and which in turn deter the development of new AF (primary prevention) or after happening once, its rate of recurrence or progression to permanent AF (secondary prevention). Best data have accumulated for primary prevention of AF in heart failure with ACEIs and ARBs and post-operative AF with statins. However, these agents have not been shown to be so effective for secondary prevention of AF recurrences in patients with little or no structural heart disease. There is no significant data at present to recommend use of PUFAs for primary or secondary prevention of AF.

Suggested Reading

1. Camm AJ, Kirchhof P, Lip GYH, et al. Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC): Guidelines for the management of atrial fibrillation. European Heart Journal 2010;12:1360-420.
2. Caterina RD, Husted S, Wallentin L, et al. ESC Working Group on Thrombolysis – Task Force on Anticoagulation in Heart Disease Position Paper. New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes. JAm Coll Cardiol 2012;59:1413-25.
3. Singh BN, Aliot E. Newer antiarrhythmic agents for maintaining sinus rhythm in atrial fibrillation: simplicity or complexity. European Heart Journal Supplements 2007:9 (Supplement G), G17-G25.
4. The perioperative management of antithrombotic therapy. Chest 2008;133(Suppl.);2995-3395.
5. Wann LS, Curtis AB, January CT, et al. Writing on behalf of 2006 ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation Writing Committee. 2011 ACCF/AHA/HRS focused update on management of patients with atrial fibrillation (updating the 2006 guideline). JAm Coll Cardiol 2011;57:223-42.

ANNEXURE

SPECIAL PROBLEMS WITH ANTITHROMBOTIC THERAPY

Absolute Indications for Lifelong Oral Anticoagulation

- Mechanical prostheses
- Chronic or intermittent AF in the presence of:
  - Native valve disease
  - Bioprostheses
  - Valve repair
  - Valvuloplasty
- Native valve disease and previous emboli
- Mitral valve stenosis, independent of rhythm, with:
  - High valve gradients
  - Thrombus in left atrium
  - Spontaneous echo contrast in left atrium
  - Large left atrium > 50 mm
  - Low cardiac output
  - Congestive heart failure.

Recommended Therapeutic Range for Oral Anticoagulant Therapy

Indications	International Normalized Ratio (INR)
Prophylaxis of venous thrombosis (high-risk surgery)	2.0–3.0
Treatment of venous thrombosis	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	
Acute myocardial infarction (to prevent systemic embolism)*	
Valvular heart disease	
Atrial fibrillation	
Mechanical prosthetic valves (high risk)	2.5–3.5
Bileaflet mechanical valve in aortic position	2.0–3.0

*If oral anticoagulant therapy is elected to prevent recurrent myocardial, an INR of 2.5 to 3.5 is recommended consistent with US Food and Drug Administration recommendations.

Management of Antithrombotic Perioperatively

High thromboembolic risk (>10% per year risk of ATE or > 10% per month risk of VTE)

- Any mechanical mitral valve
  Older aortic valve
  Recent (< 6 mo) stroke or TIA
- $CHADS_2$ score of 5 or 6
  Recent (<3 mo) stroke or TIA
  Rheumatic valvular heart disease
- (<3 mo) venous thromboembolism (VTE)
  Severe thrombophilia

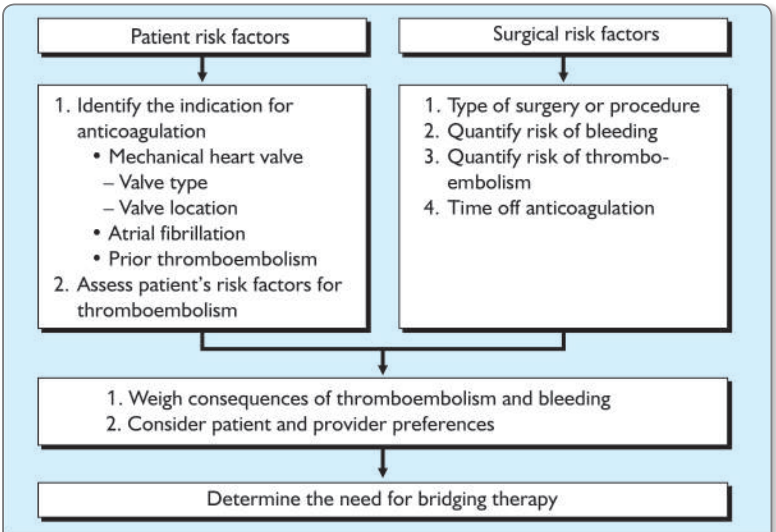
Moderate thromboembolic risk (4-10% per year risk of ATE or 4-10% per mo risk of VTE)

- Bileaflet valve and one of the following:
  Atrial fibrillation, prior stroke/TIA, hypertension, diabetes, heart failure, age >75 years
- $CHADS_2$ score of 3 or 4
- VTE within past 3-12 mo
  Recent VTE
  Non-severe thrombophilic conditions
  Active cancer

Low thromboembolic risk (<4% per year risk of ATE or <2% per mo risk of VTE)

- Bileaflet aortic valve without atrial fibrillation and no other risk factors for stroke
- $CHADS_2$ score of 0-2 (and no prior stroke or TIA)
- Single VTE within past 12 mo and no other risk factors.

[ATE: Arterial thromboembolism, VTE: Venous thromboembolism]



Assessment tool for identifying patient-specific and surgical risk factors for patients on anticoagulation therapy who are undergoing elective surgery

A Practical Approach to Bridge Therapy

Essentials of a prolonged bridge therapy for patients receiving warfarin therapy are as following:

Before Surgery

- Discontinue warfarin 5 days before surgery (i.e. hold four doses) if the preoperative international normalized ratio (INR) is 2 to 3, and 6 days before surgery (hold five doses) if the INR is 3 to 4.5.
- For bridge therapy, start LMWH (enoxparin-1 mg/kg or dalteparin 100 IU/kg subcutaneously every 12 hours) beginning 36 hours after the last dose of warfarin.
- Give the last dose of LMWH approximately 24 hours prior to surgery.

After Surgery

- For minor surgery, reinitiate LMWH at full dose approximately 24 hours after surgery. For major surgery and for patients at high risk of bleeding, consider using prophylactic doses on the first two postoperative days.
- Discuss the timing of anticoagulant reinitiation with the surgeon.
- Restart warfarin at preoperative dose 1 day after surgery.

- Order daily prothrombin time/INR tests until the patient is discharged and periodically after discharge until the INR is within the therapeutic range.
- Order a complete blood cell count with platelets on days 3 and 7.
- Discontinue LMWH when the INR is between 2 and 3 for 2 consecutive days.
- Additionally, the plan should be discussed in advance with the patient, surgeon, and anesthesiologist, along with the risk and benefits associated with LMWH.

When to Stop Warfarin

Warfarin should be discontinued far enough in advance of surgery to achieve a preoperative target INR of less than 1.2. Patients with an initial INR of 2 to 3 tend to achieve that target after discontinuation of warfarin for about 5 days (four doses). A longer wait (6 days, or five doses) is necessary for patients with a slower rate of decrease in the INR, and there is wide interpatient variation. The INR should always be checked prior to surgery.

Procedures than can be performed without discontinuing warfarin

Ophthalmic	Dental	Dermatologic	Gastrointestinal
Cataract surgery	Restorations	Mohs' surgery	Diagnostic esophagogastro-duodenoscopy
Trabeculectomy extractions	Uncomplained extractions	Simple excisions	Colonoscopy without biopsy
	Endodontics		Diagnostic endoscopic retrograde cholangiopancreatography
	Prosthetics		Biliary stent without sphincterotomy
	Periodontal therapy		Endoscopic ultrasonography without biopsy
	Dental hygiene		Push enteroscopy

If Warfarin is Stopped for Minor Procedures, Bridging may be Counterproductive

At the same time, a recent prospective observational study evaluated the effects of brief (≤ 5 days) interruption of warfarin among more than 1,000 patients undergoing minor outpatient procedures and found low rates of both thromboembolism (9.7%) and major bleeding (0.6%). The risk of major bleeding was significantly higher among the small proportion of patients who received bridge therapy with UFH or LMWH. The study concluded that interrupting warfarin for 5 days or less for minor outpatient procedures carries a low risk of thromboembolism and that the risk of clinically significant bleeding should be weighed before bridge therapy is considered in this setting.

Problem 1: *Patient with permanent atrial fibrillation on chronic warfarin therapy presents with sudden onset hemiparesis and drowsiness, i.e. has a recent cerebrovascular accident (CVA).*

Possible Scenarios

- Non-cardioembolic CVA
- Breakthrough embolic CVA
- Intracerebral hemorrhage.

Antithrombotic Therapy for the Secondary Prevention of Noncardioembolic Stroke

- In patients with a history of noncardioembolic ischemic stroke or TIA, long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid) or cilostazol (100 mg bid) is recommended over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), combination of clopidogrel plus aspirin (Grade 1B), or trifusal (Grade 2B).
- Of the recommended antiplatelet regiments, clopidogrel, or aspirin/extended release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C).

Initiation/Resumption of Oral Anticoagulation After an Ischemic Stroke

- Patients should be treated (i.e. bridged) with aspirin until anticoagulation has reached a therapeutic level.
- Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset.
- Earlier anticoagulation can be considered for patients at low risk of bleeding complications (e.g. those with a small infarct burden and no evidence of hemorrhage on brain imaging).
- Delayed anticoagulation should be considered for patients at high risk of haemorraghic complications (e.g. those with extensive infarct burden or evidence of significant hemorrhagic transformation on brain imaging).

Breakthrough Embolic Stroke

Acute management

- In patients with acute ischemic stroke due to proximal cerebral artery occlusion, intra-arterial (IA) r-tPA initiated within 6 hours of symptom-onset is suggested over no IA r-tPA (Grade 2C).
- In patients with acute ischemic stroke, we suggest against the use of mechanical thrombectomy.

Long-term Management of Breakthrough Embolic Stroke

i. Switching to dabigatran/oral anti-XA inhibitors (especially, Apixaban when it becomes available) from VKA.
ii. Aiming higher INR values with VKA if option – is not available/feasible.
iii. Considering LA appendage occlusion device in addition to anticoagulation.

Antithrombotic Therapy for Secondary Prevention of Cardioembolic Stroke

- In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, oral anticoagulation is recommended over no antithrombotic therapy (Grade 1A), aspirin (Grade 1B) or combination therapy with aspirin and clopidogrel (Grade 1B).
- In patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal AF, oral anticoagulation with dabigatran 150 mg bid is suggested over adjusted-dose VKA therapy (target 2.0 – 3.0) (Grade 2B).

Intracerebral hemorrhage

Once a patient is diagnosed with warfarin-related ICH, decision regarding further management hinges around two key questions.

- In the acute phase, how does the risk of further bleeding (hematoma expansion) compare against short-term risk of thromboembolism ?
- In the chronic phase, how does the risk of recurrent hemorrhage compare to risk of thromboembolism if the patient does not resume anticoagulation.

Some Important Points to be Noted

- Higher the INR at presentation, greater the risk of death, earlier correction of INR is associated with better outcome.
- While emergency reversal of warfarin is widely considered standard treatment, concern persists about its safety in patients at high risk of thromboembolism.
- Continued bleeding is common after ICH; 25 percent of hematomas expand more than 33 percent over first hour and another 12 percent expand this amount over the next 20 hours. In warfarin-associated ICH, up to 50 percent of patients develop this level of hematoma expansion, but it appears to take place over a more prolonged period of time.
- Over 70 percent of patients presenting acutely develop at least some amount of expansion within 24 hours. Therefore, the risk of hematoma expansion in the first 24 hours is likely so high that patients cannot safely receive anticoagulants during this time frame.

But not all patients are at equal risk of hematoma expansion, several features are suggestive:

- A large hematoma volume on presentation is a significant predictor of expansion, possibly reflecting a more severe underlying insult.
- Early presentation, especially within 3 hours of symptom onset, also appears to mark those at higher risk, presumably because such patients undergo computed tomography (CT) while still bleeding.
- For those on warfarin, a higher INR is a significant predictor, not just of higher risk, but also of a more delayed expansion.
- Certain radiographic findings indicate higher risk. One is the 'spot sign', i.e. contrast exvasation after contrast-enhanced CT. Apparently, the more spots present, and the denser the contrast, the greater the risk, an observation that has led to a proposed 'spot-sign score' that may predict both expansion and poor outcome.

Given the risk of hematoma expansion in the early phase, and given our inability to predict hematoma expansion, most authorities recommend immediate reversal of anticoagulation typically includes intravenous vitamin K, which begins to act within several hours, and repletion of coagulation factors, which act within minutes (prothrombin complex concentrates and recombinant factor VIIa [Novo Seven] or a few hours (fresh frozen plasma).

Dosages

- Vitamin K 5 to 10 mg intravenously
- Prothrombin complex concentrates 10 to 50 U/kg
- Recombinant factor VIIa 40 to 80 µg/kg
- Fresh frozen plasma 10 to 50 U/kg.

Studies of in-hospital anticoagulation after ICH

- As the benefit appears to outweigh the risk, national guidelines suggest starting subcutaneous heparin early in all ICH patients, including those not previously on warfarin
- Commonly used heparinoid regimens include UFH 5000 u subcutaneous twice a day, enoxaparin 40 mg subcutaneous once a day and dalteparin 5000 u subcutaneous once a day.
- After first few days or a week, consider increasing to a full anticoagulation or starting an oral anticoagulant and subsequently discontinuing heparin when INR is in the therapeutic range.

When to Start Anticoagulation?

- **European stroke Initiative:** In patients with a strong indication for anticoagulation start warfarin 10 to 14 days after an ICH.
- **American Heart Association:** In patients at very high risk of thromboembolism, start warfarin 7 to 10 days after ICH onset.

- **American College of Chest Physician:** Start prophylactic dose heparin the day after an ICH, with no clear guidance on restarting warfarin.
- Alternatives to warfarin that show promise in reducing bleeding risk are factor Xa and direct thrombin inhibitors with similar reduction in risk of thromboembolism.

Antiplatelet Therapy after Hypertensive Intracranial Hemorrhage

- There are no recommended guidelines as to whether and when to start secondary stroke prophylaxis after hypertensive intracranial hemorrhage.
- Although the risk factors remain identical and risk of recurrence of stroke which may be ischemic exists in these patients, the risk of recurrence of hemorrhage versus infarct in these patients, risk of hemorrhage due to antiplatelet agents remain nebulous at best.
- Most strokologists verbally promulgate use of antiplatelet agents on an average 6 months after ICH.

Problem 2: *Perioperative antithrombotic therapy for surgery with 'High Bleeding Risk', e.g. spinal surgery*.

Perioperative Antithrombotic Therapy for Spinal Surgery

- Because of the hazardous risk of symptomatic epidural hematoma, potential consequences of antithrombotic therapy may contradict the benefits of these agents.
- In patients who are being treated with chemical anticoagulants for a non-spine related disorder (e.g. Valve replacement, atrial fibrillation), literature reviewed does not support an ideal perioperative 'bridge' therapy.
- Candidate agents, such as warfarin, therapeutic heparin, LMWH, clopidogrel or acetylsalicyclic (ASA) all increase bleeding risk in post-operative spinal surgery patients.

Problem 3: *Management of antiplatelet therapy perioperatively in patients with intracoronary stent.*

Key to Management: Assessing and Balancing

i. Individual risk for thromboembolism if antiplatelet therapy is stopped
ii. Individual risk for bleeding if antiplatelet therapy is continued.

Surgical Hemorrhagic Risk

Low risk: Transfusion normally not required; peripheral pelvic and general surgery, biopsies; minor orthopedic, ENT, and general surgery, endoscopy; eye anterior chamber; dental extrusion and surgery, urosurgery.

Intermediate risk: Transfusion normally not required; visceral surgery, cardiovascular surgery, major orthopedic, ENT, reconstructive surgery, endoscopic surgery.

High risk: Possible bleeding in a closed space; intracranial neurosurgery, spinal canal surgery, eye posterior chamber surgery.

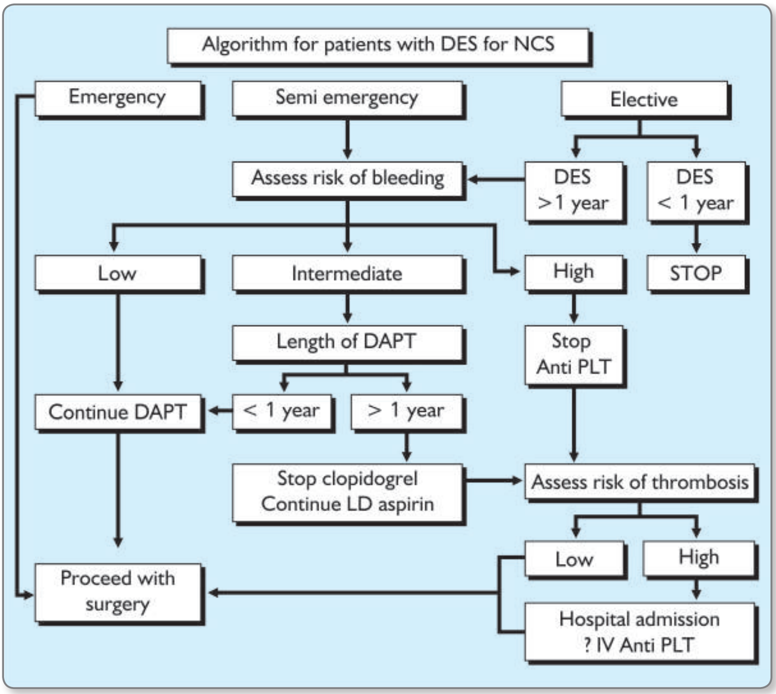
Cerebro- and Cardiovascular Risk

Low : > 6 months after MI, PCI, BMS, CABG, score >12 months in complication

Intermediate: 6-24 weeks after MI, PCI+BMS, CABG or stroke (if complications); >12 months after DES; high risk stents (long, proximal, multiple, overlapping, small vessels, bifurcation); low EF, diabetes.

High: < 6 weeks after MI, PCI, BMS, CABG, <6 months after same (if complications) <12 months after high risk DES; <2 weeks after stroke.

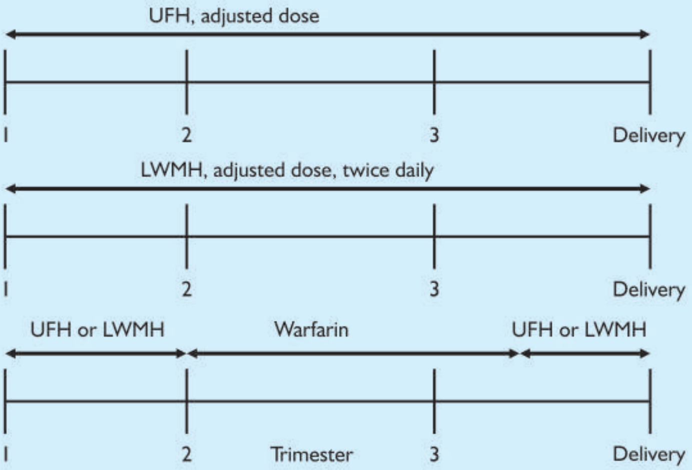
Surgical Hemorrhagic risk	**Cerebro- and Cardiovascular Risk**		
	Low	*Intermediate*	*High*
Low	Elective surgery; OK; maintain aspirin	Elective surgery; OK, maintain aspirin, Clopidogrel (if prescribed)	Elective surgery; postpone, vital or emergency surgeryl; OK, maintain aspirin and clopidogrel
Intermediate	Elective surgery; OK maintain aspirin	Elective surgery; postpone; surgery absolutely required: OK, maintain aspirin, clopidogrel (if prescribed)	Elective surgery; postpone vital or emergency surgery; OK: maintain aspirin and clopidogrel
High	Elective surgery; OK; Maintain statin, withdraw Aspirin (maximum 7 days)	Elective surgery: postpone surgery absolutely required; OK: maintain aspirin, or replace aspirin by Ibuprofen, stop clopidogrel	Ok only not vital or emergency surgery; maintain aspirin, bridge with tirofiban eptifibatide and heparin



Management of Anticoagulants in Pregnancy

Anticoagulants in Pregnancy

- **Warfarin:** Freely crosses placenta and affect fetal development. Incidence of warfarin embryopathy is 4 to 10 percent. Risk is highest when warfarin is administered during 6th through 12th weeks of gestation.
- **UFH:** The UFH does not cross placenta and unlike warfarin does not have teratogenic effects and is therefore considered safer. It is, however, associated with maternal osteoporosis, hemorrhage, thrombocytopenia or HIT syndrome and a high incidence of thromboembolic events with older generation mechanical valves.
- **LMWH:** Use of LMWH during pregnancy is still controversial as it has not been adequately studied. Use in pregnant patients with prosthetic valves is to be done with caution.



Anticoagulation options during pregnancy

In patients with a mechanical heart valve with high risk of thrombosis (first-generation prosthesis; e.g. Starr-Edwards, Bjork-Shiley in mitral position, atrial fibrillation, and history of thromboembolism) one of the following algorithms may be used:

- Continuous IV UFH (aPTT 2.5 – 3.5 times) for 12 weeks followed by Coumadin (INR 2.5 – 3.5) for up to 35 weeks followed by IV UFH (aPTT 2.5 – 3.5) until delivery or subscutaneous (SC) LMWH (anti-Xa level ~ 0.7) for 12 weeks followed by coumadin (INR 2.5 – 3.5) for up to 35 weeks followed by IV UFH (aPTT of 2.5 – 3.5 times) or SC LMWH (anti-Xa ~ 0.7).
- In patients with a mechanical heart valve with relatively lower risk of thrombosis (second-generation prosthesis; e.g. St Judge Medical, Medtronic-Hall and any mechanical prosthesis in aortic position) algorithm options include:

  Subcutaneous (SC) LMWH (anti-Xa ~ 0.6) or SC UFH (aPTT 2.0 – 3.0 times) for 12 weeks followed by coumadin (INR 2.5 – 3.0) for up to 35 weeks followed by IV UFH (aPTT 2.0 – 3.0 times) or SC LMWH (anti-Xa ~ 0.6)

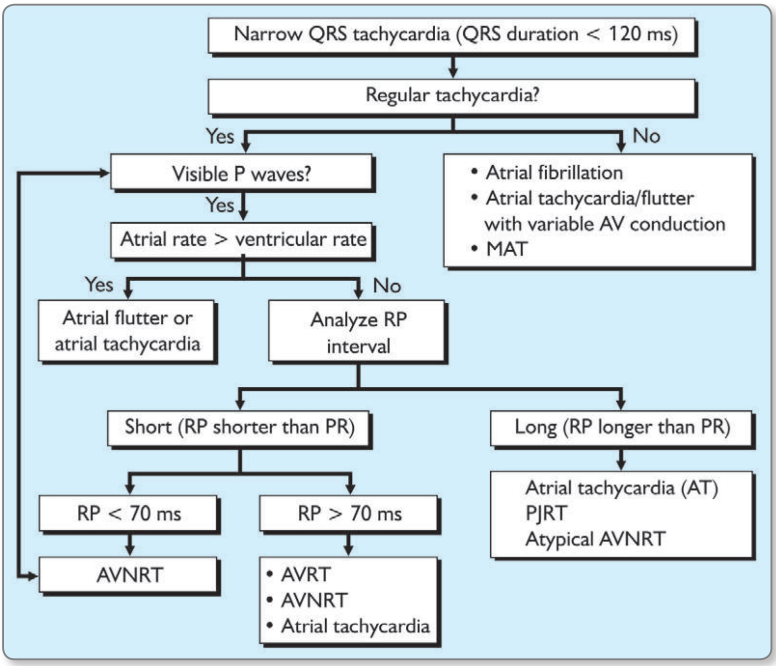
  SC UFH or SC LMWH throughout pregnancy (data supporting this algorithm are limited).

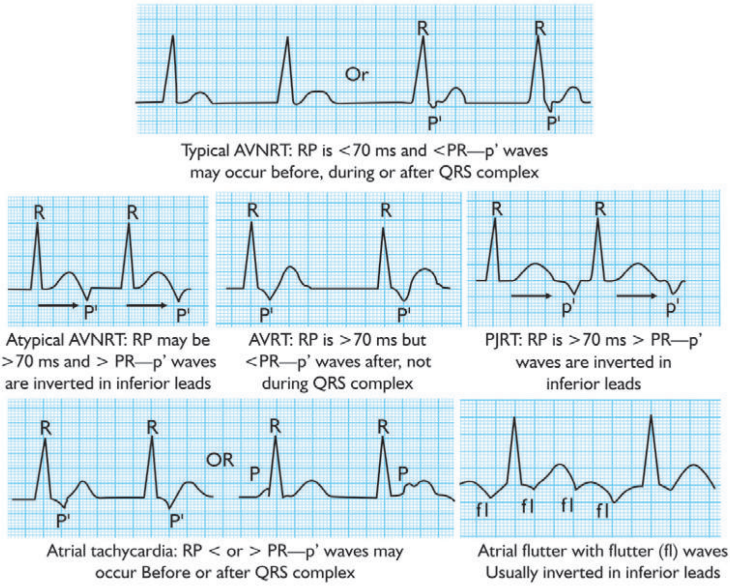
chapter 8

Tachycardias

Dipankar Mondal, Soumitra Kumar

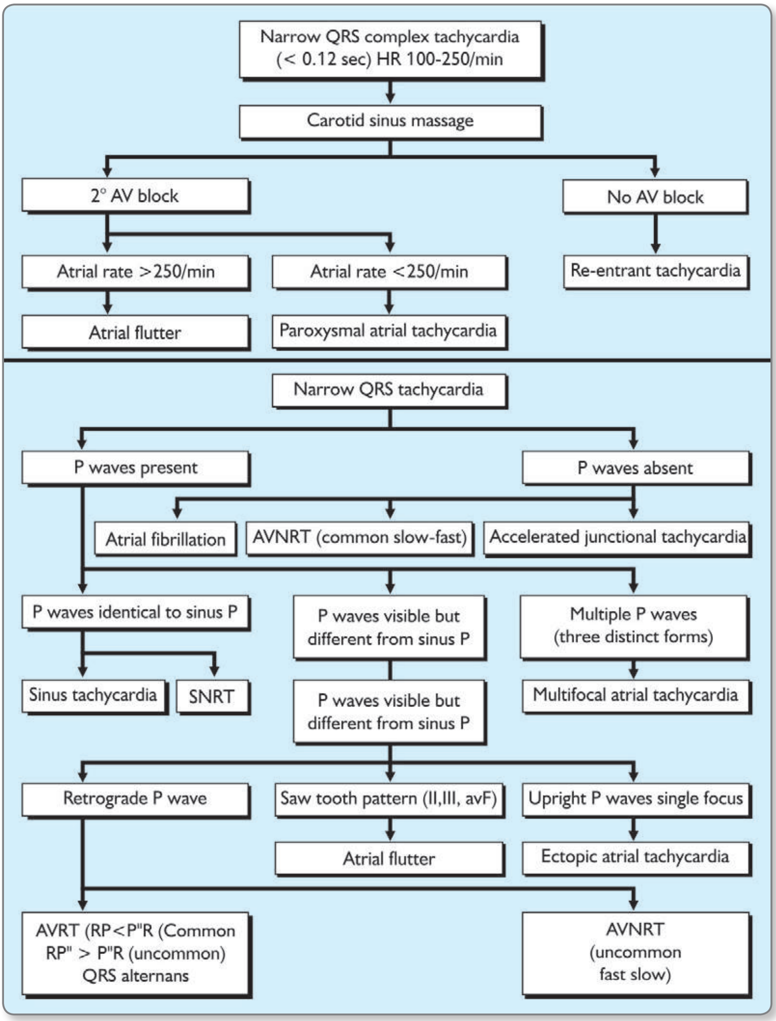
Approach to the patient with narrow QRS tachycardia (QRS duration < 120 ms)





P wave morphology and its relation with RP and PR intervals in narrow QRS tachycardia–AVNRT: AV nodal re-entrant tachycardia, AVRT: AV re-entry tachycardia, PJRT: permanent from of AV junctional reciprocating tachycardia

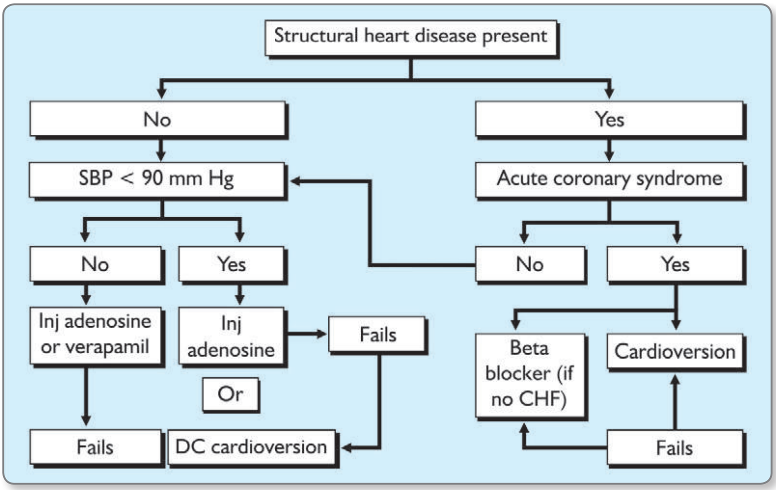
Approach to the Patient with Narrow QRS Complex Tachycardia



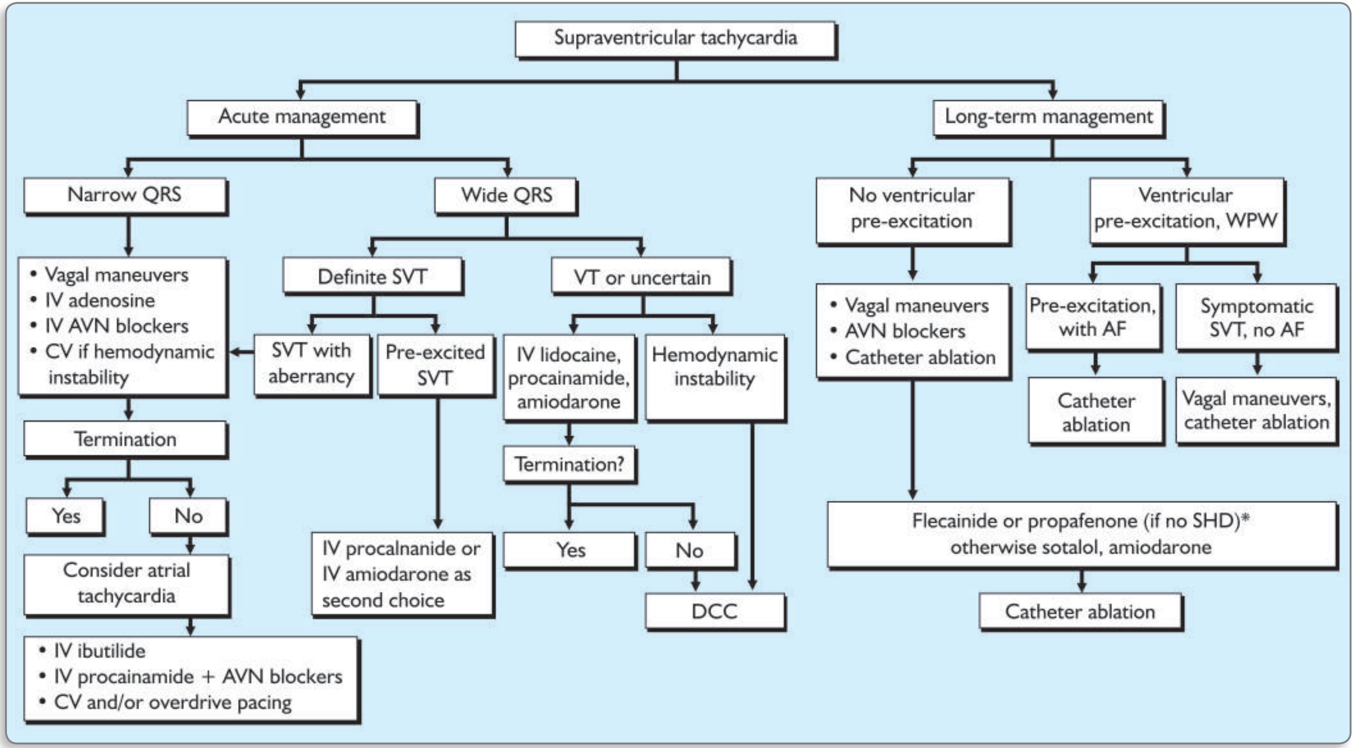
Effect of vagal maneuvers, adenosine and verapamil in narrow complex tachycardia

	Vagal maneuvers	IV adenosine	IV verapamil
AVNRT	Terminates (+)	Terminates (++)	Terminates (++)
AVRT	Terminates (+)	Terminates (++)	Terminates (++)
Atrial flutter	Slows (+)	Slows (++) Terminates (±)	Slows (++)
Atrial tachycardia (±)	Slows (+)	Slows (++)	Slows (++)
SNRT	Terminates (±)	Terminates (++)	No effect
Sinus tachycardia	Slows (±)	Slow (+)	No effect

Initial Treatment of AVNRT (AV Nodal Re-entry Tachycardia)



Management of Narrow QRS Tachycardia



*SHD—Structural heart disease

Management of Patients with AVNRT

Acute Treatment, Stable

- *Vagal maneuvers (by physician):* Valsalva (with patient in supine position) or carotid sinus massage (in absence of carotid bruits or history or evidence of cerebrovascular disease). If hypotensive (BP <90-100 mmHg) and rate is >220 bpm, carotid massage is unlikely to be effective but Valsalva may work in supine or Trendelenburg positions. If stable, the patient can be advised to perform vagal maneuvers at home in the following order: Valsalva maneuver, diving reflex (immerse head in cold water for 1 to 2 seconds), gag reflex, cold water on face, and self-carotid sinus massage, provided that there is no known carotid disease or bruits (as checked by physician previously).
- Adenosine 6-mg rapid IV bolus with a saline flush. If ineffective within 30 to 60 seconds, give a 12 to 18 mg bolus. If still ineffective, reconsider the rhythm diagnosis. If the tachycardia just slows in response to adenosine, it may be sinus tachycardia. Adenosine is successful in terminating AVNRT in >90% of patients if given properly. Side effects occur in >40% but usually last <1 minute, and include flushing, chest pain, and dyspnea (due to bronchospasm). Bronchospasm is the most serious side effects and can require immediate attention. Drug half-life is 10 seconds. Adenosine effects are potentiated by dipyridamole and inhibited significantly by theophylline. Adenosine can precipitate atrial fibrillation but this is usually transient and tends to occur at large doses. Adenosine should not be administered to patients with heart transplant, as asystole may result.
- Verapamil 5 to 15 mg IV over 5 minutes. Effects is seen within seconds to minutes. Success rate exceeds 90%. Not to be used in wide complex tachycardia (QRS >0.12 sec), as the diagnosis of AVNRT may be wrong in the first place. Verapamil is now usually reserved for patients who have recurrent episodes of AVNRT after termination with adenosine.
- Other drugs that may be effective but are rarely needed these days include diltiazem 0.25 to 0.35 mg/kg IV (compared with verapamil, less effective but also more likely to cause hypotension), metoprolol to 8 mg IV titrated over 15 to 30 minutes, or esmolol (50 to 250 μg/kg/min), especially if the AVNRT is typically exercise or anxiety induced.
- *Nonresponders to above measures:* DC cardioversion synchronized to the QRS complex (anesthetize*, then 50 J first shock).

Acute Therapy, Unstable (Chest Pain, Severe Dyspnea, Hypotension, Syncope, Impaired Consciousness)

- *Blood pressure (BP) > 90 mmHg, awake:* Vagal maneuvers, it unsuccessful, adenosine 6 mg (additional 12 mg in 5 minutes if necessary). If unsuccessful, follow with synchronized DC cardioversion with anesthesia*.

- *BP < 90 mmHg but rate > 220 bpm and/or highly symptomatic, CHF or severe underlying cardiac disease:* DC cardioversion.

Congestive Heart Failure

- *If acute pulmonary edema:* Cardiovert
- *If not in pulmonary edema:* Vagal maneuvers, as above, adenosine, as above.

Recurs Shortly after Conversion to Sinus Rhythm

- *Drug therapy to stabilize the rhythm:* IV diltiazem infusion or IV verapamil (preferable); metoprolol or esmolol if a short-acting β-adrenergic blocker is deemed preferable.
- Further therapy based on frequency of episodes, severity of symptoms, and tachycardia rate.

Chronic Prevention in Infrequent, Well-tolerated, Short-lived Episodes

- No specific therapy for a single or first episode.
- Patients to be advised to avoid activities and stimulants (including caffeine) that are thought to initiate episodes.
- Train patient on vagal maneuvers (vide acute therapy, stable comments above).
- Consider medications such as β-adrenergic blockers, diltiazem, or verapamil, to be taken when episodes occurs.
- EP study with RF ablation explained as an option.

Chronic Prevention in all others (Frequent Episodes, Poorly Tolerated or Rapid Rates (>220/mm)

- *First line:* Catheter ablation of the slow pathway. Slow AV node pathway modification has a success rate >95% and has a low (<1%) risk of the need for a permanent pacemaker, and can be performed on an outpatient (23 hour admission) basis. The cost-benefit ratio favors ablation if the patient is young and would otherwise require long-term drug therapy.
- *Second line:* Drug therapy
  - *No CHF:* Preferred drug class: β-adrenergic blocker (atenolol, acebutolol, metoprolol), esp. if episodes are exertion or stress related. Alternatives (perhaps less effective but better tolerated)—verapamil (long-acting preparation) or diltiazem.
  - *CHF or low LVEF:* β-adrenergic blockers, if tolerated, also for survival benefit in heart failure; digoxin (less effective).
  - If patients chooses trial of drug therapy but fails with more than one drug proceed to ablation.

*DC cardioversion should be performed under general anesthesia with propofol, methohexital, etomidate etc. by a person certified in deep sedation or alternatively, deep sedation by IV midazolam may be acceptable.

Nonresponder

- *First line:* Catheter ablation.
- *Second line: Drug therapy:* AV nodal blockers first (β-adrenergic blockers, calcium channel blockers, digoxin).
  - *No structural heart disease:* Monotherapy with class IC drug (propafenone, flecainide), class IA drug (quinidine, procainamide, disopyramide) given with one of drugs listed above (see chronic prevention, all others). Disopyramide can cause urinary retention and exacerbation of CHF. Class IA antiarrhythmic drugs are rarely used these days for AVNRT.
  - *Structural heart disease:* Monotherapy with class III drug (sotalol or amiodarone). Sotalol therapy should be initiated in the hospital, and should be avoided in patients with renal insufficiency. Amiodarone may be started as an outpatient. Class IC drugs should not be given to patients with structural heart disease or CAD.

Management of Patients with Pre-excitation

AF with Ventricular Pre-excitation and Rapid Ventricular Rates: Acute Therapy Unstable (Hypotension, Angina, Heart Failure Symptoms)

- *First line:* Synchronized DC cardioversion (50 to 200J) with anesthesia.
- *Second line:* IV procainamide or IV amiodarone can be tried to block conduction in the accessory pathway, provided the patient can tolerate the medication due to low blood pressure and if there is sufficient time before complete hemodynamic collapse.
- *Not to administer:* digoxin, adenosine, or verapamil. Avoid β-adrenergic blockers as well. All these block AV nodal conduction, allowing more impulse conduction down the accessory pathway.
- This approach is useful not only for a patient who presents to the emergency department but also for a post-operative patient with rapid rates due to pre-excitation.

AF with Ventricular Pre-excitation and Controlled Ventricular Rates without Hemodynamic Instability: Acute Therapy

- *First line:* IV procainamide or IV amiodarone. Procainamide is preferred but is often not available.
- *Second line:* Anesthesia and synchronized cardioversion.
- Not administered: AV nodal blockers.

Orthodromic AVRT: Acute Therapy

- *First line:* Carotid sinus massage or Valsalva maneuvers.
- *Second line:* Adenosine 6 mg IV and, if ineffective, 12 mg IV.
- *Caution:* High doses of adenosine may initiate AF.

- *Third line:* Verapamil 5 to 15 mg IV in any cases, it is not clear whether or not the patient will have ventricular pre-excitation in sinus rhythm when presenting with orthodontic AVRT. If there is evidence for ventricular pre-excitation from ECGs recorded in sinus rhythm, verapamil may not necessary be the most ideal therapy but treating this particular rhythm with verapamil does not precipitate rapid rates in AF, and if the QRS is narrow during orthodontic SVT, the AV node is generally part of the circuit and hence responsive to verapamil.
- *Fourth line:* Intravenous β-adrenergic blockade preferably with esmolol because it is short-acting or metoprolol.
- *Fifth line:* Synchronized electrical cardioversion; this is the first-line therapy if the tachycardia is associated with hemodynamic collapse.

Antidromic AVRT: Acute Therapy

- *First line:* IV procainamide or IV amiodarone with procainamide being preferable. May perform carotid massage first if blood pressure is over 100 mmHg or Valsalva maneuver.
- *Second line:* Synchronized electrical cardioversion, this is the first-line if the patient has hemodynamic collapse.
- Digoxin, β-adrenergic blocker, and calcium channel blocker to be avoided.

Long-term Therapy: WPW Syndrome due to an Accessory Pathway

- *Symptomatic patients:* Catheter ablation is successful in >90% of patients. Ablation is first-line therapy for patients with symptomatic pre-excitation syndromes especially those presenting with AF.
- *Asymptomatic patients:* Consider catheter ablation in young patients, especially if highly active or in a high-risk profession.
- For those, who do not prefer to have ablation or for those patients who have difficult or impossible to ablate accessory pathways, drug therapy is second-line treatment for patients with normal hearts. Flecainide, propafenone, sotalol, amiodarone, and procainamide (in that order of preference), could be used, should there be no evidence for structural heart disease. In some instances, drug therapy is used in place of ablation of the pathway in "high risk", zones such as those accessory pathways that are mid septal and near the His-Purkinje system.
- For patients, who have structurally abnormal hearts, class IC antiarrhythmic drugs are not recommended. For patients with intact ventricular function, sotalol is the first-line therapy and if ineffective, amiodarone is the second-line treatment.
- For patients with poor ventricular function in whom ablation is not recommended or is impossible due to other confounding medical conditions amiodarone is the first-line treatment.

Mahaim Fiber Tachycardias

- Acute management is similar to that for AVNRT.
- *First line:* Carotid sinus massage or another vagal maneuver.
- *Second line:* Adenosine.
- *Third line:* Procainamide IV or amiodarone IV.
- AV nodal blockers to be avoided.
- Long-term therapy includes, ablation. If ablation is not reasonable due to other concomitant medical problems or is not preferred by the patient, or is ineffective, the first-line treatment includes sotalol, flecainide, or propafenone. β-adrenergic blockers alone may work as well.

Lown-Ganong-Levine Syndrome (with SVTs)

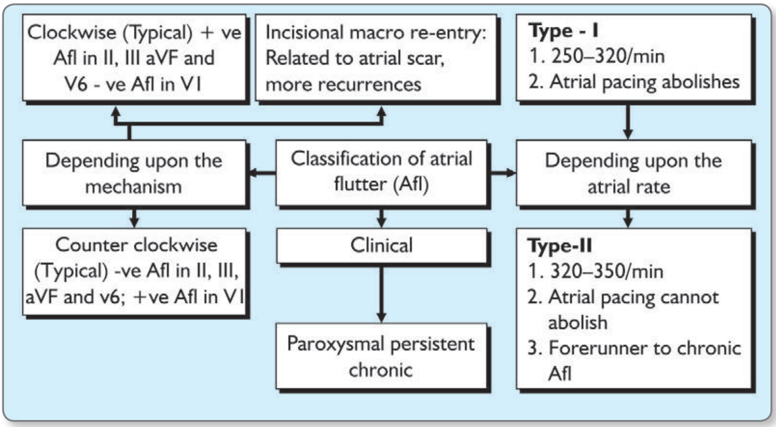
EP study followed by ablation of the responsible tachycardia. If the arrhythmia is AF, AFL, or AT with rapid conduction through the AV node, rate control using a β-adrenergic blocker or a calcium channel blocker may be effective.

Permanent Junctional Reciprocating Tachycardia (PJRT)

Ablation is the first line. Pharmacologic alternatives include AV nodal blockers (β-adrenergic blockers, diltiazem, verapamil, or digoxin), flecainide, propafenone, sotalol or amiodarone. Flecainide and propafenone should be avoided if there is structural heart disease, such as cardiomyopathy or CAD.

Atrial Flutter

The second most common of the atrial tachycarrhythmias after atrial fibrillation (0.4 to 1.2% in hospital records of ECG reports).



Typical Counter Clockwise Atrial Flutter with Variable AV Block

Atrial flutter is characterized by an atrial rate of 250 to 350 bpm with characteristic "flutter" waves (saw tooth – like waves) that are usually most evident in the inferior leads (II, III, aVF) or V1. The atrial rate of 300 bpm and negative flutter waves in lead II are characteristic of typical (type I) atrial flutter that involves counterclockwise re-entrant activation in the cavotricuspid isthmus.

Typical Clockwise Atrial Flutter

The flutter waves in lead II are upright, consistent with re-entry around the cavotricuspid isthmus in a clockwise direction.

Atypical Atrial Flutter

Atypical atrial flutter does not involve cavotricuspid isthmus. The flutter waves have more variable contour and rate than typical atrial flutter. There is a variable degree of AV block (frequently 4:1 but at times 5:1). Flutter waves can deform the QRS complexes and initial portions of the ST segments.

Other Forms of Atrial Flutter

These are nonisthmus dependent right atrial flutters including "upper loop re-entry" and "lower loop re-entry" tachycardias. These are macrore-entrant tachycardias that use other circuits within the right atrium. Although these atrial flutters are also ablatable, they are more challenging than typical isthmus-dependent right atrial flutters.

Other forms of atrial flutter include nonisthmus-dependent macrore-entrant atrial tachycardias originating from the left atrium. This type of flutter, is often associated with atrial fibrillation; it is also associated with ablation of AF in which new anatomic pathways are created, determined by the ablation lesion themselves. Left atrial flutters tend to occur in patients following cardiac surgery, especially mitral valve surgery. These types of flutters can be ablatable but they are more challenging than isthmus-dependent right atrial flutters.

Atrial flutter may also be due to re-entry around areas of right or left atrial scars, including those caused by prior surgical incisions (e.g. following atrial septal defect repair).

Management of Atrial Flutter

Acute Therapy for Poorly Tolerated Atrial Flutter (AFL) or Continuous High Ventricular Rate

- If prolonged (i.e. >48 to 72 hours), anticoagulation with heparin followed by therapeutic warfarin or dabigatran as cardioversion may be associated with thromboembolic risk. Anticoagulation guidelines for cardioversion are the same as for atrial fibrillation and may indicate need for a TEE for prolonged episodes).
- *First line:* DC cardioversion under anesthesia. Consider the length of the episode.
- *Second line:* Ibutilide or procainamide may be attempted for conversion prior to DC cardioversion attempts. Ibutilide may be 70% effective if AFL

has been present for < 48 hours, although often this is not known with certainty. Procainamide may help maintain sinus rhythm.

- *Alternative treatment:* Rapid atrial pacing (esophageal, epicardial, or endocardial depending on the situation). To terminate by pacing, pace for 10 to 15 seconds at a rate of 10 to 20% faster than rate of flutter. If ineffective, burst pace 10 bpm faster at a time for 10 to 15 seconds until conversion to AF or sinus rhythm. Adding procainamide may help pace termination efficacy; however, it may accentuate AV conduction if the ventricular response is not adequately controlled with AV nodal blocker drugs (see chronic prevention, below); 20 to 30% will convert to AF and 10 to 20% will have no effect from pacing, depending on patient selection for the procedure. When AF occurs, it is usually short-lasting and terminates spontaneously within 24 hours. If persistent, DC cardioversion can be attempted with or without antiarrhythmic drugs. Rapid AFL (atrial rate >350) and atrial fib/flutter usually cannot be pace terminated. However, slower AFL (rate <350) of any flutter wave morphology can often be pace-terminated.
- Oral drug loading alone to terminate AFL is rarely effective.
- If episodes are recurrent, then attempt cardioversion. These drugs (particularly IC drugs) may stabilize the flutter circuit. It may also create another form of AFL – IUC. AFL from AF. Ablation remains the first-line therapy, especially if AFL is isthmus dependent.
- Ablation to be considered for all persistent, refractory, or symptomatic AFL. Despite AFL ablation however, AFL may recur, especially in individuals with underlying structural heart disease.
- AV nodal ablation, although not desirable is to be considered when ventricular rate control cannot be achieved and flutter cannot be ablated, or if symptomatic, refractory, and/or if associated with tachycardia-induced cardiomyopathy. This option may be considered in cases where individuals have multiple forms of nonablatable AFL or AF and especially for those, who do have nonisthmus-dependent AFL.

Long-term Prevention

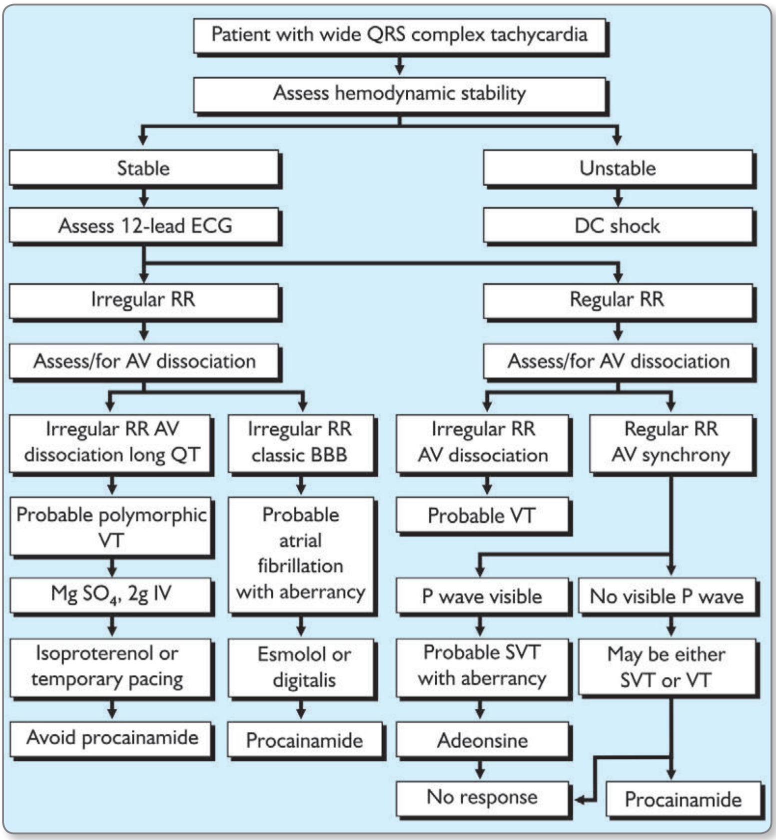
- *If structure heart disease without CHF:* Sotalol (to be initiated in the hospital), dofetilide, amiodarone.
- *If structural heart disease with CHF:* Amiodarone, dofetilide.
- If no structural heart disease, propafenone, flecainide, sotalol, dofetilide, or amiodarone, but propafenone or flecainide may need concomitant AV nodal blocking drugs to prevent 1:1 conduction.
- If class IA or IC drugs are used, first control the ventricular response rate with AV nodal blocking drug. Otherwise, the vagolytic effects of class IA drugs can enhance AV nodal conduction, and both IA and IC drugs can lead to AFL with 1:1 AV conduction.
- Drugs therapy alone for pure AFL flutter is usually ineffective.

- Consider radiofrequency catheter ablation early; it has become the first-line therapy.

Nonresponders having Severe Symptoms

- If type I AFL, radiofrequency ablation of the right atrial isthmus
- Atypical AFL is more difficult to ablate, and depends on the location of re-entrant circuit. Success rates are definitely lower than that for typical AFL. It is more difficult when there is congenital heart disease, valve disease, or prior surgery in which significant amount scan tissues are present.
- Ventricular rate control, antiarrhythmic drugs, or AV node ablation (less preferable) can be performed for atypical, nonablatable AFL.
- If AV node ablation and pacing is performed and AFL is intermittent, mode-switching function should be turned "ON".

Approach to the patient with wide QRS complex tachycardia (QRS duration > 120 ms)



Wide Complex Tachycardia

Clinical Assessment

History

- *Age:*
  Younger: Pre-excited tachycardia.
  Prone to coronary artery disease: Ventricular tachycardia (VT).
- *Structural heart disease:*
  Coronary artery disease
  or
  Myocardial infarction VT
  or
  Congestive heart failure
- *Duration:* Of > 3 years or from childhood—SVT
- *Symptoms:* Not of much help
- *Medications:* Antiarrhythmic drugs may increase QRS duration.

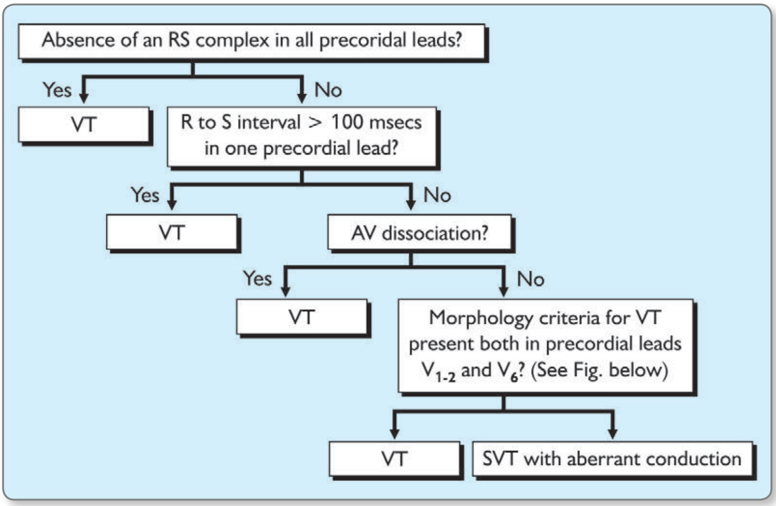
Physical Assessment

- *Neck vein:* Irregular cannon wave—VT.
- *Blood pressure:* Beat to beat variation—VT.
- *Variable the first heart sound:* VT or AF with aberrancy
- *Carotid sinus massage:*
  Termination of tachycardia — Supra ventricular tachycardia (SVT).
  Slowing of rate —

Investigations

- *Chest X-ray:* Cardiomegaly—VT
- *Electrocardiogram (ECG):* 12 lead ECG is a must
  a. Comparison with ECG in sinus rhythm if possible
     Same QRS axis and duration—SVT
     Altered pattern—VT
  b. Regularity: Regular—VT/SVT
     Irregular—Pre-excitation in AF
     (especially if H/R > 220 bpm)
  c. Atrioventricular dissociation: —VT
     Dissociated P waves at rates slower than the ventricular rates
     fusion beats
     Capture beats
     Irregular changes in ST-T waves
     (suggesting presence of dissociated P waves)
     P wave and QRS complexes at different rates on recording through esophageal electrode, which is passed through nasogastric tube.

Classic Morphology Criteria for Ventricular Tachycardia

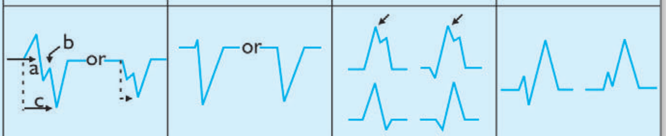


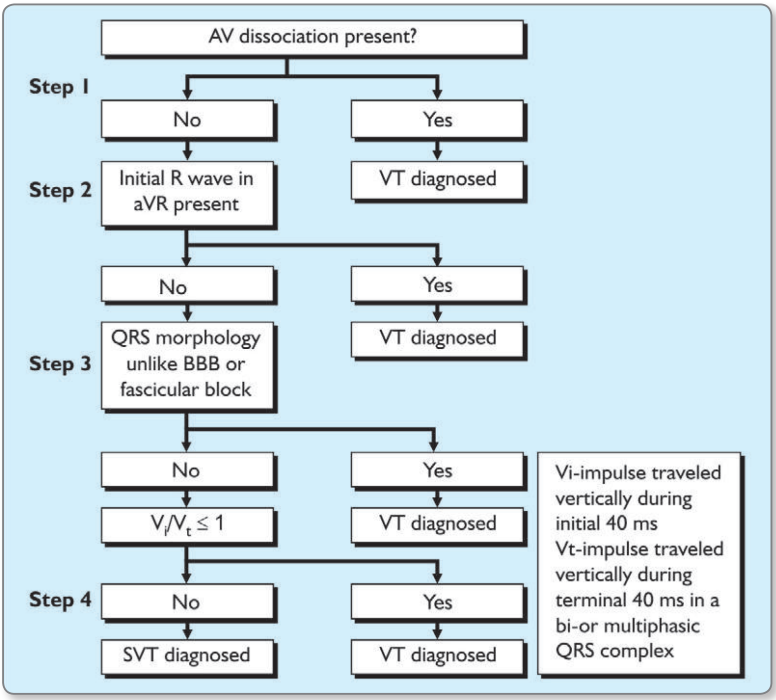
In recent times, Vereckei has proposed a new algorithm in the differential diagnosis of wide QRS complex tachycardia which has been claimed to have a greater sensitivity and predictive value for VT diagnosis and greater specificity and predictive value than those of Brugada criteria.

Brief summary of the new algorithm of vereckei is as following:

Brugadd criteria for distinguishing ventricular tachycardia from supraventricular tachycardia with aberrancy in wide-complex tachycardias

	LBBB		RBBB	
	VT	**SVT**	**VT**	**SVT**
Lead VI	In VI, V2 any of: (a) r ≥ 0.04 sec (b) Notched s downstroke (c) Delayed S nadir > 0.06 sec	In VI, V2 absence of: (a) r ≥ 0.04 sec (b) Notched s downstroke (c) Delayed S nadir > 0.06 sec	Taller left peak biphasic RS or QR	Triphasic rsR' or rR'
Lead V6	Monophasic QS		Biphasic rS	Triphasic qRs





Classification of Ventricular Tachyarrhythmias

On the basis of association:

- Ventricular tachyarrhythmias related to ischemic heart disease
- Ventricular tachyarrhythmias related to nonischemic heart disease
  - Related to His-Purkinje system disease
  - Arrhythmogenic right ventricular dysplasia
  - Acute myocarditis
  - Chagas's disease
  - Sarcoidosis
  - Muscular dystrophy
  - Related to Wolff-Parkinson-White syndrome
- Ventricular tachyarrhythmias in the structurally normal heart
  - Monomorphic
    - Right ventricular outflow tract ventricular tachycardia
    - Fascicular ventricular tachycardia
    - Miscellaneous forms

- Polymorphic
  - Long Q-T syndrome
  - Brugada syndrome
  - Other
- Ventricular tachyarrhythmias related to drugs.

Classification of Ventricular Tachyarrhythmias by Electrocardiography

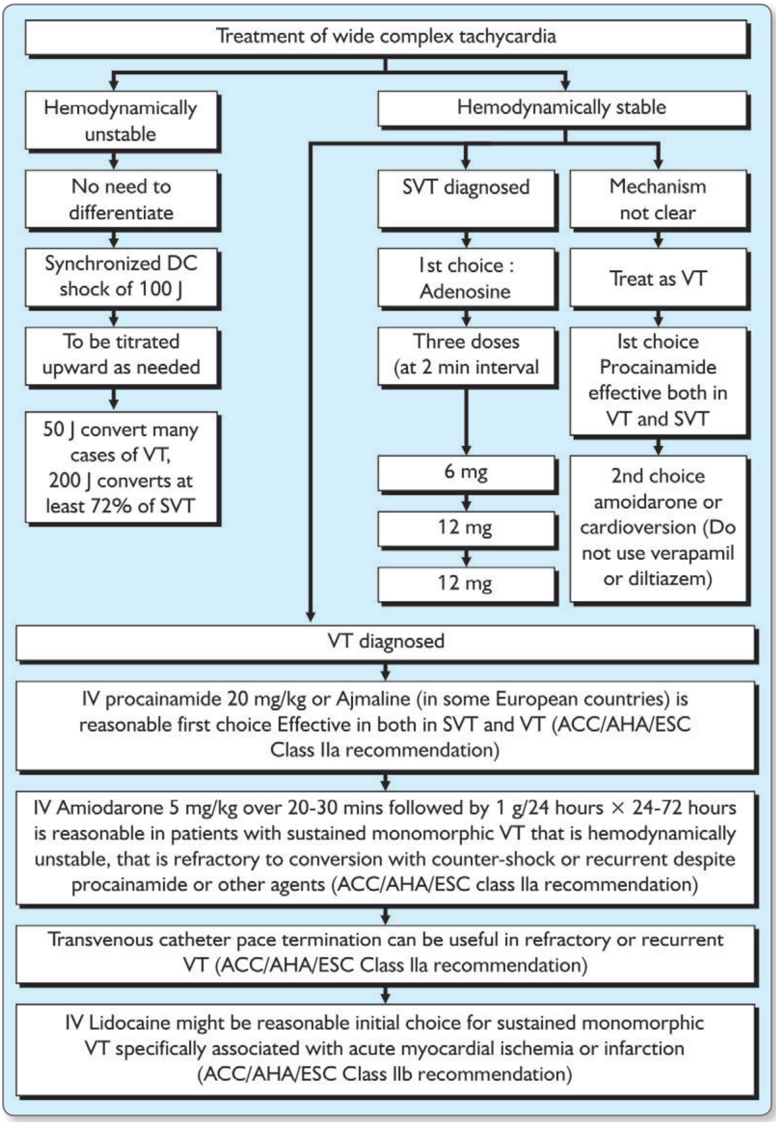
Ventricular tachyarrhythmias (VT) is a cardiac arrhythmias of ≥ 3 consecutive complexes in duration emanating from the ventricles at a rate of greater than 100 bpm (cycle length < 600 ms).

• Nonsustained VT (NSVT) (Duration < 30 secs)	1. Monomorphic 2. Polymorphic (Changing QRS morphology at cycle length between 600 and 180 ms)
• Sustained VT (Duration > 30 secs)	1. Monomorphic 2. Polymorphic
• Bundle branch re-entrant tachycardia	(VT due to re-entry involving the His-Purkinje system, usually with LBBB morphology, usually occurring in setting of cardiomyopathy)
• Bidirectional VT	(Beat to beat alternans in QRS frontal plane axis, often associated with digitalis toxicity)
• Torsade de pointes	(Characterized by VT associated with QT or QTc prolongation and ECG characterized by twisting of peaks of QRS complexes around the isoelectric line)
• Ventricular flutter	(Regular ventricular arrhythmia of cycle length ≤ 30 ms approximately 300 bpm with monomorphic appearance)
• Ventricular fibrillation	Rapid > 300 bpm, grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology and amplitude

Pharmacological Aids for the Diagnosis of Wide QRS Tachycardia

Adenosine has been proposed to be an ideal pharmacological agent to help distinguish wide complex SVT from VT because:

i. Most SV circuits encompass the AV node
ii. Adenosine blocks transmission at AV node
iii. Pharmacologic effect is too short (seconds) to have any serious adverse consequences



Caution

Adenosine has been reported to precipitate ventricular fibrillation when administrated during pre-excited atrial fibrillation (Hence avoid in irregular wide QRS complex tachycardia).

Incessant Ventricular Tachycardia

- Revascularization and beta blockade followed by IV antiarrhythmic drugs such as procainamide or amiodarone are recommended for patients with recurrent or incessant polymorphic VT due to acute myocardial ischemia (ACC/AHA/ESC class I recommendation)
- IV amiodarone or procainamide followed by VT ablation can be effective in the management of patients with frequently recurring or incessant monomorphic VT (ACC/AHA/ESC Class IIa recommendation)
- IV amiodarone and IV beta blockers separately or together may be reasonable in patients with VT storm (ACC/AHA/ESC Class IIb recommendation)
- Overdrive pacing or general anesthesia may be considered for patients with frequently recurring or incessant VT (ACC/AHA/ESC Class IIb recommendation)
- Spinal cord modulation may be considered for some patients with frequently recurring or incessant VT (ACC/AHA/ESC Class IIb recommendation)

Ventricular Tachycardia Related to Ischemic Heart Disease

Postmyocardial Infarction

i. *VT within 24 hours:* If following therapy no recurrence occurs within 48 to 72 hours, no treatment required.
ii. *VT within 6 weeks:* Very high recurrence rate (convalescence period). Treatment: (a) Acute phase, (b) Long-term.
iii. *VT between 7 and 8 weeks:* Prognosis in between (i) and (ii).

Risk stratification in post MI with/without HF

Class I	Class IIa	Class IIb
• Demographic variables • LVEF • HRV or BRS • LVV	• PVCs • VTns • Resting HR	• LP • PES • TWA • HRT • Patency of infarct related artery

LVEF = Left ventricular ejection fraction; HRV = Heart rate variability; BRS = Baroreflex sensitivity; LVV = Left ventricular volume; PVCs = Premature ventricular contractions; VTns = Nonsustained ventricular tachycardia; HR = Heart rate; LP = Late potentials; PES = Programmed electrical stimulation; TWA = T wave alternans; HRT = Heart rate turbulence analysis.

Recommendations of Electrophysiological Testing in Patients with Coronary Heart Disease

ACC/AHA/ESC Guidelines 2006

Class I

- Diagnostic evaluation of patients with remote MI with symptoms suggestive of ventricular tachyarrhythmias including palpitations, presyncope and syncope.
- In patients with CHD to guide and assess efficacy of VT ablation.
- In patients with CHD for the diagnostic evaluation of wide QRS complex tachycardias of unclear mechanism.

Class IIa

- For risk-satisfication in patients with remote MI, nonsustained VT and LV ejection fraction (LVEF) ≤ 40%

Primary prophylaxis of sudden cardiac death in post MI patients with/without HF

Conditions	Class I	Class IIa	Class IIb
Post MI	• Beta blockers • ACE inhibitors • Lipid lowering drugs • Aspirin	• PUFA (EPS+DHA) • Amiodarone	
MI+	• Beta blockers	• Amiodarone	
LV dysfunction	• ACE inhibitors • Aldosterone	• ICD (if EF ≤ 30%)	
Hemodynamically tolerated VTs		• Amodarone • Beta blockers	• ICD • Ablation • Surgery
EF ≤ 40% (≤35%) + Spont. VTns + VTs inducible at PES	• ICD		

LV=Left ventricular; VTs=Sustained ventricular tachycardia; PUFA=Polyunsaturated fatty acids; rec=receptor; VTns=Nonsustained ventricular tachycardia; EF=Ejection fraction; ACE inhibitors=Angiotensin converting enzyme inhibitors; EPA=Eicosapentaenoic acid; DHA=Docosahexenoic acid; PES=Programmed electrical stimulation.

Secondary prophylaxis in post MI with or without HF

Conditions	Class I	Class IIa	Class IIb
VF Nonhemodynamically tolerated VTs	• ICD • ICD	• PUFA • Amiodarone • Beta blockers	

Recommendations for Treatment of Ventricular Arrhythmias in Patients with Prior MI

- Aggressive attempts should be made to treat heart failure in patients with LV dysfunction due to prior MI and ventricular tachyarrhythmias (Class I level of evidence C)
- Coronary revascularization is indicated to reduce risk of SCD in patients with VF when direct, clear evidence of acute myocardial ischemia is documented to immediately precede the onset of VF (Class I level of evidence B)
- ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with LV dysfunction due to prior MI and i) who are at least 40 days post-MI, have an LVEF ≤ 30-40%, are NYHA Class II or III or ii) who present with hemodynamically unstable sustained VT and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year (Class I level of evidence B)
- Implantation of an ICD is reasonable in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30-35%, are NYHA functional Class I on chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year (Class IIa level of evidence B).
- ICD implantation is resonable for treatment of recurrent sustained VT in patients post MI with normal or near normal ventricular function, who

Treatment of ventricular arrhythmias in dilated cardiomyopathy

Risk stratification:	Class I: (ESC)	VT, VF
	Class IIa: (ESC)	Syncope
	Class IIb: (ESC)	Decreased ejection fraction Nonsustained VT
Primary prophylaxis:	Class I: (ESC)	ACEI, Beta-blockers
	Class IIa: (ESC)	Aldosterone receptor blockers
	Class IIb: (ESC)	Amiodarone, ICD
Secondary prophylaxis:	Class I: (ESC)	ICD, ACEI, Beta-blockers
	Class IIa: (ESC)	Aldosterone receptor blockers
	Class IIb: (ESC)	Amiodarone

are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year (Class IIa level of evidence C)

- In patients with frequent episodes of sustained VT or VF in patients with LV dysfunction due to prior MI, adjunctive therapies to ICD including catheter ablation or surgical resection and pharmacological therapy (amiodarone/sotalol) are reasonable (Class IIa level of evidence C)

Bundle-branch re-entrant tachycardia (BBRT) as the cause of sustained VT is more likely to occur in patients with nonischemic cardiomyopathy. Of the inducible VTs in the electrophysiology laboratory, BBRT is the underlying mechanism in 30 to 50% of patients with dilated nonischemic cardiomyopathy, whereas it accounts for only 5 to 6% in patients with ischemic cardiac disease. Clinically, this tachycardia tends to have a high rate, generally greater than 200 beats/min with most commonly a LBBB pattern on surface ECG. There are, however, three types of re-entrant circuit involving the His-Purkinje system.

Type	Antegrade limb	Retrograde limb	ECG morphology	Comment
A	RBB	LBB	LBB	Most common
B (fascicular re-entry)	Left anterior or posterior fascicle	The other fascicle	RBBB with LAD or RAD	Rare
C	LBB	RBB	RBBB	Rare

Treatment consists of ablation of one bundle branch or fascicle. It is debatable whether these patients should undergo ICD implantation even after successful ablation. With the advent of biventricular pacing as a potential adjunctive therapy for patients with cardiomyopathy and dual-chamber ICD in more recent years, one might consider implantation of a DDDR-biventricular ICD implantation.

Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disorder [most common mode of inheritance is autosomal dominant but a rarer autosomal recessive form in conjunction with keratoderma and woolly hair (Naxos disease) has been reported]. At least eight loci for autosomal dominant ARVC have been mapped and three genes (RYR2, DSP and JUP) have been identified. It is also likely that familial polymorphic VT and stress induced (or catecholaminergic) polymorphic VT are phenotypic variants of ARVC.

Identification

ECG during sinus rhythm: T wave inversion in right precordial leads and Epsilon wave.
ECG during tachycardia: LBBB type.

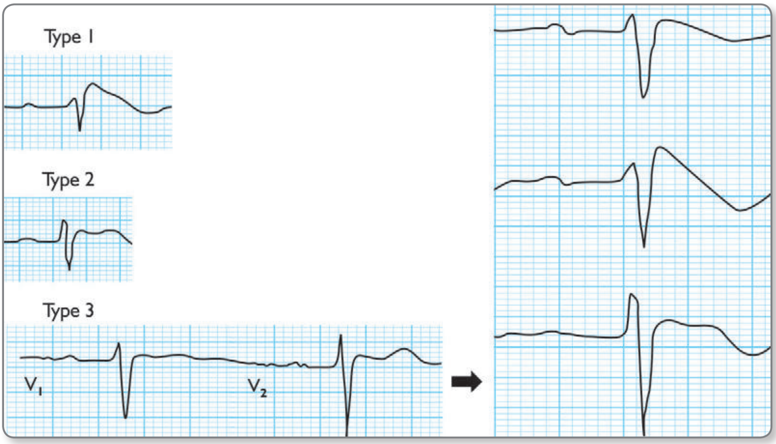
	Risk stratification:
Class IIa	VTs/VF
(ESC recommendation)	RV dilatation
	RVdysfunction
	Programmed electrical stimulation (PES)
Class IIb	Family history of sudden cardiac death
(ESC recommendation)	Late potential + RV dysfunction
	VT
	PES inducibility
Primary prophylaxis:	Class IIa: ICD
	(ESC)
	Class IIb: Antiarrhythmic drugs
	(ESC)
Secondary prophylaxis:	Class I: ICD
	(ESC)

Ventricular Arrhythmias in Hypertrophic Cardiomyopathy

Risk stratification:	Class I:	VTs, VF
	(ESC)	
	Class IIa:	Family history of SCD
	(ESC)	Syncope
		LV hypertrophy (>30 mm septum)
		Nonsustained VT
		Hypotensive response during exercise stress test
	Class IIb:	High-risk mutations
	(ESC)	(e.g. Arg 403 Gln)
Primary prophylaxis:	Class IIa:	ICD
	(ESC)	
	Class IIb:	Amiodarone
	(ESC)	
Secondary prophylaxis:	Class I:	ICD
	(ESC)	

Brugada Syndrome

The Brugada syndrome is an inherited arrhythmogenic disease characterized by the typical ECG pattern of ST-segment elevation > 2 mm (transient or persistent) in the leads V1 through V3, incomplete RBBB in the right precordial leads and an increased risk of sudden cardiac death as a result of VF. Most patients do not show evidence of structural heart disease. It has also become apparent that the electrocardiographic pattern noted with the Brugada syndrome (the "Brugada sign") may be present in individuals with no symptoms or may be associated with a variety of structural defects and functional cardiac challenges, including drug effects. Patients with no symptoms and ECG abnormality alone are said to have an 'Asymptomatic Brugada syndrome'. Despite familial clustering and presumed autosomal dominant inheritance, approximately 50% of the cases seem to be sporadic. In 15 to 30% of patients with Brugada syndrome, mutations have been found in SCN5A, the cardiac channel alpha subunit gene located on chromosome 3. The sensitivity of the ECG for Brugada syndrome can be increased with placement of ECG leads in intercostal leads above V1 and V2 (V1 ic 3 and V2ic3). Lead positions of leads V3 and V5 can be changed to V1 ic3 and V2ic3 rspectively to catch Brugada pattern on the ECG.



Spectrum of Individuals Who Exhibit Brugada ECG Pattern

Brugada Syndrome

BrS1	SCNSA – Cardiac sodium channel α-submit – Loss of function – reduced Na^+ current
BrS2	GPD1-L – Glycerol-6 – phosphate dehydrozenes Loss of function – Reduced Na^{++} current
BrS3	CACNA1C – L-type calcium channel α-submit – Loss of function – Reduced Ca^{++} current

BrS4	CACNV2 – L-type Calcium channel β-submit – Loss of function – Reduced Ca^{++} current
BrS5	SCN1B – Cardiac sodium channel β1-submit – Loss of function – Reduced Na^{+} current
BrS6	KCNE3 – Transient outward current β submit K Ito current
BrS7	SCN3B – Cardiac sodium channel β3 submit – Loss of function – Reduced Na^{+} current.

Brugada ECG Pattern and High-risk Features

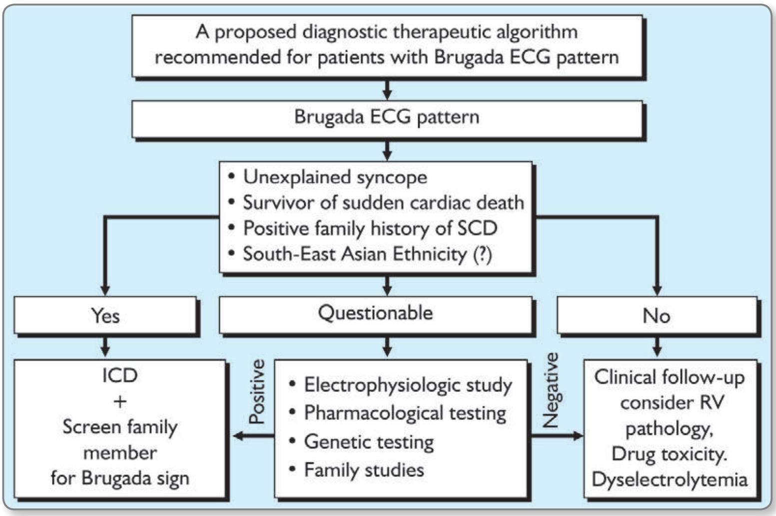
- Family history of SCD
- Unexplained syncope
- South-east Asian ethnicity

Brugada ECG Pattern Provoked by

- RV pathology (Mediastinal tumors or hemopericardium compressing RV, Hyperacute RV ischemia or infarction, ARVC)
- Sodium channel blockade (Class IA and IC drugs cannot only unmask the Brugada ECG sign in latent Brugada syndrome but also can induce it in individuals without symptoms)
- Drugs, e.g. Cocaine, Tricyclic antidepressants; Lithium; Venlafaxine; Dimenhydrinate.
- Electrolyte abnormalities (Severe hyperkalemia, hypercalcemia)

Brugada ECG Pattern without above Features

Currently, there is no evidence that individuals without clinical risk factors have a higher risk of sudden cardiac death than the general population.



Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an autosomal dominant inherited disease with a mortality rate of approximately 30 percent by age of 30 years. Phenotypically, it is characterized by runs of bidirectional and polymorphic ventricular tachycardia in response to vigorous exercise in the absence of evidence of structural myocardial disease. A rare recessive form has also been described.

	Class I	Class IIa	Class IIb
Risk stratification	• VF	• Family history of SCD • VTns/syncope in pediatric age	• Syncope
Primary prophylaxis		• Beta-blockers	• ICD
Secondary prophylaxis	• ICD + Beta-blockers	• Beta-blockers	

Genetic Pattern of CPVT

Gene involved in inherited arrhythmia.

CPVT-1 RyR2 Cardiac ryanodine receptor (RyH2) – Gain of function – diastolic Ca^{++} release form SR.

CPVT-2 CASQ2 Cardiac calsequestrin – Loss of $SRCa^{2+}$ – buffering capacity

CPVT-3 KCNJ2 Inward rectifier. Potassium current α-submit – Loss of function – Reduced IK1K + current

CPVT4 KNKB – Ankyrin 2 gene – affects multiple current – not definitely established.

Digoxin Induced Toxic Fascicular Tachycardia

Commonly monomorphic but may be polymorphic.

Mechanism: Triggered activity through generation of delayed after depolarization; responds to verapamil (misdiagnosed as SVT)

Rx:
- Withdrawal of digoxin
- Administration of digoxin specific Fab fragments.

Ventricular Tachycardia in Normal Heart

Idiopathic Ventricular Tachycardia

Repetitive Monomorphic Ventricular Tachycardia

Also referred to as right ventricular outflow tract VT (RVOT VT).

Identification

- Occurs frequently in young or middle aged patients without structural disease.
- Usually provoked by exercise and emotional stress; in women, occurs in perimenopausal and gestational periods.
- Normal baseline ECG and normal echocardiography.
- Normal SAECG.
- ECG during VT-LBBB type with inferior axis.
- MRI—Myocardial thinning at RVOT.

Rx:
1. Calcium channel blockers, e.g. Verapamil (effective in approximately 25-30%) and beta-blockers (effective in approximately 25-50%)
2. Catheter ablation technique utililizing pace mapping (High success rate, approximately 80-100%) has emerged as an alternative to life long medication.

Annular Ventricular Tachyardia

VTs arising from the mitral or tricuspid annulus account for between 4 and 7% of idiopathic VTs. They are of repetitive monomorphic type. Mitral annular VTs have a right bundle branch block pattern and tricuspid annular VTs have a left bundle branch block pattern. These VTs behave similarly to outflow tract VT, both in prognosis and in drug response. Annular VTs are amenable to ablation.

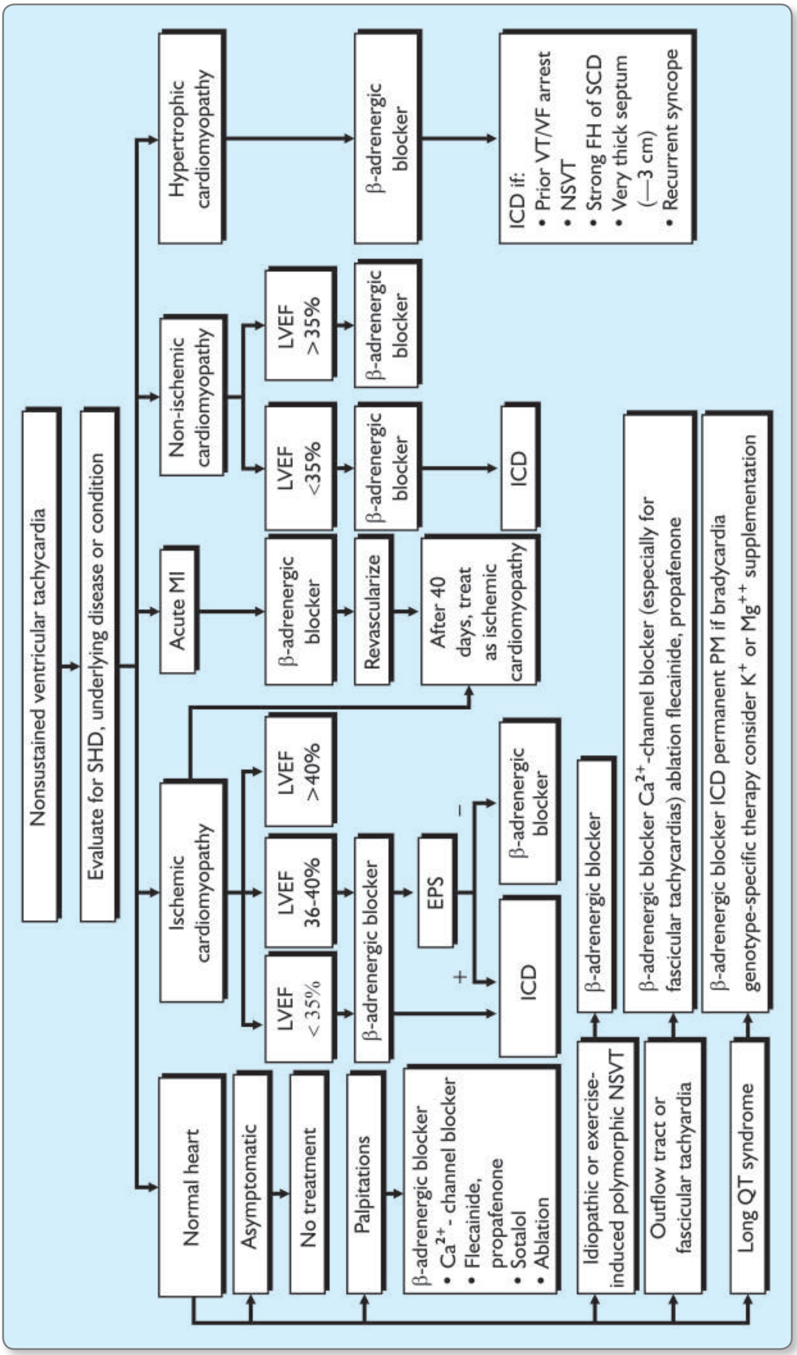
Idiopathic Left Ventricular Tachycardia

Also referred to as fascicular VT since the site of origin is usually in the region of the left posterior fascicle (inferoposterior LV septum).

Identification

- 70% of patients are men (usually between 15 and 40 years of age).
- Structurally normal heart.
- Resting ECG is usually normal except for occasional T-wave inversion in inferolateral wall.
- RBBB pattern, left superior axis VT with a relatively narrow QRS (<140 ms).
- Can be induced by atrial pacing.

Rx:
1. Responds well to verapamil for acute termination of VT as well as for long-term arrhythmia control.
2. In patients with poor control on verapamil or who desire potential cure, radiofrequency catheter ablation is performed with acute success rates ranging from 85 to 100%.



Approach to nonsustained ventricular tachycardia (NSVT)

Classification of Polymorphic VT (PMVT)

Prolonged QT Interval (Torsade De Pointes)

a. Congenital long QT syndrome
b. Acquired long QT syndrome
   - Drugs
   - Electrolyte disturbances: Hypokalemia
Hypomagnesemia
Hypocalcemia (association not well established)
   - Bradyarrhythmias: Sinus bradycardia
High-grade AV block
   - Cerebrovascular abnormalities
   - Intrinsic heart disease: Congestive heart failure
Myocardial ischemia or infarction
Myocarditis

c. Normal QT interval
   Ischemia
   Reperfusion
   Organic heart disease
   Catecholaminergic PMVT
   Idiopathic PMVT
   Short-coupled variant or torsade de pointes
   Brugada syndrome

Congenital long Q-T syndrome diagnostic criteria (Schwartz et al)

Criteria	Points
1. ECG finding	
a. QT_C	
≥ 480 ms	3
460-470 ms	2
450 ms (Male)	1
b. Torsade de pointes	2
c. T wave alternans	1
d. Notched T wave in 3 leads	1
e. Low heart rate for age	0.5
2. Clinical history	
a. Syncope	
with stress	2
without stress	1
b. Congenital deafness	0.5
3. Family history	
a. Family members with definite LQTS	1
b. Unexplained SCD at < 30 yrs among immediate family members	0.5

Scoring ≤ 1 low probability 2-3 intermediate ≥ 4 high probability.

Congenital Long Q-T Syndrome

Genetic Long-QT Syndromes

Type	Mutation (Channel)	Frequency of LQT	Phenotype	Miscellaneous
LQT1	KCNQ1 (Kslow)	50%	During exercise, swimming syndactyly Broad-based T waves	Beta blockers most effective
LQT2	KCNE2 (Krapid)	35%	Auditory stimuli Emotional stimuli Postpartum Low-amplitude notched T waves	Highest female risk (0.82%/year)
LQT3	SCN5A (Na)	5%–10%	During sleep, rest Long JT segment, normal T wave	Highest male risk (0.96%/year) Most common LQT found in sudden infant death syndrome Least responsive to beta blocker
LQT4	ANKB (anchors Na)	Rare	During exercise	
LQT5	KCNE1 (Kslow)	2%-3%		
LQT6	KCNE2 (Krapid)	Rare	Associated with QT-prolonging drug sensitivity	
LQT7	KCNJ2 (K)	Rare	Periodic paralysis Distinct facial features Often normal QT interval but long QU interval Bidirectional VT	Andersen-Tawil syndrome
LQT8	CACNA1C (Ca)	Rare	Long JT segment, normal T wave	Timothy syndrome (infants)
JLN1	KCNQ1 (Kslow)	Rare	Deafness	Autosomal recessive
JLN2	KCNE1 (Kslow)	Rare	Deafness	Autosomal recessive

ECG Patterns

LQT1	Wide based slow upstroke	
LQT2	Wide base, double hump	
LQT3	Discrete T after long ST	

	Class I	**Class IIa**	**Class IIb**
Risk stratification	• TdP/VF/CA • Syncope • JLN • LQT3	• QT_c > 60 ms • CE in infants • Postpartum • Syndactyly + AV block • TWA • Female gender	• Fam. Hist SCD • ↑QT dispersion
Primary prophylaxis	• Avoid QT Prolonging drugs • Avoid sports[1] • Beta-blockers[1]		• LCSD • Pacemaker
Secondary prophylaxis	• ICD + Beta-blockers + Avoid QT Prolonging drugs • Avoid sports		

(1) IIa in patient without syncope or silent carriers of genetic defects TdP=Torsade de Pointes, VF=Ventricular fibrillation, CA=Cardiac arrest, JLN=Jervell and Lange Nielsen, CE=Cardiac event TWA=Macroscopic T-wave alternans, Fam.hist SCD= Familial history of sudden cardiac death, LCSD=Left cardiac sympathetic denervation.

PMVT Associated with Ischemic Heart Disease

PMVT associated with acute coronary syndrome usually presents with additional ECG evidence of ischemia or signs and symptoms supportive of the diagnosis. Although prolongation of the Q-T interval and PMVT may be seen with myocardial ischemia or infarction, the Q-T interval usually is normal with acute coronary syndromes. The relative contributions of ischemia and structural abnormalities, such as aneurysms and infarct-related scar, may be difficult to distinguish and so the benefit of restoring flow to ischemic regions is questionable. Role of revascularization in prevention of recurrences of PMVT has been evaluated by several small studies with conflicting results. With such sparse data available on the subject, no firm conclusions concerning the role of revascularization in preventing PMVT recurrences can be made. The most prudent course likely should include an evaluation and treatment for coronary artery disease, with the expectation that revascularization alone may not be sufficient in preventing PMVT recurrences.

Long Q-T Syndrome—Rx

For PMVT unresponsive to other therapies, IV amiodarone (150 mg bolus over 10 minutes, then 1 mg/min infusion) may be given. Although amiodarone may increase the QT interval and has been implicated in initiation of torsade de pointes, successful suppression of drug induced torsade de pointes also has been reported.

Short QT Syndrome

Recently, short QT (≤ 300 msec) syndrome has been identified as a cause of familial sudden death, short refractory periods and inducible ventricular fibrillation. Mutations identified so far have involved a gain-of-function mutation in KCNH2 and a mutation in KCNQ1 encoding the K^+ channel K_V LQT1. Quinidine can prolong the QT interval and is under investigation for its efficacy in decreasing the incidence of life-threatening ventricular arrhythmias. This could prove useful in very young patients with the disorder in whom ICD therapy may not be feasible.

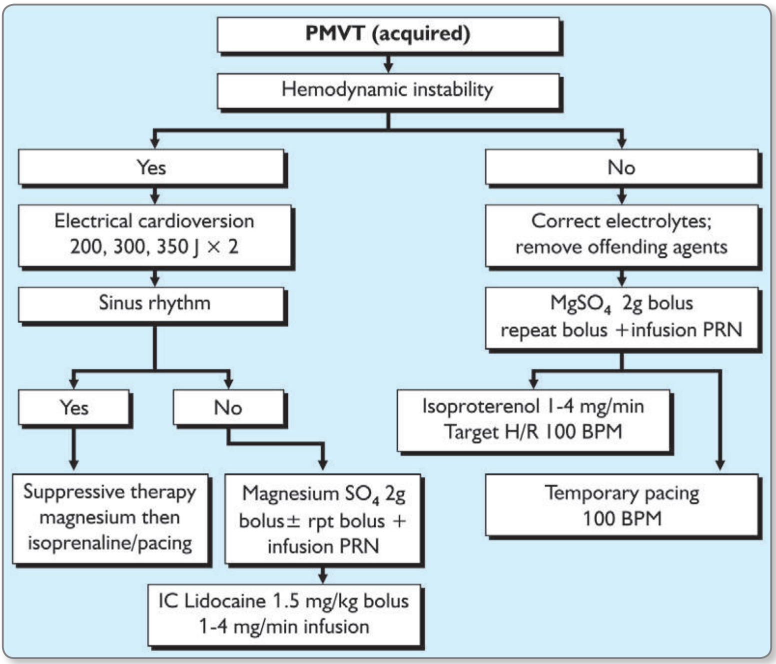
Indications for implantable cardioverter-defibrillator (ICD) therapy (ACC/AHA/HRS 2008 Guidelines)

Class I

1. Survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable sustained VT (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes (Level of Evidence A).
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable (Level of Evidence B).
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study (Level of Evidence B).
4. LVEF < 35% due to prior myocardial infarction in patients who are at least 40 days post-myocardial infarction and are in NYHA functional class II or III (Level of Evidence A).
5. Nonischemic dilated cardiomyopathy in patients who have an LVEF ≤ 35% and who are in NYHA functional class II or III (Level of Evidence B).
6. LV dysfunction due to prior myocardial infarction in patients who are at least 40 days postmyocardial infarction, have an LVEF < 30% post-myocardial infarction, have an LVEF < 30% are in NYHA function class I (Level of Evidence A).
7. Nonsustianed VT due to prior myocardial infarction, LVEF < 40% and inducible VF or sustained VT at electrophysiologic study (Level of Evidence B).

Class IIa

1. Unexplained syncope, significant LV dysfunction and nonischemic dilated cardiomyopathy (Level of Evidence C).
2. Sustained VT and normal or near-normal ventricular function (Level of Evidence C).
3. Hypertrophic cardiomyopathy in patients who have 1 or more major risk factors for sudden cardiac death (Level of Evidence C).
4. Arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients who have 1 or more risk factors for sudden cardiac death (Level of Evidence C).
5. Long-QT syndrome in patients who are experiencing syncope and/or VT while receiving beta-blockers (Level of Evidence B).
6. Nonhospitalized patients awaiting transplantation (Level of Evidence C).
7. Brugada syndrome in patients who have had syncope (Level of Evidence C).
8. Brugada syndrome in patients who have documented VT that has not resulted in cardiac arrest (Level of Evidence C).



9. Catecholaminergic polymorphic VT in patients who have syncope and/or documented sustained VT while receiving beta-blockers (Level of Evidence C).
10. Cardiac sarcoidosis, giant cell myocarditis or Chagas disease (Level of Evidence C).

Class IIb

1. Nonischemic heart disease in patients who have an LVEF of ≤35% and who are in NYHA functional class I (Level of Evidence C).
2. Long-QT syndrome and risk factors for sudden cardiac death (Level of Evidence B).
3. Syncope and advanced structural heart disease in patients in whom through invasive and noninvasive investigations have failed to define a cause (Level of Evidence C).
4. Familial cardiomyopathy associated with sudden death (Level of Evidence C).
5. LV noncompaction (Level of Evidence C).

Suggested Reading

1. Cannom DS, et al. Management of ventricular arrhythmias. JAMA. 1999;28:172.
2. Chiang CE, et al. The long QT syndromes: genetic basis and clinical implications. J Am Coll Cardiol. 2000;36:1.
3. Epstein AE, DIMarco JP, Ellenbrogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the ACC/AHA Task Force on Practice Guidelines. Circulation. 2008;117:e350.
4. ESC Guidelines on Sudden Cardiac Death. European Heart Journal. 2001;22:1374-1450.
5. Greene HL. The implantable cardioverter defibrillator. Clin Cardiol. 2000;23:315.
6. Gregoratos G, et al. ACC/AHA guidelines for implantation of cardiac pacemakers and arrhythmia devices. Circulation. 1998;97:1325.
7. Koplan BA, Stevens on WG. Ventricular tachycardia and sudden cardiac death Mayo Clin Proc. 2009;84(3):289-97.
8. Mark Ester NA. Weinstock J. Guidelines for Cardiac Arrhythmias. Circulation: Arrhythmia and Electrophysiology 2011;4:119-22..
9. Roden DM. A practical approach to torsade de pointes. Clin Cardiol. 1997;20:285.
10. Update of the ESC Guidelines on Sudden Cardiac Death. European Heart Journal. 2003;24:13-5.
11. Viskin S. Long QT syndromes and torsade de pointes. Lancet. 1999;354:1625.
12. Welch PJ, et al. Management of ventricular arrhythmias. J Am Coll Cardiol. 1999;34:62J.
13. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the ACC/AHA Task Force and the ESC Committee for Practice Guidelines. Circulation. 2006;114:e385.
14. Zipes DP, et al. Sudden Cardiac Death. Circulation. 1998;98:2334.

Cardiopulmonary Resuscitation

chapter 9

Sujata Majumder, Amitava Majumder, Soumitra Kumar

Definition

Cardiopulmonary resuscitation (CPR) is a series of life saving actions that improve the chance of survival following cardiac arrest.

The newest development in the guidelines of CPR is a change in basic life support (BLS) sequence of steps from **A-B-C** (airway, breathing, chest compression) to **C-A-B** (chest compression, airway, breathing)

Goals

1. To recognize cardiopulmonary arrest immediately.
2. To maintain cerebral perfusion until cardiopulmonary function is restored
3. To return the patient to baseline neurological function.

Key Principles in Resuscitation: Stengthening the Links in the Chain of Survival

1. Immediate recognition of cardiac arrest and activation of the emergency response system
2. Early **CPR** with an emphasis on chest compression
3. Rapid **defibrillation**
4. Effective **advanced life support**
5. Integrated **postcardiac arrest care**

Adult Basic Life Support

1. Make sure the victim, any bystanders and you are safe

   ↓

   Check the victim for a response
   - shake his shoulders
   - ask loudly

   ↓

   No response

   ↓

   Shout for help

2. Turn the victim on to his back and then open the airway using head tilt and chin lift.
   - Place hand on his forehead and gently tilt his head back
   - Lift chin

     ↓
   - Keeping airway open; look, listen and feel for normal breathing (take not >10 seconds)
   - Look for any chest movements, listen for breath sounds.

     ↓

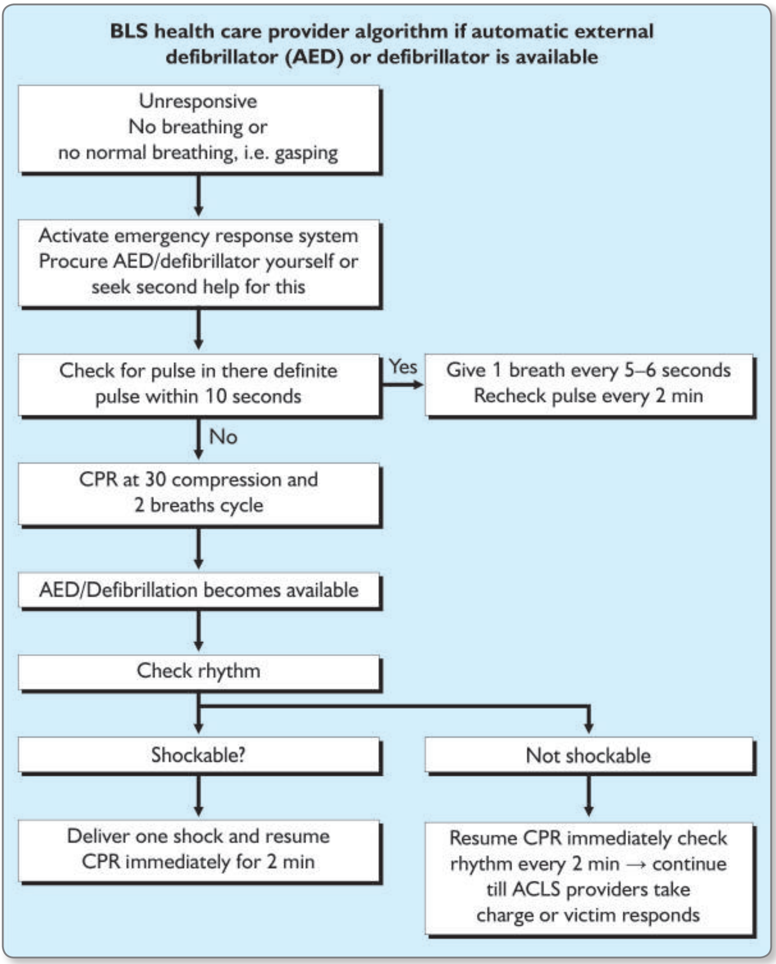
     Not breathing
   - Kneel by side of victim
   - Start chest compression @ 100 times/minute, {a little less than 2 compressions for a second}. — 1″ above xiphoid, depth should be 1½–2″ for adults, 1–1½″ for children, ½–1″ for infants.

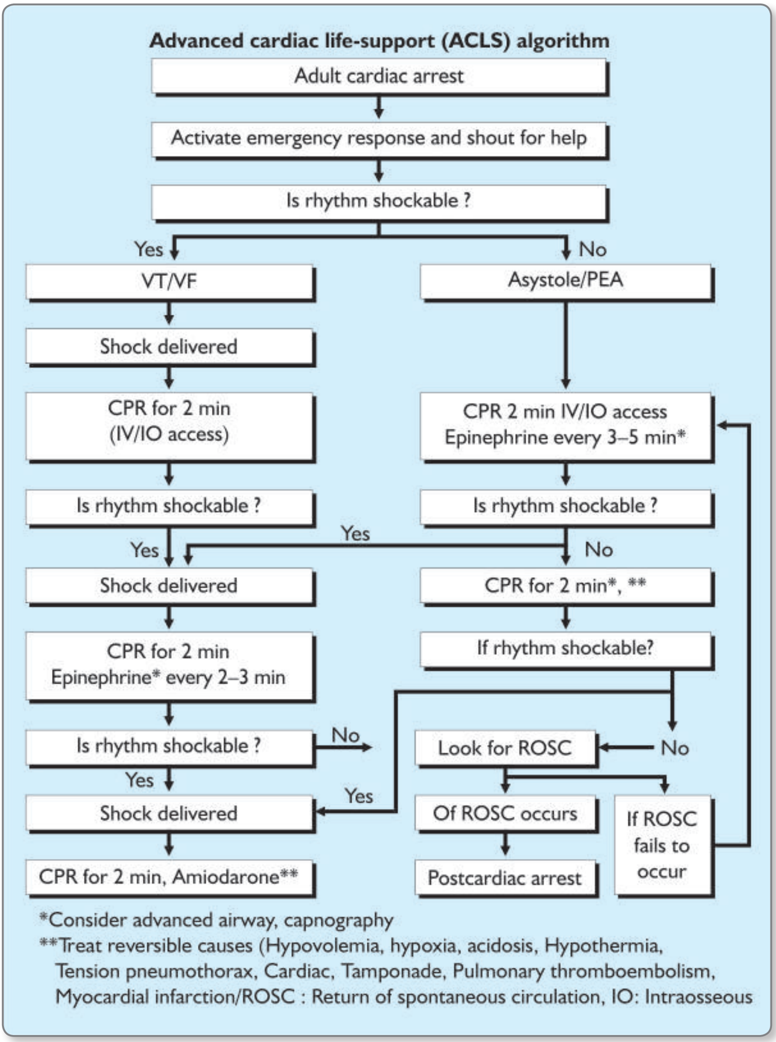
     ↓
3. Combined chest compression with rescue breaths
   - Blow into victim's mouth taking about 1sec to make his chest rise as in normal breathing.
   - Continued chest compression rescue breath in a ratio of 30: 2.

     ↓
4. Stop to check only if he starts breathing normally. Otherwise, do not interrupt resuscitation.

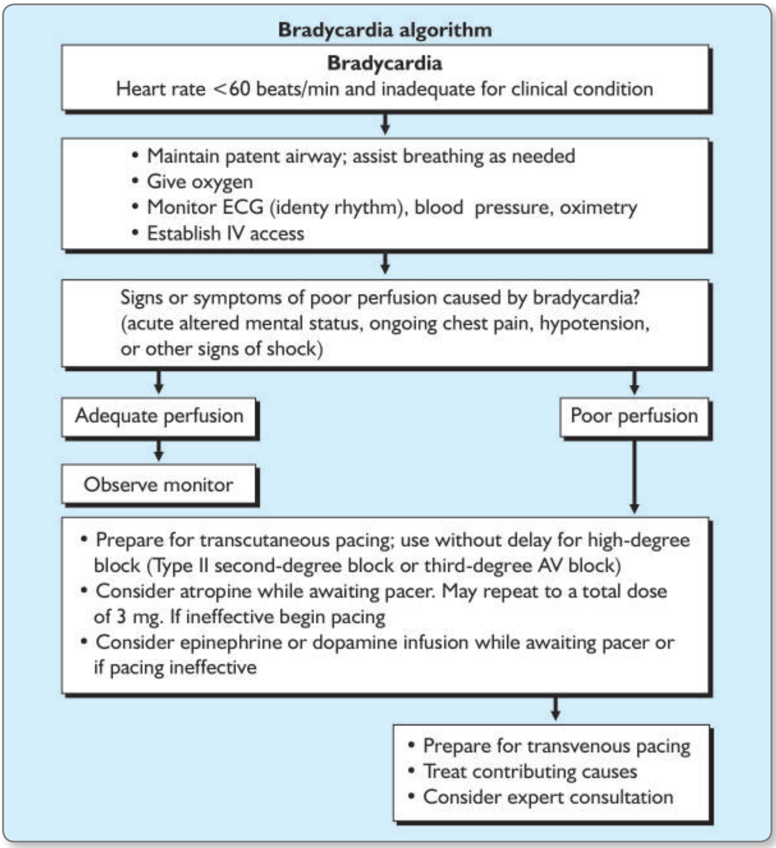
   ↓

   Continue resuscitation until
   - Qualified help arrives and takes over
   - The victim starts breathing normally
   - You become exhausted.

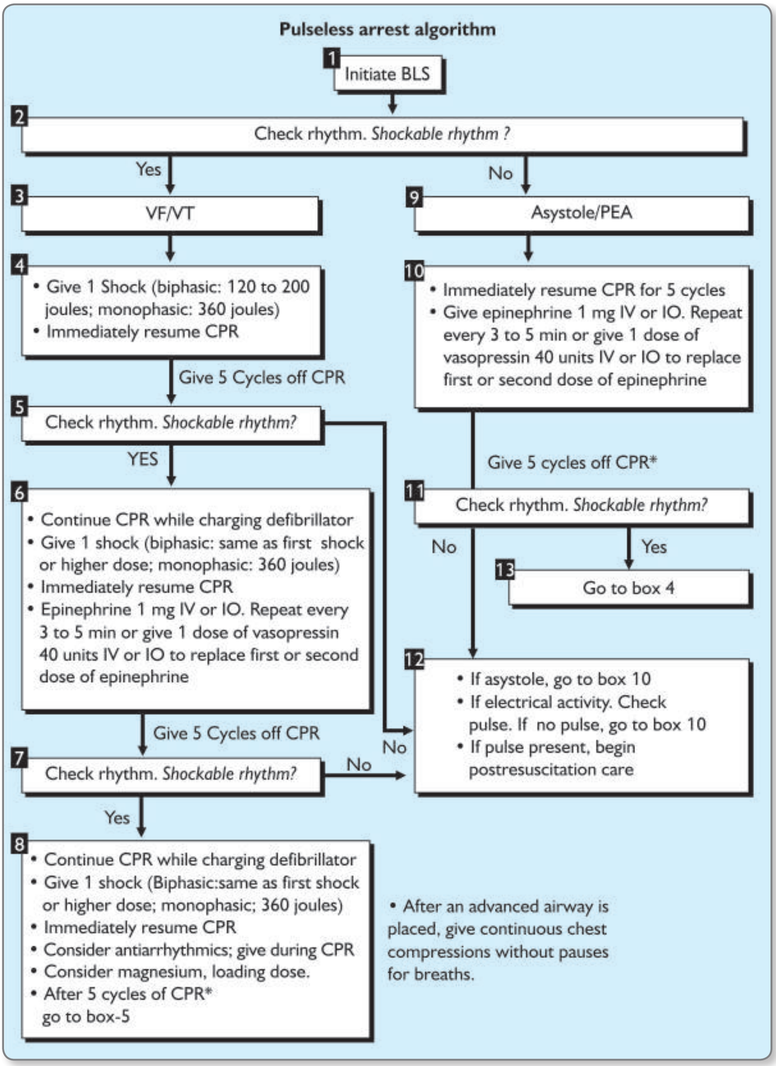

BLS health care provider algorithm if automatic external defibrillator (AED) or defibrillator is available
Unresponsive
No breathing or
no normal breathing, i.e. gasping
Activate emergency response system
Procure AED/defibrillator yourself or
seek second help for this
Check for pulse in there definite
pulse within 10 seconds
Yes
Give 1 breath every 5–6 seconds
Recheck pulse every 2 min
No
CPR at 30 compression and
2 breaths cycle
AED/Defibrillation becomes available
Check rhythm
Shockable?
Not shockable
Deliver one shock and resume
CPR immediately for 2 min
Resume CPR immediately check
rhythm every 2 min → continue
till ACLS providers take
charge or victim responds


Advanced cardiac life-support (ACLS) algorithm
Adult cardiac arrest
Activate emergency response and shout for help
Is rhythm shockable ?
Yes
No
VT/VF
Asystole/PEA
Shock delivered
CPR for 2 min (IV/IO access)
CPR 2 min IV/IO access Epinephrine every 3–5 min*
Is rhythm shockable ?
Is rhythm shockable ?
Yes
Yes
No
Shock delivered
CPR for 2 min*, **
CPR for 2 min Epinephrine* every 2–3 min
If rhythm shockable?
Is rhythm shockable ?
No
Look for ROSC
No
Yes
Yes
Shock delivered
Of ROSC occurs
If ROSC fails to occur
CPR for 2 min, Amiodarone**
Postcardiac arrest
*Consider advanced airway, capnography
**Treat reversible causes (Hypovolemia, hypoxia, acidosis, Hypothermia, Tension pneumothorax, Cardiac, Tamponade, Pulmonary thromboembolism, Myocardial infarction/ROSC : Return of spontaneous circulation, IO: Intraosseous

Advanced Cardiac Life Support (ACLS)



Advanced Cardiac Life Support (ACLS)



Tachycardia algorithm

1 **Tachycardia with pulses**

2
- Assess and support ABCs as needed
- Give oxygen
- Monitor ECG (identify rhythm), blood pressure, oximetry
- Identify and treat reversible causes

3 **Symptoms persist**

Is patient stable ?
Unstable signs include altered mental status, ongoing chest pain, hypotension or other signs of shock

Unstable

4 **Perform immediate synchronized cardioversion**
- Establish IV access and give sedation if patient is conscious; do not delay cardioversion
- Consider expert consultation
- If pulseless arrest develops, see pulseless arrest algorithm

5 **Stable**
- Establish IV access
- Obtain 12-lead ECG (when available) or rhythm strip

Is QRS narrow?

6 **Narrow (<0.12 sec)**
- ***Narrow QRS***

Is rhythm regular?

12 **Wide (≥0.12 sec)**

Wide QRS
Is rhythm regular?
Expert consultation advised

7 **Regular**
- Attempt vagal maneuvers
- Give adenosine 6 mg rapid IV push. If no conversion, give 12 mg rapid IV push; may repeat 12 mg dose once

11 **Irregular**

Irregular Narrow-Complex Tachycardia
Probable atrial fibrillation or possible atrial flutter or multifocal atrial tachycardia
- Consider expert consultation
- Control rate (diltiazem, beta blocker; use beta blockers with caution in pulmonary disease or CHF)

8 **Stable**

Does rhythm convert ?
Note : Consider expert consultation

9 **Converts**

If rhythm converts, probably re-entry Supraventricular tachycardia (SVT)
- Observe for recurrence
- Treat recurrence with adenosine or longer-acting AV nodal blocking agents (such as diltiazem or beta blockers)

10 **Do not convert**

If rhythm does NOT convert, atrial flutter, ectopic atrial tachycardia, or junctional tachycardia
- Control rate (diltiazem, beta blockers; use beta blockers with caution in pulmonary disease of CHF).
- Treat underlying cause.
- Consider expert consultaion

13 **Regular**

If ventricular tachycardia or uncertain rhythm
- Amiodarone 150 mg IV over 10 min.

Repeat as needed to maximum dose of 2.2g/24 hours
- Prepare for elective synchronized cardioversion.

IF SVT with aberrancy
- Give adenosine (go to box 7)

14 **Irregular**

If atrial fibrillation with aberrancy
- see Irregular narrow-Complex tachycardia (Box 11)

If pre-excited atrial fibrillation (AF+WPW)
- Expert consultation advised
- Avoid AV nodal blocking agents (adnosine, digoxin, diltiazem, verapamil).

If recurrent polymorphic VT
- Seek expert consultation

If torsades de pointes
- Give magnesium (load with 1 to 2 g over 5 to 60 min, then infusion)

Cardio-cerebral Resuscitation

Cardiocerebral resuscitation (CCR) was begun in November 2003 in Tucson, Arizona and by 2007 was being used throughout the majority of the state. In 2005, the AHA updated their guidelines and incorporated some of the changes made with CCR. In 2008, the AHA published a science advisory statement supporting chest compression only for bystander response to adult cardiac arrest.

Three Pillars of Cardiocerebral Resuscitation

1. Compression-only cardiopulmonary resuscitation by anyone who witnesses unexpected collapse with abnormal breathing (cardiac arrest).
2. Cardiocerebral resuscitation by emergency medical services (arriving during circulatory phrase of untreated ventricular fibrillation [e.g. > 5 min].
   a. 200 continuous chest compressions (CCCs): delay intubation, second person applies defibrillation pads and initiates passive oxygen insufflation.
   b. Single direct current shock if indicated without postdefibrillation pulse check.
   c. 200 CCCs prior to pulse check or rhythm analysis.
   d. Epinephrine (intravenous or intraosseus) as soon as possible.
   e. Repeat (b) and (c) 3 times. Intubate if no return of spontaneous circulation after 3 cycles.
   f. Continue resuscitation efforts with minimal interruptions of chest compressions until successful or pronounced dead.
3. Post-resuscitation care to include mild hypothermia (32°C to 34°C) for patients in coma postarrest.

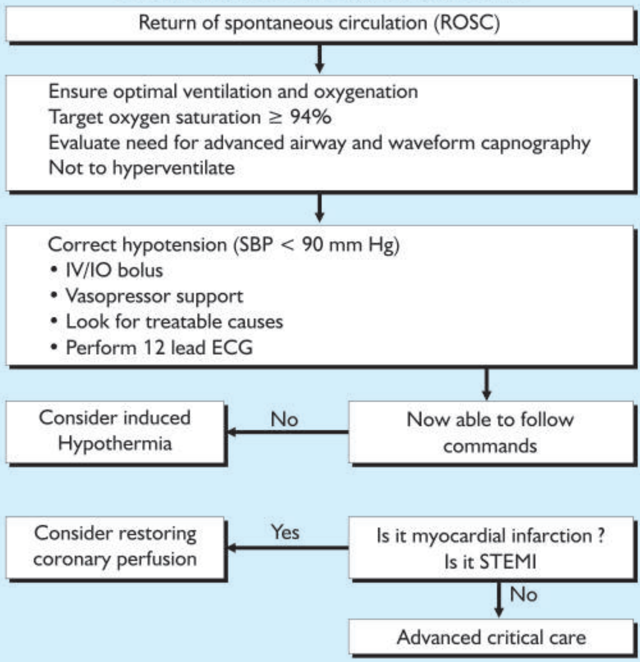
Urgent cardiac catheterization and percutaneous coronary intervention unless contraindicated.

The concept of CCC CPR by bystanders came into being with the expectation that eliminating mouth-to-mouth "rescue brathing" will go on a long way toward increasing the incidence of bystander-initiated resuscitation efforts. CCR also changes the approach of those delivering ACLS. These changes resulted in dramatic (250 to 300%) improvement in survival of patients most likely to survive with witnessed cardiac arrest and shockable rhythm. Most aggressive postresuscitation care, including hypothermia and emergent cardiac catheterization and PCI, is required to save even more victims of sudden cardiac arrest.

Comparison between cardiocerebral resuscitation (CCR) and AHA CPR

CCR 2003	AHA 2005 Guidelines and 2005 Advisory Statement
Continuous chest compression (CCC) for bystanders	Bystander "hands-only" CPR
Decrease rescue breathing	Decrease CCC interruption
BLS: No rescue breaths	BLS:30:2 CCs to ventilations
ACLS: Passive oxygen insufflation or limited breaths/min	ACLS : 8-10 breaths/min
200 CCCs prior to shock	Optimal 5 cycles of 30-2 prior to shock
Single shock	Single shock
200 CCCs immediately after shock	5 cycles of 30:2 immediately after shock
Therapeutic hypothermia for all unconscious post-resuscitation	Therapeutic hypothermia for all unconscious post-resuscitation from VF-induced cardiac arrest
Early, emergent catheterization and PCI for all resuscitated victims regardless of electrocardiographic findings	No official statement

Postcardiac arrest care algorithm in adults



Initial and late key objectives of postcardiac arrest care include:

- Optimizing cardiopulmonary function and vital organ perfusion after ROSC; anticipate, treat and prevent multiple organ dysfunction.
- Transportation to an appropriate hospital or critical care unit with a comprehensive postcardiac arrest treatment system of care.
- Institute measures to improve long-term neurologically intact survival; temperative control to optimize neurological recovery.
- Identification and intervention for acute coronary syndrome.
- Identify causes of arrest and institute measures to prevent recurrence.

Prognostic Factors after CPR

Of 4 of these 5 predictors are present 24 hours – after CPR a poor prognosis is implied:

- Absent corneal reflex at 24 hours
- Absent papillary reflex at 24 hours
- Absent withdrawal reflex at 24 hours
- No motor response at 24 hours and 72 hours
- EEG > 24 to 48 hours provide useful predictive information.

Therapeutic Hypothermia after Cardiac Arrest

Death from brain injury is common after cardiac arrest, but the patient is more likely to survive and to have a better neurologic outcome when mild hypothermia – in which the patient is cooled to a core temperature between 89.6°F (32°C) and 93.2°F (34°C) is induced as part of the care plan. Mild hypothermia reduced oxygen requirements of the brain. Additional protective effects of hypothermia may include enhancing stability of cellular membranes such blood-brain barrier, blood vessel walls, suppressing release of cytotoxic free radicals and stabilizing neurons by promoting ion homeostasis.

Indication: Comatose adult patient whose circulation has returned spontaneously following out-of-hospital cardiac arrest associated with ventricular fibrillation (Class I recommendation); same state following out-of-hospital cardiac arrest associated with pulseless electric activity or asystole is a Class IIb recommendation.

Three stages of therapeutic hypothermia

i. *Induction:* Either invasive (infusing up to 30 ml/Kg of normal saline or lactated Ringer's solution that has been cooled to 39.2°F (4°C) through a peripheral line or an intravascular cooling catheter in a central vein connected to an external cooling device) or noninvasive methods (surface coolants, e.g. cooling blankets, pads or ice packs).

ii. *Maintenance:* Patient kept at temperature range mentioned above for 12 to 24 hours.

iii. *Rewarming:* May be passive (accomplished solely through withdrawal of cooling devices) or actively managed (through external or invasive warming methods) at 0.2°C to 0.3°C per hour.

A Swan-Ganz catheter is used to monitor core temperature, volume status, cardiac output etc. complications include shivering, aspiration pneumonia, seizures, arrhythmias, bleeding, sepsis, pulmonary edema.

Common Interventions and Medications Used in ACLS

A. Interventions

1. **Shock: Biphasic:** Manufacturer recommendation (e.g. initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent and higher doses may be considered.
   Monophasic: 360 J
   Synchronized cardioversion: Initial recommended doses :
   - Narrow regular: 50 – 100 J
   - Narrow irregular: 120 – 200 J biphasic or 200 J monophasic
   - Wide regular: 100 J
   - Wide irregular: defibrillation dose (Not synchronized)
2. **Ventilation/Oxygenation:** Avoid excessive ventilation. Start at 10 to 12 breaths/min and titrate to target PET CO_2 of 35 to 40 mm Hg. When feasible, titrate FiO_2 to minimum necessary to achieve $SpO_2 \geq 94\%$.
3. **Advanced Airway:**
   - Supraglottic advanced airway or endotracheal intubation
   - Waveform capnography to confirm and monitor ET tube placement
   - 8 to 10 breaths/min with continuous chest compressions.
4. **CPR quality:**
   - Push hard (≥ 2 inches [5 cm] and fast (≥ 100/min) and allow complete chest recoil
   - Minimize interruptions in compressions
   - Avoid excessive ventilation
   - Rotate compressor every 2 minutes
   - If no advanced airway, 30:2 compression : ventilation ratio
   - Quantitative waveform capnography, - if PET CO_2 < 10 mm Hg, attempt to improve CPR quality
   - Intra-arterial pressure – If relaxation phase (diastolic) pressure < 20 mm Hg, attempt to improve CPR quality.

B. Medications

1. **Epinephrine:** It is an endogenous catecholamine which acts by stimulating β_1 and α_1 adrenergic receptors. Most commonly used drug during CPR.

Dose: 10 ml of a 1:10000 soln. rpt. after 3 to 5 min.; 1 mg IV/IO; for IV infusion (when indicated 2 to 10 mcg/min).

2. **Vasopressin:** Nonadrenergic peripheral vasoconstrictor
   Dose: 40 U single dose; IV/IO; can replace first or second dose of epinephrine
3. **Atropine:** Blocks parasympathetic activity at both SA node and AV node; may also increase sinus automaticity and facilitate AV node conduction.
   Indictaion symptomatic bradycardia
   Dose: 0.5 mg IV bolus; repeat every 3 to 5 minutes, maximum 3 mg.
4. **Amiodarone:** A complex drug with effects on sodium, potassium, calcium channels as well as α and β adrenergic blocking properties.
   Indications
   1. Narrow complex tachycardia if rhythm remains uncontrolled by adenosine, vagal maneuvers and AV nodal block (IIb)
   2. Control of hemodynamically stable VT, Polymorphic VT with normal QT and wide complex tachycardia of uncertain origin (IIb)
   3. Rapid ventricular rate due to accessory pathways.

   Dose: 5 mg/kg IV infusion as bolus over 20 min - 2 hr; In emergency - 150-300 mg slow IV push over > 3 min, repeat after > 15 min if needed
   ↓
   1 mg/min for 6 hrs
   ↓
   0.5 mg/min for 18 hrs
   Supplementary dose of 150 mg may be repeated every 10 minutes to a maximum of 2.2 g/24 hrs.
   Side effects: 1. Hypotension; 2. Bradycardia
5. **Procainamide:** Blocks open sodium channels and also blocks IKr prolonging action potential duration. It can be used in treating stable monomorphic VT but has been generally replaced by amiodarone for this indication. It can also be used in SVTs, particularly rapidly conducting AF and atrial flutter in WPW syndrome.
   Dose: 20-50 mg/min. until arrhythmia suppressed, hypotension ensures, QRS duration increases
   > 50% or maximum dose 17 mg/kg given. Maintenance infusion : 1-4 mg/min. Avoid if prolonged QT or CHF.
6. **Sotalol:** It is a class III antiarrhythmic drug with nonselective β-blocking properties and this combined action makes it effective for a wide range of supraventricular and ventricular arrhythmias.
   Dose: 100 mg (1.5 mg/kg) over 5 minutes. Avoid if prolonged QT.
7. **Magnesium** indicated in Torsades de pointes.
   In VF/pulseless VT - dose is 1 to 2 gm diluted in 10 ml of D/W IV; push over 5 to 20 minutes (IIA)

Pulse present - 1 to 2 gm in 50 to 100 ml of D/W IV loading over 5 to 60 minutes.

8. **Adenosine:** Endogenous purine nucleotide that depresses AV node and SA node activity.
   Indications:
   1. SVT (I)
   2. Unstable SVT (IIb)
   3. Undefined stable narrow complex SVT.

   Dose: 6 mg IV as rapid IV push given over 1 to 3 seconds through a large vein followed by 20 ml saline flush and elevation of the arm.
   ↓ if not corrected by 2 minutes
   12 mg stat
   ↓ 1-2 minutes
   12 mg stat again
   5 to 10 mg over 15 to 30 min up to total 20 mg.
9. **Norepinephrine:** is predominantly a α-1 adrenergic stimulant with mild β-receptor agonism and thus is best categorized as a vasopressor.
   Dose: 0.1 to 0.5 mcg/kg/min (in 70 kg adult: 7-35 mcg per minute)
10. **Dopamine:** It evokes most of its effects through activation of adrenergic receptors (β_1, β_2 and α) and also acts via stimulation of dopaminergic receptors (D1 and D2) at low dosage (< 4.0 μg/Kg/min).
    Dose: 5 to 10 mcg/kg/min as a vasopressor.
11. **Lignocaine:** It may be considered as an alternative to amiodarone in stable monomorphic VT, polymorphic VT with normal QT and if ventricular function is preserved.
    Dose: Initial 1.0 to 1.5 mg/kg IV bolus; additional doses of 0.5 to 0.75 mg/Kg IV every 10 to 15 minutes can be given up to maximum of 3 mg/kg. A maintenance IV infusion of 2 to 4 mg/min may be acceptable.
    Side effects include slurred speech, altered sensorium, seizures, bradycardia, muscle twitching.

Suggested Reading

1. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation (Suppl.) 2010.
2. Erb, Jessica L, Hravnak, Marilyn et al. Therapeutic Hypothermia after Cardiac Arrest. American Journal of Nursing 2012;112(7):38-44.
3. Ewy GA, Kern KB. Recent Advances in Cardiopulmonary Resuscitation, Cardiocerebral resuscitation. J.Am.Coll.Cardiol 2009;53(2),149-57.

Percutaneous Coronary Intervention in Acute Myocardial Infarction

chapter **10**

Shuvanan Ray

Acute ST elevation MI (STEMI) results from sudden occlusion of a major epicardial artery which leads to time dependent myocardial necrosis extending from endocardium to epicardium in a wavefront manner. Coronary reperfusion means opening of the artery permitting blood flow uninterruptedly into the microvascular, and into the microvasculature, and it can be achieved in a timely manner either by primary percutaneous intervention or by fibrinolysis. Reperfusion improves clinical outcomes compared to no reperfusion in nearly all groups of patients presenting with STEMI. A number of mega trials of fibrinolysis proved that myocardial salvage and related mortality reduction with fibrinolysis gradually declines with the time passed between the onset of chest pain and introduction of the drug. Initial studies of primary PCI did not show this trend and rather stressed a 'door to balloon time, i.e. time between the first medical contact and balloon dilatation which if prolonged denied any survival benefit after the procedure. A report from NRMI data, which included a cohort of 29,222 patients with STEMI treated with PCI within 6 hours of presentation. In hospital, mortality was 3%, 4.2%, 5.7% and 7.4% for door to balloon intervals of 90 minutes or less, 91 to 120 minutes, 121 to 150 minutes and more than 150 minutes respectively ($P<.001$). Nevertheless the data comparing primary PCI and thrombolysis do not mean that myocardial salvage after primary PCI is not time dependent. They merely indicate that time window for myocardial salvage is wider with primary PCI than thrombolysis. Recent data demonstrated that a shorter door to balloon time (<90 minutes) with a shorter symptom onset to doortime (<4 hours) was associated with lowest longer term mortality and short door to balloon time (<90 minutes) are associated with lower mortality in early presenters but not in late presenters. Based upon the randomized clinical trials, primary PCI is preferred when performed in a timely fashion by an expert operator in patients with ST elevation MI, or an MI with a new or presumably new LBBB or a true posterior MI.

Why Primary PCI is different from an Elective PCI?

Primary PCI involves opening of a thrombus laden large epicardial artery in a patient with unstable hemodynamics in a time dependent manner to establish undeterred flow through the microcirculation. It requires a cognitive knowledge base and a technical skill that is some what different from that required to perform elective PCI.

Criteria for the performance of primary PCI: The American College of Cardiology/American Heart Association 2004 guidelines recommended that Primary PCI should be performed in patients with STEMI with following features:

1. Less than 12 hours duration.
2. Door to balloon time < 90 minutes.
3. Operator should have a volume of (> 75/year elective PCI and > 11/year Primary PCI).
4. Laboratory volume should exceed (> 200/year elective PCI and > 36 Primary PCI cases/year).
5. If symptom duration is less than 3 hours, PCI is recommended in the event that the procedure is carried out < 1 hour of diagnosis.
6. PCI is the treatment of choice if the patient arrives > 3 hours from symptom onset.
7. PCI is recommended between 12 to 24 hours of symptom onset if there is
   i. Heart failure
   ii. Hemodynamic instability
   iii. Persistent ischemic symptoms.

Risk stratification for primary PCI: Two multivariable models have been devised and validated for patients undergoing primary PCI: The Zwolle primary PCI risk Index and the cardiac risk score.* The Zwolle index was based upon a primary PCI population in Zwolle, the Netherlands from data on 1791 patients undergoing primary PCI between 1994-2001. CADILLAC risk score was derived from the 2082 patients in the CADILLAC trial of abciximab or placebo and stenting or angioplasty in primary PCI and then validated using data from the 900 patients in the STENTPAMI trial. Seven variables, *which* are readily available at the time of intervention, were weighted according to their odds ratio for 1 year mortality:

- LVEF <40% – 4 points
- Killip class 2/3 – 3 points
- Renal insufficiency – (estimated CrCl <60 ml/min) – 3 points
- TIMI flow grade after PCI 0-2 – 2 points
- Age > 65 years – 2 point
- Anemia (hematocrit – <39% in men, <36% in women) – 2 points
- Triple vessel CAD – 2 points.

Patients could be stratified into three risk groups:

- Low risk (score 0-2) – 0.1 to 0.2% at 30 days and 08 to 0.9% at 1 year
- Intermediate risk (3-5) – 1.3 to 1.9% at 30 days and 4 to 4.5% at 1 year
- High risk (>6) – 6.6 to 8.1% at 30 days and 12.4 to 13.2% in 1 year.

Protocol for Primary PCI

Preprocedural Protocol

At Home

- Chew aspirin 325 mg (not enteric coated)
- Call emergency service
- Prehospital ECG (if available immediately).

At Hospital

- Establish a primary PCI orientation.
- All patients with confirmed or suspected AMI undergo emergency angiography; thrombolysis withheld.

Referring physicians (e.g. physicians, internists, noninvasive cardiologists) and catheterization laboratory staffs are educated about invasive treatment.

PTCA should be performed as rapidly as possible.

Catheterization laboratory team is called in as soon as notice is received that a patient of myocardial infarction is being transported or has arrived at the ER.

An abbreviated history is taken and a physical examination is performed in the ER; laboratory samples are drawn and medications are given.

Adjunctive Pharmacology

Anti Platelets

a. *Aspirin:* An initial loading dose of 162 to 325 mg of uncoated aspirin should be given as soon as possible to any patient thought to have an ACS. At this dose, aspirin produces a rapid antithrombotic effect due to immediate and almost complete inhibition of thromboxane A2 production. The first tablet should be chewed or crushed to establish a high blood level quickly. Aspirin 75 to 162 mg once a day shuld be continued daily indefinitely for secondary prevention. Higher dose does not produce greater benefit (OASIS-7). For patients taking ticagrelor aspirin should be given at a dose of 8 mg/day.

Newer Platelet

b. Three antiplatelet drugs appeared in the field one after another. Each one is backed by one or more large RCT. Clopidogrel is the oldest molecule and is fairly effective but with a slower onset of action and a peculiar metabolic pattern causing nonresponse in 10 to 15% of cases. In patients undergoing an invasive approach, ticagrelor or prasugrel is preferred to clopidogrel (Grade 2B). The loading dose of ticagrelor is 180 mg and prasugrel is 60 mg . Prasugrel is contraindicated in prior stroke, or TIA or those with active pathological bleeding.

c. *Glycoprotein IIb/IIIa receptor blocker:* In the era of very powerful antiplatelet agents like P_2Y_{12} inhibitors and antithrombotics like bivaluridine, the role of Gp_{2b3a} receptor blockers are uncertain. A few trials (In fuse AMI) have shown benefit of IC abciximab in primary PCI, while others have not. The judicial recommendation of anti-platelets in primary PCI will be:
   i. P_2Y_{12} receptor blockers Ticagrelor loading before angiography (Prasugrel only in patients with low risk of bleeding : Age <75 years : Weight >65 kg : DM, no histories of TIA/Cerebro-vascular disease).
   ii. Aspirin loading in all cases.
   iii. Gp_{2b3a} receptor blocker should be given during the procedure if patient received clopidogrel loading on the table and if heparin is being used for the procedure. Abciximab and Eptifibatide both are equally established.

d. *Betablocker:* In CADILLAC trial, preprocedural beta blockade enhanced myocardial recovery and 30-day mortality following primary PCI.

e. *Statins:* Extrapolating data from the benefit of high-dose statin in patients with ACS, 80 mg atorvastatin should be administered in patients with STEMI.

f. In diabetics, IV fluids should contain dextrose with neutralizing dose of insulin in the bottle or running infusion of insulin depending on baseline level of glucose on admission. Indirect evidence suggets that a glycemic target of less than 145 mg/dL (8 mmol) in STEMI will improve vascular function, limit myocardial cell apoptosis and increase the success of reperfusion therapy.

Procedural Protocol

a. *Arterial access:* Femoral artery is most commonly used since it is most quickly accessible and allows use of large guide-catheters, venous access (Shock, bradycardia or angio-jet use) Seven french sheath is most commonly used. Radial artery access is the alternative much less commonly used. Advantages are minimal access site problems, e.g. hematoma, AV fistula etc and quicker mobilization. Disadvantages include arterial spasm and inaccessibility of larger guiding catheters (if required).

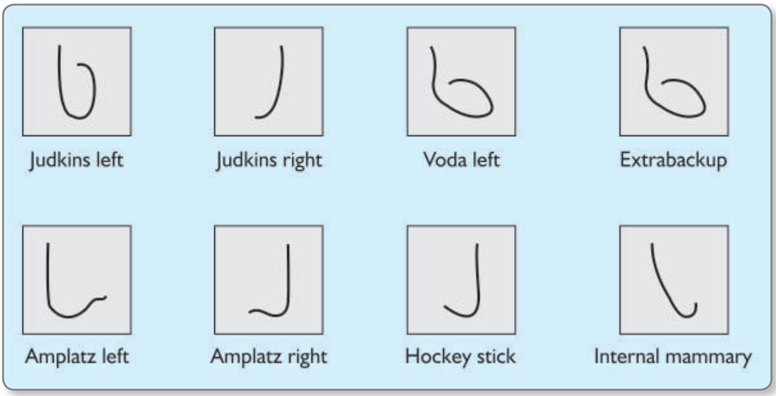
b. Check ACT after access and q 20 min.
   (>250 secs with GPIIb/IIIa, >350 secs if none)

c. Ionic low osmolar/nonosmolar contrast should be used to minimize hemodynamic and arrhythmic disturbances. The contrast agent of choice is ioxagalate (Hexabrix) which is the only ionic, low osmolar agent currently available. Its use reduces emboli risk and reduces mortality in comparison with nonionic contrast.

d. Coronary angiography should be performed after establishing arterial access; first the noninfarct artery is visualized using a diagnostic catheter. The infarct-related artery (IRA) is visualized last, using a guiding-catheter.

Choice of Guiding Catheter

Some commonly used guiding-catheter



JL: Judkins left; JR: Judkins right; VL: Voda left; XB: Extrabackup; AL: Amplatz left; AR: Amplatz right; HS: Hockey stick; IMA: Internal mammary.

Guiding catheter selection (Based on aortic root width and coronary artery orientation)

Target vessel	Configuration	Guiding catheters
Right coronary artery (RCA)	*Aortic Root* Normal Dilated Narrow	 JR4, AL1, AR1 JR ≥ 5, AL ≤ 2, AR ≤ 2 JR3, AL ≤ 0.75
	Orientation Normal Anterior, superior Inferior Shepherd cook Horizontal	 JR, AL, AR AL, HS, MP MP, AR, JR AL, SCR, VR, IMA JR, HS
Left coronary artery (LCA)	*Aortic Root* Normal Dilated Narrow	 JL4, AL2, XB3.5 JL ≥ 5, AL ≥ 2, VL ≥ 4, XB ≥ 4 JL3.5, VL3.5, XB3.0
	Orientation Normal, anterior Posterior Superior	 JL, AV, VL, XB AL, VL, XB JL, VL, XB

Contd…

Contd...

	Superselect LAD LCX	 JL3.5, JL (Anterior) JL4.5, AL, JL (Posterior)
SVG to RCA	*Orientation* Inferior Horizontal	 MP, AL, AR, JR JR, AL, MP
SVG to LCA	*Orientation* Horizontal Superior	 JR, HS, MP, AL HS, LCB, MP

Abbreviations: MP: Multipurpose; LCB: Left coronary bypass; SCR: Shepherd cook right; JL: Judkins left; JR: Judkins right; VL: Voda left; XB: Extrabackup; AL: Amplatz left; AR: Amplatz right; HS: Hockey stick; IMA: Internal mammary; SVG: Saphenous vein graft.

Size of Guiding Catheters

Through femoral route atleast a 7F guiding catheter should be introduced. Since, it provides a more stable position and back-up compared to 6 or 5F catheter. Complex anatomy in an unknown situation demands larger lumen for use of different devices.

e. *Choice of Guide wires:* Basic advice to use floppy guide wires as stiffer guide wires may pass subintimally producing no reflow after balloon dilatation. Floppy and hydrophilic (whisper, choice floppy) wires are particularly effective in most of the cases (some useful wires):

   Floppy
   - BMW, nontapered tip (Abott Vascular) (Nitinol core)

   Floppy and Hydrophilic
   - Whisper: Nontapered tip, durasteel core (Abott Vascular)
   - Fielder XT: Tapered tip, trutorque steel core (Asahi)
   - Choice Floppy: Polymer tip, nontapered, stainless steel core (Boston Scientific).

Choice of Balloon Dilatation Catheters

Angioplasty balloon catheters are arbitrarily classified into three different categories: over-the-wire (OTW) systems, “Monorail” or “Rapid-exchange” balloons and fixed wire systems (formerly called “balloon-on-a-wire”). Of these “Monorail” balloons (also called single-operator exchange systems) comprise the overwhelming majority of balloon catheters commonly used. These balloons have a lower profile and are better suited for single operator use. Standard length (175 cm) guidewires are recommended using a bare-wire technique; exchange-length guidewires are not necessary. Disadvantages of a rapid-exchange system include less pushability and trackability, inability to reshape or exchange the guidewire without a transfer catheter and difficulty using the balloon catheter for additional guidewire back-up support while crossing a difficult lesion (**Figures 10.1 and 10.2**).

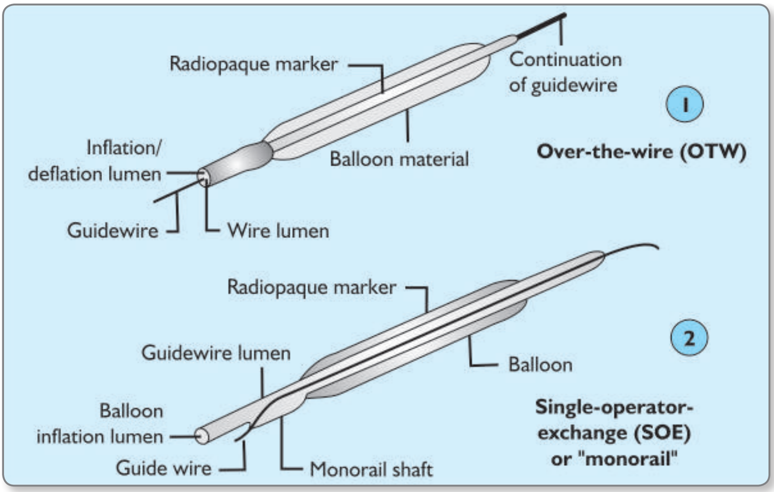


Fig. 10.1 Balloon dilatation catheter design

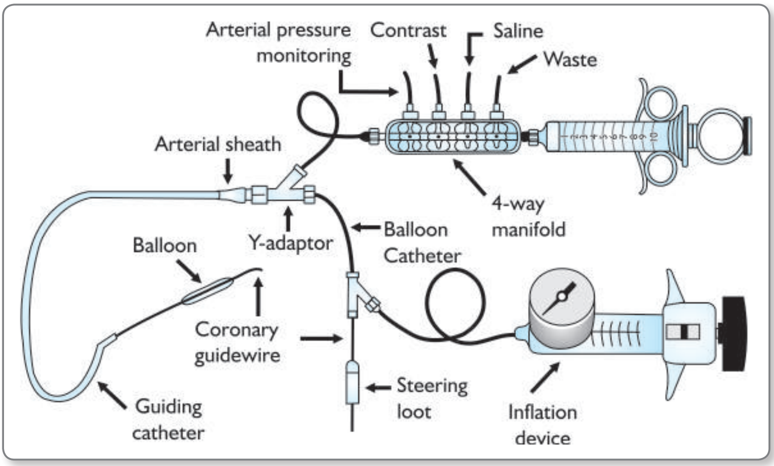


Fig. 10.2 Basic angioplasty equipment and set-up

Coronary Stenting

The availability of low profile stent delivery systems has led to the consideration of direct stenting (i.e. without predilatation). Advantages are for example less radiation exposure, contrast use, reduced embolization of plaque constituents, lowering the incidence of no-reflow. Direct stenting is advised in most cases except heavy calcification of the vessel and poor visualization of the distal edge. The facts to be remembered:

i. Sizing of the stent should be proper and stent should match the proximal diameter.
ii. As the vessel is underfilled and may be thrombus laden even after manual thrombo-suction adequate dosage of NTG/adenosine/nicorandil should be given IC before sizing.
iii. Stent should be deployed at a nominal pressures, may be postdilated with a high pressure balloon if required.

Type of stents: Initially BMS were used, then came 1st generation DES. A meta-analysis in 2012 used 11 randomized trials comparing BMS and DES (both sirolimus and paclitaxel eluting stents) from nearly 6,300 patients and these facts came out:

- There is no significant difference in mortality
- Target vessel revascularization was lower with DES
- No difference in stent thrombosis. Very late thrombosis is higher with DES.

However, recent trials like COMFORTABLE AMI or EXAMINATION establish the superiority of second generation DES (Biolimus and everolimus) to BMS with regard to target vessel revascularization. While more data, including longer follow-up are needed to confirm the finding of a lower rate of stent thrombosis, this finding is reassuring. So, second generation DES are reasonable choice for patients treated with primary PCI, who are able to comply with dual antiplatelet drugs for atleast 1 year.

Management of Thrombus

In all myocardial infarctions, IRA is expected to contain thrombus in variable amounts. Presence of thrombus in infarct lesions is strongly associated with a high-risk of distal embolization and no-reflow events leading to poor angiographic and clinical outcomes.

Angiographic features of 'high thrombus burden' are:

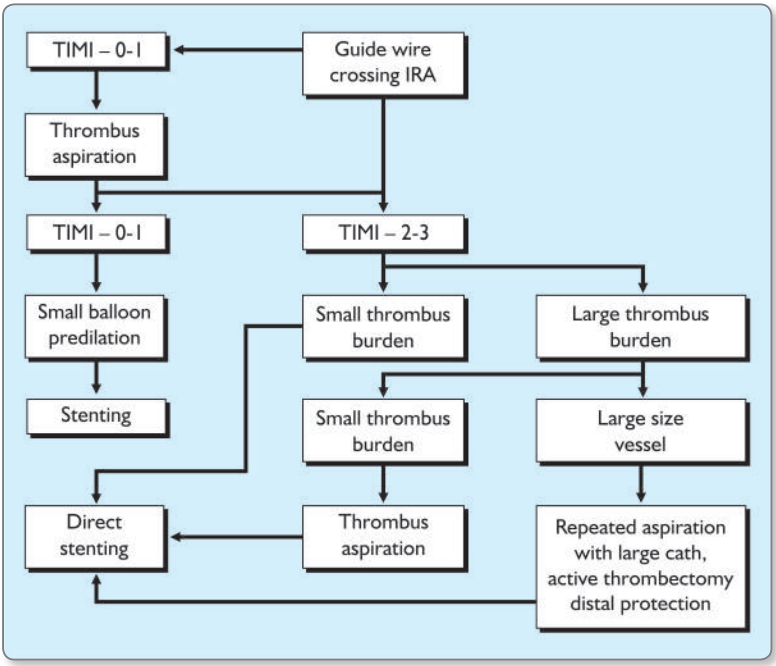
1. Large IRA (>4 mm)
2. Cut-off pattern (abrupt cut-off IRA)
3. Accumulated thrombus (>5 mm)
4. Floating thrombus proximal to the occlusion
5. Persistent dye stasis distal to the occlusion.

Thrombectomy and Thrombus Aspiration

As primary PCI almost always involves management of thrombus, both manual thrombus aspiration (By Pronto, Export, Diver) or mechanical thrombectomy were tried in different clinical studies. TAPAS is the largest trial (1071 patients) which showed angiographic as well as clinical benefits with manual thrombosuction. Blush grade zero to one (no or minimal reperfusion) occurred significantly less often in the thrombus aspiration group (17.1% vs. 26.3%) as did the secondary end-point of cardiac death or nonfatal MI) at one year (5.6% vs. 9.9% hazard ratio 0.6, 95% C.I.). Most of the benefit of thrombosuction was attributable to significantly lower rate of cardiac death (3.6% vs. 6.7%). The benefits of manual aspiration have been confirmed in meta-analysis. A meta-analysis of mechanical thrombectomy did not find a significant benefit.

Long-term prognosis may vary with the age of the aspirated thrombus. A retrospective study showed four year mortality was higher in patients with thrombus age of more than 24 hours (16% vs. 7.4%). So, most patients with STEMI undergoing primary PCI should undergo manual aspiration thrombectomy as aoon as possible. Thrombus aspiration is not appropriate for

Stemi in Cath Lab

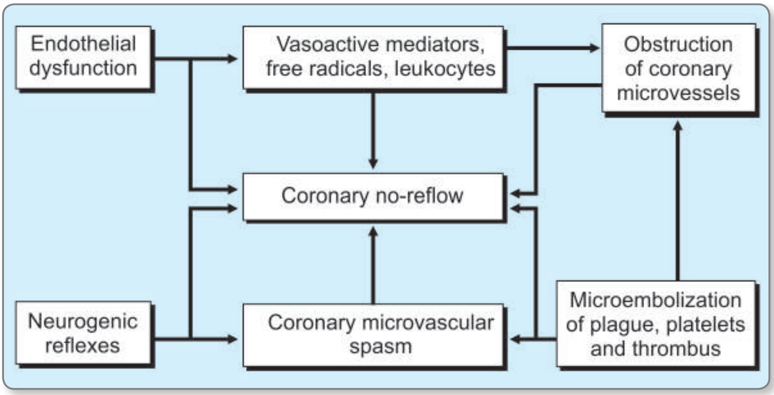


all patients, such as those who have patent arteries with culprit lesions not associated with significant thrombus, also in patients with severe coronary tortuosity or calcifications where the delivery of these large caliber catheters may not be possible.

Management of No-reflow

No-reflow is defined as inadequate myocardial perfusion without angiographic evidence of mechanical vessel obstruction. TIMI-0 to 1 is considered as no-reflow and grade II flow is slow flow.

Various factors involved in etiology of no-reflow



Treatment of No-reflow

May include one or more of the following:

i. Repeated boluses of intracoronary adenosine (60 µg boluses to a total of 1200-2400 µg) for no reflow in the patient with AMI because it can have the additional benefit of limiting infarct size. Heart block is frequent but resolves in seconds.
ii. Intracoronary nitroprusside (50 µg doses up to 200 µg total) [watch for hypotension].
iii. Intracoronary abciximab (bolus dose).
iv. Repeated bolus of intracoronary verapamil (100-200 µg) [Watch for bradycardia].
v. Nicorandil 1 to 2 mg over 30 to 60 seconds
vi. Intracoronary epinephrine, if no reflow occurs with hypotension (watch for hypertension and ventricular arrhythmia).

vii. Placement of intra-aortic balloon pump if blood pressure is low or multivessel disease is present with severe ventricular dysfunction.

Prevention of No-reflow

Pharmacological Strategies

VAPOR trial demonstrated benefit of verapamil pretreatment before saphenous vein graft PCI. There is conflicting data regarding utility of adenosine to prevent no-reflow.

Initial small reports have shown that no-reflow/slow flow phenomenon in primary PCI can be effectively prevented by pretreatment with intravenous nicorandil followed by intracoronary bolus of 2 mg of nicorandil at the time of balloon inflation during PCI and postprocedure nicorandil infusion (1-2 mg IV infusion/hour) for 24 to 48 hours as tolerated. The drug is safe and does not require intensive monitoring. Improvement in TIMI frame count translates into better patient outcomes and lower MACE.

Management of Reperfusion Injury

The process of myocardial repefusion itself, however, can induce injury to the myocardium , thereby reducing the beneficial effects of myocardial reperfusion. The cardiomyocyte death associated with the irreversible, lethal form of myocardial reperfusion injury diminishes the infarct-reducing effects of myocardial reperfusion by independently inducing cardiomyocyte death. Hence, reperfusion injury may contribute to the mortality despite early and successful reperfusion. Until recently, the efficacy that has been shown for most cardioprotective agents in animal models has been difficult to confirm in clinical trials. There is, however, general agreement that ischemic preconditioning (low-pressure balloon inflations and deflations after stent deployment) and postconditioning are cardioprotective not only in animal hearts but also in human hearts. The increasing understanding of the mechanism of the protection, particularly with regard to the risk pathway (Group of protein kinases which when specifically activated confer cardioprotection by preventing lethal reperfusion injury) has led to new pharmacologic interventions. These are glucagon-like peptide 1, erythropoietin, atorvastatin, atrial natriuretic peptide, all of which by activating RISK pathway have the potential to prevent reperfusion injury. A preliminary clinical study with inhibitor of proinjurious protein kinase C delta isoform (KAI-9803) was shown to reduce infarct size in patients undergoing primary PCI. Another, strategy deals with mitochondrial PTP inhibition with intravenous cyclosporine. Preliminary data with these cardioprotective strategies are encouraging but they remain to confirmed in large-scale clinical studies.

Supportive Management in the Cath-Lab

i. Management of arrhythmias:
   a. *Ventricular fibrillation and tachycardia:* Prompt defibrillation/ DC cardioversion and CPR, amiodarone bolus IV and then drip, lignocaine (prophylactic lignocaine should not be used)
   b. *Bradyarrhythmias, persistent bradycardia and hypotension (Bezold-Jarisch reflex):* atropine, temporary transvenous pacing.
   c. *Atrial fibrillation:* Beta-blocker (if no hypotension)
   d. *Ideoventricular rhythm:* No treatment needed.

ii. Management of hypotension during PCI
   a. Ensure that the guide catheter is removed from the coronary ostium and the system is airtight (Y-connector is tightened down)
   b. *Administer fluids:* Volume can be administered both intravenously and intra-arterially (hand delivered boluses through the arterial sheath) simultaneously.
   c. Raise legs
   d. Reverse any potentially offending medications
   e. Administer a vasoconstrictive medication
      - Phenylephrine 100 mcg bolus or >10 mcg/min infusion (max 200 mcg/min)
      - Epinephrine 1 to 10 mcg/min infusion or for suspected anaphylaxis 0.1 mg of the 1:10,000 solution
      - Dopamine 5 to 20 mcg/kg/min infusion.
   f. Support the rate
      - Cardiovert for fast tachyarrhythmias
      - Pacing for significant bradycardia if unresponsive to atropine (1 mg)
   g. Search for specific cause and treat accordingly.

iii. Use of hemodynamic support devices
   a. *IABP (Intra-aortic balloon pump):* Routine use of routine IABP has not been shown to be beneficial in routine management of patients with AMI (PAMI-2). However, continued ischemia, hypotension, congestive heart failure, severe ventricular dysfunction with multivessel disease and mechanical complications such as VSDs or severe MR remain indications for adjunctive use of patients with IABP.
   b. *Percutaneous left ventricular assist devices (p-VAD):* A recent study comparing IABP support to p-VAD in 41 patients with revascularized AMI complicated by cardiogenic shock demonstrated that hemodynamic and metabolic parameters could be reversed more effectively with p-VAD. However, this was at the expense of a higher incidence of complications as severe bleeding and limb ischemia and

no difference in 30 days mortality (IABP 45% vs pVAD 43%, P=0.86). Of the p-VADs, Impella device which is almost like a miniaturized water pump, have show particular promise for use in cardiogenic shock (despite IABP) and during high-risk PCI.

iv. Need for emergency CABG

Left main disease, failed angioplasty, presence of mechanical complications and three vessel proximal coronary artery disease (particularly with a low ejection fraction and diabetes) remain the gold standard for referral to bypass surgery as reported in the guidelines. Surgery is rarely immediately performed after restoration of coronary flow with only angioplasty (failed PCI, subtotal occlusion of left main). Most patients with three vessel CAD can be treated wtih PCI and infact, stenting of IRA converts three vessel disease into two vessel disease and CABG can be avoided. Of those referred for primary PCI, only 5% are initially referred for CABG and these patients have a patent IRA and additional complex vessel anatomy not amenable to PCI. These situations are:

a. Unprotected left main > 60%
b. Proximal three vessel disease with TIMI 3 flow in IRA and CABG is considered the superior choice
c. IRA stenosis < 70% and TIMI 3 flow
d. IRA supplies only small amout of myocardium.

Vascular Access Management

Arterial sheath should be removed as early as possible, i.e. whenever ACT is < 190 seconds. Various vascular closure devices like angioseal, perclose, vasoseal, duett, femostop, etc. are now available. While these have facilitated early mobilization and discharge from hospital, vascular complication rates have not decreased.They should not be used when double punctures are suspected.

Anticoagulation may be resumed after 4 to 6 hours from sheath removal for other indications (atrial fibrillation, prosthetic valves, large MI, poor LV function, residual thrombus). If GPIIb/IIIa inhibitors are being used, heparin should not be restarted after the procedure. Minidose heparin may be given subcutaneously while patients are in bed rest for prophylaxis against deep venous thrombosis.

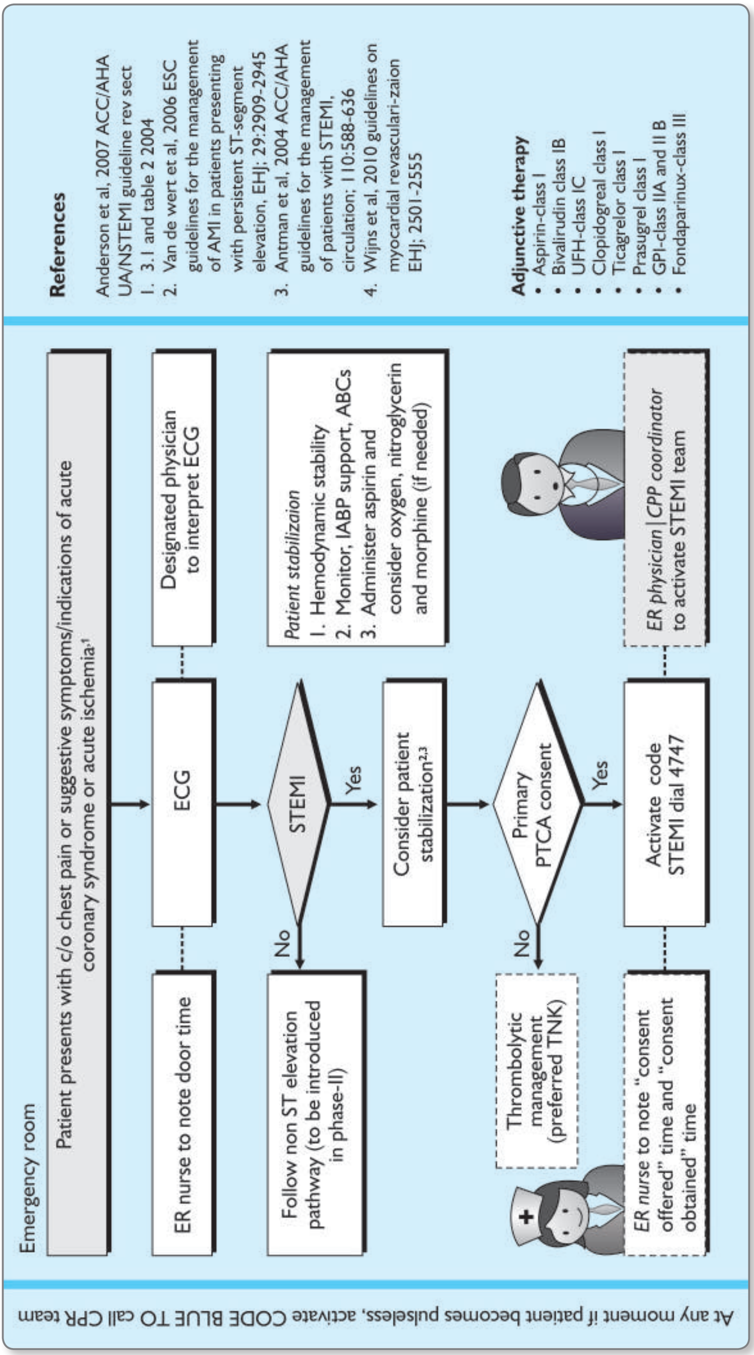
Discharge

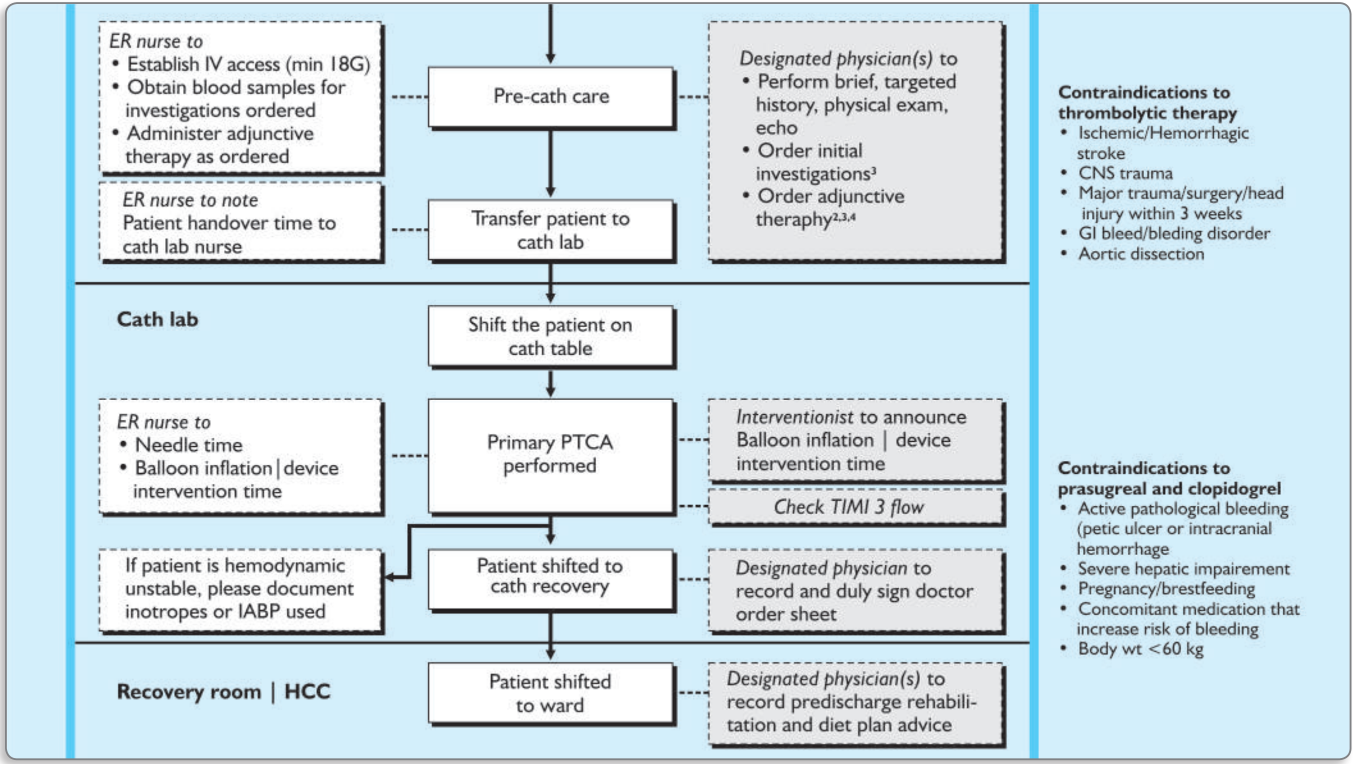
Several risk scores have been described to prognosticate about patients' outcomes and in-hospital placement and discharge. These are:

PAMI risk score and CADILLAC risk score.

If patients has low-risk features by PAMI risk score (e.g. age < 70 yrs, EF > 45%, < 3-vessel CAD, no SVG occlusion and no persistent arrhythmias) or

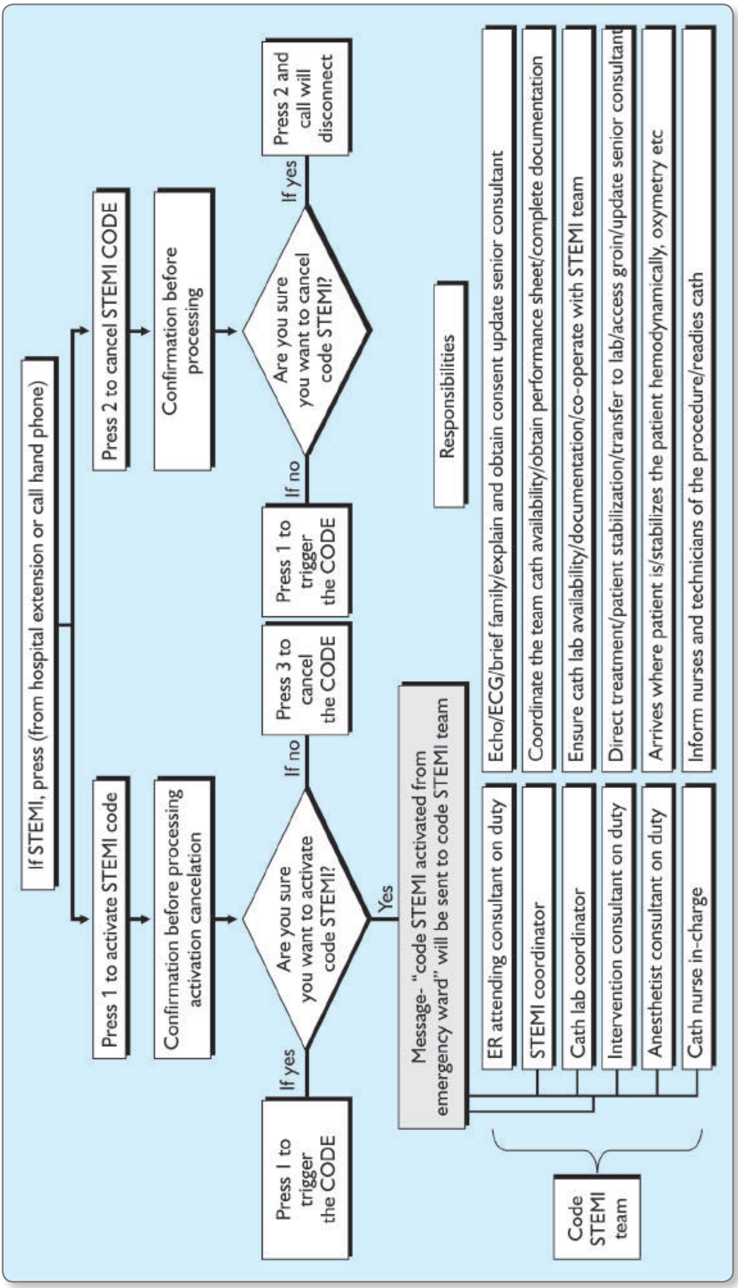
A model chest pain pathway—STEMI management control





STEMI management protocol of Fortis group of hospitals

A model chest pain pathways—STEMI code activation protocol



Fortis group of hospitals

by CADILLAC risk score (EF > 40%, no renal insufficiency, Killip Class I, final TIMI flow III, age < 65, no anemias, < 3 vessel disease), patient can be safely transferred to a step-down unit with target discharge of 3 days. However, high-risk patients require CCU admission with a target discharge of 5 days.

Aspirin, clopidogrel, beta-blockers, statins, ACEIs and aldosterone antagonists have all been shown to improve clinical outcomes, include mortality, following primary PCI and should be routinely prescribed at discharge, unless any specific contraindication exists. Cardiac rehabilitation (psychological and physical) is of utmost importance following AMI and should be persued with all sincerity.

Suggested Reading

1. Antman EM, Anbe DT, Armstrong PW, et al. ACA/AHA guidelines for management of patients with acute myocardial infarction-executive summary. Circulation. 2004; 110:588-636.
2. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. European Heart J. 2008;29:2989-3001.
3. De Luca G, Dudek D, Sardella G, et al. Adjunctive manual thrombectomy improves myocardial perfusion and mortality in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis of randomized trials. European J. 2008;29:3002-10.
4. Ezhilan J, Manjeet S, et al. Prevention of No flow/Slow reflow phenomenon in Primary PCI by Nicorandil. Indian Heart J. 2007;59(3):246-9.
5. Francesco Burzotta, Carlo T, et al. Feasibility of sequential thrombus aspiration and filter distal protection in the management of high thrombus burden lesion. J Invasive Cardiol. 2007;19:317-23.
6. Haranath SP, Grines C. Percutaneous Coronary Interventions for AMI: Current strategy in the lab: Indian Heart J. 2007;Suppl. B:B86-B98.
7. Henriques JP, Remmelink M, Baan J Jr, et al. Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. Am J Cardiol. 2006;97(7):990-2.
8. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. Lancet. 2003;361:13-20.
9. Reffelmann T, Kloner RA. The "No-reflow" phenomenon: Basic science and clinical correlates. Heart. 2002;87:162-8.
10. www.uptodate.com for
    - Primary percutaneous coronary intervention in acute STEMI pericardial management (2013)
    - Suboptimal reperfusion after PPCI in acute STEMI (2013)
    - Antiplatelet agents in acute non-ST elevation and acute coronary syndrome (2013)

Vascular Emergencies

chapter 11

Shuvanan Ray, Aniket Niyogi, Soumitra Kumar

Venous Thromboembolic Disorders

Average annual incidence in developed countries is 1 in 1000. Commonly occurs in legs but also occurs in other veins, such as cerebral sinus, retina, arms and mesentery.

Etiology

i. *Clinical risk factors:* Age (higher risk in older patients, obesity, surgery, pregnancy and drugs, e.g. oral contraceptive pills, tamoxifen), long haul flights.

ii. *Thrombophilias:* a. Inherited (genetic)
b. Acquired

a. **Inherited thrombophilias**

Inherited thrombophilias		**Prevalence in first VTE episode**
Elevated factor VIII levels		25%
Factor V Leiden:	Heterozygous	18.8%
	Homozygous	Rare
Hyperhomocysteinemia (>18.5 mcmol/l)		10%
Prothrombin G 20210A Allele		7.1%
Protein C deficiency		3.7%
Protein S deficiency		2.3%
Antithrombin III deficiency		1.9%

b. **Acquired thrombophilia**
- Mucin secreting carcinomas
- Antiphospholipid antibody syndrome
- Myeloproliferative disorders
- Paroxysmal nocturnal hemoglobinuria

Clinical Diagnosis of Deep Venous Thrombosis of Lower Limb

Clinical diagnosis of deep venous thrombosis (DVT) of lower limb is unreliable. Individual signs and symptoms are of limited value. Homan's sign is of no value.

Clinical Model for Predicting Pretest Probability of DVT

Clinical Feature	Score
• Active cancer (Rx ongoing or within previous 6 months or palliative)	1
• Paralysis, paresis or recent plaster immobilization of legs	1
• Recently bedridden for > 3 days or major surgery within 4 weeks	1
• Localized tenderness along distribution of deep venous system	1
• Entire leg swollen	1
• Calf swelling > 3 cm compared to asymptomatic leg (measured 10 cm below tibial tuberosity)	1
• Pitting edema (greater in asymptomatic leg)	1
• Collateral superficial veins (non-varicose)	1
• Alternative diagnosis as likely or wider than that of DVT	–2
• Low probability	0 or less
• Moderate probability	1-2
• High probability	3 or more

Differential Diagnosis of Deep Venous Thrombosis

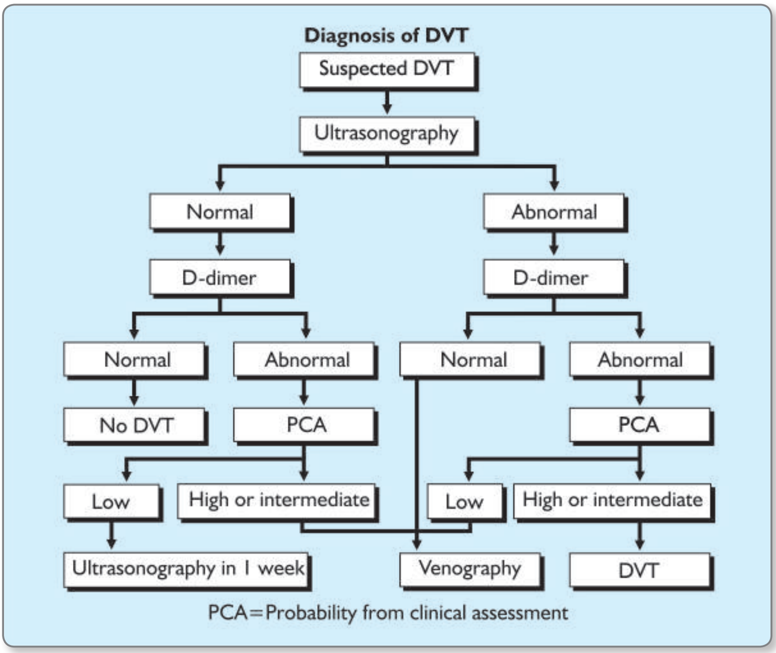
- Superficial thrombophlebitis
- Muscle or tendon tear, muscle cramps.
- Popliteal inflammatory cysts (Baker's cysts)
- Cellulitis (without lymphangitis)
- Internal derangement of the knee
- Postphlebitic syndrome
- Cutaneous vasculitis
- Lymphedema

Investigations for DVT

A. **Screening investigations:**
   - *D-dimer tests:* Sensitive but nonspecific; has high negative predictive value.
     i. Laboratory tests ELISA
        Latex agglutination tests
     ii. Bedside tests Simpli-RED (agglutination)
        Simplify (immunochromatography)
   - *Plesthysmography:* Recording of changes in the size of the limb due to tissue fluid or pooled blood in the veins.

B. **Definitive investigations (directly visualize the thrombus)**
   - *Venography:* Gold standard
   - Ultrasonography
     i. Compression ultrasound

ii. Duplex ultrasonography
iii. Color coded Doppler ultrasonography
- Computed tomography
- Magnetic resonance imaging



[D-dimer > 400 ng/ml : positive; ≤ 400 ng/ml; negative]

Treatment of DVT

The main goals in the treatment of venous thromboembolism (VTE), which comprises DVT and pulmonary embolism (PE), are to restore perfusion of the occluded vessel, to inhibit progression and embolization of the thrombus, and to prevent recurrence.

Initial Treatment

a. **Antithrombotics:**
   i. Unfractionated heparin (UFH)
      - Remains the drug of choice in symptomatic DVT
      - Aim for APTT within 1.5 to 2.5 times upper limit of normal
      - Therapeutic APTT to be achieved within 24 hours.
   ii. Low molecular weight heparin (LMWH)

- Stable patients may benefit from LMWH and it may even be superior to UFH.
- No monitoring required.
- Likely to replace UFH in near future.

iii. The mainstay of initial treatment for DVT is anticoagulation. Nonetheless, anticoagulation therapy does not actually treat DVT by dissolution of thrombus but instead prevents the propagation of the existing acute DVT. In selected patients with extensive acute proximal DVT (e.g. those with iliofemoral DVT, upper extremity DVT, symptoms of less than 14 days' duration, good functional status, of a life expectancy exceeding 1 year whose bleeding risk is low, catheter-directed thrombolysis (CDT) may be used to reduce symptoms and post-thrombotic morbidity if appropriate resources are available.

The CDT is performed under imaging guidance; the procedure delivers the thrombolytic agent directly to the clot through a catheter inserted in the vein. Intraclot injection of the thrombus with a fibrin-specific thrombolytic agent, such as alteplase is an alternative to continuous infusion and minimizes the duration of systemic exposure to thrombolytic agents.

Efficacy and safety of urokinase, alteplase and reteplase in CDT for the treatment of symptomatic DVT concluded that the three thrombolytic agents had similar success and complication rates. Tenecteplase was reported to achieve significant or complete lysis in 83.3 percent of cases.

Despite the known effectiveness of thrombolysis, widespread use of thrombolytics in the treatment of DVT is limited by the long infusion times required and the substantial risk of hemorrhagic complications associated with large doses of these agents.

Pharmacomechanical CDT (PCDT) refers to combination of CDT and mechanical thrombectomy to fragment, macerate or aspirate the thrombus. With use of such devices, thrombus removal can be performed with reduced dose of thrombolytic drug and in a single procedure session. However, there are no rigorously performed prospective studies to validate this finding and there may be risks associated with greater mechanical manipulation of thrombus and vein. The CDT or PCDT should be given to patients with IFDVT associated with limb-threatening circulatory compromise (i.e. phlegmasia cerulea dolens).

Thrombolytic Regimens

Alteplase: For lysis of venous thrombus, catheter-directed infusion of alteplase 1-1.5 mg/hr for 12 to 24 hours has been used; regimens may vary, depending on local expertise.

Urokinase: The usual systemic urokinase regimen for DVT consists of 4400 U/kg as an IV bolus followed by a maintenance drip of 4400 U/kg/h. The drip is continued for 1 to 3 days, until clinical or laboratory investigations demonstrate thrombus resolution. When available, intrathrombus delivery of urokinase can avoid a systemic lytic state; via this route, the drug is given in a loading dose of 250,000 U IV followed by infusion of 500 U/kg/h. If clot lysis is inadequate, the infusion rate can be gradually increased up to 2000 U/kg/h.

Streptokinase: The usual streptokinase regimen for DVT consists of an IV bolus of 250,000 U followed by a maintenance drip at 100,000 U/h. The drip is continued for 1 to 3 days, until clinical or laboratory investigation shows thrombus resolution.

Reteplase: Reteplase is not approved by the US Food and Drug Administration (FDA) for lysis of venous thrombus in DVT but is often used off label. Catheter-directed infusion of 1 U/h is maintained for 18 to 36 hours.

iv. IVC interruption by the insertion of an IVC filter (Greenfield filter) is only indicated in the following settings:

Patients with acute venous thromboembolism who have an absolute contraindication to anticoagulant therapy (e.g. recent surgery, hemorrhagic stroke, significant active or recent bleeding).

Patients with massive pulmonary embolism who survived but in whom recurrent embolism invariably will be fatal.

Patients who have objectively documented recurrent venous thromboembolism, adequate anticoagulant therapy notwithstanding.

In patients with a time-limited indication for IVC filter placement (e.g. a short-term contraindication to anticoagulation), it is reasonable to select a retrievable IVC filter and evaluate the patient periodically for filter retrieval. After placement of an IVC filter, AHA guidelines recommend that anticoagulation be resumed once contraindications to anticoagulation or active bleeding complications have resolved.

v. New antithrombotic agents for initial treatment of DVT

a. *Fondaparinux - synthetic selective antifactor Xa:*
 5 mg for body weight < 50 kg
 7.5 mg for body weight 50-100 kg
 10 mg for body weight > 100 kg

b. *Ximelagatran - oral direct thrombin inhibitor*: Ximelagatran- not marketed due to liver damage

c. *Oral factor Xa inhibitor:* Rivaroxaban has been approved for acute treatment of DVT and PE at dosage of 15 mg twice daily with food for the first 21 days; 22nd day onward, it is to be given at 20 mg once daily with food at same time every day for remaining/extended period of treatment. Avoid its use in patients with creatinine clearance < 30 ml/min, patients with moderate and severe hepatic impairment (Child Pugh B & C), inhibitors or inducers of P-gp and CYP3A4. In pregnant women, rivaroxaban should be used only if potential benefit justifies the potential risk to mother and fetus (It has not been studied in pregnancy). Another upcoming oral, reversible and selective factor Xa inhibitor is Apixaban. It is being evaluated for treatment in these conditions.

Long-term Treatment of Acute-DVT

The patients with acute DVT require long-term treatment (Tables 11.1 and 11.2) to prevent high frequency of symptomatic extension (15-50%) of thrombosis and/or recurrent venous thromboembolic events in patients of proximal vein thrombosis (popliteal, femoral, iliac veins) and also deep veins of the calf.

Treatment with oral vitamin K antagonists (VKA) is the preferred approach in long-term anticoagulation except in pregnancy, where VKAs are contraindicated. Dose of VKA has to be adjusted to maintain a target INR of 2.0 to 3.0.

Dabigatran is an oral direct thrombin inhibitor with a dose of 150 mg bid, is superior to warfarin with similar bleeding rate but with a 110 mg bid, is noninferior to warfarin with significantly less major bleeding. No need to monitor PT regularly. Ecarin clotting time is best indicator of efficacy. It has an approximate. lesser risk of bleeds (major and minor) than warfarin but GI upset and dyspepsia seen in many.

Complications of Anticoagulant Therapy

- **Bleeding**
- **Failure of anticoagulation:** Recurrent VTE may occur despite adequate anticoagulation in patients with overt or occult cancer and possibly APLA syndrome.
- **Heparin-induced thrombocytopenia (HIT):** Frequency is < 1 percent when UFH or LMWH is given no more than 5 to 7 days. Recombinant hirudin (lepirudin) has been specifically approved for HIT accompanied by thrombosis.
- **Post-phlebitic syndrome:** occurs in 20 to 50 percent of patients after a documented episode of DVT.
  Prevention: Use of elastic compression stockings with pressure of 30 to 40 mm Hg for 2 years after a DVT episode
  Treatment: Physical: Severe edema leg—intermittent pneumatic compression; Mild edema leg—elastic compression stocking
  Drugs: Rotusides may be tried.

Table 11.1 Duration of anticoagulation after a venous thromboembolism episode

Groups		Duration of anticoagulation	
a.	Transient major or risk factor (i.e. surgery, hospitalization, trauma, general anesthesia)	a.	3-6 months of conventional intensity anticoagulation (INR 2-3)
b.	Unprovoked events (with or without common thrombophilia risk factor V Leiden, prothrombin mutation, etc.)	b.	2-4 years with either: INR 1.5-2 (better than placebo) or INR 2-3 (better than low-intensity anticoagulation)
c.	Recurrent unprovoked events or severe underlying prothrombotic factor • Active cancer • Antiphospholipid antibodies • Protein C or S deficiency – Antithrombin deficiency – Homozygous factor V Leiden – G20210A Prothrombin gene mutation – Combined thrombophilic abnormalities – Pulmonary hypertension	c.	Long-term therapy • At least one year but, likely indefinitely (risk-benefit to be reassessed, depending on patient preference and/or if risk of bleeding increases) • Most experts recommend life long therapy in active cancer or at least until cancer is cured. Therapy with low molecular weight heparin might be superior to coumadin in this group

Table 11.2 Prevention of venous thromboembolism in medical patients

Groups	Recommendations
AMI	Prophylactic or therapeutic anticoagulant therapy with SC UFH or LMWH.
Ischemic stroke (and impaired mobility)	SC UFH or LMWH or a heparinoid (danaparoid)
Other medical conditions (cancer, bedrest, heart failure, severe lung disease)	SC UFH or LMWH If anticoagulant prophylaxis is contraindicated, elastic stockings or IPC are recommended.
SC = Subcutaneous, IPC = Intermittent pneumatic compression	

Oral rivaroxaban is approved for surgical prophylaxis of DVT which may lead to PE after knee or hip replacement surgery at 10 mg once daily (12 days for knee replacement and 35 days for hip replacement).

Use of Compression Therapy

Patients with ileofemoral DVT (IFDVT) should wear 30 to 40 mm Hg knee-high graduated external compression stocking (ECS) on a daily basis for at least 2 years. In patients with prior IFDVT and severe edema, intermittent sequential pneumatic compression followed by daily use of ECS is recommended.

Pulmonary Embolism

The deep veins of the lower extremities and pelvis are the most common sources of pulmonary emboli. Thrombi dislodge from these veins and embolize to the pulmonary arterial tree where they trigger pathophysiologic changes in hemodynamic and gas exchange.

Clinical Features

- Dyspnea is the most frequent symptom and tachypnea is the most common sign.
- Pleuritic chest pain, cough or hemoptysis most often indicates a small peripherally located pulmonary embolism (PE)
- Massive PE may present with hypotension, syncope, cardiogenic shock or cardiac arrest.
- Classic signs, e.g. tachycardia, fever, neck vein distension, tricuspid regurgitation and an accentuated pulmonic valve closure sound are often conspicuous by their absence.

Investigations

i. **Cardiac biomarkers:** These include troponin and BNP and are not specific for the diagnosis of acute PE. D-dimer assay (ELISA) has a high sensitivity and high negative predictive value. Hence , D-dimer ELISA alone can exclude PE in patients with low to moderate clinical suspicion without the need for further costly imaging tests.

ii. **Electrocardiography (ECG):** Findings in PE are:
   - Sinus tachycardia
   - T-wave inversions in lead III and aVF or in leads VI-V4
   - Incomplete or complete RBBB
   - QRS axis greater than 90º or indeterminate axis.
   - Concurrent deep S wave in lead I with Q wave and T wave inversion in lead III (S1 Q3 T3).
   - S waves in lead I and aVL greater than 1.5 mm.
   - Q waves in leads III and aVF but not in lead II.
   - Transition zone shift to V5
   - Low limb lead voltage
   - AF

iii. **Chest radiography:** Classically described radiographic findings in PE include:
   a. Focal oligemia (Westermark sign)
   b. Peripheral wedge-shaped density above diaphragm (Hampton's hump)
   c. An enlarged right descending pulmonary artery.

iv. **Echocardiography:** Findings in patients with pulmonary embolism are:
   - RV dilatation and hypokinesis. In acute PE, severe RV wall hypokinesis is seen sparing the apex (McConnell's sign)
   - Interventricular septal flattening and paradoxical motion.
   - Tricuspid regurgitation
   - Pulmonary hypertension as identified by a tricuspid regurgitant jet velocity greater than 2.6 m/sec.
   - Loss of respiratory phasic collapse of the inferior vena cava with inspiration.
   - Decrease in the difference between LV area during diastole and systole (indicates low cardiac output state).
   - Patent foramen ovale.

v. **Chest CT:** Spiral or helical chest CT scanning with contrast has become the initial imaging test of choice in the evaluation of patients with suspected PE. Sensitivity of chest CT is highest in detecting PE in proximal pulmonary arteries; newer generation multidetector CT scanners may diagnose segmental or subsequental PEs but also have increased frequency of indeterminate studies.

vi. **Ventilation-Perfusion (V/Q) lung scanning:** While a high probablity scan in the setting of moderate to high clinical suspicion virtually ensures the diagnosis of PE and a normal scan excludes it; the majority of patients have non-diagnostic scan. Lung scanning is still used for patients with renal failure, anaphylaxis to IV contrast or pregnancy.

vii. **MR Angiography:** MR angiography avoids the risk of iodinated contrast and ionizing radiation. MR angiography holds promise for imaging proximal pulmonary arteries.

viii. **Contrast pulmonary angiography** is indicated when chest V/Q scanning, lower extremity ultrasonography for DVT and echocardiography are non-diagnostic in setting of high clinical suspicion for PE.

   Immediate bedside clinical assessment for the presence or absence of clinical hemodynamic compromise allows for stratification into 'high-risk' and 'non-high-risk' PE.

Principal Markers Useful for Risk Stratification

1. **Clinical markers:** Shock, hypotension [SBP < 90 mm Hg or a pressure drop of > 40 mmHg for > 15 minutes if not caused by new-onset arrhythmia, hypovolemia or sepsis]
2. **Markers of RV dysfunction:** RV dilatation (4-chamber RV diameter divided by LV diameter > 0.9 on echo), hypokinesia or pressure overload on echocardiography.

   RV dilatation on spiral computed tomography (same as echo with 4-chamber slice)

BNP or NT-proBNP elevation (BNP > 90 pg/ml or NT pro BNP > 500 pg/ml.

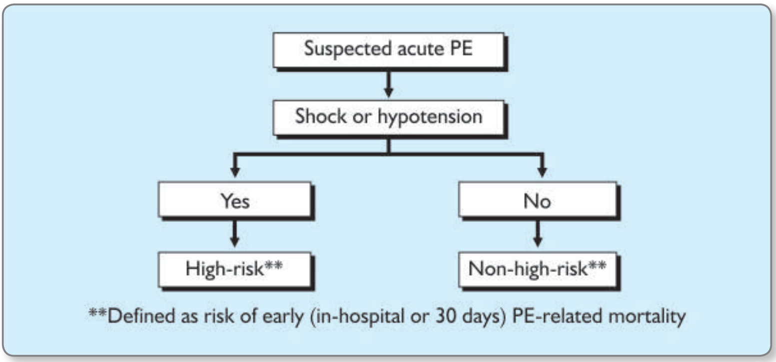
Elevated right heart pressures at right heart catheterization.

3. **Markers of myocardial injury:** Cardiac troponin T or I positive (Heart-type fatty-acids binding protein is an emerging marker) (Troponin I > 0.4 ng/ml, Troponin T > 0.1 ng/ml).

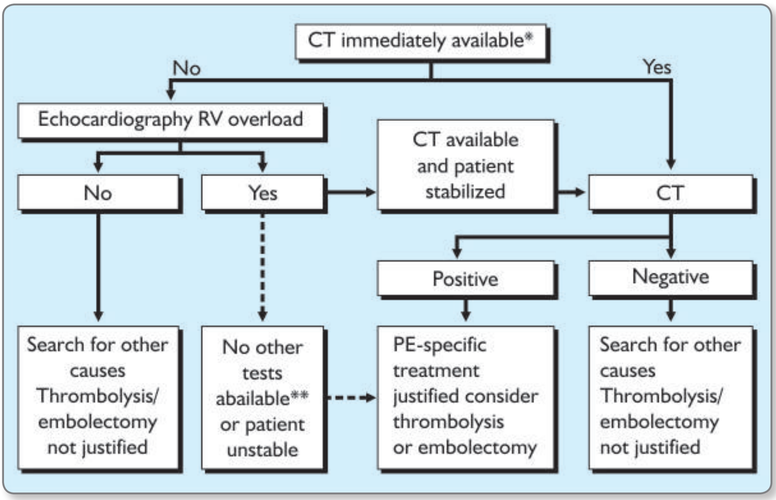
Risk Stratification in Pulmonary Embolism

Independent predictors of increased mortality at three months after pulmonary embolism

- Age greater than 70 years
- Cancer
- Clinical CHF
- Chronic obstructive pulmonary disease
- Systolic BP less than 90 mm Hg

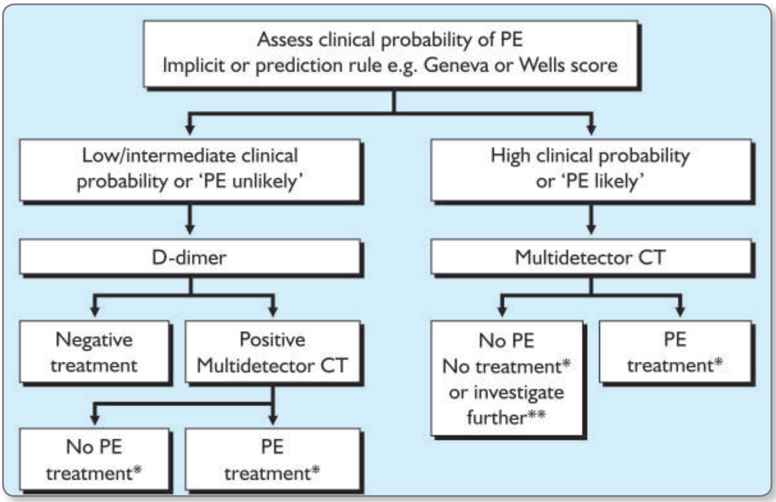


Suspected High-risk PE, i.e. with Shock or Hypotension [ESC 2008 Guidelines]



* CT is considered not immediately available also if critical condition of a patient allows only bedside diagnostic tests.
** Note that transesophageal echocardiography may detect thrombi in the pulmonary arteries in a significant proportion of patients with RV overload and PE ultimately confirmed at spiral CT and that confirmation of DVT might also help in decision-making.

Suspected Non-high risk PE, i.e. without Shock or Hypotension [ESC 2008 Guidelines]



*Treatment refers to anticoagulant treatment for PE.
**V/Q scan, Doppler study of lower limb veins, pulmonary angiography.

Table 11.3 Risk stratification according to expected PE-related early mortality rate

<table>
<tr><th colspan="6">Risk markers</th></tr>
<tr><td colspan="2">PE-related early mortality risk</td><td>Clinical (shock or hyotension)</td><td>RV dysfunction</td><td>Myocardial injury</td><td>Potential treatment implications</td></tr>
<tr><td colspan="2">High > 15%</td><td>+</td><td>(+)*</td><td>(+)*</td><td>Thrombolysis or embolectomy</td></tr>
<tr><td rowspan="2">Non-high</td><td>Inter-mediate 3-15%</td><td>–</td><td>+
+
–</td><td>+
–
+</td><td>Hospital administration</td></tr>
<tr><td>Low <1%</td><td>–</td><td>–</td><td>–</td><td>Early discharge or home treatment</td></tr>
</table>

*In the presence of shock or hypotension it is not mandatory to confirm RV dysfunction/ injury to classify as high risk for PE-related early mortality.
An ongoing multicenter randomized trial is evaluating the potential benefit of thrombolysis in normotensive patients with predefined echocardiographic signs of RVD and troponin levels.

Thrombolysis: In patients with high-risk PE (and selected intermediate-risk PE patients with features of RV dysfunction and Troponin positivity combined), thrombolysis administered systematically may be life-saving (Table 11.3). Approved thrombolytic regimens for pulmonary embolism (Task Force on Acute Pulmonary Embolism of ESC, 2008):

i. *rtPA:* 100 mg over 2 hours or 0.6 mg/kg over 15 minutes (maximum dose 50 mg). According to the British Thoracic Society 2003 recommendations, immediate administration of 50 mg of alteplase may be life-saving for patients in cardiac arrest believed to be caused by PE. Some centers prefer to use an accelerated 90 minute regimen that appears to be faster-acting, safer, and more efficacious than the 2-hour infusion. For patients weighing less than 67 kg, the drug is administered as a 15 mg IV bolus followed by 0.75 mg/kg over the next 30 minutes (maximum, 50 g) and then 0.50 mg/kg over the next 60 minutes (maximum 35 mg). For patients weighing more than 67 kg, 100 mg is administered as an 15 mg IV bolus followed by 50 mg over the next 30 minutes and then 35 mg over the next 60 minutes.

ii. *Streptokinase:* 250,000 IU as a loading dose over 30 minutes, followed by 100,000 IU/h over 12 to 24 hours. Accelerated regimen 1.5 million IU over 2 hours.

iii. *Urokinase:* 4,400 IU/kg as a loading dose over 10 minutes, followed by 4,400 IU/kg/h over 12 to 24 hours. Accelerated regimen: 3 million IU over 2 hours.

Reteplase has not been approved by the FDA for any indication except AMI, but it is widely used for acute deep vein thrombosis and PE. The dosing used is the same as that approved for patients with AMI: Two IV boluses of 10 U each, administered 30 minutes apart. Tenecteplase too is not approved by FDA for use in acute DVT and PE. It has been used in trials at weight-adjusted IV bolus (over 5 secs.) of 30 to 50 mg with a 5 mg step every 10 kg from < 60 to > 90 kg body weight. Analysis of pooled results of fibrinolysis by Wan et al showed that there was a significant reduction in recurrent PE or death from 19.0 percent with heparin alone to 9.4 percent with fibrinolysis when the analysis was restricted to trials with massive PE.

Data from MAPPET, ICOPER, RIETE and EMPEROR registries suggest that in contrast to massive PE, short-term mortality rate directly attributable to submassive PE treated with heparin anticoagulation is probably < 3.0 percent. Hence, secondary adverse outcomes such as persistent RV dysfunction, chronic thromboembolic pulmonary hypertension and impaired quality of life represent appropriate surrogate goals of treatment in submassive PE rather than mortality of the two trials (involving tenecteplase vs placebo). PEITHO and TOPCOAT, are addressing the controversial question about which patients with submassive PE will benefit from fibrinolysis, PEITHO was recently presented at ACC 2013. It enrolled 1006 patients with confirmed acute pulmonary embolism. The primary end-point of death from any cause or hemodynamic collapse after 7 days of randomization was reduced by 56 percent in patients assigned heparin plus tenectplase compared with heparin plus placebo. Death rates were low and similar in both groups. However, major bleeding was increased with tenecteplase 6.3 percent vs 1.5 percent.

In contrast to thrombolysis in myocardial infarction, IV unfractionated heparin (UFH) is withheld during the administration of alteplase. Every patients being considered for thrombolysis should be meticulously screened for contraindication [Intracranial disease, recent surgery, recent trauma, severe or uncontrolled hypertension, recent prolonged CPR, active or recent bleeding].

Open surgical embolectomy: Open surgical embolectomy may be considered in patients with massive and submassive PE in whom thrombolytics have failed or are contraindicated. Open surgical embolectomy is most effective in the treatment of saddle or main pulmonary artery embolism. IVC filters are routinely placed perioperatively. The procedure can be performed off bypass, with normothermia and without aortic cross-clamping or cardioplegic or fibrillatory arrest.

Catheter-based strategies: Catheter-based strategies have been applied to both DVT and PE. Catheter-based pulmonary embolectomy may be considered when thrombolysis and open-surgical embolectomy are containdicated. Catheter-based strategies work best on fresh thrombus within the first five days of symptoms of PE or DVT. There are three general categories of interventions that are done : (i) Aspiration thrombectomy (with Greenfield suction embolectomy catheter), (ii) Thrombus fragmentation with balloon angioplasty, a pigtail rotational catheter or Amplatz catheter using an impeller, (iii) Rheolytic thrombectomy catheters like Angio Jet and Oasis. ***Anticoagulation:*** Anticoagulation is the mainstay of therapy for patients with acute PE.

Unfractionated heparin (UFH): IV UFH is usually administered as a bolus followed by continuous infusion and titrated to a goal-activated partial thromboplastin time (aPTT) between two to three times the upper limit of normal (e.g. approximately 60-80 seconds). Various weight-based heparin nomograms may be used to achieve therapeutic anticoagulation more quickly (Table 11.4). IV UFH is continued for at least five days with simultaneously initiated oral anticoagulations. UFH is preferred in patients undergoing thrombolysis or embolectomy.

Table 11.4: Modified Raschke weight-based heparin nomogram

Variable	Heparin dosage Initial dose → maintenance infusion (IV)
Initial heparin dose	80 u/kg bolus, then 18 u/kg/hour
aPTT < 35 sec (<1.2 × control)	80 u/kg bolus, then increase infusion by 18 u/kg/hour
aPTT 35-59 sec (1.2-1.9 × control)	40 u/kg bolus, then increase infusion by 2 u/kg/hour
aPTT 60-89 sec (2.0-2.9 × control)	No change
aPTT 90-100 sec (3.0-3.3 × control)	Decrease infusion by 3 u/kg/hour
aPTT >110 sec (>3.3 × control)	Hold infusion one hour, then decrease infusion rate by 4 u/kg/hour

Low molecular weight heparin (LMWH): LMWHs offer several advantages over UFH including longer half-life, better bioavailability and more predictable dose response. In contrast to UFH, the LMWHs are dosed by weight and usually do not require dose adjustments or laboratory monitoring.

Pentasaccharides: The synthetic pentasaccharide, fondaparinux, is approved by the FDA for treatment of acute DVT and acute PE. Administered subcutaneously on a once daily basis, the fixed dose of fondaparinux is 5 mg for body weight less than 50 kg, 7.5 mg for body weight of 50 to 100 kg and 10 mg for body weight greater than 100 kg. As with IV UFH and LMWH, fondaparinux is initiated concurrently with warfarin and continued for at least 5 days. Fondaparinux does not require dose-adjustment or monitoring of aPTT or anti-Xa activity. It does not cause heparin-included thrombocytopenia (HIT). Fondaparinux is contraindicated in patient with severe renal impairment. In a recent study, Idraparinux, a long-acting inhibitor of activated factor X, given once-weekly subcutaneously had an efficacy similar to that of heparin plus a vitamin K antagonist. However, in patients with pulmonary embolism, idraparinux was less efficacious than standard therapy. During a 6-month extension of thromboprophylaxis, idraparinux was effective in preventing recurrent thromboembolism but was associated with an increased risk of a major hemorrhage.

Warfarin: Oral vitamin K antagonists, such as warfarin, are started concurrently with heparin, LMWH or fondaparinux and overlapped until full therapeutic efficacy has been achieved. For majority of patients, target INR is between 2.0 and 3.0. Management of warfarin anticoagulation is often challenging because of many dietary and drug-drug interaction.

Upper extremity DVT, this can be primary(due to thoracic outlet syndrome or Paget-Schrotter syndrome) or secondary, which can be genetic (hypercoagulable states) or acquired (malignancy, SVC syndrome, due to central lines or peripherally introduced central lines, PPM implantation).

Signs and symptoms include pain, tenderness, erythema and discoloration over the affected area, swelling, etc.

Diagnostic modalities are similar to lower limb DVT, as is the treatment. However if the DVT is found to be due to a central catheter, instilling a fibrinolytic such as streptokinase for a few hours and then withdrawing the fibrinolytic solution may be a better alternative to removing the catheter in some.

Aortic Dissection

Acute aortic dissection is the most common catastrophic event affecting the aorta, with an estimated annual incidence of 5 to 30 per million. In a necropsy series, the prevalence is 0.2 to 0.8 percent. The early mortality is very high.

Dissection of the aorta is characterized by separation of the layers of the aortic wall, due to blood entering through a tear in the intimal layer. 'Acute' aortic dissection is arbitrarily defined as those identified less than 14 days from onset; the remainder are considered 'chronic'.

Etiology/Associations

The main associations for aortic dissection are as follows:

- A connective tissue disorder, such as Marfan's or Ehlers-Danlos syndromes.
- Medial degeneration secondary to age
- Hypertension
- Iatrogenic (e.g. through using an intravascular catheter).

Classification: Two Schemes are Utilized

Debakey, in 1965, identified three types of dissection:

Type I: Involves the ascending aorta and a variable portion of the thoracic and thoracoabdominal aorta

Type II: Limited to ascending aorta

Type III: Involves the decending thoracic aorta without (IIIa) or with (IIIb) extension into the abdominal aorta

Subsequently, in 1970, Daily et al proposed the **Stanford classification**; those dissections involving the ascending aorta were classified as Type A and those without ascending aorta involvement, Type B.

Presentation

Symptoms

Sudden, excruciating chest and/or interscapular back pain, sometimes radiating into lower back or abdomen.

- Syncope
- Neurological phenomena (including paraplegia)

Signs

- Hypertension
- Pulse deficits (e.g. BP differences between the arms, and/or loss of the leg pulses)
- Early diastolic murmur, suggesting aortic regurgitation
- Neurological signs.

Few Important Facts

- Occurs most commonly between 50 to 60 years (ascending aorta) a decade later in descending aorta
- M:F = 2:1
- Most common symptom is pain—severe and sudden onset maximum at the onset, sharp and tearing in nature may have wide radiation in the back, abdomen, lower extremities.
- *Associated features:* CCF (7%), syncope (9%), stroke (6%), AMI, Paraplegia, cardiac arrest and SCD.
- Painless in diabetes, prior cardiac surgery
- Hypertension is present in 70 percent, mostly in Type B but many Type A patients may be normotensive or hypotensive
- Hypotension demands exclusion of cardiac tamponade
- Absent pulses, aortic regurgitation may be associated
- Acute aortic regurgitation is a feature of Type A dissection.

Investigations

1. *ECG:* This may be normal or show LV hypertrophy and inferior ST-elevation (if right coronary artery is involved in dissection flap [Dissections involving left main coronary artery die immediately].
2. *Chest X-ray:* This may show widening of aortic silhouette or pleural effusion or may be normal. Widened mediastinum: Chest > 0.25 – 0.31, mediastinum

width ≥ 8 cm at level of aortic knob) and displacement of intimal aortic calcification > 6 mm are diagnostic. Sensitivity and specificity of X-ray are 64 and 86 percent respectively. If negative, does not rule out dissection.

3. *Echocardiography:* (a) Transthoracic (TTE) diagnoses a minority of dissections and hence a normal TTE does not exclude dissection. Pericardial effusion and aortic regurgitation suggests possible dissection. (b) Transesophageal (TEE) is a very sensitive and specific method for detection of aortic dissection especially concomitant coronary and aortic valve involvement. It should be performed only in a high dependency area if dissection is suspected.
4. *Computed tomography scanning:* This is currently the most widely used technique for diagnosis of aortic dissection. It identifies two distinct aortic lumens that are separated by a flap. In future, MRI may take the place of CT scanning, particularly as no IV contrast is necessary.
5. *Aortography:* Long considered to be the 'gold standard' for the diagnosis of dissection, aortography is often not necessary if a clear picture has emerged from noninvasive investigations. It may be required by the surgeon to investigate branch vessel involvement and delinate coronary disease, but does carry a significant risk and should only be performed with surgical team standing by.

A recent study has shown that levels of a smooth muscle troponin-like protein, calponin in blood is elevated in acute aortic dissection compared with controls. This biomarker has the potential for use as an early diagnostic biomarker for acute aortic dissection. Serum D-dimer increases is till date the most promising marker. Patients with low pre-test probability who have serum D-dimer < 500 ng/ml can be ruled out for the disease.

Risk-stratification: The risk of early death from those dissections involving the ascending aorta (De Bakey Type I and II, Stanford Type A) is substantially higher than for lesions isolated to the descending aorta (De Bakey Type III, Standford Type B) because life-threatening complications like acute AR, coronary occlusion and intrapericardial rupture may occur with dissections involving ascending aorta. Hence, treatment of dissections involving ascending aorta is typically surgical and that of uncomplicated Type B dissection is medical.

Medical Treatment

i. *Control of pain:* Generally with IV opioid analgesia plus an antiemetic.
ii. *Control of blood pressure:* Systolic BP should be lowered to less than 120 mm Hg. IV Labetolol is the drug of choice. Initial dose is 40 to 80 mg/IV every 10 minutes. Start 20 mg IV over two minutes up to maximum of 300 mg IV. Alternatively, IV nitroprusside (0.1-5 mg/kg/min or even up to 10 mg/kg/min) may be used. Other options are IV esmolol or IV verapamil or Diltiazem. IV Enalaprilat 0.625 mg or 1.25 mg over 5 minute every 6 hours up to maximum of 5 mg qid.

Surgical Treatment: It is the definitive therapy for dissection of the ascending aorta. Objectives of surgery for acute ascending aortic dissections (i.e. **type A dissections)** are:

- Excision of the intimal tear
- Resection of the most damaged part of the aorta
- Obliteration of the entry into the false lumen by suturing the edges of the dissected aorta both proximally and distally.
- Restoration of aortic continuity by the insertion of prosthetic graft.
- Resuspension or replacement of the aortic valve—sometimes necessary in the presence of aortic regurgitation.
- Open surgery is considered treatment of choice in type A to prevent life-threatening complications.

Treatment of type B dissection is evolving and may require endovascular therapy. Medical therapy is the treatment of choice for majority (> 90%) of patients with type B aortic dissection. A few patients with complicated type B dissection need emergency surgical or endovascular management. The term 'complicated' means persisting or recurrent pain, uncontrolled hypertension despite full medication, early aortic expansion, malperfusion and signs of rupture (hemothroax, increasing periaortic and mediastinal hematoma). Choice between surgery and endovascular repair should be decided by a multidisciplinary team. For endovascular repair, the stent-graft diameter should exceed the diameter of the landing zones by at least 10-15 percent of reference aortic diameter. Technical challenge, especially in complicated type B dissections, may be to cannulate the narrowed, sometimes collapsed true lumen. To assure access to the true lumen, TEE may be necessary. Procedure-related difficulties may be overcome by an antegrade approach via the brachial artery with the guidewire being snared in the aorta. Ballooning of the stent-graft is not recommended even if it is not fully expanded. Retrograde dissection and rupture of the dissection membrane has been reported due to ballooning. Pharmacological lowering of blood pressure < 80 mm Hg (systolic) during stent-graft deployment may be sufficient in many cases to avoid displacement of the device. Combined surgical and endovascular techniques, so-called hybrid procedures, have become popularized during the last decade.

Management of Pericardial Tamponade

Pericardial tamponade should be managed as an emergency with open surgical repair of aorta and drainage of pericardium under direct vision. Closed pericardiocentesis may lead to sudden cardiac death, as gross reduction of pericardial pressure may lead to increase in intra-aortic pressure. So if pericardiocentesis is at all needed, a small amount should be removed, just to stabilize the patient.

Acute Limb Ischemia

Though many of the acute vascular occlusion occur without the patient noting either sudden pain or altered appearance of the limb, acute lower limb ischemia sometimes presents as a dramatic event.

- The onset is painfully obvious to the patient
- The appearance of the limb is frightening to the patient and the doctor
- The patient intuitively fears for the survival of the limb.

Acute Lower Limb Ischemia (ALLI) occurs mainly due to two factors:

i. Embolism
ii. *In situ* thrombosis
   - Previously surgical revascularization (Thromboembolectomy) was the treatment of choice but it was seen later that surgical revascularization has a higher mortality (10-20%) and historically amputation rate in the survivors of emergency surgical revascularization was also frustratingly high (10-20%).
   - As the occluding thrombus is always fresh, thrombolysis with a catheter placed near the thrombus becomes an option with excellent result and is considered as the treatment of choice
   - Patients with embolic ALLI are more likely to die than those with thrombolysis, usually secondary to underlying cardiac disease, where as thrombotic ALLI are more likely to lose their limbs when compared with embolic ALLI.

Management Strategies

Clinical History

Symptoms

Pain

i. Sudden onset produced by minimal exertion but clears with rest/ immobilization; involves foot only.
ii. Persistent rest pain, persisting, involving foot and calf Coldness, paresthesia which can progress to anesthesia or paralysis

Signs: Pulselessness, absence of pulse which can progress to absence of capillary refill, fixed skin mottling, bullae and necrosis.

Clinical categories of ischemia are:

i. Viable
ii. Threatened
iii. Irreversible

Lab

- Chemistry panel, coagulation screen (INR, APTT) and CBC
- Typing and screening for possible blood transfusion

Imaging

- CXR (Pulmonary edema ?)
- Echocardiogram (? Embolism)
- Vascular ultrasound with Doppler
- Angiography (single segment of occlusion, two segment of occlusion (or equivalent) and > 1 trifurcation patent, greater than two segment of occlusion and no trifurcation patent).

Classification

Rutherford Clinical Classification of ALI

Class	Category	Prognosis loss	Sensory	Muscle weakness	Arterial Doppler	Venous Doppler
1	Viable	No immediate limb threat	None	None	Audible	Audible
2A	Threatened; marginal	Salvageable if treated promptly	Minimal-none	None	± Audible	Audible
2B	Threatened; immediate	Salvageable if treated immediately	More than just toes	Mild-moderate	Rare audible	Audible
3	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

A proposed clinico-ultrasonographic–angiographic correlation

Category	Description	Neuromuscular finding	Doppler	Angio
I	Viable	No sensory loss or muscular weakness	Audible arterial and venous	Single segment occlusion
II	Threatened	Rest pain, moderate sensory loss, mild to moderate muscle weakness	Inaudible arterial audible venous	Two segment occlusion and distal trifurcation patent
III	Irreversible	Profound deficit	No signal	> 2 segment occlusion, no distal trifurcation patent

Management Pathways

i. *Viable:* Heparinization, angiography, wire and catheter placement and thrombolysis

ii. *Threatened:* Like viable ± mechanical thrombectomy ± GP2b3a receptor blocker (abciximab)
iii. *Irreversible:* Heparinization
Do not lyse if calf muscles are not viable (rigid and nonfunctioning)
Delayed revascularization surgery/amputation

Heparinization

- Heparinize to prevent worsening of ischemia due to clot propagation/extension
- Improvement is associated with improvement of color and comfort.

Dose: Bolus of 3000 – 5000 units IV
Target APTT – 80 to 100 sec.
Maintenance dose: 1000 u/hour IV to keep
APTT – 80 to 100 sec prior to lysis
APTT around – 60 sec when hyperesthesia only present
Therapeutic levels of heparin anticoagulation not deemed critical during lysis.

Thrombolysis

- Access from contralateral femoral artery
- Contralateral sheath to reach common femoral artery of the affected side
- Try with regular guidewire (non-hydrophilic); if the occlusion is crossed it confirms a new clot (0-14 days)
- Nowadays thrombolytic therapy is delivered through an infusion catheter that combines multiple side holes plus ultrasound emissions.

Dose of thrombolytic drugs

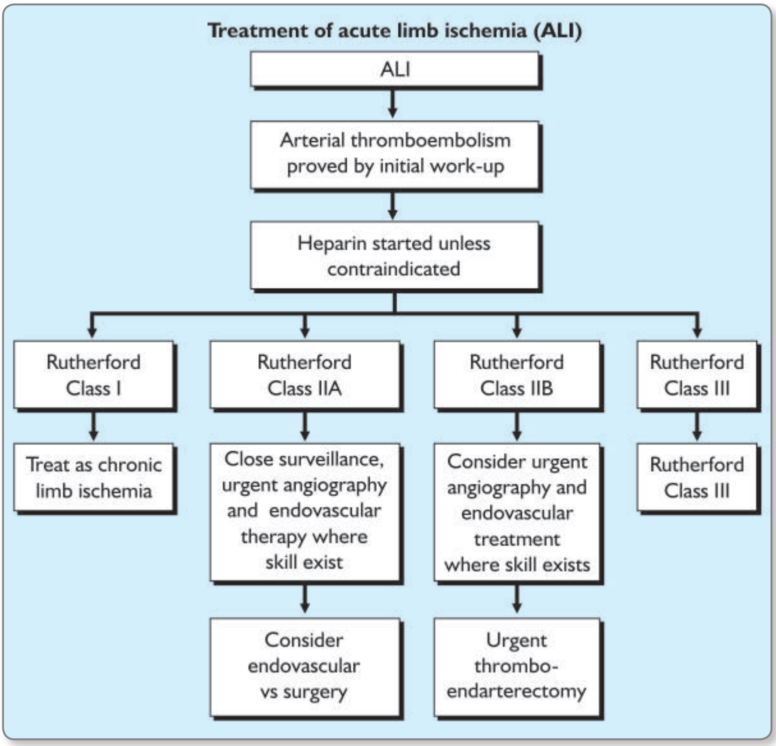
- In a viable limb with no or minimal sensorimotor impairment, begin with low dose of lytic and re-examine after over-night infusion
- In a threatened limb short-term high dose (4 hours may be tried) if either sensory deficit is more than hyperesthesia or if there is some motor impairment (High dose = 2 to 4 times low dose)
- After 4 hours re-angio with intent to finish by aspirating any residual clot (Possis) or just switch to low dose for overnight infusion if clinical examination has improved, and no easy access to the interventional site
- Lytic low dose:
  Urokinase = 50,000 to 60,000 units/h.
  Tenecteplase (TNK-tpA) = 0.2 mg/h.
  Alteplase = 0.5 mg/h.
  Reteplase (rPA) = 0.20 to 0.24 mg/h.

Heparin is not necessary with tpA
With TNK or rPA 150 units/hour via sheath
With urokinae: IV heparin (with APTT 60 – 80 seconds).

Endovascular therapy

Percutaneous intervention can offer limb-salvage success rates that rival those for surgical management for ALI and a strong consideration for endovascular management of ALI can be made where skilled personnel and facilities exist. The Rochester trial showed a significant mortality benefit at 1 year, with thrombolysis (catheter directed) mostly due to decreased complications compared to an open operative procedure. The STILE trial showed modest amputation-free survival with catheter-directed thrombolysis (CDT) compared with surgery. Largest of these trials, TOPAS, failed to reveal any mortality benefit over open embolectomy at 1-year follow-up. Although no statistical difference was noted in the rate of amputation between the two groups in these three trials, CDT did avoid the need for open surgery and can treat smaller distal vessels. Drawbacks include increased overall cost due to the need for prolonged infusion times combined with intensive care requirements and possible repeat catheterization procedures.

Catheter-directed thrombolysis (CDT) remains an initial treatment option for patients presenting with Rutherford category 1 or 2 ALI. Percutaneous mechanical thrombectomy (PMT) using Angiojet rheolytic thrombectomy system is also often used as first-line therapy. Percutaneous aspiration thrombectomy (PAT) using Pronto extraction catheter has been used in ALI but its success in ALI has mostly been anecdotal (unlike coronary interventions in AMI) and is limited to primarily managing embolization during peripheral interventions. A relatively novel isolated pharmaco-mechanical thrombolysis-thrombectomy (IMPT) system using Trellis PIS has been extensively described in treating DVT and there are reports for treatment of either *de novo* supra-inguinal arterial lesions or infrainguinal peripheral arterial bypass graft occlusion with successful clinical outcomes achievable in up to 95% of cases. Successful endovascular treatment of ALI also requires careful post-procedure observation for compartment syndrome or any other complication.



Suggested Reading

1. Apostolakis E, Baikoussis NG, Georgiopoulous M. Acute Type-B Aortic Dissection: The Treatment Strategy. Hellenie J Cardiol 2010;51:338-47.
2. ESC guidelines for Diagnosis and Management of Acute Pulmonary Embolism. European Heart Journal 2008doi:10.1093/eur.hearty/edn 310.
3. Grabenwoger M, Alfonso F, Bachet J, et al. Thoracic Endovascular Aortic Repair (TEVAR_ for treatment of aortic diseases: a position statement from EACTS and ESC in collaboration with EAPCI. European Heart Journal 2012;33:1558-63.
4. Hebballi R, Swanevelder J. Diagnosis and Management of aortic dissection. Br J of Anaesthesia 2009;9:14-8.
5. Hirsh J, Guyatt G, Albers G, et al. Antithrombotic and thrombolytic therapy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:71S-109S.
6. Jaff MR, McMurty MS, Archer SL, et al. AHA Scientific Statement. Management of massive and submassive pulmonary embolism, ileofemoral deep venous thrombosis and chronic thromboembolic pulmonary hypertension. Circulation 2011;123:1788-1830.

Acute Cardiac Care in Pediatric Practice

chapter **12**

Achyut Sarkar

Cardiovascular emergencies in pediatric population are a vast subject, which cannot be compiled in this limited space. We have selected a few cases, which we face relatively commonly in our day-to-day practice and which even a cardiologist engaged in adult-practice may be called upon to attend as the "best-available" person at that point of time.

Case 1

A male child, weighing 3.2 kg at birth with an uncomplicated normal delivery and good APGAR score, suddenly became cyanosed six hours after birth in the nursery. During initial assessment, the SPO_2 was 76% with Head-box O_2. Over next two hours, SPO_2 came down to 58%; the baby became tachypneic; no murmur; black lungs in the chest X-ray, with a narrow pedicle. A PDA-dependent congenital cyanotic disease was diagnosed.

Management

- ABG showed severe hypoxia along with metabolic acidosis.
- Baby was put on mechanical ventilation.
- Ventilatory strategies: ventilating at a lower tidal volume (as low as 6 ml/kg) to maintain a permissive hypercapnea and a low FiO_2 (around 60%). All these help to keep the ductus open.
- Volume.
- Sodium bicarbonate.
- To keep the glycemic status and electrolytes optimum.
- Then the echocardiogram was available and the cardiac lesion was confirmed as d-TGA, restrictive ASD and a patent ductus.
- Prostaglandin was started and the baby was shifted from nursery to pediatric cardiology unit.
- ***Prostaglandin:***
    1. Alprostadil (Prostin VR)
    2. To start with the lowest dose (0.01mcg/kg/min)
    3. To increase up to 0.1mcg/kg/min.
    4. To maintain at lowest effective dose.
    5. Precaution: apnea in 10 to 20% cases.

6. Side effects: Inhibition of platelet aggregation, hypotension, bradycardia, other rhythm disorder, fever, seizure-like activities.

- Even after all these efforts, the saturation started coming down, and a decision of balloon atrial septostomy was taken.
- **Balloon Atrial Septostomy**
  1. Indication:
     a. to increase further admixture: TGA*
     b. To vent RA/LA: Tricuspid atresia, TAPVC/HLHS.*
  2. Where to do: NICU (echo guided)/in the CATH-LAB.
  3. Route: transfemoral vein/umbilical vein.
  4. Indications of success: equalization of both atrial pressures, rise in SaO_2 by 10% and ASD size around 8 mm in echo.
  5. Complications: Failure, arrhythmia, cardiac perforation, laceration of the AV valve, balloon embolization.
- On the D3, arterial switch operation was done.
  *[*TGA = Transposition of great arteries, *TAPVC = Total anomalous pulmonary venous connection, *HLHS=Hypoplastic left heart syndrome]*

Case 2

A male child, aged 5 months was admitted in the pediatric cardiology unit with spells of hyperpnea, deepening cyanosis and transient loss of consciousness on crying, feeding or any form of straining. On examination, the baby was found cyanosed and polycythemic. ECG, chest X-ray and echocardiogram were done and a diagnosis of TOF complicated with hypoxic spell was done.

Hypoxic spell is commonest between second to sixth months of age, becoming infrequent after two years of age. It usually occurs after a prolonged deep sleep when the vulnerable respiratory center remains very sensitive. Physical stress results in increased cardiac output. On the face of already existing right outflow obstruction and probably superadded dynamic contraction, increased cardiac output results in enhanced right to left shunt, deepening cyanosis and hypoxia. The sleep-sensitive respiratory center overreacts and results in hyperpnea, which further increases the cardiac output and precipitates the vicious cycle.

Management of Hypoxic Spell

Aims: To decrease right to left shunt either by decreasing the venous return or by increasing the systemic vascular resistance.

Step 1

- Moist O_2 inhalation
- Knee-chest position.

Step 2

Propranolol: 0.1 mg/kg diluted in 10 ml of water/half the dose as bolus/rest, over next 15 to 10 minutes (alternatively, IV Metoprolol: 0.2 mg/kg slowly over 30 minutes can be used).

Step 3

- ***Morphine:*** 0.1 mg/kg/dose, IM/SC/IV (to decrease the venous return).
- ***NaHCO$_3$:*** 1mEq (1 ml)/kg (to combat metabolic acidosis).

Step 4

- Volumes
- ***Phenylephrine:*** 0.1mg/kg SC/IM or 0.01 mg/kg IV or as a drip 0.1-0.5 mcg/kg/min (to increase the systemic vascular resistance).

Step 5

- General anesthesia
- Emergency shunt.

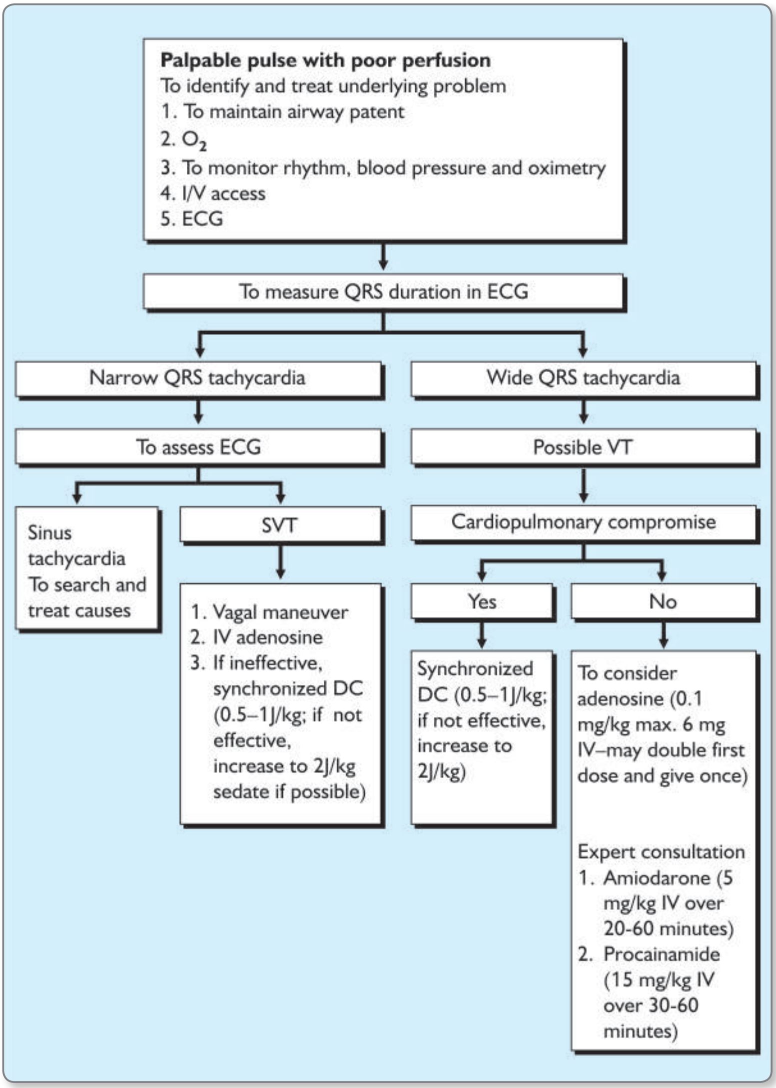
Case 3

A 5 years old male child was admitted in the pediatric cardiology unit with persistent uneasiness along with palpitation for the preceding four hours. This was his first of this ailment. The child was afebrile. His heart rate was above 230/min. BP was 100/70 mm Hg. Chest was clear. An ECG was done showing a narrow-complex regular tachycardia, rate 250/min. A diagnosis of PSVT with a normal hemodynamic status was made.

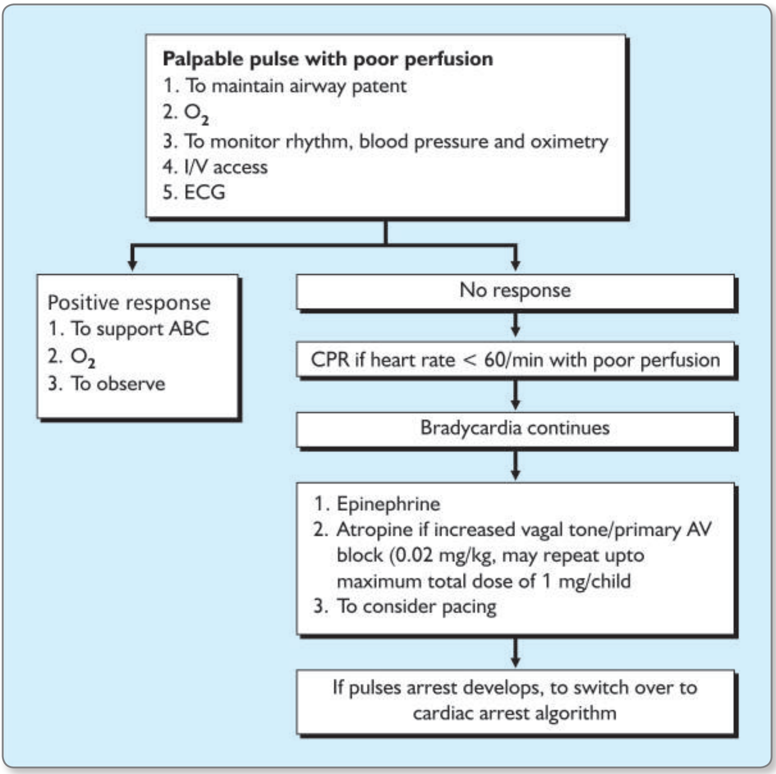
Management of Supraventricular Tachycardia

- Ice pack on face to stimulate gag reflex (one must avoid pressing on eyeball)
- Valsalva
- Carotid sinus massage
- *No response:* Adenosine 0.1 mg/kg was given in central line followed immediately with rapid fluid flush.
- No response, the dose was doubled (may be given maximum up to 12 mg).
- No response; the child became listless; BP started falling.
- Synchronized cardioversion with 0.5 to 1 Joule/kg; it was not effective, and the dose was increased up to 2 Joule/kg.
- After initial conversion to sinus rhythm, the PSVT restarted. IV Amiodarone infusion 5 mg/kg over 30 to 60 minute ultimately terminated the PSVT.

Pediatric tachycardia



Pediatric pulse with poor perfusion



Case 4

A 4 years old male child was admitted in the pediatric cardiology unit with severe respiratory distress for the preceding 5 days. He came from a remote health center without any initial work up. Clinical examination revealed all features of CHF: anasarca, raised JVP, LV S3 and enlarged tender liver. His BP was 140/100 mm Hg and pulse rate was 38/minute. When the child was being examined, suddenly he developed cardiac arrest. Subsequent management was:

- CPR was started
- He was put on monitor, which showed complete asystole
- IV Epinephrine was given 0.01 mg/kg and was repeated
- The child came up; put on a temporary pacemaker; there was, however a persistent capture failure with child's own rhythm as 40/min, absent p wave and tall T wave

- Subsequent work up revealed blood urea 118 mg/dl, creatinine 4.9 mg/dl, K+6.7 mmol/L, urine alb 1.2 gm/24 hrs, R.B.C ++, ECG typical of hyperkalemia.
- There was no structural lesion in echocardiogram
- Acute nephritic syndrome was diagnosed; managed accordingly and sinus rhythm was restored.

Case 5

A female child aged 6 years was admitted in the pediatric cardiology unit with a history of three syncope over preceding two days. She had flu-like ailments for which her regular pediatrician attended her. He witnessed the last syncope when she became pulseless and came up only after CPR at his chamber. There was no warning symptoms or convulsive movements; two of this syncope was in lying posture. There was no prior history of syncope. Clinical examination did not reveal specific abnormalities of any of the system. Subsequent work up was done according to the protocol of the unit.

Common Cause of Cardiac Syncope in Pediatric Age Range

A. Neurogenic
B. Dysrhythmic
   - PSVT (including Pre-excitation)
   - VT/VF
   - LQTS
   - Short QT syndrome
   - Brugada syndrome
   - Catecholamine-sensitive monomorphic VT
   - Arrhythmogenic right ventricular dysplasia
   - Repaired TOF
   - Myocarditis/DCM
   - Congenital or acquired coronary artery anomalies.

C. Mechanical
   - RVOT or LVOT obstruction
   - PAH
   - HCM
   - Cardiac tumor

Work Up

- ECG
- Echocardiogram
- Routine electrolytes
- 24 hours Holter monitoring
- Head up tilt test

- Transtelephonic ECG
- Implantable loop recorder
- Neurological assessment
- EP study
- When this initial work up was going on, suddenly she had another pulseless syncope; monitor revealed a polymorphic VT. She was resuscitated. The 12-lead ECG showed a QT of about 540 msec. For her Flu-like ailments, she was prescribed antihistamines and macrolide group of antibiotics, which caused this acquired LQTS leading to polymorphic VT and syncope.

Case 6

An infant, aged 2 months, 2.8 kg, presented with "difficult feeding", excessive sweating, preferring to be picked up all the times (spoiled baby). On examination, the baby was tachypneic; cool extremities; heart rate 220/minute; low volume pulse; signs of impaired peripheral perfusion(mottled extremities and decreased capillary refill); no murmur; liver down by 4 cm.

All the features were suggestive of congestive heart failure (CHF).

Common Causes of CHF in Early Infancy

1st day of life

- *Myocardial:* Asphyxia, sepsis, Hypoglycemia, Hypocalcemia.
- *Hematological:* Anemia, Hyperviscosity
- *Heart rate:* SVT, congenital complete heart block
- Neonatal myocarditis.

1st week of life

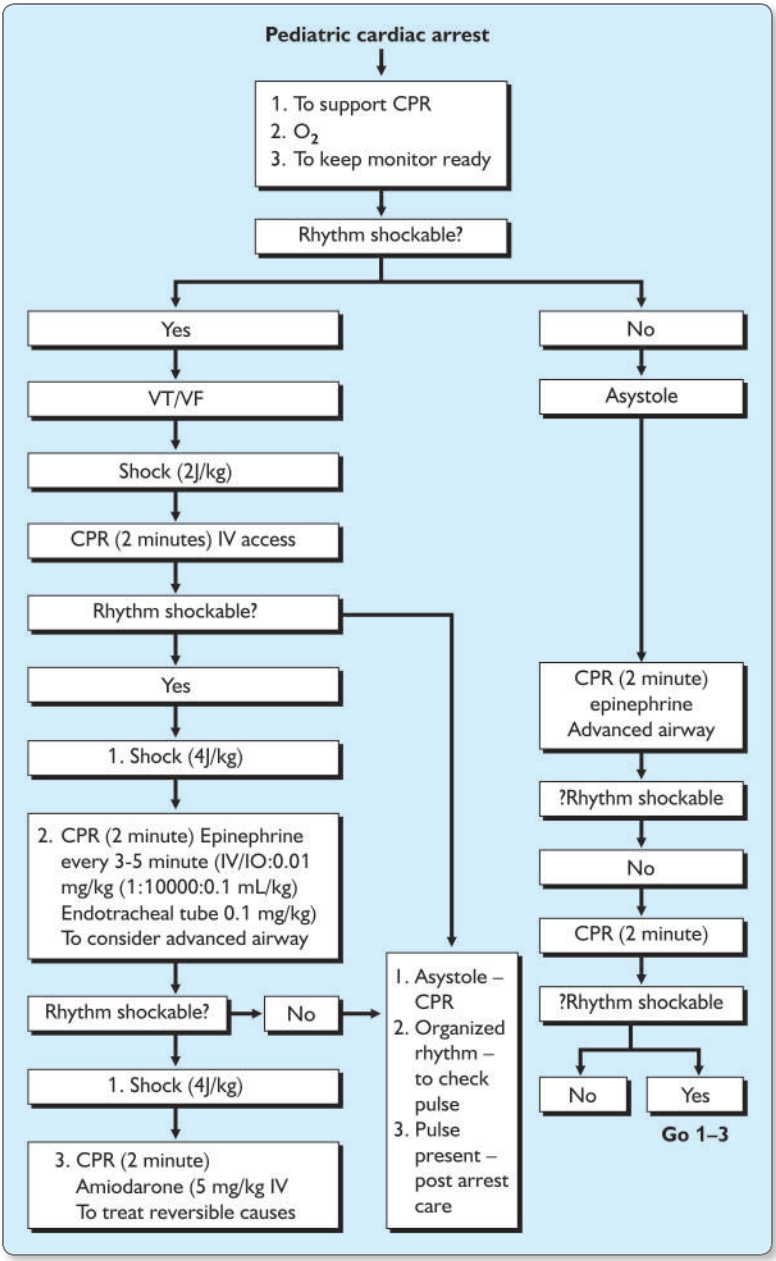
- Structural abnormalities: PDA (premature) critical AS and PS, coarctation, HLHS, TAPVC (obstructive)

1st 2 months of life

- ***Structural abnormalities:*** L-R shunt, Left sided obstructive lesions. ALCAPA. (Anomalous left coronary artery from pulmonary artery)
- ***Heart muscle abnormalities:*** Cardiomyopathy, endocardial fibroelastosis, myocarditis
- ***Endocrine: Hypothyroidism:*** On these common etiological backgrounds, the baby was investigated in accordance with the protocol.

Routine Investigation

X-ray chest	ECG
Hb Total count	Serum glucose*
Serum calcium**	Serum electrolytes***
Echocardiogram	


Pediatric cardiac arrest
1. To support CPR
2. O_2
3. To keep monitor ready
Rhythm shockable?
Yes
No
VT/VF
Asystole
Shock (2J/kg)
CPR (2 minutes) IV access
Rhythm shockable?
Yes
CPR (2 minute)
epinephrine
Advanced airway
1. Shock (4J/kg)
?Rhythm shockable
No
2. CPR (2 minute) Epinephrine every 3-5 minute (IV/IO:0.01 mg/kg (1:10000:0.1 mL/kg) Endotracheal tube 0.1 mg/kg) To consider advanced airway
CPR (2 minute)
?Rhythm shockable
Rhythm shockable?
No
1. Asystole – CPR
2. Organized rhythm – to check pulse
3. Pulse present – post arrest care
No
Yes
Go 1–3
1. Shock (4J/kg)
3. CPR (2 minute)
Amiodarone (5 mg/kg IV
To treat reversible causes

* Hypoglycemia sets in secondary to hypermetabolic state; these babies are more irritable and can have seizure. Mothers may be diabetic.

** Hypocalcemia leads to irritation, seizure and occasional tetany; ECG shows prolonged QT interval.

*** Unlike adults, infants can show hyponatremia, hypochloremia and increased bicarbonate level even before starting decongestant treatment.

X-ray chest revealed CTR ratio > 0.55 with congestive changes. ECG revealed prominent q in lead I and aVL. Echocardiogram revealed dilated globular heart, severe LV systolic dysfunction, and grade 2 MR. Initial diagnosis was congenital dilated cardiomyopathy.

Management protocol
Diuretics
Inotrops
Vasodilators
↓
After stabilization
Beta blockers

To correct anemia
To correct infection
Hyperdense calories

Management for CHF was Started as per Protocol

The initial management involved the usual assessment of the baby's airway, breathing and circulation (ABC) achieving intravenous access. Management of low cardiac output was initiated by using a dopamine infusion at 5 to 10 mcg/kg/min; acidosis was corrected with administration of fluid and bicarbonate.

After the low output state was controlled, IV furosemide was started for a few days followed by oral route, along with spironolactone; ACEI and digoxin initiated too.

A few days after stabilization, baby was put on lowest dose of Carvedilol.

When the baby was cooled down, echocardiogram was reviewed and the final diagnosis was anomalous left coronary artery from pulmonary artery (ALCAPA).The baby was referred for surgical intervention.

Pharmaceutical agents used in the treatment of CHF

Agent	Pediatric dose	Comment
Preload reduction Furosemide	1 mg/kg/dose PO or IV	BID/TID
Hydrochlorothiazide Spironolactone	2 mg/kg/d PO divided BID 2 mg/kg/day	
Metolazone	0.2 mg/kg/dose PO	Used with loop diuretic, may increase to BID

Contd...

Contd…

Agent	Pediatric dose	Comment
Inotropes Digoxin	Preterm infants: 0.005 mg/kg/d PO divided bid or 75% of this dose IV <10 yr: 0.010 mg/kg/d PO divided bid or 75% of this dose IV >10 yr: 0.005 mg/kg/d PO qd or 75% of this dose IV	
Dopamine	5-28 mcg/kg/min IV	Gradually titrate upward to desired effect
Dobutamine	5-28 mcg/kg/min IV	Gradually titrate upward to desired effect
Milrinone	0.5-1 mcg/kg/min IV	Load: 50 mcg/kg IV slowly over 15 min
Afterload reduction Captopril	0.1-0.5 mg/kg/d PO divided q8h	
Enalapril	0.1 mg/kg/d PO divided qd/bid not to exceed 0.5 mg/kg/d	Adults: 2.5-5 mg/d PO qd-bid, not to exceed 40 mg/d
Nitroprusside	0.5-10 mcg/kg/min IV	May need to monitor cyanide level
Carvedilol	0.2-0.4 mg/kg/dose	BID

Infant with CHF: Initial "Normal Echo"

- Coarctation of aorta
- ALCAPA
- Obstructed TAPVC

Suggested Reading

1. Arthur Garson, Bricker JT, Fisher DJ, Neish SR. The science and practice of pediatric cardiology. 2nd edn. Williams and Wilkins, Philadelphia. 1998:1207-56.
2. Caldwell RL. Two dimensional echocardiographic differentiation of anomalous left coronary artery from congestive cardiomyopathy. Am Heart J. 1983;106:710.

3. Garson A Jr, Gillete PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment and long-term follow-up in 217 patients. J Paediatr. 1981;98:875.
4. Gillette PC, Garson AT. Sudden cardiac death in the pediatric population. Circulation, 1992;85(suppl 1):164-9.
5. Rankin AC, Oldroyd KC, Chong E. Value and limitation of Adenosine in the diagnosis of and treatment of narrow and broad complex tachycardia. Br Heart J. 1989;62:195-203.
6. Shaddy R, Boucek M, Hsu D, et al. Pediatric Carvedilol Study Group. Multicenter, randomized, placebo-controlled, double-blind trial of Carvedilol in children with heart failure. Program and abstracts of the American College of Cardiology 55th Annual Scientific Session; March 11-14, 2006; Atlanta, Georgia. Smaller Trial Late-Breaking Clinical Trials II, Abstract 418-6.
7. Tzivoni D, Kern A, Bansi S, Stern S. Terminology of torsade de pointes. Cardiovasc drugs ther. 1991;5:505-7.

Hypertensive Crisis

chapter 13

Saptarshi Mukhopadhyay, Soumitra Kumar

Hypertensive crisis refers to clinical circumstances with life-threatening hypertension (diastolic BP > 120-130 mmHg and mean BP = 140-150 mmHg) where rapid reduction of BP is required, not necessarily to normal range, to prevent or limit target organ damage. Hypertensive crises include, hypertensive emergencies and urgencies. Hypertensive emergencies are situations wherein immediate control of BP within minutes is required usually with parenteral therapy. Hypertensive urgencies are situations wherein control of BP is needed within hours (12-24 hrs) and hence usually treatment with oral agents may suffice.

Accelerated malignant hypertension is another very commonly used term, by which we connote diastolic BP ≥ 130-140 mmHg and vascular injury, mainly renal and various fundoscopic features are also implicated, of which the most sinister entity conventionally associated with the term "Malignant hypertension" has been papilledema. But truly speaking, it has little significance as far as overall prognosis is concerned and hence the common term accelerated malignant hypertension is used now-a-days.

Chronic Hypertension results in thickening and remodeling of arteriolar walls that appears to be an adaptive mechanism to prevent vascular damage from the mechanical stress of hypertension. However, when the blood pressure rises abruptly or increases to a critical level, these compensatory mechanisms may be overwhelmed, resulting in vascular damage. As a consequence of the mechanical stress of increased transmural pressure, focal segments of the arteriolar vasculature become dilated, producing a sausage-string pattern. Endothelial permeability rises in the dilated segments, leading to extravasation of fibrinogen, fibrin deposition in the media, and necrosis of smooth muscle cells (fibrinoid necrosis). Platelet adherence to damage endothelium with release of platelet-derived growth factor triggers migration of smooth muscle cells to the intima where they proliferate (neointimal proliferation) and produce mucopolysaccharide. These cells also produce collagen, resulting in proliferative endarteritis, musculomucoid hyperplasia, and finally fibroid obliteration of the vessel lumen. Blockage of arterioles leads to accelerated glomerular obsolescence and end-stage renal disease. Other factors may also contribute to damage arterial vasculature. Renal ischemia leads to stimulation of the renin-angiogensin system that can cause further increase of blood pressure and progressive vascular damage. Spontaneous natriuresis early in the course of malignant hypertension leads to volume depletion with activation of the renin-angiotensin system or catecholamines that further aggravates blood pressure. It is also possible that angiotensin II may be directly vasculotoxic. Activation of the clotting cascade within the lumen of damaged vessels may precipitate fibrin deposition with localized intravascular coagulation. Hence, microangiopathic hemolytic anaemia is a common finding in malignant hypertension. Cigarette smoking and oral contraceptive use may contribute to the development of malignant hypertension by interfering with prostacycline production in the vessel wall and thereby inhibiting repair of hypertension-induced vascular injury. Low dietary intake of potassium may actually promote vascular smooth muscle proliferation and therefore contribute to the development of malignant hypertension in blacks with severe essential hypertension.

Vascular lesions in malignant hypertension:

(i) Retinal: Hemorrhages
Cotton-wool spots
Papilledema

(ii) CNS: Intracerebral hemorrhage
Hypertensive encephalopathy

(iii) Cardiac: Left ventricular dysfunction
Renal: Glomerulosclerosis
Tubular atrophy
Interstitial fibrosis

(iv) Gastrointestinal: Hemorrhage
Bowel necrosis

(v) Pancreatic: Necrosis
Hemorrhage

Hypertensive emergencies can be subdivided into two categories:

A. Immediate BP reduction is required but not necessarily to normal
   i. Hypertensive encephalopathy
   ii. Severe hypertension associated with acute left ventricular failure and pulmonary edema, acute aortic dissection, eclampsia
   iii. Post CABG hypertension
   iv. Hypertension associated with circulating catecholamines (e.g. pheochromocytoma, clonidine withdrawal, interaction with monoamine oxidase inhibitor (MAOI), etc.

B. Immediate BP reduction is required only when it is excessively high:
   i. Hypertensive intracerebral bleeding
   ii. Acute subarachnoid hemorrhage
   iii. Some acute brain infarcts
   iv. Unstable angina or AMI.

Hypertensive urgencies include the following:

i. Accelerated-malignant hypertension without signs of end-organ dysfunction.
ii. Severe hypertension associated with coronary artery disease.
iii. Severe hypertension in the organ transplant patient.
iv. Preoperative, postoperative hypertension.
v. Hypertension associated with burns.
vi. Severe uncontrolled hypertension.

Clinical characteristics of accelerated-malignant hypertension are the following:

Symptoms and signs are usually dramatic.

1. BP diastole ≥ 140 mmHg
2. Fundoscopy: Hemorrhages, exudates, papilledema
3. CNS: Headache, altered sensorium, visual loss, focal deficits, seizures, coma
4. CVS: Prominent apical impulse,cardiac enlargement, congestive failure.
5. Renal: Oliguria, azotemia, urine shows protein and RBCs
6. GI: Nausea and vomiting

Course and Prognosis

Prior to effective therapy:	< 25% - 1 year survival
	≤ 1% - 5 year survival
With effective therapy:	90% - 1 year survival
	80% - 5 year survival
	Death beyond 5 years is usually due to CAD

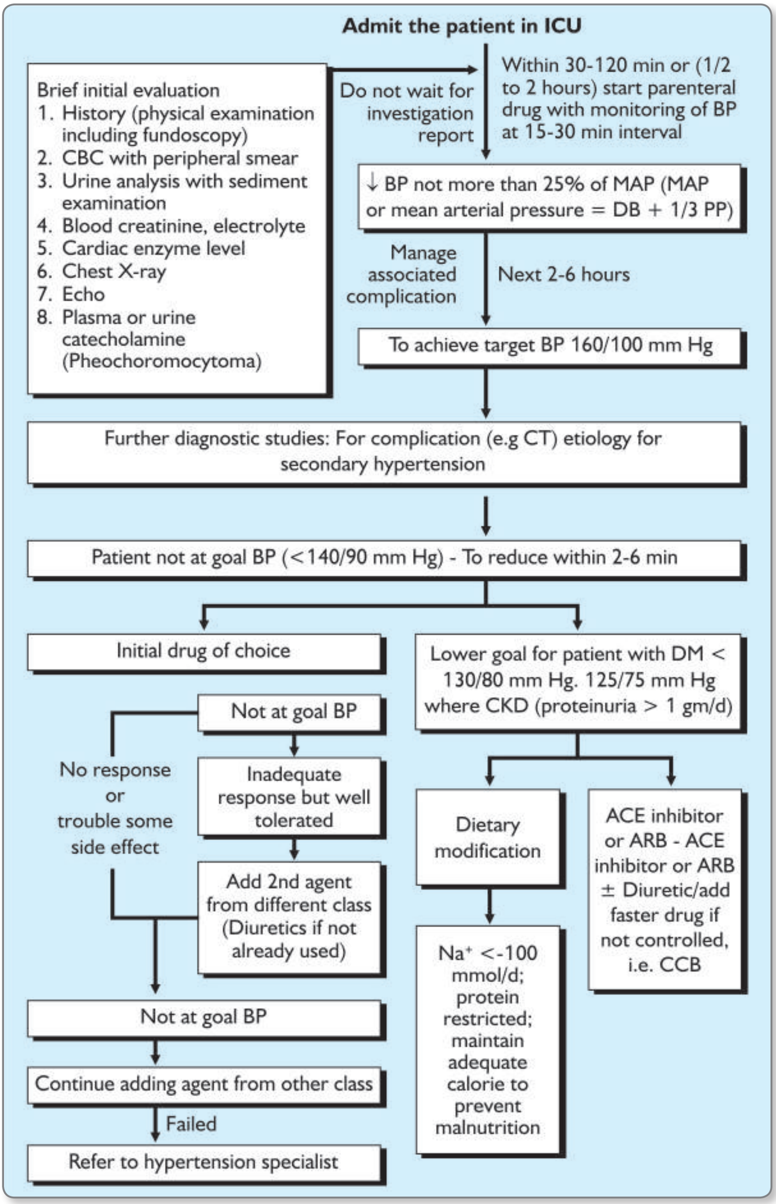
Goals of therapy:

i. Reduce mean arterial pressure by not more than 25% within minutes to 2 hours.
ii. Then aim for 160/100 mmHg within 2 to 6 hours –Avoid excessive fall in BP that may precipitate renal, cerebral or coronary ischemia.

Caution

Unpredictable fall in BP (rate and degree) with sublingual nifedipine is unacceptable and may be hazardous in severe atherosclerotic disease. Hence,routine use of sublingual nifedipine whenever BP rises beyond a predetermined level is quite inappropriate.

If BP is persistently >180/120 mmHg, long- acting agents are preferred. It should be remembered that elevated BP alone, unless abrupt and very severe, in the absence of symptoms or new or progressive target organ damage rarely requires emergency therapy.


Admit the patient in ICU
Brief initial evaluation
1. History (physical examination including fundoscopy)
2. CBC with peripheral smear
3. Urine analysis with sediment examination
4. Blood creatinine, electrolyte
5. Cardiac enzyme level
6. Chest X-ray
7. Echo
8. Plasma or urine catecholamine (Pheochoromocytoma)
Do not wait for investigation report
Within 30-120 min or (1/2 to 2 hours) start parenteral drug with monitoring of BP at 15-30 min interval
↓ BP not more than 25% of MAP (MAP or mean arterial pressure = DB + 1/3 PP)
Manage associated complication
Next 2-6 hours
To achieve target BP 160/100 mm Hg
Further diagnostic studies: For complication (e.g CT) etiology for secondary hypertension
Patient not at goal BP (<140/90 mm Hg) - To reduce within 2-6 min
Initial drug of choice
Not at goal BP
No response or trouble some side effect
Inadequate response but well tolerated
Add 2nd agent from different class (Diuretics if not already used)
Not at goal BP
Continue adding agent from other class
Failed
Refer to hypertension specialist
Lower goal for patient with DM < 130/80 mm Hg. 125/75 mm Hg where CKD (proteinuria > 1 gm/d)
Dietary modification
Na⁺ <-100 mmol/d; protein restricted; maintain adequate calorie to prevent malnutrition
ACE inhibitor or ARB - ACE inhibitor or ARB ± Diuretic/add faster drug if not controlled, i.e. CCB

Parenteral treatment for specific hypertensive emergencies

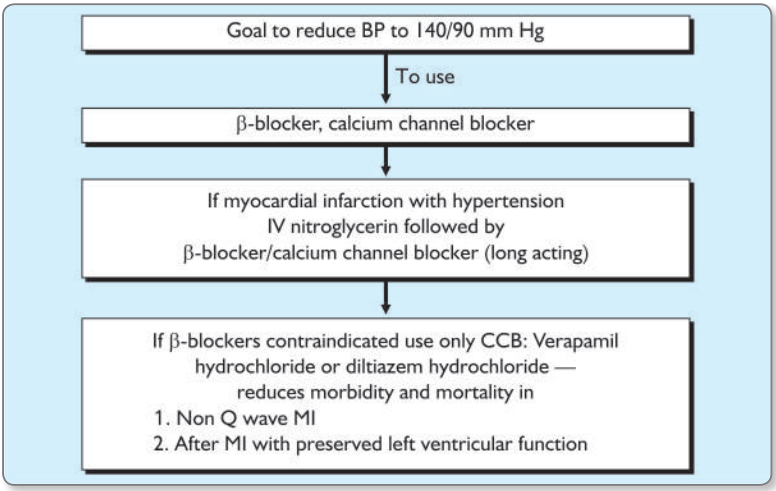
	Condition	Preferred	Avoided
1.	Hypertensive encephalopathy	Labetolol Nicardipine Nitroprusside	Methyldopa Diazoxide Reserpine
2.	Accelerated malignant hypertension	Labetolol Nicardipine Enalaprilat	Methyldopa
3.	Acute LVF	Enalaprilat Nitroglycerin Nitroprusside	Labetolol Esmolol
4.	Coronary insufficiency	Nitroglycerin Esmolol Nicardipine	Hydralazine Diazoxide Nitroprusside
5.	Dissecting aortic aneurysm	Trimethaphan Nitroprusside Esmolol	Hydralazine Diazoxide
6.	Catecholamine excess	Phentolamine Labetolol	All others
7.	Postoperative	Labetolol Nitroglycerin Nicardipine	Trimethaphan (Bladder and bowel atony)
8.	Eclampsia	Hydralazine Methyldopa Labetolol Ca-antagonists	Nitroprusside

Management of hypertensive urgencies (oral drugs generally suffice for the management of hypertensive urgencies)

	Drug	Dose	Onset of action	Duration
1.	Nifedipine	5-10 mg sublingual or swallowed	5-15 mins	3-5 hrs
2.	Captopril	6.25-50 mg sublingual or swallowed	15 mins	4-6 hrs
3.	Clonidine	0.2 mg initial then 0.1 mg/hour up to 0.8 mg	1/2-2 hrs	6-8 hrs
4.	Labetolol	200-400 mg	1/2-2 hrs	8-12 hrs

Management of Specific Situations

Patients with Coronary Artery Disease with Hypertension



Aortic Dissection

Classification of aortic dissection is based on the presence or absence of involvement of the ascending aorta. The dissection is defined as proximal if there is an involvement of the ascending aorta.

Acute aortic dissection is a hypertensive crisis requiring immediate antihypertensive treatment aimed at halting the progression of the dissecting hematoma.

Patients with acute dissection should be stabilized with intensive antihypertensive therapy to prevent life-threatening complications before diagnostic evaluation with angiography. The initial therapeutic goal is the elimination of pain that correlates with halting of dissection, and reduction of the systolic pressure to the 100 to 120 mmHg range or to the lowest level of blood pressure compatible with the maintenance of adequate renal, cardiac, and cerebral perfusion. Even in the absence of systemic hypertension, blood pressure should be reduced. Antihypertensive should be designed not only to lower the blood pressure but also to decrease the steepness of the pulse wave. The most commonly used regimens consists of initial treatments with intravenous beta-blockers such as propanolol, metoprolol or esmolol followed by treatment with sodium nitroprusside. After control of blood pressure, angiography or transesophageal echocardiography, or both should be performed. The need for surgical intervention is determined based on involvement of the ascending aorta.

Hypertensive Crisis after Coronary Artery Bypass Surgery

Paroxysmal hypertension in the immediate postoperative period is a frequent and serious complication of cardiac surgery. Paroxysmal hypertension is the most frequent complication of coronary artery bypass surgery, occurring in 30 to 50% of patients. It occurs just as in normotensive patients as it does in those with a history of chronic hypertension.

The initial management of post-bypass surgery hypertension should focus on attempts to ameliorate reversible causes of sympathetic activation, including patient agitation on recovery from anesthesia, tracheal or nasopharyngeal irritation from the endotracheal tube, pain, hypothermia with shivering, ventilator asynchrony, hypoxia, hypercarbia and volume depletion. If these general measures fail to lower blood pressure, further therapy should be guided by measurement of systemic hemodynamics. Intravenous nitroglycerin or nitroprusside is the drug of choice to provide a controlled decrease in systemic vascular resistance and blood pressure. Nitroglycerin may be the preferred drug because it dilates intracoronary collateral arteries.

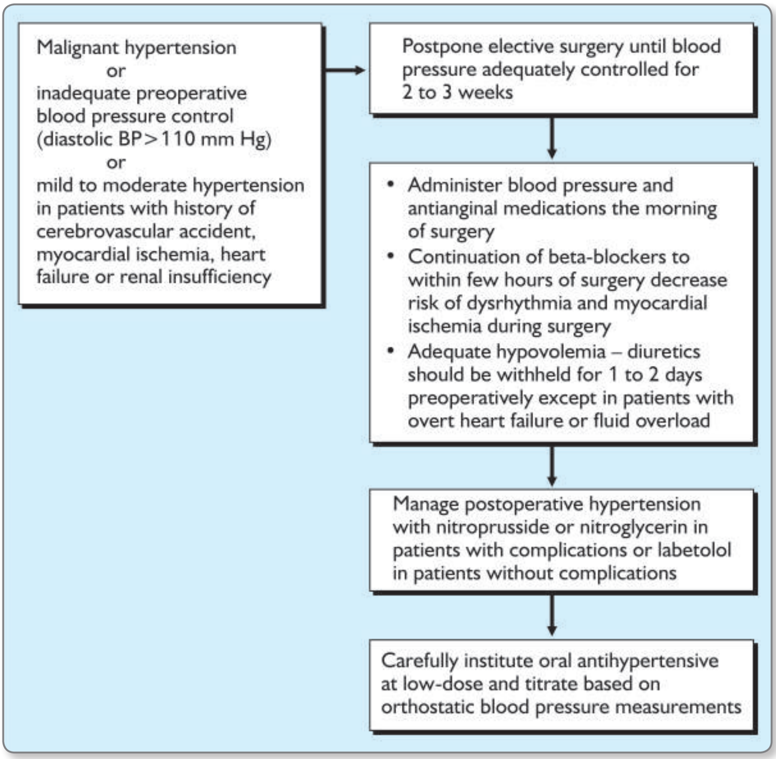
Pheochromocytoma

In most patients, pheochromocytoma causes sustained hypertension that sometimes becomes malignant as evidenced by the presence of hypertensive neuroretinopathy.

Prompt control of blood pressure is mandatory to prevent life-threatening complications. Although the nonselective alpha-blocker phentolamine often is cited as therapy of choice for pheochromocytoma-related hypertensive crisis, sodium nitroprusside is equally effective and easier to administer. After adequate alpha-blockade is achieved, based on the presence of moderate orthostatic hypotension, oral beta-blocker therapy can be initiated as needed to control tachycardia.

Poorly Controlled Hypertension in Surgical Patients

Although adequate preoperative control of blood pressure is imperative, aggressive parenteral therapy to do so can lead to precipitous fall of blood pressure which carries the risk of significant complications such as hypovolemia, electrolyte abnormalities and marked intraoperative blood pressure lability. General anesthesia is accompanied by a 30% decrease in cardiac output. In normotensive persons and patients with adequately treated hypertension, anesthesia is not associated with a decrease in systemic vascular resistance. Therefore, decrease in mean arterial pressure (MAP) is modest (25-30%). However, in patients with inadequate preoperative blood pressure control, anesthesia is associated with a concomitant decrease in systemic vascular resistance (SVR) of approximately 27%. The combined decrease in cardiac output and SVR leads to a profound decrease in MAP (45%) during anesthesia. This intraoperative hypotension predisposes to myocardial ischemia, cerebrovascular accidents and acute renal failure. Hence, more gradual and sustained adequate preoperative blood pressure control should be the goal in all hypertensive patients.



Hypertensive Emergency in Pregnancy

Classification of hypertensive disorders in pregnancy

The classification is as follows:

- Pre-eclampsia and eclampsia
- Gestational hypertension
- Chronic hypertension
  - Essential
  - Secondary
  - White coat
- Pre-eclampsia superimposed on chronic hypertension

- Pre-eclampsia: A diagnosis of pre-eclampsia can be made when hypertension arises after 20 weeks of gestation and is accompanied by one or more of the following
- Renal involvement
  - Significant proteinuria – dipstick proteinuria subsequently confirmed by a spot urine protein/creatinine ratio > 30 mcg/mmol
  - Serum or plasma creatinine > 90 mmol/l
  - Oliguria
- Hematological involvement
  - Thrombocytopenia
  - Hemolysis
  - Disseminated intravascular coagulation
- Liver involvement
  - Raised serum transaminases
  - Severe epigastric or right upper quadrant pain
  - Neurological involvement
  - Convulsions (eclampsia)
  - Hyper-reflexia with sustained clonus
  - Severe headache
  - Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)
  - Stroke
  - Pulmonary edema
  - Fetal growth restriction
  - Placental abruption

Note:

- Proteinuria is not mandatory to make the clinical diagnosis
- Hyperuricemia is a common but not diagnostic feature of pre-eclampsia
- The HELLP syndrome (hemolysis, elevated liver enzymes and a low platelet count) represents a particular presentation of severe pre-eclampsia and separating it as a distinct disorder is not helpful.

Urgent blood pressure lowering for severe hypertension ≥170/110 mmHg

	Dose	Route	Onset of action
Labetolol Nifedipine	20-50 mg 5 mg capsules 10 mg tablet	i.v. bolus over 2 min oral	5 min, repeat after 15-30 min 10-20 min, repeat after 20 min 30-45 min, repeat after 45 min
Hydralazine	5-10 mg	i.v. bolus	20 min, repeat after 30 min
Diazoxide	15-45 mg max 300 mg	i.v. rapid bolus	3-5 min, repeat after 5 min

Eclampsia

Comprehensive protocols for the management of eclampsia (and severe hypertension) should be available in all appropriate areas.

There are four main aspects to care of the woman who sustains eclampsia:

1. **Resuscitation**
2. **Prevention of further seizures**
   - Treatment should be commenced with magnesium sulfate (4 g/IV over 10–15 min) followed by an IV infusion (1–2 g/h) for 24–48 h. There is no need to measure serum magnesium levels provided renal function is normal.
   - In the event of a further seizure, a further 2 to 4 g of magnesium sulfate is given IV over ten minutes.
   - Intravenous diazepam (2 mg/min to maximum of 10 mg) or clonazepam (1–2 mg over two to five minutes) may be given while the magnesium sulfate is being prepared if the seizure is prolonged.
   - Magnesium infusion should not be used for more than 12 hours in women with oliguria or renal impairment and serum magnesium levels should be monitored during this time.
3. **Control of hypertension**
   - Control of severe hypertension to levels below 160/100 mmHg by parenteral therapy is essential.
4. **Delivery**
   - Arrangements for delivery should be decided once the woman's condition is stable.
   - In the meantime, close fetal monitoring should be maintained.

Prevention of Eclampsia in the Woman with Pre-eclampsia

The drug of choice for the prevention of eclampsia is magnesium sulfate given as described above. Although there is good evidence for the efficacy of this therapy, the case for its routine administration in women with pre-eclampsia in countries with low maternal and perinatal mortality rates is less compelling. It is appropriate for individual units to determine their own protocols and monitor outcomes.

Hepatic and Hematological Manifestations

- Epigastric or right upper quadrant pain may subside (albeit temporarily) after blood pressure lowering, particularly with vasodilators.
- Thrombocytopenia may require platelet transfusion at the time of cesarean delivery or in the case of postpartum hemorrhage, wound or vulval hematoma or other bleeding. In the presence of bleeding, administer 6 units of platelets if the platelet count is below 40×109/L.
- Fresh frozen plasma is required for management of coagulopathy as indicated by active bleeding and a prolonged activated partial thromboplastin time or international normalized ratio (prothrombin time).

- Steroid therapy (other than for fetal lung maturation) is not indicated for the management of thrombocytopenia or hepatic dysfunction.

Acute Stroke and Hypertension

Guidelines on how to manage BP in acute stroke are regularly published but so far have not been evidence based. No association has been found between blood pressure at admission and recovery, in a series of patients with acute stroke. Ten days after an ischemic stroke, two-thirds of patients become normotensive. Since perfusion in the ischemic penumbra (potentially viable) is pressure-dependent, one should preferably hold-off hypotensive therapy for 10 days in acute stroke, unless there is hypertensive encephalopathy, or aortic dissection or intracerebral hemorrhage with BP > 200/120 is present.

Rough guidelines for hypertension management in stroke are:

i. *Ischemic stroke:* Lowering of BP is indicated if
   a. Systolic BP > 220 mmHg
   b. Diastolic BP > 120 mmHg
   c. Mean arterial BP > 130 mmHg
   (On two readings 15 mins apart)

   Cautious reduction of blood pressure into ranges of 160-170 mmHg systolic and 100-110 mmHg diastolic may be appropriate.

ii. *Hemorrhagic stroke:* Lowering of BP is indicated if
   a. Systolic BP > 200 mmHg and diastolic BP > 110 mmHg

   20% decrease in mean arterial pressure should be considered the maximal goal of blood pressure reductions during acute stage (preferably with intra-arterial and intracranial pressure monitoring)

iii. *Subarachnoid hemorrhage:*
   a. Mean arterial BP should be < 125 mmHg

iv. *Thrombolysis in stroke:* Permissible limits of BP are :
   Systolic BP ≤ 185 mmHg
   Diastolic BP ≤ 110 mmHg

In the setting of sudden severe hypertension, it may be difficult to distinguish hypertensive encephalopathy with focal neurologic findings from cerebral infarction. Since rapid reduction of blood pressure is life saving in patients with hypertensive encephalopathy, a cautious diagnostic trial of blood pressure reduction may be warranted. If blood pressure reduction is deemed necessary in patients with acute cerebral infarction, treatment should be initiated using parenteral agents, e.g. sodium nitroprusside or labetolol. Use of oral or sublingual nifedipine is associated with excessive risk of prolonged overshoot hypotension. Two-thirds of the patients on leaving hospital after stroke, have significantly raised BP at one year follow-up. However, long-term benefit of secondary stroke prevention by lowering BP is uncertain and extrapolating from primary prevention studies may be inappropriate. Hence, one should not be over-enthusiastic in treating hypertension after thrombotic stroke.

Parenteral drugs for treatment of hypertensive emergencies

Drug	Dose	Onset of action	Duration of action	Adverse effects	Special indication
Sodium Nitroprusside	0.25-10 μgm/kg/min as IV infusion. Max dose increment for 10 min only (Avoid exposure to light)	Immediate	1-2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication 1. Nausea, vomiting, muscle twitching are symptoms of cyanide toxicity. → Nitroprusside to be discontinued. 4-6 mg of 3% sodium nitrate solution IV over 2-4 min ↓ 50 ml 25% sodium thiosulfate IV 2. Cyanide toxicity can be prevented by concominant administration of hydroxocobalamin	Most hypertensive emergencies. Best avoid in raised intracranial pressure or azotemia. Caution with coronary ischemia. Special preference to situations like dissection of aorta, subarachnoid hemorrhage with very high BP.
Nicardipine hydrochloride	5-15 mg/hr. IV	5-10 min	1-4 hr.	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure. Caution with coronary ishchemia.
Fenoldopam mesylate	0.1-0.3 μgm/kg/min IV infusion	< 5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma

Contd…

Drug	Dose	Onset of action	Duration of action	Adverse effects	Special indication
Nitroglycerin	5-100 μgm/min as IV infusion	2-5 min	3-5 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia and LVF; contraindicated raised intracranial tension
Enalaprilat (free form of Prodrug Enalapril]	1.25–5 mg every 6 hr IV	15-30 min	6 hrs.	Precipitous fall in pressure; in high renin states response is variable.	Acute left ventricular failure. Avoid in acute myocardial infarction
Hydralazine hydrochloride	10-20 mg IV 10-50 mg IM	10-20 min 20-30 min	3-8 hrs.	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Diazoxide	50-100 mg IV bolus repeated or 15-30 mg/min infusion	2-4 min	6-12 hrs.	Nausea, flushing, tachycardia, chest pain	Now obsolete when no intensive monitoring available.
Labetolol hydrochloride	20-80 mg IV bolus every 10 min 0.5-2.0 mg/min IV infusion	5-10 min	3-6 hrs.	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure which could be worsened by predominantly β-blockade.
Esmolol hydrochloride	250-500 μgm/kg/min for 1 min then 50-100 μgm/kg/min for 4 min repeat sequence	1-2 min	10-20 min	Hypotension, nausea	Aortic dissection, Peri-operative.

Contd…

Contd…

Drug	Dose	Onset of action	Duration of action	Adverse effects	Special indication
Phentolamine	5-15 mg IV	1-2 min	3-10 min	Tachycardia, flushing, headache	Catecholamine excess.
Clevidipine	1-2 mg/hr IV increase up to 32 mg/hr with doubling of dose every 5-10 min or 90 secs in emergency	2-4 min	5-15 min	Headache, nausea, vomiting	Reduction of BP when oral therapy is not feasible or desirable

Suggested Reading

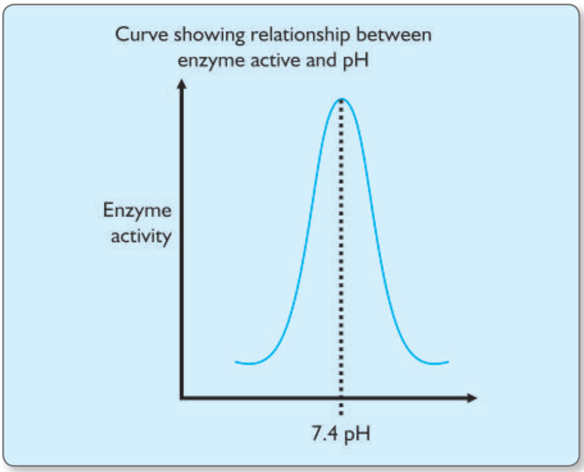
1. Angelats EG, Bragulat Baur E. Hypertension, hypertensive crisis and hypertensive emergency: approaches to emergency department care. Emergencis 2010;22:209-19.
2. Bodman KF, Troster S, Clemens R, et al. Hemodynamic profile of intravenous fenoldopam in patients with hypertensive crisis. Clin Investig. 1993;72:60-74.
3. Bodriquez G Varon J. Clevidipine: a unique agent for the critical care practitioner. Crit care shock. 2006;9:9-15.
4. Chalmers J. What to do about blood pressure in acute stroke? J Hypertens. 2005;23: 277-8.
5. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC VII report JAMA. 2003;289:2560-72.
6. Fenves AZ, Ram CVS. Drug treatment of hypertensive urgencies and emergencies. Semin Nephrol. 2005;25:272-280.
7. Henry CS, Biedermann SA, Camphell MF, et al. Spectrum of hypertensive emergencies in pregnancy. Crit Care Clin. 2004;20:697-712.
8. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood Pressure and stroke: an overview of published trials: Stroke. 2004;35:776-85.
9. Marik PE, Varon J. Hypertensive Crises : Challenges and Management. Chest. 2007; 131;1949-62.
10. Rodriguez MA, Kumar SK, Cara MD. Hypertensive Crisis- Cardiology in Review; 2010;18(2):102-7.
11. Tuncel M, Ram CVS. Hypertensive emergencies. Etiology and Management. Am J Cardiovasc Drugs. 2003;3:21-31.
12. Zampaglione B, et al. Hypertensive urgencies and emergencies. Prevalence and clinical presentation. Hypertension. 1996;27:114.

Acid-base Disturbances

chapter 14

Joydeep Mukherjee, Debashis Sarkar

The objective is to detect acid-base disorder from ABG analysis and correlate with clinical and other laboratory findings to reach at a definite diagnosis. Sometimes multiple acid-base disorders are present due to presence of either multiple diseases at a time or multiple components of a disease at a time. Body tries to maintain pH in physiologic range (7.35–7.45) to maintain all the enzymes to remain active.



Whenever any disease process makes the pH to any extreme then body tries by compensatory means to bring the pH towards physiology range. In extreme pH, people cannot survive.

Types of Acid-base Disorder

- Metabolic acidosis: pH low, HCO_3^- low
- Metabolic alkalosis: pH h igh, HCO_3^- high
- Respiratory acidosis: pH low, $PaCO_2$ high
- Respiratory alkalosis: pH high, $PaCO_2$ low.

Table 14.1 Compensatory changes

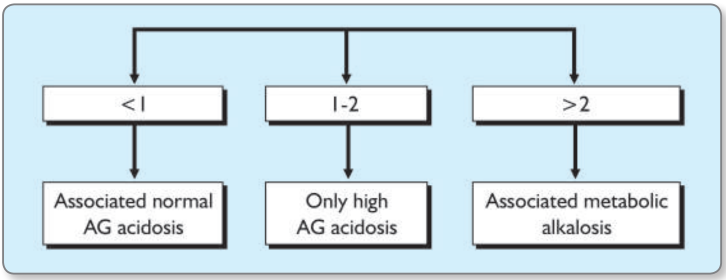
Acid-base disorder	Method of compensation	Prediction of compensation	pH	$PaCO_2$	HCO_3^-
Met acidosis	Hyperventilation	↓$PaCO_2$ 1.25 mmHg per mmol/L in [HCO_3^-]	↓	↓	↓
Met alkalosis	Hypoventilation	↑$PaCO_2$ 0.75 mmHg per mmol/L in [HCO_3^-]	↑	↑	↑
Acute res acidosis	*1, 2, 3	[HCO_3–]0.1 mmol/L per mmHg in $PaCO_2$	↓	↑	↑
Chronic res acidosis	*1, 2, 3	↑[HCO_3–]0.4 mmol/L per mmHg in $PaCO_2$	↓	↑	↑
Acute res alkalosis	Opposite of *1, 2, 3	↓[HCO_3–]0.2 mmol/L per mmHg in $PaCO_2$	↑	↓	↓
Chronic res alkalosis	Opposite of *1, 2, 3	↓[HCO_3–]0.4 mmol/L per mmHg in $PaCO_2$	↑	↓	↓

*The kidneys regulate plasma [HCO_3^-] through three main processes: (1) "re-absorption" of filtered HCO_3^-, (2) formation of titratable acid, and (3) excretion of NH_4^+ in the urine.

Normal Values

- pH = 7.35 – 7.45
- $PaCO_2$ = 35 – 45 mmHg
- HCO_3^- = 22 – 26 mmol/L
- BE = +2 to −2

Approach to Diagnose Mixed Acid-base Disorders

- ***CO_2 – bicarbonate (boston) approach:*** Check pH → Check $PaCO_2$ and HCO_3^- → Determine primary acid-base disorder from Table 14.1 a measure compensation from second column of the table → look for overshoot changes → that will be the second disorder.
- **Anion gap approach:** Measure anion gap ($Na^+ - Cl^- - HCO_3^-$) → measure corrected AG = AG – 2.5* (reduction in albumin from 4.5 gm/dl) → if >10 then high AG acidosis is present → measure delta AG (AG-10) and delta HCO_3^- (24 – HCO_3^-) → measure their ratio.
- 

- **Base deficit/excess (Copenhagen) approach:**

Disturbance	BDE vs $PaCO_2$
Acute respiratory acidosis	$\Delta BDE = 0$
Acute respiratory alkalosis	$\Delta BDE = 0$
Chronic respiratory acidosis	$\Delta BDE = 0.4, \Delta PaCO_2$
Metabolic acidosis	$\Delta PaCO_2 = \Delta BDE$
Metabolic alkalosis	$\Delta PaCO_2 = 0.6, \Delta BDE$

BDE = Base deficit/excess
Change of $PaCO_2$ more/less than above equation will indicate mixed disorder.

- **Stewart's approach:** There are three independent variables, namely $PaCO_2$, SID (Strong ion difference), A_{TOT}.* In respiratory disorders, there is change in $PaCO_2$. Metabolic disorders are addressed with SID and A_{TOT}. In metabolic alkalosis, SID in increased and in metabolic acidosis, SID is decreased.

$$\textbf{SID} = [Na^+] + [K^+] + [Ca^{+2}] + [Mg^{+2}] - [Cl^-] - [\text{lactate}^-] - [\text{other strong ions}] = [HCO_3^-] + [A^-]$$

Under normal conditions, concentration of lactate and other strong ions is very low and can be ignored. The formula could therefore be simplified to

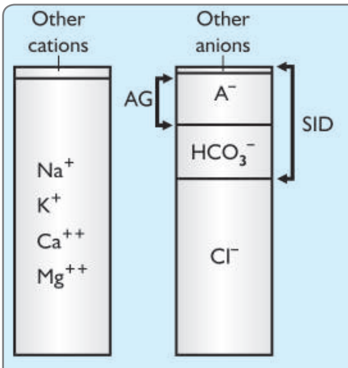
$$\textbf{SID} = [Na^+] + [K^+] + [Ca^{+2}] + [Mg^{+2}] - [Cl^-] = [HCO_3^-] + [A^-]$$

SID, therefore, can be calculated as the difference between fully dissociated cations and anions or sum of bicarbonate and [A⁻], where [A⁻] represents total charges contributed by all nonbicarbonate buffers, primarily albumin, phosphate, and, in whole blood, hemoglobin.

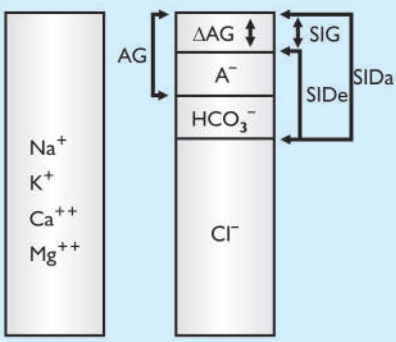
SIG (strong ion gap) = apparent SID (SID_a) – effective SID (SID_e)

$$SID_a = [Na^+] + [K^+] + [Ca^{+2}] + [Mg^{+2}] - [Cl^-]$$

$$SID_e = [HCO_3^-] + [A^-]$$



Relationship between SID, anion gap (AG), and bicarbonate in normal individuals.



Relationship between strong ion gap (SIG) and ΔAG.

*A_{TOT} = [HA + A⁻] **(all nonbicarbonate buffer pairs)** contributed primarily by serum proteins with phosphate and other buffers playing a minor role. An increase in serum protein would result in metabolic acidosis and a decrease, metabolic alkalosis.

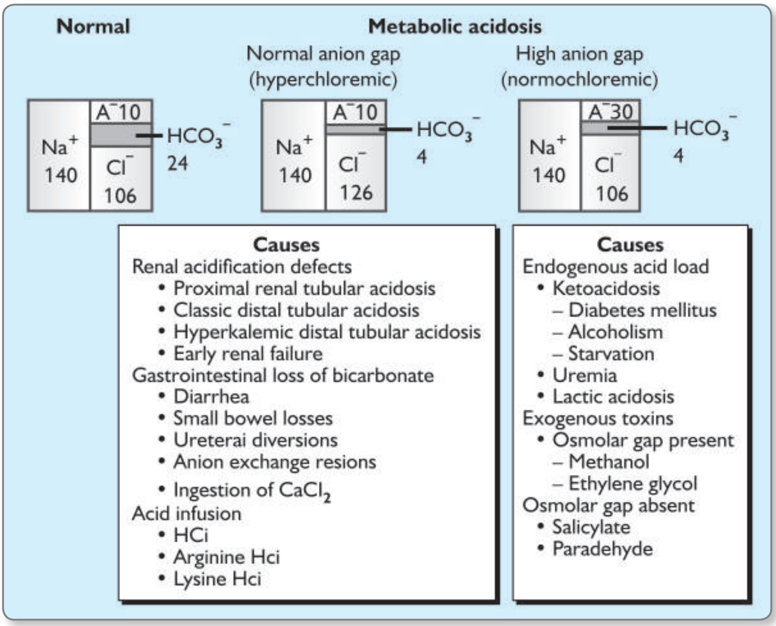
Classification of primary acid-base disturbances

Parameter	Acidosis	Alkalosis
Respiratory	↑PCO_2	↓PCO_2
Nonrespiratory (metabolic)		
Abnormal SID		
Water excess/deficit	↓SID, ↓[Na]	↑SID, ↑[Na]
Imbalance of strong anions		
Chloride excess/deficit	↓SID, ↑[Cl]	↑SID, ↓[Cl]
Unidentified anion excess	↓SID, ↑[XA]	
Nonvolatile weak acids		
Serum albumin	↑[Alb]	↓[Alb]
Inorganic phosphate	↑[Pi]	↓[Pi]

[Alb], albumin concentration; [Pi] inorganic phosphate concentration; XA, concentration of unidentified strong anion.

Individual Acid-base Disorders

Metabolic Acidosis—High AG and Normal AG



Signs and symptoms of metabolic acidosis

Respiratory system	Cardiovascular system	Metabolism	Central nervous system	Skeleton
Hyperventilation Respiratory distress and dyspnea Decreased strength of respiratory muscles and promotion of muscle fatigue	Impairment of cardiac contractility, venoconstriction, and centralization of blood volume Reductions in cardiac output, arterial blood pressure, and hepatic and renal blood flow Sensitization to re-entrant arrhythmias and reduction in threshold for ventricular fibrillation Increased sympathetic discharge but attenuation of cardiovascular responsiveness to catecholamines	Increased metabolic demands Insulin resistance Inhibition of anaerobic glycolysis Reduction in adenosine triphosphate synthesis Hyperkalemia Increased protein degradation	Impaired metabolism Inhibition of cell volume regulation Progressive obtundation Coma	Osteomalacia Fractures

High AG acidosis	Diagnostic clue	Treatment plan
Lactic Acidosis L-lactate → (type A) poor tissue perfusion, (type B) aerobic disorders, D-lactate → ↑formation by gut bacteria	Serum lactate > 5 mmol/L	• Underlying condition correction • Tissue perfusion restoration • Vasoconstrictors should be avoided • Alkali therapy when pH < 7.15, to make pH 7.2 over 30-40 min • Cautious fluid administration • After correction risk of overshoot alkalosis (lactate will convert to HCO_3^-)
Keto-acidosis **Diabetic K** **Alcoholic K**	Blood sugar high, history of missed insulin, pancreatitis, AMI, sepsis, pain abdomen History of alcoholism/ alcohol withdrawal, poor nutrition, vomiting	• IV Fluid • Insulin in DKA • Underlying condition correction in DKA • Electrolytes correction • Dextrose when needed

Contd…

Contd…

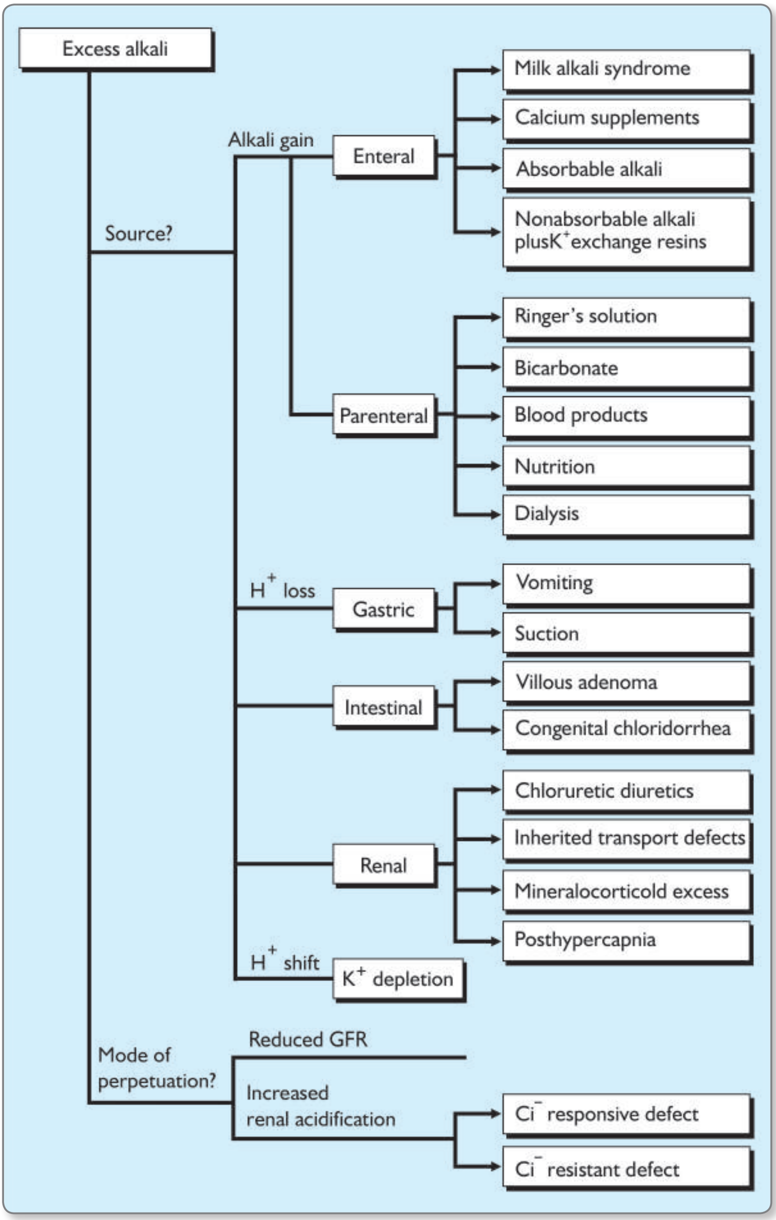
Starvation **Renal Failure** **Ethylene glycol**	High serum creatinine, low urine output, sometimes combined high and normal AG acidosis Associated osmolar gap (measured osmolality—calculated osmolality >15-20 mmol/L), oxalate crystal in urine	• Alkali supplement • Hemodialysis, if needed • General measures • Fomepizole • Hemodialysis
Methanol **Salicylate**	Associated osmolar gap Associated respiratory alkalosis	• Gastric lavage, activated charcoal • Alkali replacement (if no alkalemia) • Acetazolamide (if alkalemia) • Treat hypokalemia, hypoglycemia • Hemodialysis (bicarbonate dialysate)

Metabolic Alkalosis

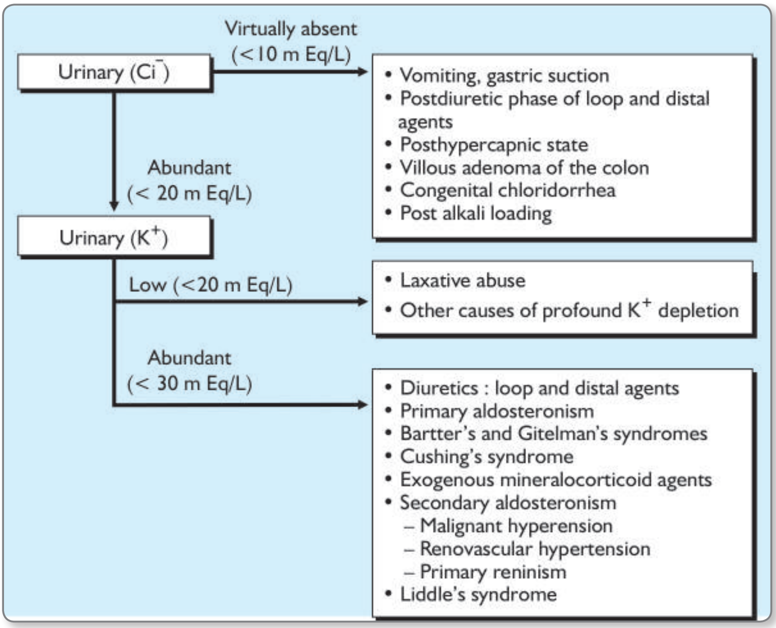
Signs and symptoms of metabolic alkalosis

Central nervous system	Cardiovascular system	Respiratory system	Neuromuscular system	Metabolic effects	Renal (Associated potassium depletion)
Headache Lethargy Stupor Delirium Tetany Seizures Potentiation of hepatic encephalopathy	Supraventricular and ventricular arrhythmias Potentiation of digitalis toxicity Positive inotropic ventricular effect	Hypoventilation with attendant hypercapnia and hypoxemia	Chvostek's sign Trousseau's sign Weakness (severity depends on degree of potassium depletion)	Increased organic acid and ammonia production Hypokalemia Hypocalcemia Hypomagnesemia Hypophosphatemia	Polyuria Polydipsia Urinary concentration defect

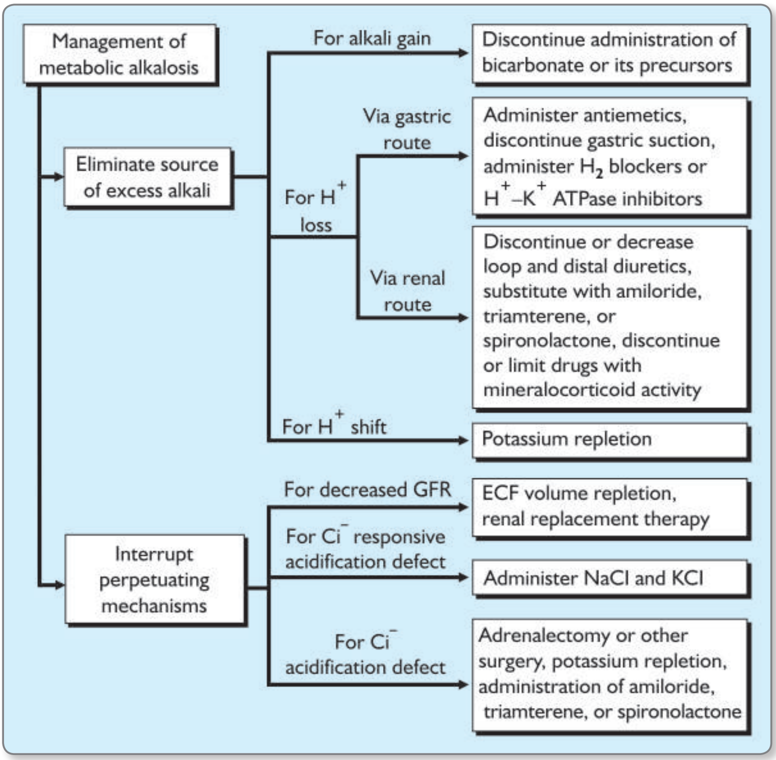
Causes


Excess alkali
Source?
Alkali gain
Enteral
Milk alkali syndrome
Calcium supplements
Absorbable alkali
Nonabsorbable alkali plusK+exchange resins
Parenteral
Ringer's solution
Bicarbonate
Blood products
Nutrition
Dialysis
H+ loss
Gastric
Vomiting
Suction
Intestinal
Villous adenoma
Congenital chloridorrhea
Renal
Chloruretic diuretics
Inherited transport defects
Mineralocorticold excess
Posthypercapnia
H+ shift
K+ depletion
Mode of perpetuation?
Reduced GFR
Increased renal acidification
Ci- responsive defect
Ci- resistant defect

Diagnostic Clue of Metabolic Alkalosis



Treatment



Respiratory Acidosis

Chronic respiratory acidosis management: Therapeutic measures are guided by the presence or absence of severe hypercapnic encephalopathy or hemodynamic instability. An aggressive approach that favors the early use of ventilator assistance is most appropriate for patients with acute respiratory acidosis. In contrast, a more conservative approach is advisable in patients with chronic hypercapnia because of the great difficulty often encountered in weaning these patients from ventilators. As a rule, the lowest possible inspired fraction of oxygen that achieves adequate oxygenation (PaO_2 on the order of 60 mmHg) is used. Unlike acute respiratory acidosis, the underlying cause of chronic respiratory acidosis only rarely can be resolved.

Signs and symptoms of respiratory acidosis

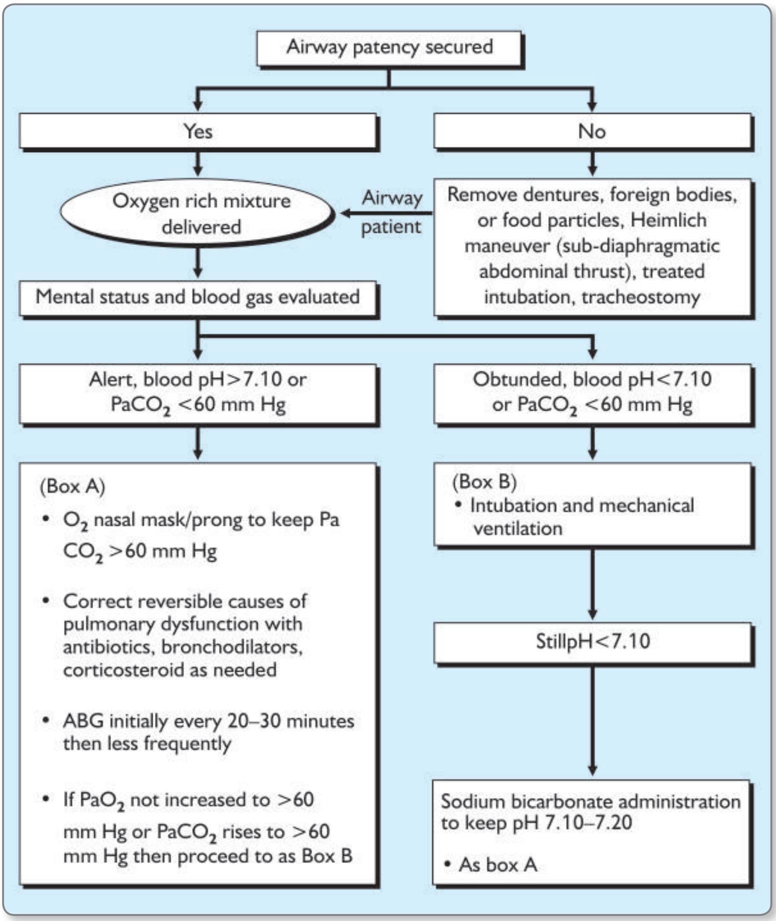
Central nervous system	Respiratory system	Cardiovascular system
Mild to moderate hypercapnia Cerebral vasodilation Increased intracranial pressure Headache Confusion Combativeness Hallucinations Transient psychosis Myoclonic jerks Flapping tremor Severe hypercapnia Manifestations of pseudotumor cerebri Stupor Coma Constricted pupils Depressed tendon reflexes Extensor plantar response Seizures Papilledema	Breathlessness Central and peripheral cyanosis (especially when breathing room air) Pulmonary hypertension	Mild to moderate hypercapnia Warm and flushed skin Bounding pulse Well maintained cardiac output and blood pressure Diaphoresis Severe hypercapnia Cor pulmonale Decreased cardiac output Systemic hypotension Cardiac arrhythmias Prerenal azotemia Peripheral edema

Respiratory Alkalosis

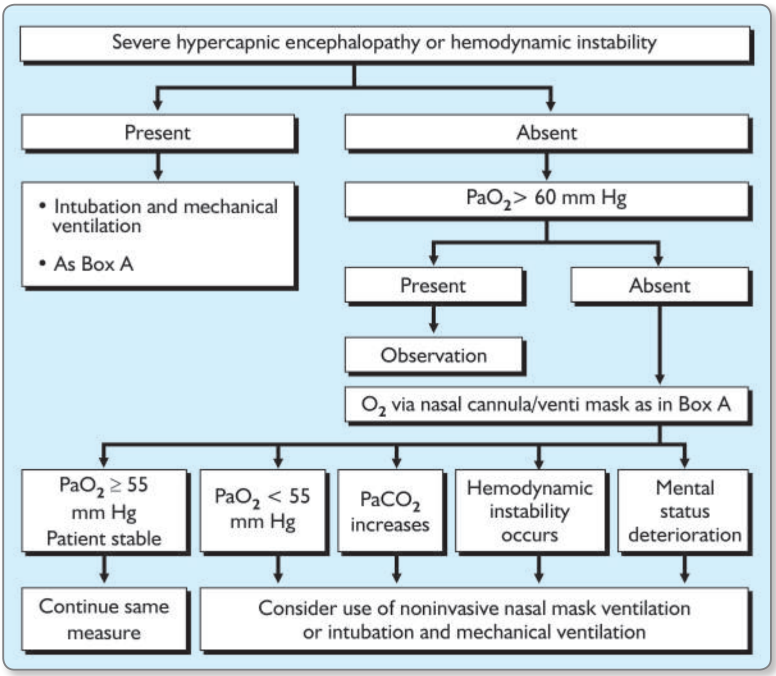
Signs and symptoms of respiratory alkalosis

Central nervous system	Cardiovascular system	Neuromuscular system
Cerebral vasoconstriction Reduction in intracranial pressure Light-headedness Confusion Increased deep tendon reflexes Generalized seizures	Chest oppression Angina pectoris Ischemic electrocardiographic changes Normal or decreased blood pressure Cardiac arrhythmias Peripheral vasoconstriction	Numbness and paresthesias of the extremities Circumoral numbness Laryngeal spasm Manifestations of tetany Muscle cramps Carpopedal spasm Trousseau's sign Chvostek's sign

Acute respiratory acidosis management



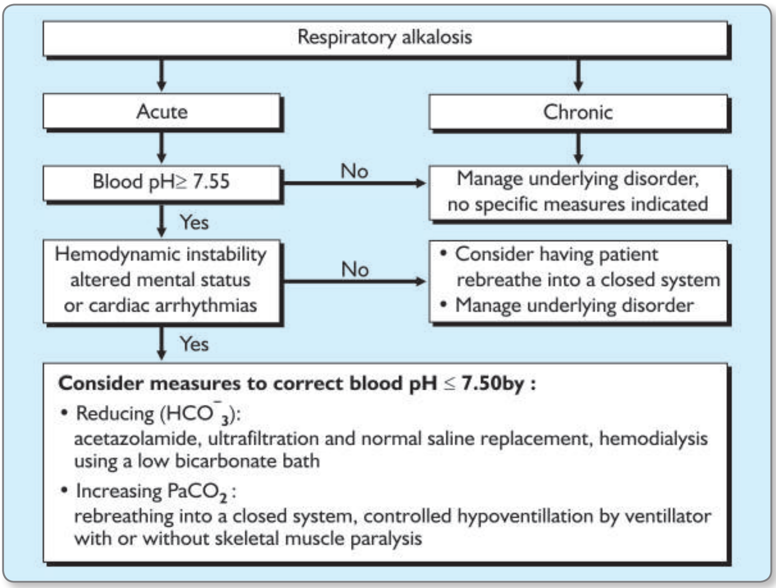
Chronic respiratory acidosis management



Causes of respiratory alkalosis

Hypoxemia or tissue hypoxia	Central nervous system stimulation	Drugs or hormones	Stimulation of chest receptors	Miscellaneous
Decreased inspired oxygen tension High attitude Bacterial or viral pneumonia Aspiration of food, foreign object, or vomitus Laryngospasm Drowning Cyanotic heart disease Severe anemia Left shift deviation of oxyhemoglobin curve Hypotension Severe circulatory failure Pulmonary edema	Voluntary Pain Anxiety syndrome-hyperventilation syndrome Psychosis Fever Subarachnoid hemorrhage Cerebrovascular accident Meningoencephalitis Tumor Trauma	Analeptics Doxapram Xanthines Salicylates Catecholamines Angiotensin II Vasopressor agents Progesterone Medroxyprogesterone Dinitrophenol Nicotine	Pneumonia Asthma Pneumothorax Hemothorax Flail chest Acute respiratory distress syndrome Cardiogenic and noncardiogenic pulmonary edema Pulmonary embolism Pulmonary fibrosis	Pregnancy Early sepsis Hepatic failure Mechanical hyperventilation Heat exposure Recovery from metabolic acidosis

Management of Respiratory Alkalosis



Role of dialysis in acid-base disorders: In Ethyl glycol poisoning, when the arterial pH is <7.3, or the osmolar gap exceeds 20 mOsm/kg.

Suggested Reading

1. Adrogene HJ, et al. Management of life-threatening acid-base disorders (Part I). N Engl J Med. 1998;338:26.
2. Adrogne HJ, et al. Management of life-threatening acid-base disorders. Second of two parts. N Engl J Med. 1998;338:107.
3. Bruno CM, Valenti M. Acid-Base Disorders in Patients with Chronic Obstructive Pulmonary Disease : A Pathophysiological Review Journal of Biomedicine and Biotechnology. (2012), Article ID 915150.doi:10.1155/2012/915150.
4. Hood VL, et al. Protection of acid-base balance by pH regulation of acid production. N Engl J Med. 1998;39-819.

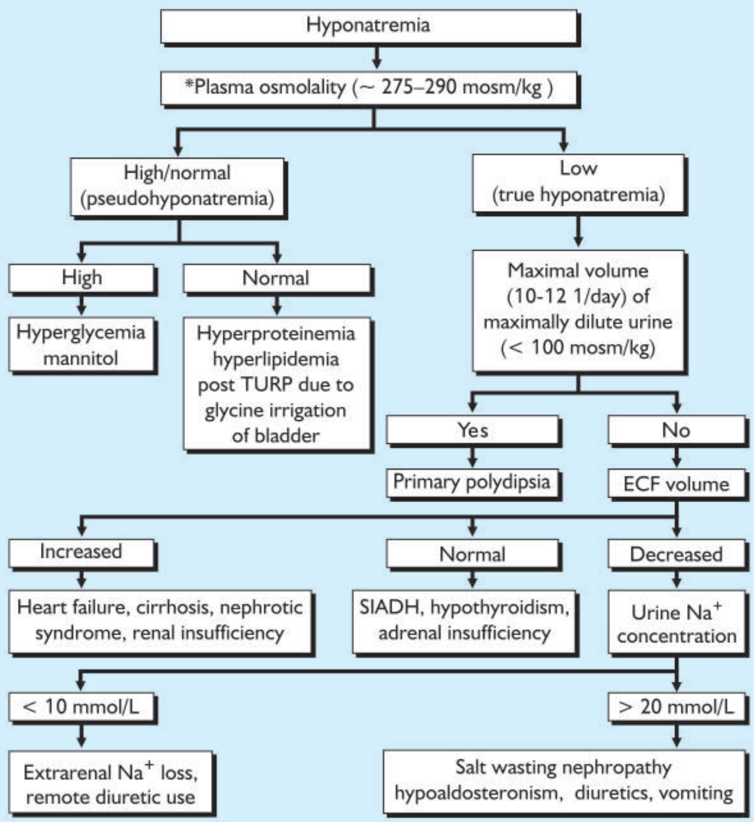
chapter 15

Electrolyte Imbalance

Sudip Mondal, Basab Bijoy Sarkar

Hyponatremia

Hyponatremia: Plasma (Na^+) < 135 mmol/L
Clinical features: Primarily neurologic due to cerebral edema and depends on acuity and magnitude of fall in plasma Na^+.



*Serum Osmolality (mosm/kg) $= 2Na + \frac{BUN}{2.8} + \frac{Glucose}{18}$

Clinical Approach

Asymptomatic, nausea, malaise, headache, lethargy, confusion, obtundation, stupor, seizures, coma → excess mortality in hospitalized patients.

Adaptive mechanism in chronic hyponatremia minimizes symptoms.

What is Pseudohyponatremia?

Serum osmolality is governed by conributions from all molecules in the body that cannot easily move between the intracellular and extracellular space. Sodium is the most abundant electrolyte, but glucose, urea, plasma proteins and lipids are also important. A patient with diabetic ketoacidosis may have hyponatremia, but normal osmolality, due to hyperglycemia, hypertriglyceridemia and ketonemia. Patients with acute renal failure may have hyponatremia due to uremia.

If a patient has hyponatremia, with low measured and calculated serum osmolality, we call this hypotonic hypernatremia. If serum osmolality is normal or high, this is isotonic or hypertonic hyponatremia-pseudohyponatremia.

Hyponatremia: Treatment

Goals

I. To increase plasma Na^+ concentration by decreasing water intake and promoting water loss.
II. To correct the underlying disorder.

Individual Situations

i. Mild, asymptomatic case → no treatment
ii. Mild, asymptomatic cases with ECF volume contraction → Na^+ repletion with isotonic saline (raise plasma Na^+ by 0.5-1 mmol/L/hr and < 10-12 mmol/L/24 hrs).
iii. Mild, asymptomatic cases with edematous states → restriction of Na^+ and water intake, correction of hypokalemia, loss of free water in excess of Na^+ using loop diuretics.
iv. Hyponatremia with renal failure, SIADH and primary polydipsia → dietary water restriction to less than urine output.
v. Severe symptomatic acute (< 2 days) hyponatremia (plasma Na^+ 110-115 mEq/L) suffers from altered mental status, seizure. In this case, correction is indicated with hypertonic normal saline IV over 2 to 4 hours. The principle of treatment is to raise serum Na^+ concentration 1 mEq/L for first 3 to 4 hours and not more than 10 to 12 mEq/L in 24 hours.

Repleting the Sodium Deficit

4 Steps:

1. Find the patient's normal body weight

2. Calculate the serum sodium deficit, divide by half to find how much you will replace: from this calculate the total body sodium deficit (serum deficit × total body water)
3. Calculate the rate of replacement (replace the serum deficit at 0.5 mEq/hour)
4. Calculate how much of your chosen fluid is required.

If you are going to use hypertonic saline, you must calculate the sodium deficit: it is conventional only to correct half of the deficit. The normal serum sodium is 140 mEq/L.

Step 1: Find out the patient's weight in kilograms prior to illness.

Step 2: Calculate the sodium deficit

It is usual to crrect only half the sodium deficit (NaD): (hence the deficit/2)

NaD = (Desired Sodium-Patient's Sodium /2)

If the patient's weight is 70 kg, and the serum sodium is 120, then the desired change is 10 mEq/L

Total body deficit of sodium is the sodium deficit × total body water (TBW)

NaD × (weight in kg × 0.6) = Total deficit (TD)

Using the formula: 10 × (70 × 0.6) = 420 mEq.

Step 3: Calculate the rate of replacement

Most physicians replace the deficit at no more than 0.5 mEq per hour. The patient has a deficit of 10 mEq, so at this rate, it will be replaced over 20 hours (10/0.5).

Rate of replacement (ROR) in hours = NaD/0.5

Step 4: Replace the sodium deficit with the fluid of your choice.

The amount of fluid required depends on the sodium content of that fluid:

Fluid (infusate)	Na content mEq/L	Sodium concentration per mL
Lactated ringers	130	0.13 mEq/ml
0.9 % NaCl	154	0.154 mEq/ml
1.8 %	30*	0.38 mEq/L
3 % NaCl	513	0.513 mEq/ml
5 % NaCl	855	0.855 mEq/ml

So, TD/[Na fluid/ml] ROR = per hour fluid replacement.

If we are using 3% saline in this 70 kg male patient with a serum sodium of 120 (420/0.513)/20 = 41 ml/hour

That is after 20 hours, assuming no other fluids are given, the patient's serum sodium will rise to 130 mEq/L. If 0.9% saline is given:

(420/0.13)/20 = 160 ml/hour

In case of chronic hyponatremia serum Na^+ concentration is to be increased more slowly 5 to 8 mEq/L in 24 hours. Osmotic demylination syndrome (ODS) develops on rapid correction of hyponatremia.

Uses of Vasopressin Receptor Antagonists (Vaptans)

V_2R (Vasopressin Receptor V_2) antagonists have become a mainstay of treatment of *euvolemic* (i.e., *SIADH*, postoperative *hyponatremia*) and *hypervolemic hyponatremia* (i.e., *CHF* and *cirrhosis*). V_2RAs predictably cause *aquaresis* leading to increased $[Na^+]$ in majority of patients with hyponatremia due to SIADH, CHF, and cirrhosis. The optimum use of VRAs has not yet been determined, but some predictions can be made with reasonable certainty. For hyponatremia in hospitalized patients, who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, *conivaptan* (V_1/V_2R antagonist) will likely be the preferred agent. Selective V_2R antagonists such as *tolvaptan*, *lixivaptan*, etc. will likely be useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia. Tolvaptan is the one most commonly used and available in India. Start with 15 mg POq day and do not exceed 30 mg q day or 30 days of treatment to avoid liver injury. Not studied in patients with creatinine clearance <10 mL/min. Avoid use of tolvaptan in patients with underlying liver disease.

Hypernatremia - Plasma (Na^+) > 145 mmol

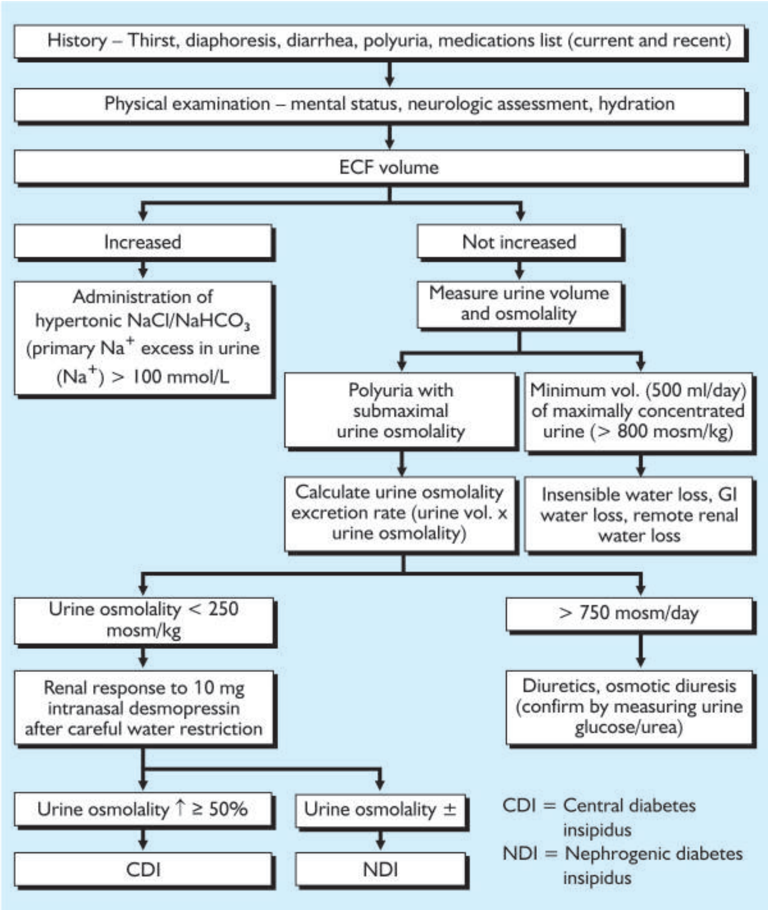
Clinical Features

Severity depends on acuity - magnitude of rise in plasma (Na^+).

Neurologic - altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, coma or seizures, ↑ risk of SAH or ICH.

Others - Polyuria, thirst, signs and symptoms of volume depletion.

Clinical Approach



Example

For a 60 kg man with Na = 160 mEq/L, K = 3.0 mEq/L ideal fluid is 5% dextrose or ½ NS with 20 mEq/L KCl

$$\text{Change in Na} = \frac{\text{Na infused} + \text{K infused} - \text{Sodium Na}}{\text{TBW} + 1}$$

$$= \frac{0 + 20 - 160}{(60 \times 0.5) + 1} = \frac{140}{31}$$

$$= 4.5 \text{ mEq/L}$$

So, 2.66 liters of 5% D reduce 12 mEq/L that means 2.66 liters/24 hours or 110 ml/hour of 5% dextrose reduces sodium at 0.5 mEq/L per hour.

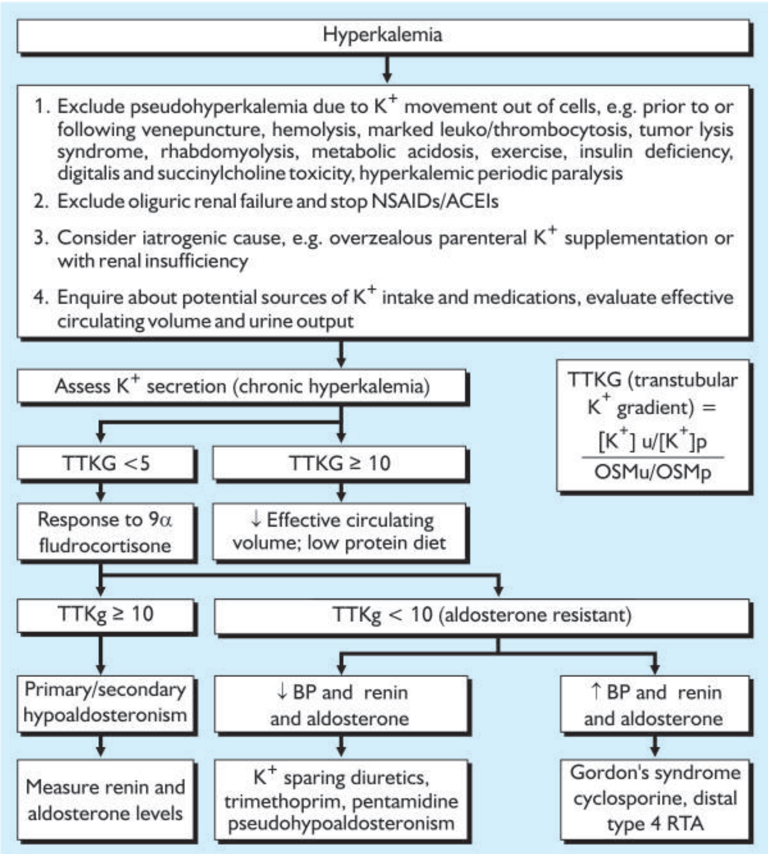
However, not included in this equation so insensible loss 10 ml/kg and GI loss should be included every day in addition to calculated total fluid.

Hyperkalemia

Plasma $[K^+]$ > 5.0 mEq/L

Clinical Features

Impaired membrane excitability → weakness of muscles, flaccid paralysis, hypoventilation → metabolic acidosis.



Cardiac toxicity → ECG changes of increased T wave amplitude, increased PR interval and QRS duration, loss of P waves, sinewave pattern, VF or asystole.

Clinical Approach

Treatment

Depends on severity (> 7.5 mmol/L - potentially fatal)

i. Exogenous K^+ intake and antikaliuretic drugs discontinued.
ii. ↓ membrane excitability by IV calcium gluconate -10 ml of a 10% soln over 2-3 mins → repeat if no ECG change after 5 to 10 mins.
iii. Shifting K^+ into cells by insulin - 10U of regular insulin in 100 ml of 25% dextrose → effect within 15 to 30 mins and lasts for several hrs.
iv. IV $NaHCO_3$ (alkali therapy) in cases of severe hyperkalemia with metabolic acidosis - isotonic solution of 3 amp per liter (134 mmol/L)
v. β_2 adrenergic agonists ↑ cellular uptake of K^+ either parenterally or in nebulized form → onset of action in 30 mins and effect lasts for 2 to 4 hours.
vi. Loop and thiazide diuretics, often in combination, ↑ K^+ excretion if renal function is adequate.
vii. Sodium polystyrene sulfonate (Kayexalate/K - Bind powder) - a cation exchange resin which promotes exchange of Na^+ for K^+ in GIT → by mouth, usual dose is 25 to 50 gm mixed with 100 ml of 20% sorbitol to prevent constipation → effect within 1 to 2 hours and lasts for 4 to 6 hours → retention enema also available.
viii. Hemodialysis is most rapid and effective way → reserved for patients with renal failure and those with severe life threatening hyperkalemia unresponsive to conservative measures.
ix. Treatment of underlying cause by either dietary modification, volume expansion, correction of acidosis or exogenous mineralocorticoid.

Hypokalemia

Plasma [K^+] < 3.5 mEq/L

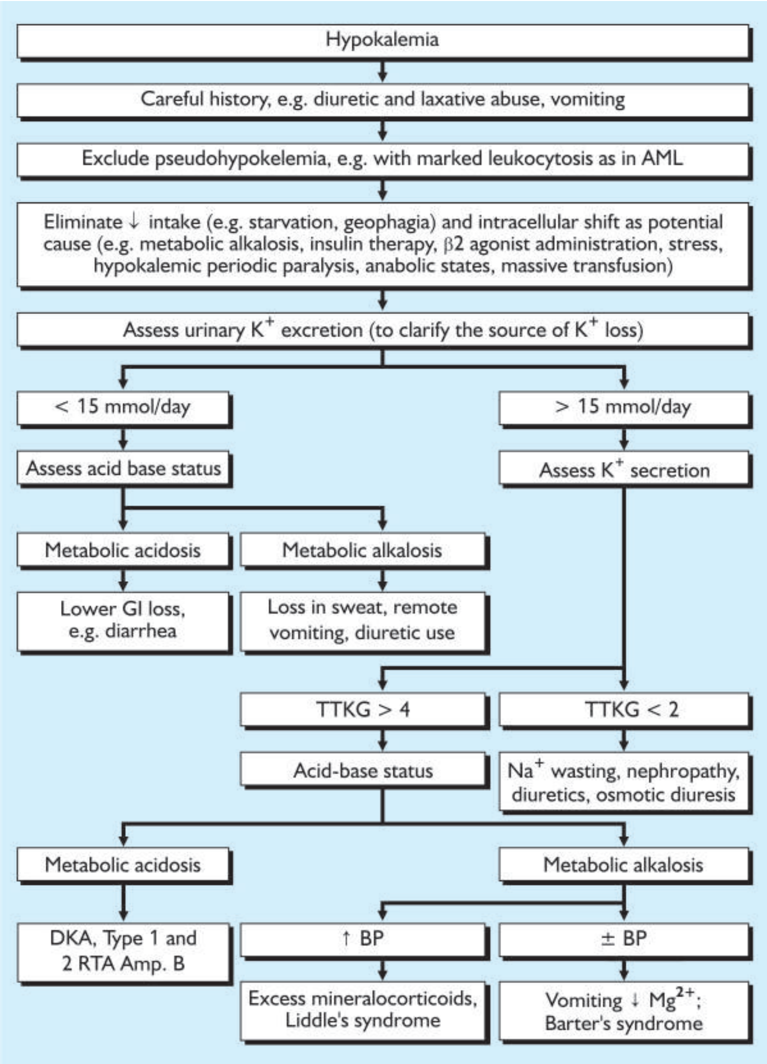
Clinical features with serum K^+ < 3 mEq/L: Vary greatly and depends on degree of hypokalemia.

Fatigue, myalgia, muscular weakness of lower limbs, hypoventilation, eventually paralysis, risk of rhabdomyolysis, paralytic ileus.

ECG changes – flattening or inversion of the T wave, prominent U wave, ST segment depression, ↑ PR interval, ↓ amplitude and widening of QRS complex, ↑ risk of VT/VF, predispose to digitalis toxicity.

↑ Prevalence of hypertension, metabolic alkalosis, nephrogenic DI, glucose intolerance.

Clinical Approach



Treatment

To Correct K^+ Deficit and Decreased Ongoing Losses

Oral correction for mild to moderate hypokalemia (serum potassium 3.0 to 3.5 mEq/L) is suggested. When the average deficit of potassium is about 200 to 400 mEq, 50 to 100 mEq/day of potassium correction is recommended. Average oral dose is 60 to 80 mEq per day. 10 mEq potassium salt are given for each 0.1 mEq/L reduction in serum potassium.

IV replacement: IV potassium administered in case of severe hypokalemia, i.e. serum $K^+ < 3$ mEq/L. The maximum concentration of administered K^+ should be 40 mEq/L via peripheral vein and 100 mEq/L via central vein. The rate of infusion should not be more than 20 mEq/hr. Average rise of K level 0.25 mEq/L occurs when 20 mEq/L is given within 1 hour. Treat judiciously and under close observation of ECG and neuromuscular examination.

Hypermagnesemia

Etiology - renal failure therapy with Mg containing antacids and laxatives and during treatment of pre-eclampsia with IV Mg.

Clinical Features

Only if > 4 mEq/L

Neuromuscular, e.g. areflexia, lethargy, weakness, paralysis and respiratory failure, cardiac, e.g. hypotension, bradycardia, prolonged PR, QRS and QT intervals, complete heart block and asystole.

Therapy

Just withdrawal of Mg preparation suffice if asymptomatic. In case of severe symptomatic hypermagnesemia symptomatic 10% Ca – gluconate, 10 to 20 ml IV over 10 minutes. to be administered. If renal function is normal IV frusemide after rehydration with NS will increase renal clearance of magnesium. Mechanical ventilation, temporary pacing and hemodialysis may be required.

Hypomagnesemia

Etiology

Decreased intestinal absorption, e.g. malnutrition, malabsorption, chronic diarrhea, NG aspiration, ↑ renal excretion, e.g. hypercalcemia, osmotic diuresis, drugs, alcoholism and alcohol withdrawal.

Clinical Features

Neurologic, e.g. lethargy, confusion, tremor, fasciculations, ataxia, nystagmus, tetany, seizures. ECG, e.g. prolonged PR and QT interval, atrial and ventricular arrhythmias.

Therapy

Mild hypomagnesemia (serum Mg 1.5 mEq/L) 240 mg elemental mg required in 24 hours.

While more severe hypomagnesemia (K^+ serum level 1.2 – 1.5 mEq/L). 720 mg elemental mg required in 24 hours. In severe hypomagnesemia (< 1.2 mEq/L of serum Mg) – 1 – 2 gm $MgSO_4$ IV slowly over 15 minutes followed by 1 mEq/kg body weight in 24 hours. After first day, the dose 0.5 mEq/Kg/days for three consecutive days to correct intracellular deficit.

1 amp = 2 ml of the 50% solution = 1 gm = 8.12 mEq of magnesium 8 mEq Mg^{++}

Deep tendon reflex should be examined frequently and ideal serum magnesium level is <2.5 mEq/L.

Hypercalcemia

A serum calcium > 11 mg/dl with normal serum albumin or an ionized calcium > 5.2 mg/dl defines hypercalcemia.

Causes of Hypercalcemia

1. Primary hyperparathyroidism
2. Secondary hyperparathyroidism (CKD)
3. Malignancy (Lung, breast, multiple myeloma)
4. Sarcoidosis
5. Vitamin D intoxication, milk alkali syndrome
6. Familial hypocalciuric hypercalcemia
7. Drug like: Lithium, thiazide
8. Thyrotoxicosis.

Clinical Features

Anorexia, vomiting, constipation, abdominal pain, polyuria, nephrolithiasis, weakness, depression, confusion.

Diagnosis

PTH↑, PO_4↓ in hyperparathyroidism, serum Cl : HCO_3 = 33:1 suggestive of primary hyperparathyroidism.

BUN↑, Cl↑, HCO_3↑ in milk alkali syndrome. PTH↓, ↑PO_4, ↑1,25 $(OH)_2$ D_3 in Vitamin D intoxication and chronic granulomatous disease.

ECG: Shortened QT interval.

Treatment

Isotonic saline (0.9% NS) for correction of dehydration and excretion of calcium. Maintenance fluid adjusted if urine as produced at 100 to 150 ml/hour. Fluid to be cautiously used in elderly patient.
Frusemide: It is used after volume correction.
IV Bisphonate
Calcitonin
Steroid
Oral phosphate by increasing Ca^{2+} deposition.

Hypocalcemia

A serum calcium < 8.4 mg/dl with normal sodium albumin or an ionized calcium <1.2 mg/dl is called hypocalcemia.

Causes of Hypocalcemic

- Hypoalbuminemia
- Hypoparathyroidism due to postsurgical hungry bone syndrome
- Hypomagnesemia
- Liver disease and kidney disease
- Nutritional deficiency of Vitamin D3. Lack of sun-exposure
- Respiratory and metabolic alkalosis
- Severe acute hyperphosphatemia, i.e. conditions like tumor lysis syndrome, rhabdomyolysis, acute renal failure
- Invasive blood transfusion and anticonvulsant drug.

Clinical Features

Paresthesia, muscle spasm, irritability, depression, psychosis. Chvostek's syndrome, Trousseau's sign, lethargy, laryngeal spasm, seizure. ECG : prolonged OT interval.

Treatment

Before correcting hypocalcemia first hypomagnesemia and hyperphosphatemia should be corrected.

Mild hypocalcemia treated with 1 amp of 10 ml 10% Ca-gluconate (containing 90 mg elemental calcium slowly over 10 minutes). Severe hypocalcemia treated with 6 amp of calcium-gluconate (60 ml) dissolved in 500 ml of 5% Dextrose. Now 1 ml of solution contains 1 mg calcium. Infusion rate 0.5 to 2 mg/kg/hour.

Chronic Treatment

- Salt (1 to 2 gm elemental calcium) TDS.
- Six weeks of ergocalciferol 50000 IV weekly in CKD patient.
- Calcitriol to be taken as it increase phosphate absorption.

Hypophosphatemia

A serum phosphate <2.8 mg/dl defines hypophosphatemia. Causes are:

A. *Increased renal excretion:* Hyperparathyroidism, ECF volume expansion with diuresis, osmotic proximal tubular transport defect (e.g. Fanconi's syndrome), cancer-induced hypophosphatemia, familial hypophosphatemic rickets).

B. *Inadequate intake or absorption:* Malabsorption, chronic diarrhea, malnutrition, phosphate-binding antacids, vitamin D deficiency or resistance.

C. *Redistribution into cells:* Refeeding after starvation, treatment for diabetic keto-acidosis, respiratory alkalosis.

Clinical Features

Proximal muscle weakness, impaired diaphragmatic function, confusion, paresthesia, dysarthria, seizure, coma, heart failure, hypoxia (due to decreased concentration of 2,3 DPG).

Investigation

Renal excretion of >100 mg by 24 hours urine collection, serum 25 (OH) D3↓, PTH↑.

Treatment

Management involves administering oral phosphate supplements and high-protein/high-dairy dietary supplements which are rich in naturally occurring phosphate. In severe hypophosphatemia (< 1 mg/dl) intravenous treatment with sodium or potassium phosphate 0.08 mmol/kg – 0.16 mmol/kg in 0.45% saline administered over 6 hours is indicated. However, intravenous phosphate administration is associated with the risk of precipitating hypocalcemia and metastatic calcification.

Hyperphosphatemia

A serum phosphate level > 5 mg/dl defines hyperphosphatemia.

1. Acute and chronic renal failure
2. Tumor lysis syndrome and rhabdomyolysis, crush injury.
3. Hypoparathyroidism
4. Acromegaly

5. Thyrotoxicosis
6. Vitamin D intoxication
7. Metabolic acidosis.

Clinical Features

Relate to hypocalcemia and metastatic calcification, particularly in chronic renal failure with tertiary hyperparathyroidism.

Treatment

Phosphate binders are calcium acetate and calcium carbonate. Aluminium hydroxide may be used with caution in chronic kidney disease patient. Management also involves volume expansion with intravenous normal saline and dialysis in extreme cases.

Suggested Reading

1. Adrogue HJ, et al. Hypernatremia, N Engl J Med. 2000;342:1493.
2. Adrogue HJ, et al. Hyponatremia N Engl J Med. 2000;342:1581.
3. Cadnapaphoenchai MA, et al. Pathogenesis and management of hyponatremia. Am J Med. 2000;109:688.
4. Charytan D, et al. Indications for hospitalization of patients with hyperkalemia. Arch Intern Med. 2000;160:1605.
5. Gennari FJ. Hypokalemia. N Engl J Med. 1998;339:451.
6. Halperin ML, et al. Potassium. Lancet. 1998;352:135.
7. Weisinger JR, et al. Magnesium and Phosphorus, Lancet. 1998;352-91.
8. Palm C, Pistrosch F, Herbig K. Vasopressin antagonists as aquaretic agents for treatment of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S87-92.

Management of Adult Severe Acute Asthma

chapter 16

Dinobandhu Naga, Sumit Sen Gupta

Diagnosis of Asthma

- Episodic wheezy attacks in a nonsmoker
- Symptoms starting from childhood or before the age of 55
- Symptoms of house dust allergy with history of rhinitis and eczema
- Expectoration is a minor component and no history of hemoptysis
- Prominent nocturnal and early morning symptoms
- Response to bronchodilators.

Probably prudent to treat all wheezy attacks as acute asthma in nonsmokers with normal Chest X-ray.

Differential Diagnosis of Acute Asthma

- COPD
  - Chronic obstructive bronchitis and emphysema
  - Bronchiectasis, specially post-tubercular - quite common in India
  - Rarer diseases like bronchiolitis
  - Postviral, drug-induced or autoimmune
- Recurrent LVF
  - 'Silent' mitral stenosis
- Upper Airways obstruction
  - Tumor/stenosis - look out for unilateral wheeze
  - Vocal chord dysfunction
- Pulmonary Embolism (PE)
- Pulmonary Hypertension.

Watch out for concurrent
- Sepsis (Pneumonia)
- Left ventricular failure
- PE
- Pneumothorax.

Levels of Severity of Acute Asthma Exacerbations

Moderate asthma exacerbation	Increasing symptoms FEV1/PEFR > 50% best or predicted No features of acute severe asthma

Acute severe asthma	Any one of: FEV1/PEFR 30-50% best or predicted Respiratory rate > 25/min Heart rate >110/min Inability to complete sentences in one breath
Life-threatening asthma	Any one of the following in a patient with severe asthma: FEV1/PEFR < 30% best or predicted SpO_2 < 92% PaO_2 < 8 kPa (60 mmHg) $PaCO_2$ > 6 kPa (45 mmHg) Silent chest Cyanosis Feeble respiratory effort, exhaustion Confusion or coma Hypotension or bradycardia
Near fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures

(FEV1: Forced expiratory volume in 1s; PaO_2, $PaCO_2$: arterial oxygen and carbon dioxide tension; SpO_2: Oxygen saturation).

Assessment

Features of Acute Severe Asthma

- Peak expiratory flow (PEF) 33-50% of best (use % predicted if recent best unknown; see chart and prediction equations below)
- Cannot complete sentences in one breath
- Respirations ≥ 25 breaths/min
- Pulse ≥ 110 beats/min

Life-threatening Features

- PEF < 33% of best or predicted
- SpO_2 < 92%
- Silent chest, cyanosis or feeble respiratory effort
- Bradycardia, dysrhythmia or hypotension
- Exhaustion, confusion or coma.

Caution: Patients with severe attacks may not be distressed and may not have all these abnormalities. The presence of any should alert the doctor.

Blood Gas Markers of a Life-threatening Attack

If a patient has any life-threatening feature, measure arterial blood gases. No other investigations are needed for immediate management.

Blood gas markers of a life-threatening attack:

- Normal (35-45 mmHg) $PaCO_2$
- *Severe hypoxia:* $PaO_2 < 60$ mmHg irrespective of treatment with oxygen
- A low pH (or high H^+).

Near Fatal Asthma (NFA) Acute Asthma

- Associated with a respiratory arrest on $PaCO_2 > 50$ mmHg, with or without altered consciousness
- 80-85% of NFA is associated with eosinophilic inflammation associated with gradual deterioration and slow to respond to therapy
- Rest of the NFA is associated with—
  Neutrophilic inflammation
  and has both rapid onset
  and response to therapy

Immediate Treatment

- Oxygen 40 to 60% (CO_2 retention is not usually aggravated by oxygen therapy in asthma however, some recent data suggest otherwise)
- Salbutamol 5 mg or terbutaline 10 mg via an oxygen-driven nebulizer
- Ipratropium bromide 0.5 mg via an oxygen-driven nebulizer
- Prednisolone tablets 40 to 50 mg or IV hydrocortisone 100 mg or both if very ill
- No sedatives of any kind
- Chest radiograph if pneumothorax or consolidation are suspected or patient requires IPPV.

If Life-threatening Features are Present

- Discuss with senior clinician
- Add IV magnesium sulphate 2 g infusion over 20 minutes
- Give nebulized β2 agonist more frequently, e.g. salbutamol 2.5 to 5 mg up to every 15 to 30 minutes or 10 mg continuously hourly, or Levosalbutamol 1.25 every 20 minutes (continuously).

Subsequent Management

If Patient is Improving Continuously

- 40 to 60% oxygen
- Prednisolone 40 to 50 mg daily or IV hydrocortisone 100 mg 6 hourly
- Nebulized β2-agonist and ipratropium 4 to 6 hourly.

If Patient Not Improving After 15 to 30 Minutes

- Continue oxygen and steroids

- Give nebulized β2-agonist more frequently, e.g. salbutamol 2.5 to 5 mg up to every 15 to 30 minutes or 10 mg continuously hourly or Levosalbutamol 1.25 mg every 20 minutes (continuously)
- Continue ipratropium 0.5 mg 4 hourly until patient is improving.

If Patient is Still Not Improving

- Discuss patient with senior clinician and ICU team
- IV magnesium sulphate 2 g over 20 minutes (unless already given)
- Senior clinician may consider use of IV β2-agonist or IV aminophylline or progression to IPPV.

Monitoring

- Repeat measurement of PEF 15 to 30 minutes after starting treatment
- Oximetry: Maintain $SpO_2 > 92\%$
- Repeat blood gas measurements within 2 hours of starting treatment if:
  - Initial PaO_2 <60 mmHg unless subsequent SpO_2 >92%
  - $PaCO_2$ normal or raised
  - Patient deteriorates
- Chart PEF before and after giving β2-agonists and at least four times daily throughout hospital stay.

Referral of Adults with Acute Asthma to Intensive Care

Transfer to ICU accompanied by a doctor prepared to intubate if:

- Deteriorating PEF, worsening or persisting hypoxia, or hypercapnea
- Exhaustion, feeble respiration, confusion or drowsiness
- Coma or respiratory arrest.

Ventilatory management of asthma is discussed in the chapter on invasive ventilation.

Noninvasive Ventilation in Asthma

Though asthma is not proven to be a good substrate for noninvasive ventilation there are small randomized studies, which have shown that it works in asthma and the current practise is to use it in hypercapnic patients, who are not ill enough to be invasively ventilated but have nonresponding severe or life threatening asthma. Extreme caution needs to be taken to ensure that noninvasive ventilation does not delay intubation when it becomes necessary.

Discharge

When discharged from hospital, patients should have:

- Been on discharge medication for 24 hours and have had inhaler technique checked and recorded
- PEF > 75% of best or predicted and PEF diurnal variability < 25% unless discharge is agreed with respiratory physician

- Treatment with oral and inhaled steroids in addition to bronchodilators
- Own PEF meter and written asthma action plan
- GP follow-up arrangement within two working days
- Follow-up appointment in respiratory clinic within four weeks

  Patients with severe asthma (indicated by need for admission) and adverse behavioural or psychosocial features are at risk of further severe or fatal attacks
- Determine reason(s) for exacerbation and admission
- Send details of admission, discharge and potential best PEF to GP.

Other Treatments

- Magnesium as solvent for nebulized β-stimulants
- Montelukast
- Heliox
- Extra Corporeal Membrane Oxygenation
- Nebulized DNAase/acetylcysteine
- Lung lavage
- Cardiopulmonary bypass
- Nebulized frusemide/lignocaine.

This protocol is based on the British Thoracic Society guidelines for asthma accessible from the British Thoracic Society website and also published in Thorax 2004 as a supplement.

For North Indians, a prediction equation (based on Aggarwal et al Chest. 2006;130(5):1454-61) may be used.

Men	PEF	$42.3 + 5.0\ A - 0.08\ A^2 + 2.4\ H$
Women	PEF	$52.0 + 1.5\ A - 0.04\ A^2 + 2.1\ H$

A = age in years; H = height in centimeters

A simpler prediction formula can also be used (based on Prasad et al Indian J Chest Dis Allied Sci. 2006;48:103-6)

Males:	PEFR = –2.924 (Age) + 3.38 (Height)
Females:	PEFR = –2.8 (Age) + 3.05 (Height)

Advanced in Current Management and Future Therapy

A. **SMART Strategies (single inhaler only):** For moderate to severe asthmatic only. Here, inhaler formoterol + budesonide combination is used as reliever therapy instead of a short-acting β2-agonist and budesonide/formoterol inhaler twice daily as maintenance therapy.

B. **Newer corticosteroids:**

   Ciclesonide: Prodrug, activated in lungs. Less systemic effect, more local effect.

   Mapracorat, AL-438: Nonsteroidal selective glucocorticoid receptor activator.

C. **Once daily B2-agonist: Ultra long-acting β2-agonist (LABA):** Indacaterol, carmoterol, vilanterol, olodaterol.
Now combination of fluticasone, +vilanterol, mometasone + indacaterol, are in clinical development for once daily combination inhaler.

D. **Long-acting Muscarinic Antagonist:**
- *Tiotropium bromide:* Recent studies have shown that once daily Tiotropium provides useful additional bronchodilation when used with LABA in severe asthma
- Glycopyrrolate, GSK 573719 $\rightarrow$ once daily dosage
- *Aclidinium bromide:* Twice daily dose.

E. **Novel classel of Bronchodilator:**
- Ro 25 – 1553 (Vasoactive intestinal peptide analog)
- TAS 2RS (Bitter taste receptor agonist) like quinine, saccharine, chloroquine
- PDE3 – inhibition – Cilostazol, milrinone (Phosphodiesterase-3)

F. **Anti-IgE:** Omalizumab, lumiliximab, omlizumab, lumileximab

G. **Inflammatory mediator antagonists:**
i. Only ones current available are antileukotrienes
ii. Anticytokines
Pitrakinra: IL-4 receptor α-blocker.
Lebrikizumab: A blocking mAb to IL-13.
Mepolizumab
Reslizumab
Benralizumab
$\}$ IL-5 blocker (IL5 is of critical importance in eosinophilic inflammation)
MEDI blocker 528 : Anti IL-9
iii. Other cytokine antagonists
Infliximab: TNF alpha-blocker, but recent multicenter trial with humanized antibody golimumab has shown no beneficial effect on lung function and there were increased reports of pneumonia and cancer.
Mogamulizumab a defucosylated antibody to CCR4.
Navarixin: Oral CXCRI/CXCR2 antagonist.

H. Broad-spectrum anti-inflammatory treatments

I. **New PDE-4 inhibitor:** Roflumilast

J. **Kinase Inhibitor:** IKK2/IKKβ (inhibitor of K-beta-kinase) – now in preclinical testing. P38 Mitogen-activated protein kinase (-P38 MARK) inhibitor are now in clinical development; could be useful in cases of corticosteroid resistance

K. Peroxisome proliferators activated receptor – Rosiglitazone

L. **Mast cell:** Inhibitor, C-kit inhinbitor – Mastinib

M. **Macrolides:** Antibiotic – clarithromycin, Nonantibiotic EM-703

Sedation, Analgesia, Paralysis in Patients with Status Asthmatices

Drug: Regimen

Midazolam: Bolus 0.03–0.1 mg/Kg, iv, followed-up by : an infusion 3 to 10 mg/hour

Propofol: 60 to 80 mg/min iv up to 2 mg/kg followed by infusion of 5 to 10 mg/kg/hour as needed

Fentanyl: Bolus 50 to 100 ug/kg, iv followed up infusion of 50 to 1000 ug/hour

Remifentanil: 1 ug/kg iv, followed up by infusion 0.25 to 0.5 mg/min

Ketamine: Bolus : 1 mg/ml/iv, followed-up by infusion 0.1 to 0.5 mg/min

Cisatracurium: Bolus : 0.1 to 0.2 mg/kg/iv, followed-up by infusion of 3 µg/kg/min.

Dexmedetomidine: Loading dose I µg/kg over 10 to 30 min. iv – followed up by 0.2 to 0.7 µg/kg/hour

Specific Pharmacological Therapy of Ventilated Patients with Status Asthmaticus

Salbutamol: 2.5 mg by Nebulization continuously or 4 to 6 puffs by MDI with spacer every 15 to 20 min for 1st 3 hour, titrate dose

Corticosteroids: Methyl prednisolone: 40 to 60 mg iv, 6 hourly indicated (total dose 4 mg)

Ipratropium Bromide: 4 puffs (0.8 mg) every 20 min delivered by MDI with spacer or 0.5 mg every 20 mints in nebulized form along with Salbutamol.

Theophylline: 5 mg/kg iv loading dose in 30 min infusion 0.4 mg/kg/hour (Blood level 8–12 µg/ml)

Heliox: 80 : 20 or 70 : 30 helium oxygen mix.

Initial ventilator settings in status asthamaticus (CUS):

Mode	Volume controlled ventilation
Tidal volume	7–8 ml/kg ideal body weight
Respiratory rate	8–10/min
Minute ventilation	< 10 L/min
Inspiratory flow rate	60–80 L/min
Inspiratory to expiratory ratio	> 1:3
Inspiratory flow wave form	Decelerating
Plateau pressure	< 30 cm – H_2O
PEEP	0 cm H_2O
FiO_2	FiO_2 – 100% initially, then titrate to achieve SaO_2 > 90%

Suggested Reading

1. Barnes PJ. Severe asthma: Advances in current management and future therapy. J. Allergy Clin. Immunol. 2012;129:48-59.
2. British thoracic society 2007 guidelines for asthma accessible at http://www.brit-thoracic.org.uk/c2/uploads/asthma_fullguideline2007.
3. Emergency Medicine Australia. 2009;21:259-68.
4. NAEPP prepublication 2007 guidelines for asthma accessible at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
5. Papiris SA, Manali ED, Kollekas L, et al. Acute Severe Asthma. New Approaches to Assessment and Treatment. Drugs. 2009;69(17):2363-91.

chapter 17

Management of Acute Exacerbation of COPD

Dinobandhu Naga, Sumit Sen Gupta

An exacerbation of COPD (AECOPD) is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.

Diagnosis—Is it AECOPD?

Recurrent (wheezy) shortness of breath during RTIs on a background of slowly progressive exertional dyspnea (with or without chronic expectoration) in a patient with significant history of smoking (10-20 pack years). Usually, symptoms start after the age of 45.

Precipitating Factors for AECOPD

Infectious Process

Viral: Rhinovirus, Influenzae

Bacteraial: S. pneumoniae, H. influenzae, M. catarrhalis, Pseudomonas, Enterobacteriacae

Environmental Conditions

Sudden change in temperature, humidity, air pollution, exposure to tobacco smoke, noxious gases, chemical irritants.

Host Factor

Poor general condition, nutritional status.

Immunity status, compliance with prescribed medical therapy.

Differential Diagnosis

See differential diagnosis of asthma.

Is it only AECOPD?

- Sepsis (Pneumonia)
- LVF (associated IHD - ACS, arrhythmias specially AF. The estimated prevalence of heart failure—both systolic and diastolic is between 20 to 30% in patients in acute exacerbation of COPD)

- Pneumothorax
- PE (25% prevalence in patients with AECOPD without any obvious cause for the exacerbation).

Levels of Severity of COPD Exacerbations

Indications for Hospital Assessment or Admission for Exacerbations of Chronic Obstructive Pulmonary Disease

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea, change in vital signs
- Severe underlying COPD/already receiving long-term O_2 therapy
- Onset of new physical signs (e.g. cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities (particularly arrhythmias, heart failure, and insulin-dependent diabetes)
- Frequent exacerbations
- Diagnostic uncertainty
- Older age
- Insufficient home support—difficulty in coping at home
- Poor or deteriorating general condition with little activity
- Impaired level of consciousness or confusion
- O_2 saturation < 90%
- Arterial PaO_2 – < 7KPa
- Arterial pH - <7.35.

Indications for Intensive Care Unit Admission of Patients with Exacerbations of Chronic Obstructive Pulmonary Disease

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia ($PaO_2 \leq 40$ mmHg), and/or severe/worsening hypercapnia ($PaCO_2 \geq 60$ mmHg), and/or severe/worsening respiratory acidosis (pH : 7.25) despite supplemental oxygen and noninvasive ventilation
- Need for invasive mechanical ventilation
- Hemodynamic instability—need for vasopressors.

Immediate Treatment

- Check SpO_2 on air and give Oxygen usually through nasal cannulae enough to keep SpO_2 about 90%
- Salbutamol 2.5 to 5 mg via an air-driven nebulizer
- Ipratropium bromide 0.5 mg via an air-driven nebulizer
- Prednisolone tablets 40 mg or IV equivalent (There is preliminary evidence that Budesonide 2 mg nebulized every 6 hours is as effective in moderate AECOPD)

- Consider antibiotics
- No sedatives of any kind
- Chest radiograph/ECG/Hb TC DC CRP/consider NTproBNP if diagnosis unclear/consider sputum for gram stain, culture-sensitivity if high risk of multi-drug resistant (MDR) organisms.

Antibiotics should be given to:

Patients with exacerbations of COPD with the following three cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence.

Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms.

Patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive).

Risk factors for Pseudomonas include recent hospitalization, and previous intubation (in the preceding 6 months), frequent (≥ 4 courses/year) or recent antibiotics (in the preceding 2 weeks), severe disease with 1-sec forced expiratory volume of 30% predicted, and previous isolation of Pseudomonas. Failure of noninvasive ventilation (NIV) (often occurring with the first 4 hrs of application) may be another indicator of the need for treatment for MDR organisms. The frequency of MDR organisms is 10% in severe AECOPD and up to 25% in ventilated patients. The incidence of MDR organisms may be higher in India.

There is evidence that at least fluoroquinolones should be used in severe AECOPD and consideration should be given to antipseudomonal cover in intubated patients.

If Patient Seriously Ill

- Check ABG to see if NIV (Noninvasive ventilation) criteria are met - if so institute NIV
- Give nebulized β2-agonist more frequently, e.g. salbutamol 2.5 to 5 mg up to every 15 to 30 minutes or 10 mg continuously hourly, or Levosalbutamol 1.25 every 20 minutes (continuously)
- Consider IV aminophylline infusion.

Indications for Noninvasive Ventilation

Selection criteria: Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion.

Moderate to severe acidosis (pH < 7.35) and/or hypercapnia ($PaCO_2 \geq 45$ mmHg)

Respiratory frequency ≥ 25 breaths/min

Relative Contraindications for Noninvasive Ventilation

Exclusion criteria (any may be present)

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Change in mental status; uncooperative patient
- High aspiration risk/viscous or copious secretions
- Claustrophobia
- Craniofacial/nasopharyngeal abnormalities/burns/surgery/trauma.

Noninvasive Ventilation in AECOPD

Noninvasive ventilation in severe AECOPD is accepted as a standard of care. To put it into perspective, when applied appropriately it is three times more effective than streptokinase in acute STEMI. Indications and relative contraindications are discussed above.

Hold the interface on the patient's face until the patient is fully synchronized with the ventilator before strapping the headgear on. Though nasal masks have been used, full face masks are most commonly preferred. Select the size most appropriate to the patient.

Start at low pressures for patient comfort (10 cm) and titrate the inspiratory positive airway pressure (IPAP) to achieve improvement in clinical signs (RR ≥ 25 bpm, reduced accessory muscle use) and patient comfort. Aim for a IPAP of 20, slowly increasing IPAP every 5 to 10 minutes by 2 cm. At the same time put on EPAP 4 to 5 cm. Spontaneous/timed mode is preferred.

Clinical assessment and ABGs need to be repeated one hour after initiation.

If effective, use practically continuously for first 24 hours. Wean off NIV by decreasing time on the ventilator.

Subsequent Management

If Patient is Improving

- Check ABG 1 hour after starting treatment
- Controlled oxygen
- Prednisolone 40 mg daily or IV equivalent for 7 to 10 days - no need to tail off.
- Nebulized β2-agonist and ipratropium 4 to 6 hourly (shift to inhalers with spacers at least 24 hours prior to discharge—ensure patient is properly trained in technique)
- Antibiotics to be continued for 7 to 10 days.
- Strongly consider influenza and pneumococcal vaccination prior to discharge.
- DVT prophylaxis until patient is mobilized

If Patient not Improving

- Continue above treatment
- Give nebulized β2-agonist more frequently, e.g. salbutamol 2.5 to 5 mg up to every 15 to 30 minutes or 10 mg continuously hourly or Levosalbutamol 1.25 mg every 20 minutes (continuously)
- Continue ipratropium 0.5 mg 4 hourly until patient is improving
- Discuss patient with senior clinician and ICU team
- Start NIV (unless already started)
- Consider progression to invasive ventilation.

Indications for Invasive Mechanical Ventilation

- Unable to tolerate NIV or NIV failure (or exclusion criteria)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency ≥ 35 breaths/min
- Life-threatening hypoxemia
- Severe acidosis (pH < 7.25) and/or hypercapnia ($PaCO_2$ > 8.0 kPa, 60 mmHg)
- Respiratory arrest
- Worsening in mental status despite optimal therapy
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)

Ventilatory management of AECOPD is discussed in the chapter on invasive ventilation.

Of note, the perception that severe AECOPD requiring invasive ventilation leads to ventilator dependence in a majority of patients is erroneous as all data show a median length of ventilation between 2 to 5 days. However, most data is retrospective and subject to selection bias. The most important outcome variable is premorbid performance status. In fact, prognosis of AECOPD patients needing invasive ventilation is better than ARDS. However, before proceeding to intubate and ventilate a severe COPD patient the possibility of prolonged mechanical ventilation must be discussed with the family and patient, if appropriate.

Preparation for Discharge from Hospital

To qualify for discharge, a patient should have:

- Stable clinical symptoms
- Stable or improving PaO_2 >60 mmHg for least 12 hour
- Patient should not requires short acting β_2 agonist inhaler more frequent than every 4 hours
- Patient is stable at MDI (metered dose inhaler)

- Patient is educated about general overview of COPD, available medical treatment, nutrition advanced education about when to seek medical help.
- Home support, such as oxygen concentration, nebulizer, home health nurse service should be arranged before discharge.

Prevention of Future Exacerbations

- Smoking cessation
- Immunization against *H. influenzae* and *S. pneumoniae*
- Pulmonary rehabilitation
- Long-term oxygen therapy decrease frequency and duration of hospital stay
- Long-acting inhaled bronchodilator and corticosteroid reduces risk of exacerbation in patient with stable COPD.

Suggested Reading

1. Balter MS, Forge JL, Low DE, et al. Canadian guidelines for management of acute exacerbations of chronic bronchitis: Executive summary. Can Respir J. 2003;10:5.
2. BTS NICE COPD guidelines 2004 accessible at http://www.nice.org.uk/pdf/CG012_niceguideline.pdf
3. Chronic obstructive pulmonary disease • 9: Management of ventilatory failure in COPD, Thorax. 2003;58:537-42.
4. ERS/ATS 2006 COPD guidelines accessible at http://www.ersnet.org/lrPresentations/copd/files/main/index.html
5. Evensen AE. Management of COPD Exacerbations. Am.Fam.Physician. 2010 March 1;81(5):607-13.
6. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006. Available from: http://www.goldcopd.org.
7. Lodewijckx C, Decramer M, Sermeus W, et al. Eight-step method to build the clinical content of an evidence-based care pathwy : the case for COPD exacerbation. Trials. 2012;13:229.
8. The pulmonary physician in critical care 11: Critical care management of respiratory failure resulting from COPD, Thorax. 2002;57:1079-84.

chapter 18

Mechanical Ventilation

Sumit Sen Gupta

The primary goal of ventilator support is the maintenance of adequate but not necessarily normal, gas exchange, which must be achieved with minimal injurious effects. There have been two paradigm shifts in the management of ventilation in a patient over the last few years:

1. Noninvasive ventilation, which has been shown to decrease infective complications in a number of specific diseases is increasingly being used in a variety of conditions.
2. Shift away form trying to maintain "normal" physiology to an approach, which minimizes injurious effects while maintaining 'adequate' gas exchange.

As a corollary "standard" ventilatory settings are of less use than a disease or condition specific ventilatory protocol. Here, we will try to focus on the basic set-up of ventilation, assist control mode of volume cycled ventilation along with some disease specific protocols. Weaning protocols will also be addressed.

Indications for Mechanical Ventilation

Mechanical ventilation is indicated when a patient is in respiratory failure and his respiratory rate or pCO_2 or pO_2 is worsening without ventilatory support and is likely to deteriorate further and the patient is on maximal treatment. The classical approach of initiating mechanical ventilation based on some parameters is only a guideline (Table 18.1).

Table 18.1 Initiation of mechanical ventilation

	Mode	FiO_2	PEEP	VT (ml/kg)	RR/mt	Flow rate
Normal lung	ACV/PSV	0.5	5	8-12	10	60
Asthma	ACV	0.5	0	5-7	8-14	60
AECOPD	ACV/PSV	0.5	5	5-7	24	60
ARDS	ACV	1.0	10-15	4-6	24	60
Restriction	ACV	0.5	5	5-7	20	60

Abbreviations: ACV, assist-control ventilation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; RR, respiratory rate; VT, tidal volume.

Invasive Ventilation in Asthma

Intubate—not too early not too late

- Drowsy/comatose
- Respiratory arrest
- Respiratory fatigue and decreased respiratory effort
- Decision is clinical
- No objective criteria
- Never based solely on arbitrary levels of measured parameters (e.g. pCO_2)
- Do not wait until patient moribund, i.e. avoid crash intubation.

Ventilation Strategy

Minimize Dynamic Hyperinflation (DHI)

- VE 115 ml/kg
- VT < 8 ml/kg
- Frequency 8 to 14/mt
- I:E ratio 1:3
- Flow rate 80 to 100 liters/mt
- PPLAT < 25, end inspiratory pressure <35
- Ignore peak pressure
- No/minimal extrinsic PEEP
- Permissive hypercapnia as long as pH >7.15

Pressure support has been used to ventilate patients with asthma in some centers with reasonable outcome

Problems with ventilation in asthma

- Pneumothorax
- Severe dynamic hyperinflation

If patient develops severe hypoxia and hypotension on the ventilator:

- Apnea test—disconnect from ventilator for 1 minute to relieve DHI
- Always X-ray before putting a needle in for pneumothorax unless SBP <70 mmHg since the consequences of an iatrogenic pneumothorax may be disastrous.

Practical problems during ventilation

- 125 mg/day of methylprednisolone or equivalent plus neuromuscular blockade may cause severe respiratory myopathy
- Large volume nebulization required.

Acute Cardiogenic Pulmonary Edema Protocol

Intubate and ventilate if there is refractory shock or cardiorespiratory arrest. If not, be guided by BP and ABGs

1. If systolic BP is >180 start conventional treatment—if oxygenation worsens or there is significant acidosis institute noninvasive ventilation.

2. If systolic BP is <180 and
   - If there is hypercapnia or acidosis immediately start noninvasive ventilation
   - If there is normocapnia or hypocapnia and no acidosis start conventional treatment—ventilate noninvasively if patient worsens.

   If no improvement intubate and invasively ventilate.

Acute Exacerbation of COPD

Preferably ventilated noninvasively; when intubated, the goals are:

- To rest the patient (and respiratory muscles) completely for 36 to 48 hours
- To avoid excessive ventilation (which may cause significant posthypercapnic alkalosis)
- To avoid excessive ventilatory support (which may contribute to weakness of the diaphragm) switch to pressure support within 48 hours.
- In less severely ill patients, pressure support ventilation may be used from the outset.

In patients with COPD, peak airway pressures tend to be only modestly elevated (as they have relatively smaller increases in inspiratory resistance (compared with asthma), with their expiratory flow limitation arising largely from loss of elastic recoil). Auto PEEP and its consequences are common. Be careful of the odd patient with COPD who behaves like acute asthma with markedly raised peak airway pressures—in these patients a protocol similar to the asthma protocol may be used.

Weaning

You do not wean the patient—the patient weans himself if you allow him to do it.

Weaning should be considered as early as possible in patients receiving mechanical ventilation; a majority of patients can be successfully weaned on the first attempt. SBT (Spontaneous breathing trial) is the major diagnostic test to determine if patients can be successfully extubated. The initial SBT should last 30 min and consist of either T-tube breathing or low levels of PS (5-8 cm H_2O) with or without 5 cm H_2O PEEP. SIMV should be avoided as a weaning modality.

The initial assessment involves calculation of the rapid shallow breathing index (RSBI). In general, patients should be considered as an RSBI calculation and subsequent SBT earlier rather than later, since physicians frequently underestimate the ability of patients to be successfully weaned. Discontinuation of sedation is a critical step that can be achieved by either daily interruption of sedation or continuous titration of sedation to a level that allows the patient to be adequately responsive. Avoid paralyzing the patient at any stage unless absolutely necessary.

Criteria for Attempting Spontaneous Breathing Trial

Clinical Assessment

- Adequate cough
- Absence of excessive tracheobronchial secretion
- Resolution of acute phase for which the patient was intubated
- Stable metabolic status.

Objective Measurements

- Adequate oxygenation SaO_2 >90% on FiO_2 0.4 (or PaO_2/FiO_2 <150 mmHg)
- PEEP < 8 cmH_2O
- Stable cardiovascular status
  - Heart rate <120 beats/min
  - Systolic BP 90 to 160 mmHg,
  - No or minimal vasopressors
- Frequency 35 breaths/min
- fR/VT < 105 breaths/min (fR = Respiratory frequency)
- No significant respiratory acidosis
- No sedation or adequate mentation on sedation (or stable neurologic patient).

These criteria should be viewed as considerations for probable weaning rather than strict criteria that must all be met simultaneously.

If these criteria are met then a spontaneous breathing trial is attempted. If the patient succeeds the patient is extubated.

Criteria for Failure of Spontaneous Breathing Trial

- Agitation and anxiety
- Depressed mental status
- Diaphoresis
- Cyanosis
- Evidence of increasing effort
- Increased accessory muscle activity
- Facial signs of distress
- Dyspnea.

Objective Measurements

- PaO_2 <50 to 60 mmHg on FiO_2 0.5 or SaO_2 <90% or significant desaturation
- $PaCO_2$ >50 mmHg or an increase in $PaCO_2$ >8 mmHg
- pH <7.32 or a decrease in pH > 0.07 pH units
- fR/VT >105 breaths/min
- fR >35 breaths/min or increased by >50%
- Heart rate >140 beats/min or increased by >20%
- Systolic BP >180 mmHg or increased by >20%

- Systolic BP <90 mmHg
- Cardiac arrhythmias.

In patients failing attempts at SBT, PSV or assist-control ventilation should be favored. NIV techniques to shorten the duration of intubation should be considered in selected patients, especially those with hypercapnic respiratory failure due to COPD. NIV should not be routinely used as in the event of extubation failure and should be used with caution in patients with hypoxic respiratory failure. Consider early tracheostomy.

Complications of Ventilation

Ventilator Associated Pneumonia

VAP occurs in approximately 1% of intubated patients per day. Assessment for VAP starts with (a) calculation of the CPIS score as given below.

Clinical Pulmonary Infection Score (CPIS) Calculation*

Temperature (°C)

- > or equal to 36.5 and < or equal to 38.4 = 0 point
- > or equal to 38.5 and < or equal to 38.9 = 1 point
- > or equal to 39 and < or equal to 36 = 2 points

Blood Leukocytes, mm^3

- > or equal to 4,000 and < or equal to 11,000 = 0 point
- < 4,000 or > 11,000 = 1 point + band forms > equal to 50% = add 1 point

Tracheal Secretions

- Absence of tracheal secretions = 0 point
- Presence of nonpurulent tracheal secretions = 1 point
- Presence of purulent tracheal secretions = 2 points.

Oxygenation: PaO_2/FiO_2, mmHg

- > 240 or ARDS (ARDS defined as PaO_2/FiO_2 > or equal to 200, pulmonary arterial wedge pressure < or equal to 18 mmHg and acute bilateral infiltrates) = 0 point
- < or equal to 240 and no ARDS = 2 points.

Pulmonary Radiography

- No infiltrate = 0 point
- Diffuse (or patchy) infiltrate = 1 point
- Localized infiltrate = 2 points.

Progression of Pulmonary Infiltrate

- No radiographic progression = 0 point
- Radiographic progression (after CHF and ARDS excluded) = 2 points.

Culture of Tracheal Aspirate

- Pathogenic bacteria cultured in rare or light quantity or no growth = 0 point
- Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
- Same pathogenic bacteria seen on Gram stain, add 1 point.

Definition of abbreviations: ARDS = Acute respiratory distress syndrome; CHF = Congestive heart failure; PaO_2/FiO_2 = Ratio of arterial oxygen pressure to fraction of inspired oxygen.

CPIS at baseline was assessed on the basis of the first five variables, i.e. temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate. CPIS at 72 hour was calculated based on all seven variables and took into consideration the progression of the infiltrate and culture results of the tracheal aspirate. A score > 6 at baseline or at 72 hour was considered suggestive of pneumonia.

If CPIS >/= 6 start empirical antibiotics according to presence or absence of risk factors for multidrug resistant bacteria after sending of quantitative lower respiratory tract secretions for culture and sensitivity (quantitative or semi-quantitative ET aspirate is perfectly acceptable).

Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity (Table 18.2).

Table 18.2 Initial empiric antibiotic therapy for early onset pneumonia

Potential pathogen	Recommended antibiotic*
Streptococcus pneumoniae *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* Antibiotic-sensitive enteric Gram-negative bacilli *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* species *Proteus* species *Serratia marcescens*	Ceftriaxone or Levofloxacin, moxifloxacin, or ciprofloxacin or Ampicillin/sulbactam or Ertapenem

*The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

Risk factors for multidrug-resistant pathogens causing ventilator-associated pneumonia

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more

- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Initial empiric therapy for ventilator-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity (Table 18.3).

Table 18.3 Initial empiric antibiotic therapy for late onset VAP

Potential pathogens	Combination antibiotic therapy
Pseudomonas aeruginosa *Klebsiella pneumoniae* (ESBL+)† *Acinetobacter* species†	Antipseudomonal cephalosporin (Cefepime, ceftazidime) or Antipseudomonal carbapenem or (Imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (Piperacillin-tazobactam) plus Antipseudomonal fluoroquinolone † (Ciprofloxacin or levofloxacin) or Aminoglycoside (Amikacin, gentamicin, or tobramycin) ‡
Methicillin-resistant *Staphylococcus aureus* (MRSA) Legionella pneumophila †	plus Linezolid or vancomycin

†If an ESBL+ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbepenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.
‡If MRSA risk factors are present or there is a high incidence locally.

Antibiotic dosage

Antibiotic	Dosage*
Antipseudomonal cephalosporin	
Cefepime	1-2 g every 8-12 hr
Ceftazidime	2 g every 8 hr
Carbapenem	
Imipenem	500 mg every 6 hr or 1 g every 8 hr
Meropenem	1 g every 8 hr
β-Lactam/β-lactamase inhibitor	
Piperacillin-tazobactam	4.5 g every 6 hr
Aminoglycosides	
Gentamicin	7 mg/kg per d †
Tobramycin	7 mg/kg per d †
Amikacin	20 mg/kg per d †
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 hr
Vancomycin	15 mg/kg every 12 hr ‡
Linezolid	600 mg every 12 hr

* Dosages are based on normal renal and hepatic function.
†Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4-5 μg/ml.
‡Trough levels for vancomycin should be 15-20 μg/ml.

At 72 hours, recheck clinically and recalculate CPIS

- Clinical improvement but cultures are negative—consider stopping antibiotics
- Clinical improvement and cultures positive—deescalate treatment if possible.
- No clinical improvement—search for other diagnoses, complications and sites of infection and other pathogens

d. Duration of treatment is for 8 days except for MRSA or Pseudomonas.

Prevention of VAP

General Prophylaxis

1. Compliance with alcohol-based hand disinfection and universal precautions.
2. Surveillance of ICU infections.

Intubation and Mechanical Ventilation

1. Intubation and reintubation should be avoided.
2. Noninvasive ventilation should be used whenever possible.
3. Orotracheal intubation and orogastric tubes are preferred over nasotracheal intubation and nasogastric tubes to prevent nosocomial sinusitis and to reduce the risk of VAP.

4. Continuous aspiration of subglottic secretions can reduce the risk of early-onset VAP, and should be used, if available.
5. The endotracheal tube cuff pressure should be maintained at greater than 20 cm H_2O to prevent leakage of bacterial pathogens around the cuff into the lower respiratory tract.
6. Contaminated condensate should be carefully emptied from ventilator circuits and condensate should be prevented from entering either the endotracheal tube or in-line medication nebulizers.
7. Decrease the use of sedation and utilize weaning protocols to accelerate extubation.
8. Maintaining adequate staffing levels in the ICU can reduce length of stay, improve infection control practices, and reduce duration of mechanical ventilation.

Aspiration, Body Position, and Enteral Feeding

1. Patients should be kept in the semirecumbent position (30-45°).
2. Enteral nutrition is preferred over parenteral nutrition.

Modulation of Colonization: Oral Antiseptics and Antibiotics

1. Routine prophylaxis of HAP with oral antibiotics (selective decontamination of the digestive tract or SDD), with or without systemic antibiotics, reduces the incidence of ICU-acquired VAP, has helped contain outbreaks of MDR bacteria but is not recommended for routine use, especially in patients who may be colonized with MDR pathogens.
2. Modulation of oropharyngeal colonization by the use of oral chlorhexidine has prevented ICU-acquired HAP in selected patient populations such as those undergoing coronary bypass grafting, but its routine use is not recommended until more data become available.
3. Use daily interruption or lightening of sedation to avoid constant heavy sedation and try to avoid paralytic agents, both of which can depress cough and thereby increase the risk of HAP.

Stress Bleeding Prophylaxis, Transfusion, and Hyperglycemia

1. Comparative data from randomized trials suggest a trend toward reduced VAP with sucralfate but there is a slightly higher rate of clinically significant gastric bleeding, compared with H_2 antagonists. If needed, stress bleeding prophylaxis with either H_2 antagonists or sucralfate is acceptable.
2. Transfusion of red blood cell and other allogeneic blood products should follow a restricted transfusion trigger policy; leukocyte-depleted red blood cell transfusions can help to reduce HAP in selected patient populations.

3. Intensive insulin therapy is recommended to maintain serum glucose levels between 80 and 110 mg/dl in ICU patients to reduce nosocomial blood stream infections, duration of mechanical ventilation, ICU stay, morbidity, and mortality.

Barotrauma (Pneumothorax and Pneumomediastinum)

The incidence of macrobarotraumas is currently approximately 5 to 10% in ARDS patients, a substantial decline over the years.

High plateau pressure is the most likely culprit—a ventilatory strategy that allows unlimited plateau pressure is associated with a very high rate of barotraumas. The occurrence of barotrauma is significantly reduced when plateau pressures are below 35 cm H_2O but plateau pressure is a risk factor for barotrauma only when it is too high. At the levels of plateau pressure used in the ARDS network protocol the only risk factor for barotraumas is PEEP.

Hypotension during Initiation of Positive-Pressure Ventilation

Positive-pressure ventilation raises intrathoracic pressure during inspiration, decreasing venous return. Positive end-expiratory pressure (PEEP), especially when applied to compliant lungs, further impedes venous return.

Hypotension immediately following intubation and initiation of mechanical ventilation is a common clinical consequence caused by the mechanisms just listed, particularly in the presence caused by hypovolemia. The abrupt blunting of sympathetic tone by induction of anesthesia is another mechanism, and hypotension caused by decreased venous tone, such as that seen with sepsis, spinal cord injury, or hypoglycemia, also may occur. Hypotension in these settings usually responds to crystalloid infusion, with the addition of pressors if necessary.

Hypotension (in a Previously Stable, Intubated Patient)

The list of causes of hypotension in mechanically ventilated patients is extensive. The major categories are:

- Hypovolemia
- Impediments to venous return
- Cardiac dysfunction
- The systemic inflammatory response syndrome (SIRS)
- The effects of medications.

Hypovolemia may be due to inadequacies in fluid resuscitation, inadequate maintenance hydration or increased fluid losses. Following the administration of fluids and stabilization of blood pressure, potential sites of fluid or blood loss must be investigated.

Impediments to venous return include PEEP, dynamic hyperinflation, tension pneumothorax, or massive PE.

Hypotension also may be due to myocardial ischemia/infarct or arrhythmias. An electrocardiogram, ideally compared with an old tracing, aids in determining appropriate concern for ischemia.

Patients with SIRS also often have markedly elevated cardiac outputs and low systemic vascular resistance. The hypotension should be treated initially with crystalloid infusion and appropriate antibiotic therapy. If there is no response, pressors should be added.

The use of benzodiazepines, narcotics, or anesthetic agents such as propofol or etomidate can cause blood pressure lability because of their vasodilatory properties. Acute allergic reactions to medications also can cause hypotension, along with bronchospasm, laryngeal edema, and urticaria.

Initial evaluation of the hypotensive patient should include a review of the other vital signs; a directed physical examination with special attention to volume status; use of the Trendelenburg position to maintain mean arterial blood pressure greater than 70 mmHg; administration of fluids, if necessary; and the use of pressors if the patient is not responsive to fluid administration. The clinical course before the episode then should be reviewed and other data gathered if warranted.

Acute Respiratory Distress (Fighting the Ventilator)

Assess for Ventilator Malfunction

Right mainstem bronchus intubation at the time of initial placement or secondary to tube migration. Contralateral atelectasis, worsening gas exchange, and increased risk for barotrauma from overinflation of the ipsilateral lung all can arise from right mainstem intubation. Auscultation, followed by tube repositioning, is the best initial management. A chest radiograph must confirm tube placement.

The tube also may migrate above the vocal cords, presenting as low tidal volumes, the sudden ability to phonate, and escape of air from the nose and mouth. Tube migration results from inadequate external fixation coupled with excessive neck movement. Neck flexion or extension may move the tube up to 5 cm. (Confirming adequate tube placement by a chest radiograph reduces the incidence of unrecognized endotracheal tube migration).

Cuffs can rupture/leak (presenting as low delivered tidal volume, inability to maintain PEEP, and a decreased volume of cuff air).

Lower airway obstruction also results in acute respiratory distress. Copious or thick secretions can plug the endotracheal tube or small airways, resulting in atelectasis and inadequate oxygenation. Observation of the amount and consistency of secretions during suctioning assists in the diagnosis. Treatment involves the removal of secretions to maintain lung inflation by aggressive suctioning, chest physiotherapy or even bronchoscopy.

Bronchospasm, pneumonia (discussed earlier), and pulmonary edema also can lead to dyspnea and other patient discomfort. Physical examination and serial chest radiographs help guide therapy.

Dynamic hyperinflation, or auto-PEEP, occurs in patients with airway collapse. Air-trapping arises from the inability to exhale a delivered tidal volume before the next breath is delivered (so-called stacking breaths). During assist-control ventilation, the patient must generate a preset negative inspiratory pressure to trigger the ventilator. If auto-PEEP is present, the patient must generate a force equal to the level of auto-PEEP plus the necessary circuit pressure drop to trigger the ventilator measures to prevent or reverse auto-PEEP include:

I. *Prolong expiratory time*
   Increase peak inspiratory flow rates
   Use nondistensible ventilator tubing that decreases the total tidal volume delivered so it can be delivered during a shorter period
II. *Minimize expiratory airflow obstruction*
   Use larger diameter endotracheal tubes
   Treat bronchospasm aggressively (bronchodilators, steroids)
   Suction frequently to remove secretions
III. *Employ appropriate ventilatory strategies*
   Lower tidal volumes
   Remedy respiratory alkalosis with lower rates or tidal volumes
   Use PEEP to reduce the inspiratory force necessary to trigger the ventilator, thereby decreasing work of breathing.

Pneumothorax

Inadequate pain relief or sedation. This is a diagnosis of exclusion, and administration of sedatives, and especially muscle relaxants, to a patient with new onset of acute respiratory distress during mechanical ventilation without first excluding specific life-threatening causes is contraindicated.

Repeated High-pressure Alarm

Narrowing of the inspiratory passages due to fluid or kinking in the ventilatory inspiratory tubing, smaller gauge endotracheal and tracheostomy tubes, neoplasms, stenosis, or foreign bodies in the trachea.

Secretions can occlude the endotracheal tube or the airways.

Bronchospasm secondary to underlying intrinsic airway hyper-reactivity, worsened by concurrent infection, aspiration, repetitive trauma from suction catheters, or heart failure.

Decreased respiratory system compliance also acts to elevate inspiratory pressures. Recall that compliance corresponds to the change in volume for a given change in pressure. During volume-cycled ventilation, lowering the compliance means a higher pressure will be required to deliver the tidal volume; with pressure-targeted ventilation, the peak inspiratory pressure is fixed and a drop in compliance results in decreased delivered tidal volume. Common causes of decreased compliance include cardiogenic pulmonary edema, early onset of the acute respiratory distress syndrome (ARDS), dynamic hyperinflation (from auto-PEEP or an inappropriately high tidal volume), and progression of pneumonia. Splinting of intercostal muscles, often because of pain, also can alter chest wall mechanics by inhibiting lung expansion. Atelectasis during mechanical ventilation may reduce compliance by overdistending the remaining lung.

Extrinsic lung compression: Although there are multiple causes, the most potentially serious is barotrauma (i.e. pneumothorax). Barotrauma, defined for this purpose as ventilator-associated extra-alveolar air, results from alveolar overdistention and rupture or other sources of lung parenchymal injury. Such injuries can occur from penetrating trauma, surgical procedures, bronchoscopy with transbronchial biopsy, thoracentesis, and as a complication of central line placement. Pneumothorax can present in a variety of ways, ranging from changes noticed only on a chest radiograph, to alterations in bedside monitoring, and finally to the cardiovascular collapse associated with tension pneumothorax. Chest radiographs may provide early clues, and there are several subtle radiographic signs, including an increased overall lucency in one hemithorax (suggesting an anterior pleural air collection), visualization of the epicardial fat pad, and a "deep sulcus sign." Alterations in bedside monitoring include unexplained hypoxemia, a rise in peak inspiratory pressure, or a decrease in respiratory system compliance.

The clinical syndrome of tension pneumothorax is the most dramatic presentation of barotrauma. Physical signs include unilaterally diminished breath sounds, contralateral tracheal shift, tachycardia, hyper-resonance to percussion, jugular venous distention, and hypotension. Treatment of tension pneumothorax involves rapid placement of a needle into the pleural space to allow air to escape, followed by a thoracostomy tube.

Many practical measures can be employed to reduce the incidence of barotrauma, including the use of small tidal volumes, the cautious use of PEEP in high-risk patients, monitoring closely for dynamic hyperinflation, and following changes in compliance. Pneumothoraces may result in continued air leak (bronchopleural fistula).

Acute large pleural fluid collections can raise inspiratory pressure by inhibiting lung expansion as can abdominal processes such as gastric distention, ileus, or ascites.

Hypoxia

The endotracheal or tracheostomy tube may be malpositioned, occluded with secretions, or kinked. Excessive PEEP can overdistend normal alveoli, worsening V/Q mismatching by diverting blood flow to poorly ventilated lung. The ventilator itself may malfunction, resulting in varied oxygen delivery and tidal volumes. An oxygen meter should be used to confirm the delivered FiO_2.

Progression of underlying pulmonary disease also can worsen oxygenation. ARDS, pneumonia, sepsis, and COPD exacerbations can lead to poor oxygenation. Cardiogenic pulmonary edema, from fluid overload, myocardial ischemia, or decreased cardiac output, worsens V/Q mismatch and shunt. Clinical assessment of fluid balance aids the diagnosis and diuresis may correct the problem.

Pulmonary thromboembolism may occur in up to 10% of critically ill patients.

Aspiration of oropharyngeal or gastric contents can lead to bronchospasm and nosocomial pneumonia. Ventilator-associated pneumonia is another cause of hypoxia.

Tracheal suctioning, body position changes, especially in those with unilateral lung disease, Thoracentesis has been associated with a drop in PaO_2 in some studies, possibly because of re-expansion pulmonary edema. Chest physiotherapy, which includes postural drainage, percussion, and coughing, may induce bronchospasm or move secretions into larger, more proximal airways causing hypoxia. Bronchoscopy occasionally induces hypoxemia because of bronchospasm or hypoventilation, but also acts to improve oxygenation in some through the removal of secretions.

Blood from the Endotracheal Tube

The most common cause is iatrogenic, in the form of suction catheter-related trauma. Necrotizing pneumonia and tracheobronchitis, especially combined with aggressive suctioning, can cause hemorrhage. Another common cause of hemorrhagic secretions is pulmonary edema. Classically, patients who develop cardiogenic pulmonary edema produce pink, frothy sputum. The condition can be severely exacerbated into impressive hemorrhage if a concomitant coagulopathy exists or excessive suction trauma occurs. Pulmonary thromboembolism presents with hemoptysis in a small percentage of patients. Pulmonary artery catheters also are associated with pulmonary artery dissection and rupture. These arise from distal placement and inflation of the balloon. Patients with this condition typically develop hemoptysis and a radiographically well-defined mass near the catheter tip. Prolonged use of pulmonary artery catheters may induce erosion through the arterial wall, with resulting hemorrhage. Erosions secondary to the endotracheal tube cuff also occur rarely. Cuff-associated trauma occurs when cuff pressure exceeds the capillary perfusion pressure of 20 to 30 mmHg, causing tissue ischemia and necrosis. Erosions in the trachea or, more proximally, in the larynx also induce hemorrhage. The most dramatic example is tracheoinnominate artery fistula, which presents as an acute eruption of bright red blood from the endotracheal tube. Close monitoring of the cuff volume and pressure is the best prophylaxis.

The last major cause of hemorrhagic secretions is the underlying disease. A variety of illnesses may result in pulmonary hemorrhage, a few examples being vasculitic syndromes and Goodpasture's syndrome. Primary or metastatic neoplasms may erode into vessels, inducing pulmonary hemorrhage. Disseminated intravascular coagulation, often associated with the sepsis syndrome, or other forms of acquired coagulopathy rarely result in significant spontaneous hemorrhage but, in combination, can cause impressive bleeding. Tuberculosis or bronchiectasis may also present with hemoptysis. Rarely leptospirosis may present with hemoptysis.

Suggested Reading

1. Critical Care Clinics. An entire issue devoted to mechanical ventilation, 2007;23(2):xiii-337.
2. de Wit M, Miller KB, Grcen DA, et al. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med. 2009;37:2740-2745.
3. Discontinuing Mechanical Ventilatory Support Chest. 2007;132:1049-56.
4. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia, American Journal of Respiratory and Critical Care Medicine. 2005;171:388-416.
5. Jesse Hall - Principles of Critical Care, 3rd Edition.
6. Management of mechanical ventilation in acute severe asthma: practical aspects. Intensive Care Med. 2006;32:501-10.
7. Martin Tobin - Principles and Practice of Mechanical Ventilation, 2nd Edition.
8. Mechanical ventilation in chronic obstructive pulmonary disease. Clinics in Chest Medicine. 2000;21(4).
9. Mechanical ventilation in severe asthma. Crit Care. 2005;9(6):581-7.
10. Mechanical ventilation of the patient with severe chronic obstructive pulmonary disease. Intensive Care Med. 1998;24:898-910.
11. Paul Marino - The ICU book, 3rd Edition.
12. Santanilla JJ, Daniel B, Yeow ME. Mechanical Ventilation Emerg Med Clin N Am. 2008;26:849-62.
13. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receving mechanical ventilation: a randomized trial. Lancet. 2010;375:475-480.
14. Weaning from mechanical ventilation. Eur Respir J. 2007;29:1033-56.

Acute Respiratory Distress Syndrome/ Acute Lung Injury

chapter 19

Sumit Sen Gupta

- A syndrome of inflammation and increased permeability, associated with a constellation of clinical, radiologic and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary hypertension
- Acute onset
- Bilateral infiltrates on chest radiograph (alveolar/interstitial)
- Wedge pressure < 18 mmHg (PCWP/No clinical symptom of increased left atrial pressure)
- ALI $PaO_2/FiO_2 < 300$ mmHg
- ARDS $PaO_2/FiO_2 < 200$ mmHg.

Causes of Acute Respiratory Distress Syndrome/ Acute Lung Injury

- More common
  - Sepsis and sepsis syndrome
  - Acid aspiration
  - Multiple transfusions for hypovolemic shock
- Less common
  - Near-drowning
  - Pancreatitis
  - Air or fat emboli
  - Cardiopulmonary bypass
  - Pneumonia
  - Drug reaction or overdose
  - Leukoagglutination
  - Inhalation injury
  - Infusion of biologics (e.g. interleukin 2)
  - Ischemia-reperfusion (e.g. post-thrombectomy, post-transplantation)

Imitators of ARDS [with Broncho-alveolar Lavage Findings]

Cardiogenic pulmonary edema

Acute Interstitial Pneumonia

- Organizing diffuse alveolar damage
- Idiopathic (Hamman-Rich syndrome), CVD, cytotoxic drugs, infections [Neutrophilia (> 10%)]

Acute Eosinophilic Pneumonia

- Eosinophilic infiltration and diffuse alveolar damage
- Idiopathic, drugs [Eosinophilia (> 25%)].

Acute Cryptogenic Organizing Pneumonia

- Organizing pneumonia
- Idiopathic, CVD, drugs, radiation, infections [Neutrophilia, and sometimes lymphocytosis (> 25%), eosinophilia (>25%)]

Diffuse Alveolar Hemorrhage

- Pulmonary capillaritis, bland hemorrhage, diffuse alveolar damage
- Vasculitides, CVD, coagulopathies, diffuse infections [RBCs, hemosiderin-laden macrophages]

Acute Hypersensitivity Pneumonitis

- Granulomatous and cellular pneumonitis with diffuse alveolar damage
- Environmental and workplace antigens [Lymphocytosis (> 25%) and sometimes neutrophilia (> 10%)]
- Tuberculosis is rarely a cause of ARDS
- Neurogenic pulmonary edema.

Chest X-rays in ARDS

The initial film may be normal. Within 12 to 24 hours, bilateral, scattered, parenchymal homogeneous opacities are present. Although they represent extravascular lung water, these abnormalities generally are unaccompanied by the findings typically associated with cardiogenic pulmonary edema; that is, cardiomegaly, vascular redistribution or engorgement, or pleural effusion. Rapid progression to dense homogeneous opacification may occur within the next 24 to 48 hours,

If patients survive this period, there is progression into a chronic phase. Following several days of persistent homogeneous opacification, some areas of lucency are seen scattered throughout the lungs. The “white-out” and ground-glass opacities give way to a more heterogeneous, linear or reticular pattern. The heterogeneous pattern remains stable for days or weeks. In approximately 10% of cases, persistent chronic fibrosis and low lung volumes remain as a constant chest film abnormality. In other patients, various degrees of resolution may occur, with a strong tendency toward reversion to normal.

Management of ARDS

There is no specific treatment of ARDS. Management includes:

I. Ventilatory Protocol for ARDS Management

Though not formally accepted as treatment of ARDS most hospitals would try noninvasive ventilation in early stages of ALI particularly in immunocompromised patients. However, in all but the most minimal disease one would need to intubate and invasively ventilate the patient if the patient does not stabilize and improve rapidly.

Part I: Ventilator Setup and Adjustment

1. Calculate predicted bodyweight (PBW).
   Males = 50 + 2.3 [height (inches) – 60].
   Females = 45.5 + 2.3 [height (inches) – 60].
2. Select assist control mode.
3. Set initial TV to 6 ml/kg BW.
4. Set initial rate to approximate baseline VE (not > 35 bpm).
5. Adjust TV and RR to achieve pH and plateau pressure goals below.
6. Set inspiratory flow rate above patient demand (usually > 80L/min).

Oxygenation GOAL: PaO_2 mmHg or SpO_2 88-95%

Use incremental FiO_2/PEEP combinations below to achieve GOAL

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

- *Arterial oxygenation higher than the target range:* FiO_2 or PEEP will be decreased (by 0.10 or 2.0, respectively), whichever is farther (number of step changes) from the target scale shown in the accompanying table. If both PEEP and FiO_2 are equally distanced from the scale, then PEEP will be decreased.
- *Arterial oxygenation lower than the target range:* FiO_2 or PEEP will be increased (by 0.10 or 2.0, respectively), whichever is farther from the target scale shown in the table. If both PEEP and FiO_2 are equidistant from the scale, then PEEP will be increased first.
- *Arterial oxygenation within the target range:* If a single adjustment in either FiO_2 or PEEP would correct the FiO_2/PEEP to the target scale, then FiO_2 will be adjusted. If the FiO_2/PEEP cannot be corrected to the target scale with a single adjustment, then FiO_2 will be adjusted by 0.10 and PEEP will be simultaneously adjusted in the opposite direction by 2.0, e.g. increase FiO_2 by 0.10 and decrease PEEP by 2.0, or decrease FiO_2 by 0.10 and increase PEEP by 2.0.

Plateau Pressure GOAL: < 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), SpO_2, Total RR, TV and pH (if available) at least q 4 hr and after each change in PEEP or TV.

If Pplat > 30 cm H_2O: decrease TV by 1 ml/kg steps (minimum = 4 ml/kg). If Pplat < 25 cm H_2O: TV < 6 ml/kg, increase TV by 1 ml/kg until Pplat > 25 cm H_2O or TV = 6 ml/kg.

If Pplat < 30 and breath stacking occurs may increase TV in 1 ml/kg increments (maximum = 8 ml/kg).

pH GOAL: 7.30-7.45

Acidosis Management: (pH < 7.30)

If pH 7.15-7.30: Increase RR until pH > 7.30 or $PaCO_2$ < 25 (Maximum RR = 35).
If RR = 35 and $PaCO_2$ < 25, may give $NaHCO_3$.
If pH < 7.15: Increase RR to 35.
If pH remains < 7.15 and $NaHCO_3$ considered or infused, TV may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target may be exceeded).

Alkalosis Management: (pH > 7.45)

Decrease ventilation rate if possible.

I:E RATIO GOAL: 1:1.0 - 1:3 Adjust flow rate to achieve GOAL.

If FiO_2 = 1.0 and PEEP = 24 cm H_2O, may adjust I:E to 1:1.

Part II: Weaning

A. **Conduct a CPAP trial daily when:**
   1. FiO_2 <?0.50 and PEEP <?8.
   2. PEEP and FiO_2 <?values of previous day.
   3. Patient has acceptable spontaneous breathing efforts. (May decrease ventilation rate by 50% for 5 minutes to detect effort.)
   4. Systolic BP >?90 mmHg without vasopressor support.

   Conducting the Trial: Set CPAP = 5 cm H_2O, FiO_2 = 0.50
   If RR < 35 for 5 min: advance to pressure support weaning below:
   If RR > 35 in < 5 min: may repeat trial after appropriate intervention (e.g. suctioning, analgesia, anxiolysis)
   If CPAP trial not tolerated: Return to previous A/C settings

B. **Pressure Support (PS) Weaning Procedure**
   1. Set PEEP = 5, and FiO_2 = 0.50
   2. Set initial PS based on RR during CPAP trial:
      a. If CPAP RR < 25: set PS = 5 cm H_2O and go to step 3d.
      b. If CPAP RR = 25-35: set PS =20 cm H_2O then reduce by 5 cm H_2O at ?5 min. intervals until RR = 26-35 then go to step 3a.
      c. If initial PS not tolerated: return to previous A/C settings.
   3. Reducing PS:
      a. Reduce PS by 5 cm H_2O q1-3 hr.
      b. If PS <?10 cm H_2O not tolerated, return to previous A/C settings (Reinitiate last tolerated PS level next AM and go to step 3a)
      c. If PS = 5 cm H_2O not tolerated, return to PS = 10 cm H_2O. If tolerated, 5 or 10 cm H_2O may be used overnight with further attempts at weaning the next morning
      d. If PS = 5 cm H_2O tolerated for >?2 hours assess for ability to sustain unassisted breathing below.

C. **Unassisted Breathing Trial**
   1. Place on T-piece, tracheal collar, or CPAP <?5 cm H_2O
   2. Assess for tolerance as below for two hours.
      a. SpO_2 >90% and/or PaO_2 >?60 mmHg
      b. Spontaneous TV >?4 ml/kg PBW
      c. RR <?35/min
      d. pH >?7.3
      e. No respiratory distress (distress= 2 or more)
         • ?HR > 120% of baseline
         • ?Marked accessory muscle use
         • Abdominal paradox
         • Diaphoresis
         • Marked dyspnoea
   3. If tolerated consider extubation.
   4. If not tolerated resume PS 5 cm H_2O.

II. Supportive Treatment

Treat the cause:
- Aggressive treatment of sepsis
- Source control
- Fix all fractures as appropriate.

Early Goal directed therapy, e.g. early antibiotics in septic shock.

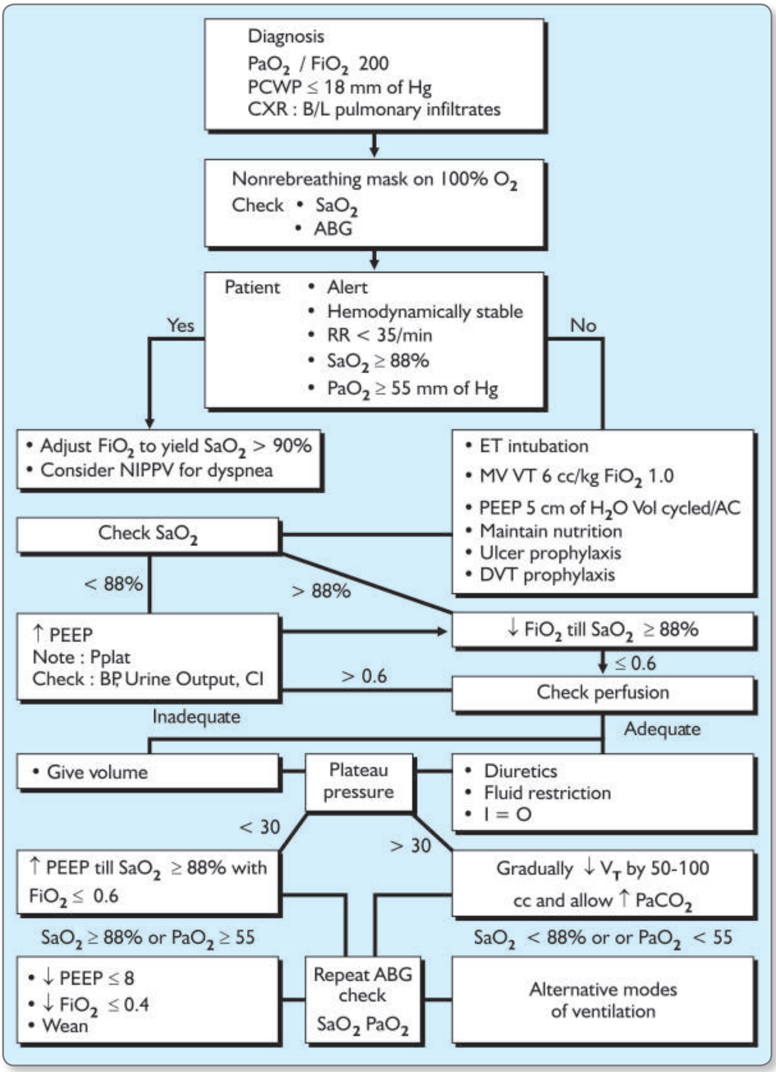
After the initial 48 hours conservative fluid strategy:
- Put in pulmonary artery catheter if feasible
- Maintain PCWP 6-14 mmHg
- Ensure euvolaemic state
- Use dopamine if PCWP as above fails to achieve MAP ≥ 65 mmHg
- Use dobutamine to ↓ SVR
- (MAP = Mean arterial pressure; SVR = Systemic vascular resistance)
  - Prophylaxis for DVT, GI bleed, aspiration, central venous catheter infection
  - Avoid unnecessary procedures and complications
  - Maintain good control of glucose with IV Insulin infusions
  - Minimize blood transfusions.

Recommendations for ARDS treatment

1. Mechanical ventilation with low VT → A
2. Optimization of left atrial filling pressure → B
3. High PEEP, prone position ventilation ECMO and recurrent maneuvers → C
4. Glucocorticosteroid, high frequency ventilation, surfactants, nitric oxide (inhaled), anti-inflammatory therapy (NSAIDS, Ketoconazole), Sivelestat (an inhibitor of neutrophil elastase) → D

A = Strong clinical evidence
B = Supportive but limited clinical data
C = Only as alternative therapy
D = Not recommended

Algorithm: Early Management of ARDS



Suggested Reading

1. ARDSNet low tidal volume trial full protocol and charts accessible at http://www.ardsnet.org/studies/arma.
2. Dushianthan A, Grocott MPW, Postle AD, Cusack R. Acute Respiratory Distress Syndrome and Acute Lung Injury. Postgrad Med J doi:10,1136/pgmj2011.118398.
3. Girand TD, Bernard GR. Mechanical ventilation in ARDS: a state-of-the-art review. Chest. 2007;131(3):921-9.
4. Santacruz JF, DiazGuzman Zavala E, Arroliga AC. Update in ARDS management: recent randomized controlled trials that changed our practice. Cleve Clin J. 2006; 73(3):217-9,223-5.
5. Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest. 2008;133(5):1120-7.

Management of Upper Gastrointestinal Bleeding

chapter 20

Sweety Trivedi, Debashis Datta

History

A. Bleeding due to suspected chronic liver disease; evaluate:
   - Alcohol consumption
   - Previous viral hepatitis, jaundice
   - Blood transfusion, etc.
   - Black tarry stool or coffee ground vomiting
   - Past history of varices.

B. Other than liver diseases
   - Pain abdomen, vomiting, medications, e.g. NSAID, warfarin, heparin, aspirin, clopidogrel, bisphosphonates, thrombolytic, GPIIb/IIIa antagonist, etc.
   - Disorder of coagulation, e.g. von Willebrand disease; Vitamin K deficiency; Disseminated Intravascular Coagulation.

Clinical Examination

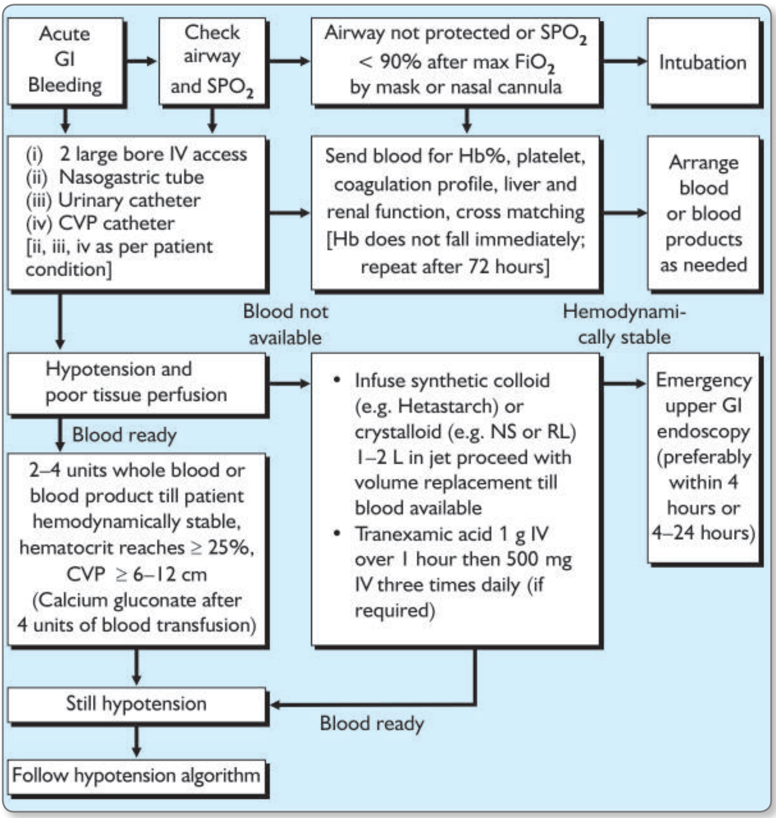
Assess Severity of Bleeding

- Hypotension, i.e. SBP < 100 mmHg
- Tachycardia, i.e. Pulse > 100 bpm
- Orthostatic hemodynamic changes, i.e. drop in SBP>10 mm Hg and/or rise in pulse rate > 15 bpm = 10 to 20 percent loss of circulatory volume supine hypotension = > 20 percent loss of volume
- Decreased urinary output < 20 mL/h
- Agitation/restlessness.

Causes of Upper GI Bleeding

- Peptic ulcer (35-62)%
- Varices (4-31)%
- Mallory-Weiss tear (4-13)%
- Gastro-duodenal erosion (3-11)%
- Erosive esophagitis (2-8)%
- Malignancy (1-4)%
- No source identified (7-25)%.

Flow chart 20.1 Resuscitation and Initial Management

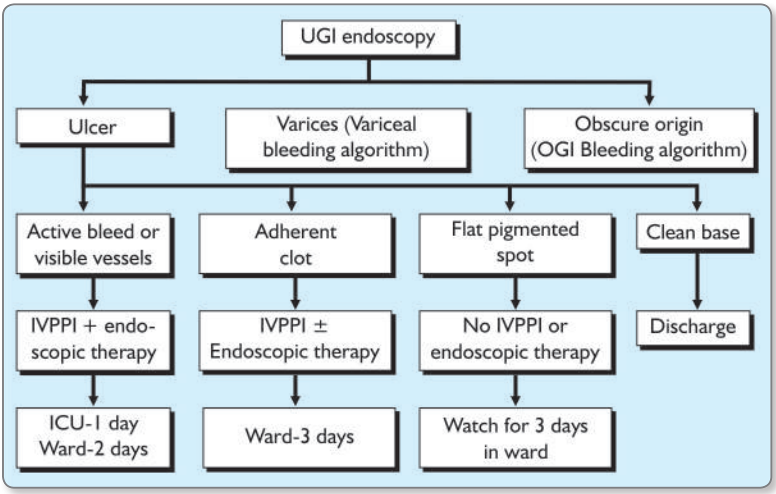


Initial Risk Assessment and Triage

The severity of blood loss can be assessed by the hemodynamic status and signs which include blood pressure, orthostatic hypotension, tachycardia, respiratory rate, urine output and sensorium. Several systems (like Baylor, Cedars-Sinai, Rockall, Blatchford, AIM565) are in use based on clinical and laboratory parameters for assessment and triage of patients presenting with upper GI bleeding. Of these following are most established and recommended.

- Blatchford Score at First-Assessment (clinical score)
- The full Rockall score after endoscopy (clinical and endoscopy)

Flow chart 20.2 Upper GI endoscopy guided management



Blatchford Score

The patients with Blatchford score of 0 can be considered for early discharge. The score can help identify patients who need early intervention.

Admission	Risk marker	Score component
• Blood urea (mg/dL)		
<18.2		0
>18.2 to < 22.4		2
>22.4 to < 28		3
>28 to < 70		4
>70		6
• Hemoglobin (men – g/dL)		
12 to < 13		1
10 to < 12		3
< 10		6
• Hemoglobin (women – g/dL)		
10 to < 12		1
< 10		6
SBP – mm Hg		
≥ 110		0
100 to 109		1
90 to 99		2
< 90		3
• Other markers:		
Pulse ≥ 100/min		1

Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac feature	2

[Adapted from: Blatchford O, Murray WR, Blatchford MA, A risk-score to predict need for treatment for UGI hemorrhage, Lancet 2000;356:1318-2].

Rockall Score

Age

- <60 years – 0 points
- 60-79 years – 1 point
- ≥ 80 years – 2 points.

Hemodynamic state

- None with systolic BP ≥ 100 and Pulse <100/min – 0 points
- Tachycardia with pulse ≥ 100/min but systolic BP ≥ 100 – 1 point
- Hypotension with systolic BP<100 – 2 points.

Major Comorbidities

- None – 0 points
- Cardiac failure, Ischemic heart disease – 2 points
- Renal failure, hepatic failure or disseminated cancer – 3 points

Diagnosis

- Mallory Weiss tear, but no major lesions and no stigmata of recent bleed – 0 points
- Other non-malignant gastrointestinal diagnosis – 1 point
- Upper gastrointestinal tract malignancy – 2 points.

Recent Hemorrhage

- None (or dark area only)—0 points
- Blood found in upper GI tract (clot adherence, spurting, bleeding vessel)—2 points.

The initial Rockall score is an appropriate tool to assess the patients for risk of re-bleeding and mortality. Patients with full Rockall score < 3 (post-endoscopic) have a low-risk of rebleeding and death and can be considered for early discharge.

Management

General Support

Patient should receive oxygen and kept 'nil by mouth'. Two large caliber peripheral cannula or central venous line should be inserted.

Elective endotracheal intubation may be necessary to decrease the risk of aspiration.

Fluid Resuscitation

Adequate resuscitation and stabilization is important prior to endosopy.

Blood Transfusion

The decision to initiate blood transfusions must be individualized. One approach is to initiate blood transfusion if hemoglobin is < 7 g/dL. The goal is to maintain hemoglobin above 9 g/dL.

However, patients with active bleeding may require blood transfusion despite an apparently normal hemoglobin.

Platelet transfusion can be considered when platelet count is < 50,000/microl and the patient is actively bleeding.

Fresh frozen plasma can also be given to patients with prolonged prothrombin time with INR> 1.5.

Place of Nasogastric Tube

Placement of nasogastric tube could be considered in selected patients who are suspected to have active UGI bleeding. Although presence of bright red blood in a gastric aspirate can be useful in identifying patients with high-risk lesion but absence of any blood does not exclude presence of active bleed.

It may also help to clear gastric field for endoscopic visualization and prevent aspiration of gastric contents.

Management of Non-variceal Bleeding

Endoscopic Therapy

- Endoscopic treatment should be given to actively bleeding lesions, non-bleeding visible vessels and when possible to adherent clots.
- Various endoscopic methods used are:
  - Adrenaline injection–usually not used as monotherapy [5-10 mL of 1:10,000 adrenaline]
  - Mechanical–clips with or without adrenaline have good efficacy and low rebleeding rates
  - Thermal coagulation using heater probe or argon coagulation with adrenaline is also a good option
  - Repeat endoscopy/endotherapy should be considered within 24 hours when initial endoscopy treatment was considered sub-optimal (because of difficult-access, poor visualization, etc.) or in patients which are at high-risk of bleeding.

High-Risk Endoscopic Stigmata

- Active bleeding
- Visible vessel
- Adherent clot

Patient with active bleeding should also receive PPI infusion at 8 mg/h for 24 to 72 hours and once bleeding settles oral high dose PPI can be started.

NSADIS, aspirin, clopidogrel, warfarin, anticoagulants should be ideally withheld, but for patients with coronary stents, ischemic heart disease cardiology opinion should be urgently requested.

Intermediate Risk Endoscopic Stigmata

- Oozing from ulcer and no other stigmata, severe comorbidity, shock on presentation: endoscopic hemostasis should be attempted.

Low-Risk Endoscopic Stigmata

- Clear base ulcer
- Flat spot

These patients usually do not need endoscopic treatment and can be started on oral PPI.

Repeat Endoscopy

Should be considered after 6–10 weeks of acid suppression in gastric ulcers to confirm healing and absence of malignancy.

Pharmacological

PPI/acid suppression

- PPI should be given to patients of non-variceal bleed if there is active bleeding, visible vessel or adherent clot
- Dose–omeprazole 80 mg bolus followed by 8 mg/h infusion for 24-72 hours or Pantoprozole same dose. Oral PPI–twice daily—4-6 weeks.

Helicobacter pylori

- Patients should be tested for *H. pylori* and treated if positive with 3 to 4 drug regime for 1 to 2 weeks.

NSAID induced/Drug induced

- Patients with H/o bleeding ulcer, healed ulcers who test negative for *H. pylori* require concomitant PPI if NSAIDs, aspirin or COX-2 inhibitors are indicated for regular intake.
- COX-2 inhibitors should be avoided in patients with cardiovascular risks.
- NSAIDs and aspirin should be discontinued when patients present with peptic ulcer bleeding and when the ulcer has healed and *H. pylori* eradication is complete, NSAIDs and aspirin should be started only when clear indications are present.
- SSRI, corticosteroids and anticoagulants should be used with caution in patients at risk of upper GI bleed.

Angiography and Surgery

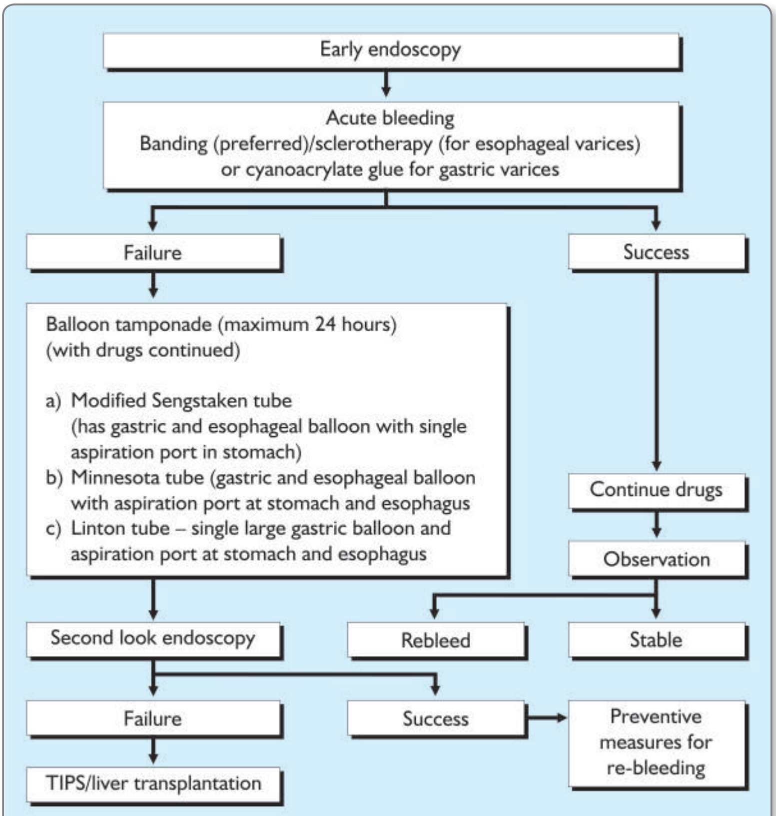
Patients with recurrent bleeding despite two sessions of endoscopic hemostasis should be considered for CT angiogram followed by embolization if bleeding vessel is identified.

Surgical intervention is required if:

- Medical management fails
- Endoscopist finds large/pulsating visible vessel.

Management of Variceal Bleeding

- Adequate initial resuscitative measures as mentioned previously
- Injection Terlipressin – 2 mg IV bolus → 2 mg IV 6 hourly till 48 hours (can cause coronary vasoconstriction, an ECG should done before starting Terlipressin)
  Or Injection Octereotide – 50 µg IV bolus → 6 mg/24 hour or 25 µg/hour for 2 to 3 days
  Or Injection Somatostatin – 250 or 500 µg/hour for 2 to 3 days
  Or Injection Vasopressin (0.1–0.4 µ/min) with GTN patch



Child's classification is used to assess hepatocellular function in cirrhosis

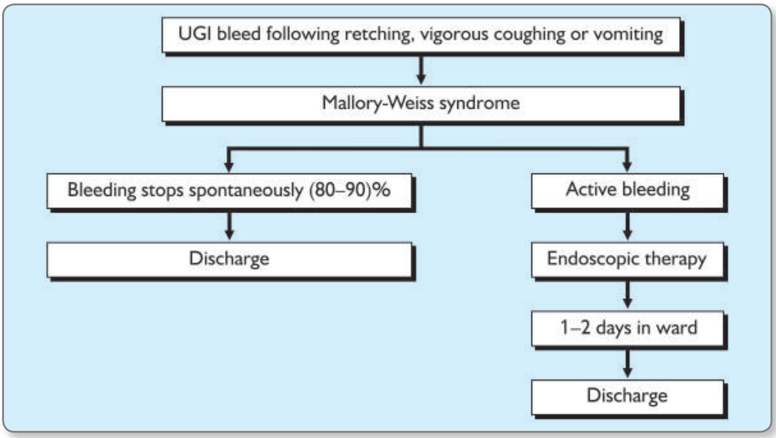
Table 20.1 Childs-Pugh Grading of Chronic Liver Disease

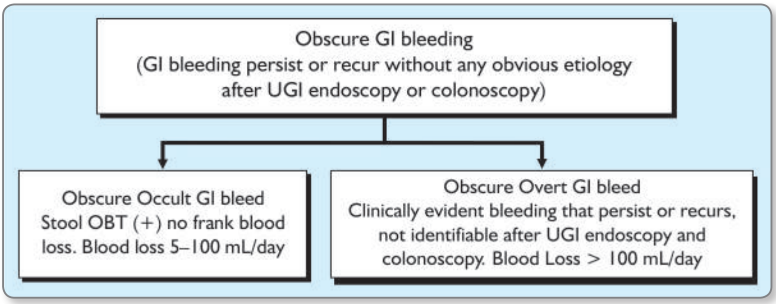
	Score		
Clinical/Laboratory findings	1	2	3
Encephalopathy	None	Mild (grade 1 to 2)	Severe (grade 3 to 4)
Ascites	None	Mid/slight	Moderate/Large
Bilirubins (micro-mol/l)	< 34	34 to 51	< 51
Albumin(g/l)	≥ 35	28 to 35	< 28
Prothrombin time Prolongation (secs) or	< 4	4 to 6	> 6
International normalized ratio	< 1.3	1.3 to1.5	> 1.5

Chronic liver diseases is classified into Child-Pugh class A to C, employing the total score from the above table.

Total points	Child-Pugh class
5 to 6	A
7 to 9	B
10 to 15	C

Mallory Weiss Tear





Obscure GI Bleeding

Common Causes

- Angiodysplasia
- Dieulafoy's Lesion
- Erosion/Ulcer
- Crohn's disease
- Small bowel varices
- Tumors
- NSAID enteropathy
- Radiation enteritis
- Small bowel diverticulosis
- Small bowel polyps
- Aortoenteric fistula
- Meckel's diverticulum

Dieulafoy's Lesion

It is a dilated aberrant vessel that erodes the overlying mucosa in the absence of a primary ulcer.The lesion is usually located in the proximal stomach along the lesser curvature.

Treatment: Dieulafoy's lesion can be difficult to identify during endoscopy due to the intermittent nature of bleed. Endoscopic treatment can be done with injection therapy, thermal treatment or clip device. Other therapies such as angiographic embolization or surgical treatment can be considered if endoscopic therapy fail.

Angiodysplasia

Treatment

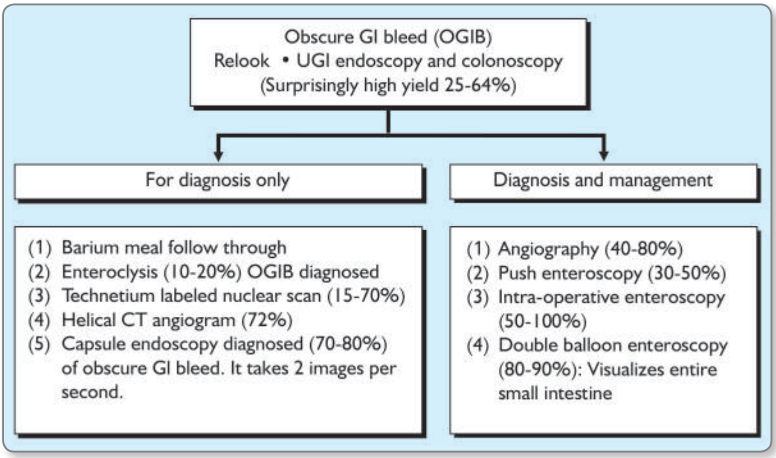
- Endoscopic ablation /Argon Plasma Coagulation (APC) for angiodysplasia.
- Combination estrogen and progesterone therapy.

Hemobilia

Causes: Latrogenic (40%), gallstone, aneurysm of hepatic artery.
Clinical Features: Hematemesis, jaundice, melena, pain and lump right hypochondrium.
Investigation: MRCP, ERCP (Clot in CBD).

Treatment

- Spontaneous remission
- Angiography with embolization.



Suggested Reading

1. Aljcbreen AM, Fallone CA, Barkun AN. Nasogastric aspirate predicts high risk endoscopic lesions in patients with acuute upper GI bleeding. Gastrointest Endosc 2004;59:172-8.
2. Barkun AN, Bardou M, Kuipers EJ, et al. Prokinetics in acute upper GI bleeding: a meta-analysis. Gastrointest Endosc 2010;72:1138-45.
3. Chen IC, Hung MS, Chiu TF, et al. Risk scoring systems to predict used for clinical intervention for patients with nonvariceal upper gastrointestinal tract bleeding. Am J Emerg Med.0 2007;25:774-9.
4. Cuellar RE, Gaveler JS, Alexander JA, et al. Gastrointestinal tract-hemorrhage. The value of a nasogastric aspirate. Arch Intern Med. 1990;150:1381-11.
5. Esrailian Eric, Gralneck Ian M. Non variceal upper gastrointestinal bleeding: Epidemiology and diagnosis. Gastroenterology Clinic North America. 2005;34:589-605.
6. Ferguson CB, Mitchell RB. Non variceal UGI bleeding: Standard and new treatment Gastroenterology Clinic North America. 2005;34:607-21.
7. Rocky Don C. Gastrointestinal bleeding: Gastroenterology Clinic North America. 2005;34:581-8.

8. Srirajaskanthan R, Conn R, Bulwer C, et al. The glasgow blatchford scoring system enables accurate risk stratification of patients with upper gastrointestinal hemorrhage. Int J Clin Pract 2010;64:868-74.
9. Stanley AJ, Ashley D, Datton HR, et al. Outpatient management of patients with low risk upper-gastrointestinal tract hemorrhage: multicenter, validation and prospective evaluation. Lancet 2009;373:42-7.
10. Stieymann GV, Goff JS, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992, 326:1527.
11. Tripathi D, Ferguson JW, Kochar N, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of first variceal bleed. Hepatology 2009;50:825-33.
12. Zoman A, Chalasani N. Bleeding caused by Portal hypertension – Gastrointerology Clinic North America 2005, 34:623-42.

chapter 21

Stroke

Dipankar Mondal, Jayanta Roy

Stroke is the second leading cause of death worldwide (9.5% cause of all deaths) and the leading cause of adult disability. World Health Organization (WHO) has defined stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". This definition proved useful for decades in clinical as well as epidemiological studies. Stroke can be of two types: Ischemic and hemorrhagic. Ischemic stroke can be arterial or venous in origin. Hemorrhagic stroke includes bleed in the brain parenchyma, within the ventricle or into the subarachnoid space.

In this chapter, management of ischemic stroke and intracerebral hemorrhage has been discussed. Treatment of subarachnoid bleed will not be discussed here.

Classification of Ischemic Stroke

TOAST (Trial of Org 10172 in Acute Stroke Treatment) Classification

- Large artery atherosclerosis (includes both extra- and intracranial diseases).
- Cardioembolic stroke.
- Lacunar stroke.
- Other determined etiology (includes dissection, vasculitis, fibromuscular dysplasia, Moyamoya, drug-induced vasospasm, etc.).
- Undetermined etiology (includes incomplete or negative work-up and cases where two mechanisms coexist).

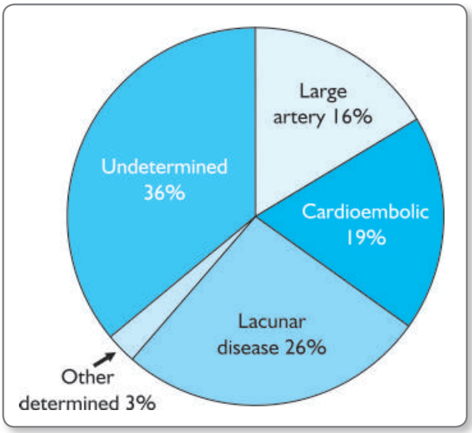


Fig. 21.1 Distribution of ischemic stroke subtypes according to TOAST criteria

Intracerebral Hemorrhage

Hemorrhage in different locations occurs in varying frequencies:

1. Putaminal 34%
2. Lobar 24%
3. Thalamic 20%
4. Cerebellar 7%
5. Pontine 6%
6. Caudate 5%
7. Putaminothalamic 4%

Prehospital Assessment of Stroke

Cincinnati Prehospital Stroke Scale: This simple scale is useful in identifying acute stroke patient at paramedical level to initiate acute stroke triage.

Facial droop:

Normal: Both sides of face move equally
Abnormal: One side of face does not move at all.

Arm drift:

Normal: Both arms move equally or not at all
Abnormal: One arm drifts compared to the other.

Speech:

Normal: Patient uses correct words with no slurring
Abnormal: Slurred or inappropriate words or mute.

Emergency Assessment of Acute Stroke

- Quick note of vitals signs.
- Rapid neurological assessment (apply NIH stroke scale—vide Appendix-1).
- Arrange for CT scan or MRI. CT scan is the most widely available scanning modality, which is very accurate in diagnosing intracerebral hemorrhage but changes of early ischemia are not always apparent. MRI is superior in diagnosis of ischemic stroke. Selected sequences like diffusion weighted images (DWIs) and FLAIR are capable of detecting early changes. T2 and gradient echo (GRE) detect acute bleed. So, an acute stroke MRI with above mentioned sequences can detect both ischemic and hemorrhagic stroke and they can be accomplished in about 8 to 10 minutes with modern MR machines. Additionally, MR angiogram can provide information about vessel status. Perfusion studies provide cerebral blood flow measurement through detection of mean transit time (MTT), cerebral blood volume (CBV) or cerebral blood flow (CBF).

4. Send lab investigations like CBC, INR, PTT, urea, creatinine, electrolytes, capillary glucose.
5. Order ECG, chest X-ray.

Management of Acute Ischemic Stroke

The landmark National Institute of Neurological Disorders and Stroke (NINDS) trial in 1995 showed an absolute increase in favorable 90-day outcomes of 11 to 13 percent for IV rtPA treatment within 3 hours of ischemic stroke onset compared with placebo, even when the 5.8 percent absolute increase in the difference in symptomatic intracranial bleeding was taken into account. The European Co-operative Acute Stroke Study (ECASSIII) showed a favorable outcome, defined as a Modified Rankin Scale (MRS) score of 0 or 1 (i.e. minimal or no deficit) at 90-day, in 52.4 percent of treated subjects versus 45.2 percent in controls ($p=0.04$).

Symptomatic intracranial hemorrhage was reported in 2.4 percent of the IV rtPA treated group compared with 0.2 percent of controls ($p=0.008$). The inclusion and exclusion criteria for ECASSIII were comparable to the original NINDS study except that those with NIHSS > 25, oral anticoagulant use, the presence of both diabetes mellitus and a previous stroke, and age > 80 years were excluded.

The American Heart Association/American Stroke Association has published (2009) a scientific advisory statement recommending its use 3 to 4.5 hours from acute ischemic stroke symptom onset for eligible patients without any additional exclusion criteria listed earlier on the basis of ECASS III.

Guidelines for Use of rtPA in Acute Ischemic Stroke

Intravenous rtPA Eligibility Criteria

Inclusion Criteria for rtPA

- Age 18 years or older
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- Time of symptom onset well-established to be < 4.5 hours before treatment.*

Exclusion Criteria for rtPA (0–4.3 hours)

- Imaging evidence of intracranial hemorrhage, mass effect, or hypodensity > one-third of hemisphere
- Minor or rapidly resolving symptoms likely to result in minimal or no residual deficit
- Clinical presentation suggestive of subarachnoid hemorrhage
- Active bleeding.

Known bleeding diathesis, including but not limited to:

- Platelet count < 10,000
- Heparin use within 48 hours and prolonged aPTT
- INR > 1.7, or anticoagulant use with residual biologic activity
- Current use of direct thrombin inhibitors or direct factor Xa-inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Intracranial surgery, serious head trauma, or previous stroke within 3 months
- Noncompressible arterial puncture within 7 days
- Lumbar puncture within 7 days
- Pretreatment SBP > 185 mm Hg or DBP > 110 mm Hg and uncontrollable BP
- Known history of intracranial hemorrhage
- Blood glucose < 50 mg/dL
- Severe underlying disease with short-term life expectancy

Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:

- Only minor or rapidly improving stroke symptoms (clearing spontaneously)
- Pregnancy

- Seizure at onset with postictal residual neurological impairments
- Major surgery or serious trauma within previous 14 days
- Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
- Recent acute myocardial infarction (within previous 3 months).

Exclusion criteria for rtPA (3.0 – 4.5 hour) : Similar to those for 0–3 hours, with any one of the following additional exclusion criteria:

- Age > 80 years
- Oral anticoagulant use, regardless of INR
- National Institutes of Health Stroke Score > 25
- Both a history of stroke and diabetes

*Time of stroke onset; time when patient's symptoms began or the time when the patient was last seen as normal; if the patient wakes up with stroke, the time of onset is defined as the time when he/she went to bed.

Procedure Prior to tPA Use

- History and physical examination consistent with an acute ischemic stroke
- Pretreatment CT scan/MRI scans of head
- *Pretreatment test:* CBC, electrolytes, glucose, PT, PTT, fibrinogen, ABO grouping and Rh typing, ECG (results not required prior to tPA infusion)
- Compatibility with the inclusion and exclusion criteria
- Foley's catheter insertion
- Two patent IV access.

Procedure for tPA Infusion and Subsequent Management

- Infuse tPA in a dose of 0.9 mg/kg (maximum 90 mg). Ten percent of total dose given IV bolus (over 2–3 minutes) and rest as IV infusion over 60 minutes.
- Monitor in an acute setting for signs of neurological change or bleeding.
- BP Q 15 minutes for 2 hours/Q 30 minutes for 6 hours/Q 1 hours for 16 hours.
- Neurovitals Q 1 hours for first 12 hours; then Q 2 hours for next 12 hours.
- Stroke assessment Q 1 hours for 6 hours; then Q 3 hours for 48 hours.
- Daily neurological evaluation after first 24 hours.
- NPO for 3 hours postinfusion, then assess.
- Bed rest for 24 hours postinfusion; then reassess.
- Maintain BP< 185/110.
- If clinical deterioration occurs:
  - Discontinue infusion
  - Immediate CT scan
  - Prepare fibrinogen and platelets.

- Repeat CT scan after 24 to 48 hours in all cases.
- No IV heparin or antiplatelets until repeat CT scan. ASA and/or heparin may be started after this period if the repeat CT free of hemorrhage (Treatment of ICH after rtPA is detailed in Appendix 2).

In case of bleeding following tPA, the infusion has to be stopped immediately. FFP (6 units), platelet concentrate (4 units) and cryoprecipitate (6 units) are considered.

Experience with newer fibrinolytics

In a trial on 75 patients, Parsons et al compared tenecteplase to alteplase and tenecteplase was shown to be associated with significantly better reperfusion and clinical outcomes than alteplase in patients with stroke who were selected on the basis of CT perfusion imaging. This trial has been criticised for a selection bias for small cerebral infarctions (~10 mL). A phase 3 trial (TASTE: Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation) that will select patients on the basis of advanced imaging and include a baseline infarct core up to 50 is underway.

Management of Blood Pressure for Thrombolyzed Patients

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:

- Labetalol 10 to 20 mg IV over 1 to 2 minutes, may repeat 1 time; or nicardipine 5 mg/hour IV, titrate up by 2.5 mg/hour every 5 to 15 minutes, maximum 15 mg/hour; when desired BP reached, adjust to maintain proper BP limits; or other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate.
- If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA.

Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:

- Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours.

If systolic BP >180 to 230 mm Hg or diastolic BP >105 to 120 mm Hg:

- Labetalol 10 mg IV followed by continuous IV infusion 2 to 8 mg/minute; or nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5 to 15 minutes, maximum 15 mg/h
- If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside.

Table 21.1 Intravenous medications for blood pressure lowering in patients with stroke

Drug	Dose/Rate
Intermittent bolus	
Labetalol	5–20 mg IVP every 14 minutes (maximum 300 mg daily)
Hydralazine	5–20 mg IVP every 30 minutes
Enalaprilat	1.25–5 mg IVP every 6 hour
Continuous infusion	
Nicardipine	5–15 mg/hour
Sodium nitroprusside	0.1–1.0 µg/kg/minute
Esmolol	25-300 µg/kg/min

a. IV labetalol can be used for rapid effect as 10 mg IV bolus at 10 minutes intervals to reach target. This should be used with cardiac monitoring only.
b. IV enalaprilat 1.25 mg bolus may be used and repeated 15 minutes interval. Enalaprilat should be avoided in patients who have received IV rtPA as it has been associated with acute life-threatening angioedema.
c. Nitrates should be avoided since they increase ICP and alter cerebral perfusion.
d. Nifedipine and nicardipine may worsen ischemia and hence should be avoided.
e. For oral medications, may start with enalapril 2.5 mg bid and titrate to maximum 20 mg bid if needed.
f. Aim to bring BP down not more that 25 percent of baseline in first 24 hours.
g. Be careful about lowering BP in patients with tight carotid or vertebrobasilar disease. They may require higher BP. Ensure imaging your patient first to know the mechanism of stroke.
h. For chronic treatment after first week, aim BP as 130/85 or lower.

Treatment of Hyperglycemia

- Patients who are diabetic or has elevated blood sugar has poorer prognosis.
- Patients with hyperglycemia bleed more frequently following thrombolysis.
- Results of NICE-Sugar Study suggests that tight glycemic control (70–110 mg/dL) has limited role in management of ICU patients. In all ICU patients, it is reasonable to maintain blood glucose concentration between 140–200 mg/dL; start insulin if it is > 180 mg/dL.

Treatment of Elevated Temperature

- Patients with high temperature are prone to have poor outcome.
- Hypothermia is a potent neuroprotectant in animal models.
- Treat all temperature above 100°F with acetaminophen 650 mg q 6h regularly scheduled to reduce temperature.
- Most importantly, investigate the cause of fever.
- An infectious source of fever should be sought as stroke patients are particularly at risk due to dysphagia, immobility and indwelling urinary and intravascular catheters. Noninfectious causes of fever associated with medications (e.g. phenytoin), venous thromboembolism and large strokes also may occur.

DVT/PE Prophylaxis

- Consider all patients confined to bed and chair or with hemiparetic limb as a candidate for DVT prophylaxis.
- Use heparin 5000 units SC bd.
- Intermittent pneumatic compression (IPC) is an effective measure and has additive effect with heparin.
- For ICH, it is safe to start heparin after 48 to 72 hours when they are stable neurologically and systemically.
- As per the PREVAIL study, there were fewer venous thromboembolic (VTE) events in the enoxaparin group compared with those receiving unfractionated heparin (10% vs 8%; p=0.0001). There was no difference in symptomatic intracranial bleeding and neurological outcomes were similar at 90 days.

Use of Antiplatelets in Acute Stroke

- Start aspirin as early as possible after diagnosis of ischemic stroke except in thrombolyzed patient where aspirin is started after the 24 hour scan excludes any bleed.
- Aspirin 75 mg (81 mg in Western countries) is standard of care. There is no evidence to support higher doses which are more effective. Two exceptions apply:
  i. Aspirin 325 mg is to be given for 6 months after carotid endarterectomy
  ii. Aspirin 325 mg is to be used in patients with lone atrial fibrillation who do not require warfarin.
- Clopidogrel is as effective as aspirin but clearly not better as monotherapy. It is appropriate for patient with aspirin intolerance.
- To date, there is no definite evidence in favor of aspirin + clopidogrel combination to be superior than aspirin/clopidogrel alone other than marginal benefit in first three months (MATCH and CHARISMA trial). Rather there was an increased risk of hemorrhage and this treatment is not recommended in stroke patients.

- Aspirin+SR dipyridamole may or may not be better that aspirin. One trial shows it is better but a meta-analysis shows no additional benefit.

Use of Statins in Stroke

Food and Drug Administration (FDA) approved 1999 the utilization of pravastatin and simvastatin in the prevention of stroke in patients with concomitant ischemic heart disease. Overall, the use of these drugs does not increase the risk of cerebral hemorrhage. According to more recent recommendations, the objective in patients with coronary artery disease or equivalent will be to maintain low-density lipoprotein cholesterol levels under 100 mg/dL; the presence of symptomatic atheromatous carotid stenosis is one of these equivalent diseases; the goal may be ≤ 70 mg/dL in high risk patients.

More recent SPARCL (2006) trial is the only clinical trial dealing specifically with secondary stroke prevention 80 mg atorvastatin reduced the risk of stroke by 16 percent overall, risk of ischemic stroke by 23 percent and risk of coronary artery disease by 43 percent versus placebo.

Antiedema Measures

- *Mannitol* (20%) is used as an initial dose of 1 to 1.5 g/kg (infused over 15 minutes) followed by 0.25 to 0.5 g/kg every 4 to 6 hourly as desired to keep ICP, 20 mm Hg or CPP > 60 mm Hg.
- Serum sodium may be used as a guide to judge the desired level of dehydration. Sodium 148 mmol/L is a goal in many centers.
- Routine use of mannitol in all strokes is not recommended since it does not improve outcome.
- *Glycerol* can be used enterally (50%) or intravenous (10%) via central line in 0.5 to 1.5 g/kg 4 to 6 hourly.
- Use of glycerol was not associated with any beneficial effects as shown in randomized control trials.
- Use of steroid is not recommended in stroke. It does not provide any benefit, rather may be harmful.
- *Hypertonic saline* (3% NaCl) effectively lowers ICP though there is no conclusive data. It probably should be reserved if mannitol proves ineffective.

Decompressive Hemicraniectomy

- Malignant MCA infarct is associated with 80 percent mortality rate.
- Pooled analysis of randomized control trials (DESTINY, DECIMAL, HAMLET) shows if surgery is undertaken within 48 hours of stroke. It reduces mortality and increase number of patients with favorable functional outcome. Evidence suggests early decompressive surgery as opposed to “wait and see” approach.

Anticonvulsants in Ischemic Stroke

Seizure occurs in 9 percent of stroke patients. Prophylactic use of anticonvulsants is debated. It is only recommended in patients, who experience seizures. Even single episode of seizure should be treated with anticonvulsant agent for 6 months.

11. Anticoagulants

- Immediate anticoagulation significantly reduces ischemic stroke within the first two weeks but chances of symptomatic intracranial hemorrhage increases too. So routine use of immediate anticoagulation is not recommended.
- There is significant increase of major extracranial hemorrhage also.
- There is no significant difference in death or dependency between treated and control group.
- So called "progressing stroke" or "stroke in evolution" is not an indication for anticoagulation.
- There is no evidence favoring immediate anticoagulation in basilar thrombosis.
- Immediate anticoagulation in suspected cardioembolic stroke does not offer any proven benefit.
- In cardioembolic stroke, the best time to start anticoagulation is not known. Most of the centers recommend starting aspirin as soon as possible. If it is a minor stroke, oral anticoagulation may be started after 48 hours and aspirin will be stopped when therapeutic INR (usually 2–3) is reached. In case of a major stroke, anticoagulation should be deferred till 2 weeks to minimize the risk of hemorrhagic transformation.

Antibiotics

Use of antibiotics should be guided by the institutional antibiotic policy but in general, routine prophylactic antibiotic has no role and probably, it facilitates emergence of resistant strains.

Intra-arterial Thrombolysis

Endovascular techniques have been employed for achieving more complete acute revascularization after ischemic stroke within a longer therapeutic window from symptom onset. The prolyse in acute cerebral thromboembolizm (PROACT) II trial randomized 180 patients within 6 hours of middle cerebral artery (MCA) occlusion to intra-arterial (IA) prourokinase plus IA heparin or IA heparin alone. Partial or complete revascularization was reported in 66 percent of the treatment group compared with 18 percent of the controls and favorable outcome without any significant increase in symptomatic intracranial bleeding. Despite this favorable trial result, the FDA did not approve prourokinase on the basis of this single study. However, many physicians have extrapolated the PROACT II findings to other IA pharmacologic agents (e.g. tPA up to 22 mg in small boluses of 2–4 mg).

A variety of devices (MERCI, PENUMBRA) have been employed for mechanical clot disruption either alone or in combination with fibrinolytic medication. Both have been approved by FDA for clot retrieval within 8 hours of symptom onset. Although the study results of the MERCI devices and PENUMBRA system compare favorably with the PROACT II control group, lack of a concurrent randomized control group limit conclusions regarding their effect on clinical outcomes.

The most important limitation to intra-arterial thrombolytic therapy is the need to perform emergency superselective angiography, which requires an interventional neurologist or neuroradiologist and a special stroke care team. The new approaches include combination therapy, with initial treatment with intravenous rtPA at the local hospital, followed by rapid transfer to the stroke treatment center for angiography and assessment of the benefits of intra-arterial fibrinolysis, if recanalization has not taken place.

There is an acute stroke during or immediately after diagnostic or therapeutic angiography or any coronary or cardiac interventions. Following should be the management:

- Do not remove femoral arterial sheaths and consider intra-arterial urokinase if sheaths can be assessed
- If not, consider IV rtPA
- Check aPTT/Hematocrit/vital signs for evidence of acute blood loss
- Sheath can be removed after 24 hours, if no bleeding occurs.

Management of Intracerebral Hemorrhage

Blood Pressure management in Intracerebral Hemorrhage Guidelines:

- In patients with a history of hypertension, mean pressure should be <130 mm Hg. If intracranial pressure (ICP) monitoring is available, CPP (cerebral perfusion pressure) should be maintained > 70 mm Hg.
- Pressor agents should be started if SBP is below 90 mm Hg.

Some suggested medications

Labetalol: 5 to 100 mg/h by intermittent bolus doses of 10 to 40 mg or continuous drip (2–8 mg/minute)

Esmolol: 500 μg/kg as a load; maintenance use, 50 to 200 μg/kg/minute

Nitroprusside: 0.5 to 10 μg/kg/minute

Hydralazine: 10 to 20 mg Q 4 to 6 hour

Enalapril: 0.625 to 1.25 mg Q 6 hour as needed.

The following algorithm adapted from guidelines of Americal Heart Association (AHA). Until ongoing clinical trials of BP intervention for intracerebral hemorrhage (ICH) are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence. Current suggested recommendations for target BP in various situations are listed below and may be considered (Class IIB; Level of Evidence : C):

- If systolic blood pressure (SBP) is >200 mm Hg or mean arterial pressure (MAP) is >150 mmHg, then consider aggressive reduction of BP with continuous intravenous infusion, with frequent BP monitoring every 5 minutes.
- If SBP is >180 mm Hg or MAP is >130 mmHg and there is the possibility of elevated ICP, then consider monitoring ICP and reducing BP using intermittent or continuous intravenous medications while maintaining a cerebral perfusion pressure >60 mm Hg.
- If SBP is >180 mmHg or MAP is >130 mm Hg and there is no evidence of elevated ICP, then consider a modest reduction of BP (e.g. MAP of 110 mm Hg or target BP of 160/90 mm Hg) using intermittent or continuous intravenous medications to control BP and clinically re-examine the patient every 15 minutes.

As per available evidence, in patients presenting with a systolic BP of 150 to 220 mm Hg, acute lowering of systolic BP to 140 mm Hg is probably safe *(Class IIa; Level of Evidence: B)*

Management of Raised Intracranial Pressure

- *Osmotherapy:* The first medical line of defence is osmotherapy. However, it should not be used prophylactically. Mannitol 20 percent (0.25–0.5 g/kg every 4 hour) is reserved for patients with type B ICP (intracranial pressure) waves, progressively increasing ICP values, or clinical deterioration associated with mass effect (Level of Evidence V, grade C recommendation). Due to its rebound phenomenon, mannitol is recommended for only 5 days. To maintain an osmotic gradient, frusemide (10 mg Q 2–8 hour) may be administered simultaneously with osmotherapy. Serum osmolality should be measured twice daily in patients receiving osmotherapy and targeted to = 310 mOsm/L.
- *No steroids:* Corticosteroids in ICH are generally avoided because multiple potential side effects must be considered and clinical studies have not shown benefit (Level of Evidence II, grade B recommendation).
- *Hyperventilation:* Hypocarbia causes cerebral vasoconstriction. Reduction of cerebral blood flow is almost immediate, although peak ICP reduction may take up to 30 minutes after pCO_2 is changed. Reduction of pCO_2 to 35–30 mm Hg, best achieved by raising ventilation rate at constant tidal volume (12–14 mL/kg), lowers ICP 25 to 30 percent in most patients (Level of Evidence III through V, grade C recommendation). Failure of elevated ICP to respond to hyperventilation indicates a poor prognosis.
- *Muscle relaxants:* Neuromuscular paralysis in combination with adequate sedation can reduce elevated ICP by preventing increases in intrathoracic and venous pressure associated with coughing, straining, suctioning, or "bucking" the ventilator (Level of Evidence III through V, grade C recommendation). Nondepolarizing agents, such

as vecuronium or pancuronium, with only minor histamine liberation and ganglion-blocking effects, are preferred in this situation (Level of Evidence III through V, grade C recommendation). Patients with critically elevated ICP should be pretreated with a bolus of a muscle relaxant before airway suctioning. Alternatively, lidocaine may be used for this purpose.

Seizure Prophylaxis

Clinical seizures should be treated with antiepileptic drugs (Class I; Level of Evidence: A).

Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury (Class IIa; Level of Evidence: B). Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiepileptic drugs (Class I; Level of Evidence: C). Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence):

DVT prophylaxis in ICH: Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism in addition to elastic stockings.

After documentation of cessation of bleeding, low dose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset.

Recombinant Factor VIIa in ICH

Phase IIB study (NEJM 2005) showed benefit of recombinant factor VIIa (rFVIIa) by reduction of mortality and improvement of outcome at the end of 3 months. It was associated with increased risk of thromboembolic events. The phase III study (FAST trial) has just been completed and the result does not show any benefit of rFVIIa over placebo (unpublished data, collected for webcast). Based on this phase III study, use of rFVIIa is not recommended in hypertensive ICH.

Surgery in ICH (AHA Guidelines)

Previous randomized controlled trials of surgery (before 1998) did not show any significant benefit except one study of endoscopic evacuation where lobar hematoma of smaller size and younger patients < 60 years showed benefit. The largest randomized controlled trial of surgical treatment in ICH (STICH trial) did not show any benefit of surgery over medical management.

Non-surgical Candidates

- Patients with small hemorrhages (> 10 cm^3) or minimal neurological deficits (Levels of Evidence II through V, grade B recommendation).

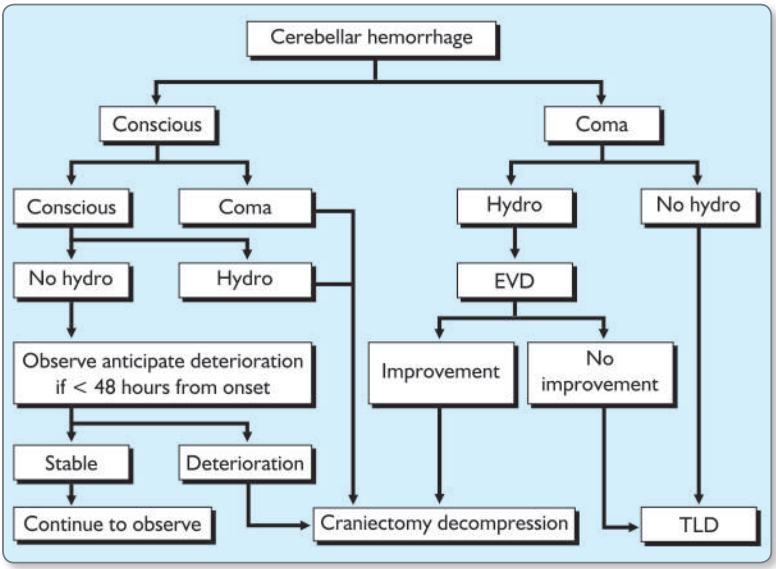
- Patients with a GCS score = 4 (Level of Evidence II through V, grade B recommendation). However, patients with a GCS score = 4 who have a cerebellar hemorrhage with brain stem compression may still be candidates for lifesaving surgery in certain clinical situations.

Surgical Candidates

- Patients with cerebellar hemorrhage > 3 cm who are neurologically deteriorating or who have brain stem compression and hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible (Level of Evidence III through V, grade C recommendation).
- ICH associated with a structural lesion such as an aneurysm, arteriovenous malformation, or cavernous angioma may be removed if the patient has a chance for a good outcome and the structural vascular lesion is surgically accessible (Level of Evidence III through V, grade C recommendation).
- Young patients with a moderate or large lobar hemorrhage who are clinically deteriorating (Level of Evidence II through V, grade B recommendation).

Best therapy unclear: All other patients.

Algorithm for Management of Cerebellar Hemorrhage



TLD: Treatment limiting decisions; EVD: External ventricular drainage.

Management of Intraventricular Hemorrhage

- Ventriculostomy with placement of external drainage catheter is done in presence of hydrocephalus.
- Catheter blockage is often a problem which can be overcome by infusing rtPA into the ventricle to dissolve the clot. 2 to 4 mg of rtPA is injected through ventricular catheter. Then the catheter is closed and opened every hour till next 24 hours. It may be repeated after 24 hours.
- Treatment of the underlying cause, if any (like AVM or aneurysm) should be undertaken.

Treatment of Cerebral Venous Thrombosis

a. Very few randomized trials are available regarding use of heparin in this situation. The safety of heparin use was evident from those studies, even in presence of hemorrhagic infarcts. But no clear benefit of outcome could be demonstrated, even with LMWH (nadroparin).

- Meta-analysis of eligible trials shows a trend of benefit favoring heparin use. It is followed by oral anticoagulation for 6 to 12 months with target INR 2 to 3.
- Case reports of successful thrombolysis in selected cases by intrasinus delivery of rtPA or urokinase are available but routine thrombolysis is not recommended.

Treatment of Arterial Dissection

a. No evidence-based data exists supporting any specific treatment for dissection.
b. Since the main mechanism of stroke in dissection is embolism from arterial tear, anticoagulation seems logical and many authorities recommend that.
c. Acute anticoagulation with heparin followed by oral anticoagulation is generally done. Duration of treatment is not defined but recanalization as demonstrated by MRA/CTA by 3 to 6 months would be a natural endpoint. Persistence of abnormality after 6 months may indicate use of antiplatelets for unspecified duration.

Appendix 1

NIH STROKE SCALE

Patient Identification............................... ....
Patient Date of Birth................................/ ..../ ....
Hospital...(...................................)
Date of Exam ..../ ..../ ....

Interval: [] Baseline [] 2 hours post-treatment [] 24 hours post-onset of symptoms ±20 minutes [] 7 to 10 days [] 3 months [] Other...(...................................)

Time:.. : .... [] am [] pm

Person administering scale...

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does not, what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e. repeated requests to patient to make a special effort).

Instructions	Scale definition	Score
1a. *Level of consciousness:* The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and flexic	
1b. *LOC questions:* The patient is asked the month and his/her age. The answer must be correct—there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given all. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or nonverbal cues	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	

Contd…

Contd...

Instructions	Scale definition	Score
1c. ***LOC commands:*** The patient is asked to open and close the eyes and then to grip and release the nonparetic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e. follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	
2. ***Best gaze:*** Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntarty or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI). Score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally, clarify the presence of a partial gaze palsy	0 = Normal 1 = Partial gaze palsy, gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver	
3. ***Visual:*** Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut a symmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	

Contd...

Contd…

Instructions	Scale definition	Score
4. ***Facial palsy:*** Ask-or use pantomime to encourage—the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or noncomprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible	0 = Normal symmetrical movements 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near-total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	
5. ***Motor arm:*** The limb is placed in the appropriate position extend the arms (palms down) 90 degree (if sitting) or 45 degree (if supine). Drift is scored, if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the nonparetic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice	0 = No drift; limb holds 90 (or 45) degree for full 10 seconds 1 = Drift; limb holds 90 (or 45) degree, but drifts down before full 10 seconds; does not hit bed or other support 2 = Some efforts against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degree, drifts down to bed, but has some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement UN = Amputation or joint fusion, explain_____ 5a. Left arm 5b. Right arm	
6. ***Motor leg:*** The limb is placed in the appropriate position—hold the leg at 30 degree (always tested supine). Drift is scored, if the leg fails before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice	0 = No drift; leg holds 30 degree position for full 5 seconds 1 = Drift; leg fails by the end of the 5-second period but does not hit bed 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity 3 = No effort against gravity; leg falls to bed immediately 4 = No movement UN = Amputation or joint fusion, explain_____ 6a. Left leg 6b. Right leg	

Contd…

Contd…

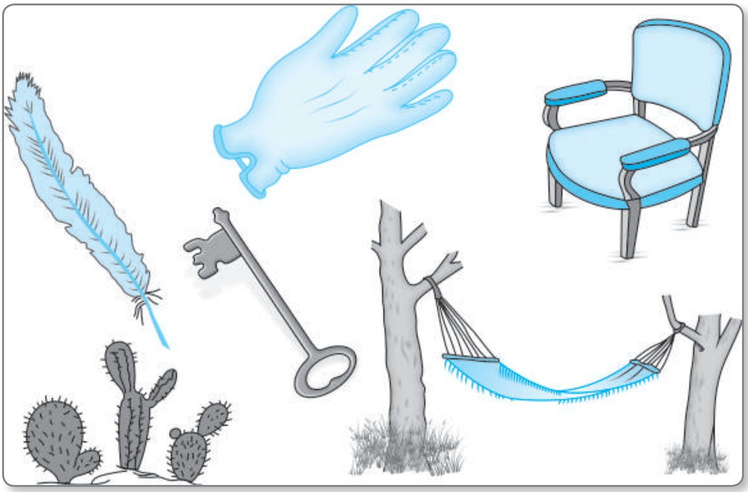
Instructions	Scale definition	Score
7. ***Limb ataxia:*** This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness test by having the patient touch nose from extended arm position	0 = Absent 1 = Present in one limb 2 = Present in two limbs UN = Amputation or joint fusion, explain_____	
8. ***Sensory:*** Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stoke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with, brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a = 3) are automatically given a 2 on this item.	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm and leg	

Contd…

Contd…

Instructions	Scale definition	Score
9. ***Best language:*** A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1 a = 3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands	0 = No aphasia; normal 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response 3 = Mute, global aphasia; no usable speech or auditory comprehension	
10. ***Dysarthria:*** If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested	0 = Normal abnormality 1 = Mild-to-moderate dysarthria; patient slurs at least some words, and, at worst, can be understood with some difficulty 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier explain_____	
11. ***Extinction and Inattention (formerly neglect):*** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosognosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space	

You know how. Down to earth. I got home from work. Near the table in the dining room. They heard him speak on the radio last night.



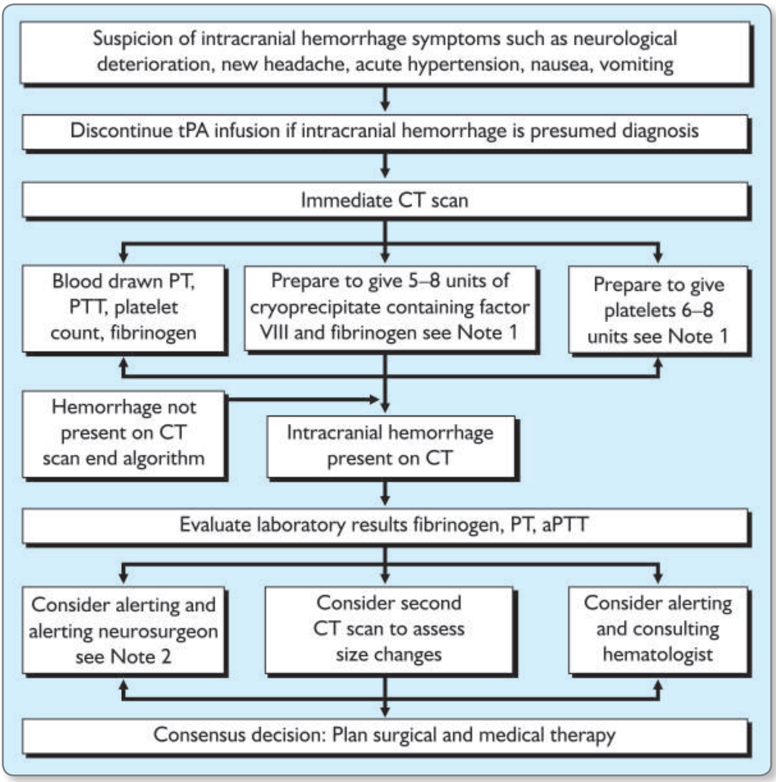
MAMA

TIP – TOP
FIFTY – FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER

Appendix 2

POST-tPA INTRACRANIAL HEMORRHAGE ALGORITHM

Hemorrhage following initiation of thrombolytic therapy for stroke the following algorithm was developed for using during a clinical trial. All or part of this algorithm may be adapted for use of thrombolytic therapy of stroke for approved indications. The application of this algorithm may have to be modified in order to function with resources available in a particular location.



Note 1: Preparations for giving platelets and cryoprecipitate can be initiated at the first suspicion of hemorrhage so that they would be ready if needed.

Note 2: It is highly recommended to have a plan for obtaining neurosurgical advice.

Suggested Reading

1. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke. A Guideline From the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guidelines as an educational tool for neurologist. Stroke. 2013;44:870-947.
2. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Circulation. 2007;115:e478-534.
3. Broderick J< Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A Guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council; Quality of Care and Outcomes in Research Intrerdisciplinary Working Group. Stroke. 2007;38:2001-23.
4. Del Zoppo GJ, Saver JL, Jauch EC, et al. On behalf of the American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke. 2009;40:2945-8.
5. Josephson SA, Saver JL, Smith WS. The Merci and Multimerci Investigations. Comparison of mechanical embolectomy and intra-arterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi-MERCT compared to PROACT II. Neurocrit Care. 2009;10:43-9.
6. Kase CS, Albers GW, Bladin C, et al. Neurological outcomes in patients with ischemic stroke receiving enoxaparin or heparin for venous thromboembolism prophylaxis: subanalysis of the prevention of VTE after Acute Ischemic Stroke with LMWH (PREVAIL) study. Stroke. 2009;40:3532-40.
7. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rtPA Stroke Study. Neurology. 2000;55:1649-55.
8. Mendelow AD, Gregson BA, Fernandes HM, et al. For the STICH Investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Hemorrhage (STICH): a randomized trial. Lancet. 2005;365:387-97.
9. Morgenstern LB, Hemphill JC III, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke. 2010;41:2108-29.
10. Parsons M, Spratt N, Bivard A, et al. A randomized trial of Tenecteplase versus Alteplase for acute Ischemic Stroke. N Engl. J Med. 2012;366:1099-107.
11. The ATLANTIS, ECASS, and NINDS rtPA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rtPA stroke trials. Lancet. 2004;363:768-74.
12. The NICE-SUGAR Study Investigators. Intensive verus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283-97.

Acute Kidney Injury

chapter 22

Sweety Trivedi, Arup Ratan Dutta

Diagnosis and Management Protocol

Definition

Acute renal failure (ARF) is defined as sudden rapid decline in renal function causing retention of nitrogenous waste products; but this definition failed to describe the dynamic process extending across the phases of initiation, maintenance and recovery.

The new terminology i.e. acute kidney injury (AKI) considers the disease as a spectrum of injury that extends from less severe forms to more advanced injury.

AKI diagnosis is made when one of the following criteria is met:

a. Serum creatinine uses by ≥ 0.3 mg/dL (26 µmol/L) from the baseline value within 48 hours

   or

b. Serum creatinine rises > 1.5 fold from the baseline value which is known or presumed to have occurred within 1 week.

   or

c. Urine output (UO) < 0.5 mL/kg/hour or > 6 consecutive hours

If a patient does not have a baseline serum creatinine more within 1 week of their admission or presentation it has been deemed acceptable to use a reference serum creatinine value within 3 months (acceptable up to 1 year).

If reference serum creatinine is not available within 3 months and AKI is suspected, repeat serum creatinine within 24 hours.

Assessment of Severity of AKI

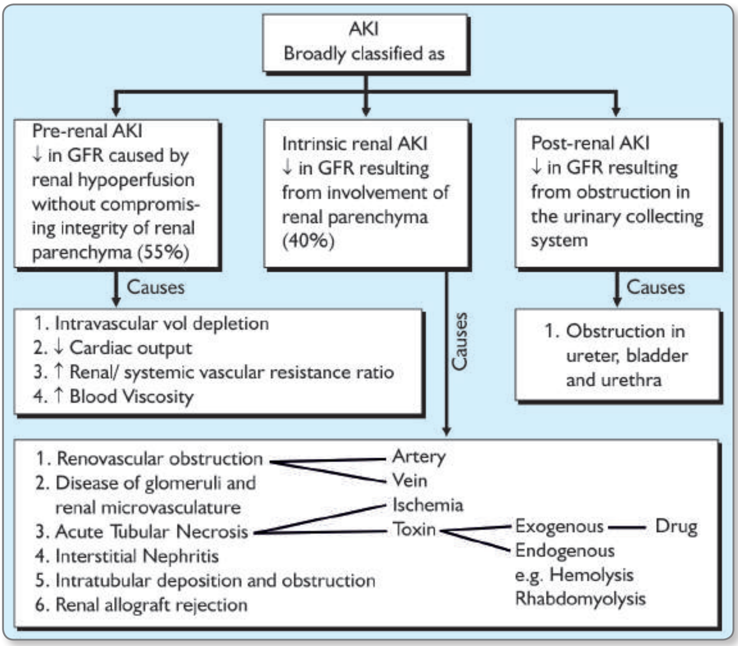
To assess the severity of a current episode of AKI, RIFLE criteria is used which is based on GFR and urine output and comprises of three levels of renal dysfunction and two clinical outcomes. The AKIN criteria, a modification of RIFLE although developed later as a potential improvement over RIFLE but it is not as sensitive as RIFLE.

RIFLE criteria	GFR	Urine output (UO)
Risk	Increase creatinine × 1.5 or GFR decrease > 2.6%	UO , 0.5 mL/kg/hour × 6 hours
Injury	Increase creatinine × 2 or GFR decrease > 50%	UO < 0.5 mL/kg/hour × 12 hours
Failure	Increase creatinine x 3 or GFR decrease > 75% or Acute rise of creatinine > 4 mg/dL	UO < 0.3 mL/kg/hour × 24 hours or Anemia × 12 hours
Loss	Persistent AKI = complete loss of renal function > 4 weeks	
ESRD	End stage renal disease (> 3 months)	

AKIN Criteria

Stages	Serum Creatinine	Urine Output
1.	Increase in serum creatinine ≥ 0.3 mg/dl (26.11 mmol/L) or increase to 1.5 – 2 times baseline	< 0.5 mL/kg/hr for 6 hours
2.	Increase in serum creatinine to 2 – 3 times from baseline	< 0.5 mL/kg/hr for > 12 hours
3.	Increase in serum creatinine to > 3 times from baseline or increase in creatinine ≥ 4 mg/dL (35 μmol/L) or the requirement for renal replacement therapy	< 0.3 mL/kg/hr for > 24 hours or anuria for ≥ 12 hours

Classification



Points for Early Detection of Impairment of Renal Function

- Regular estimation of plasma urea, creatinine and electrolyte
- Monitor fluid intake and output
- Daily weight of the patient
- Supine and standing BP.

Risk Factors

- CKD (eGFR < 60 mL/hun/1.7m^2)
- Age > 75
- Sepsis
- Cardiac failure
- Liver disease
- Diabetes mellitus
- Drugs affecting renal function
- Hypovolemia
- Atherosclerotic peripheral vascular disease.

To Exclude Possibility of Chronic Kidney Disease by

- History of pre-existing chronic renal impairment.
- Previous biochemical examination is suggestive of normal renal function.
- Absence of two small sized kidneys in USG exclude chronic kidney disease (CKD). However, CKD with normal sized kidney may be found in RPGN, leukemic infiltration, scleroderma, diabetic nephropathy, PAN, amyloidosis.
- A history of vague ill health of some month duration, h/o nocturia, pruritus, skin pigmentation, anemia, hypocalcemia, hyperphosphatemia, renal osteodystrophy, band keratopathy are signs of chronicity.

Differentiating points between AKI and CKD

	Chronic	Acute
• History of kidney disease, hypertension, abnormal urinanalysis	√	o
• Small kidney size	√	o
• Urinanalysis with broad cast	√	o
• Return of renal function to normal with time	o	√
• Signs of chronicity	√	o
• Hyperkalemia, anemia acidemia, hyperphosphatemia	+++ (more common)	+
• Low carbamylated Hb%	o	√

[Non-enzymatic carbomylation of hemoglobin occurs in direct relationship to magnitude and duration in BUN. A carbomylated hemoglobin level > 80 to 100 µg carbamyl naline per gram Hb suggests more acute cause than chronic].

Check List for Evaluation of a Patient with Suspected Acute AKI

- Evidence of genuine and recent decline in GFR.
- Sequence of deterioration in renal function with its relation to possible causative factor in history.
- Record of potential nephrotoxins.
- Estimation of adequacy of renal perfusion prior to or during decline in renal function by clinical estimation of volume status.
- Search for extrarenal manifestation.
- Examination of urine → volume, sediment, composition, chemical analysis.
- Renal imaging.
- Consideration of need for kidney biopsy.
- Detection of biochemical abnormalities common in AKI.

Diagnosis

A. **History**
   - History of fluid loss – GI, renal, skin/heat stroke, trauma
   - History of thirst, dryness of mucosa, oliguria
   - History of intake of diuretics or other potential nephrotoxic drugs
   - Syncope, dizziness
   - Shortness of breath, peripheral edema
   - Color, volume, frequency etc, other urinary complaints of patients
   - History of fever, rash, joint pain, abdomen pain, flank pain
   - Search for extrarenal manifestations.

B. **Physical examination**
   - Symptom
     - Volume depletion — Thirst, orthostatic dizziness, progressive fall of urine output, ↓ axillary sweating
     - Volume excess — Swelling of both legs and periorbital puffiness
   - Signs
     - Volume depletion:
       - i. Poor skin turgor
       - ii. Tachycardia
       - iii. ↓ JVP
       - iv. Dry mucous membrane
       - v. Decreased temperature of extremity
       - vi. Postural sign—↓ BP > 10 mm Hg
↑ Pulse rate > 10/min
     - Volume excess
       - i. S3 gallop
       - ii. Cardiomegaly

iii. Jugular venous distension
iv. Pulmonary congestion
v. Liver congestion
vi. Peripheral edema, ascites, pleural effusion.

Investigations

A. **Blood**

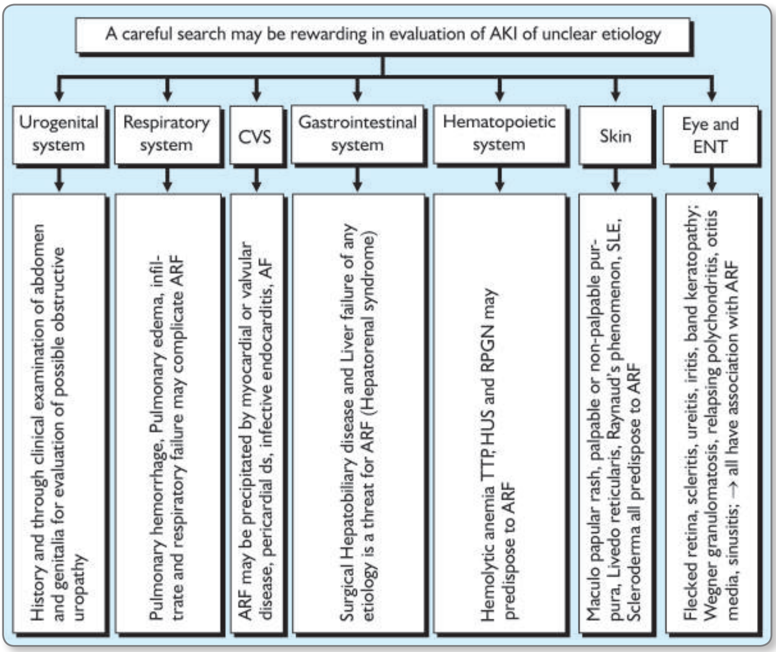
i. CBC – anemia – bleeding, hemolysis, multiple myeloma etc., acute on chronic renal failure
   - thrombocytopenia – TTP, HUS
   - peripheral eosinophilia – Churg Strauss, PAN
   - interstitial nephritis

ii. Blood urea, creatinine – baseline value and daily rate of rise

iii. Electrolytes
   - hypercalcemia, hypocalcemia, hyperphosphatemia
   - marked ↑PO_4^{-3} with low Ca^{+2} – rhabdomyolysis (CPK ↑, Uric acid ↑, or tumor lysis syndrome (CPK normal, uric acid ↑)

iv. Anion gap and osmolal gap

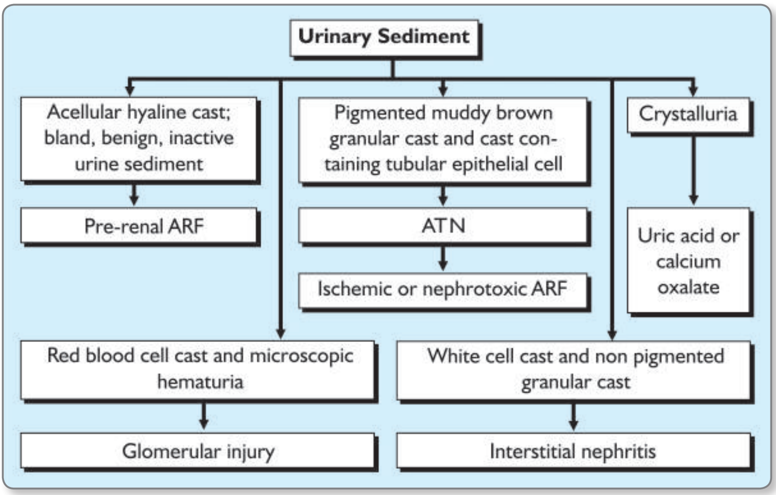
v. Serum C3 complement, cANCA, pANCA, Anti-GBM cryoglobulin, etc.

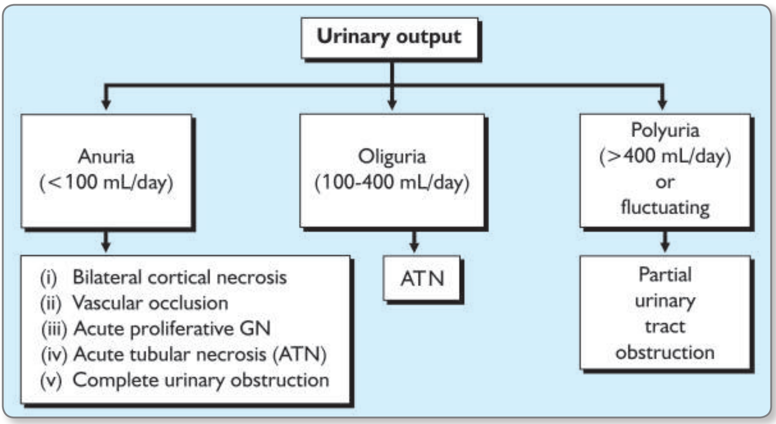


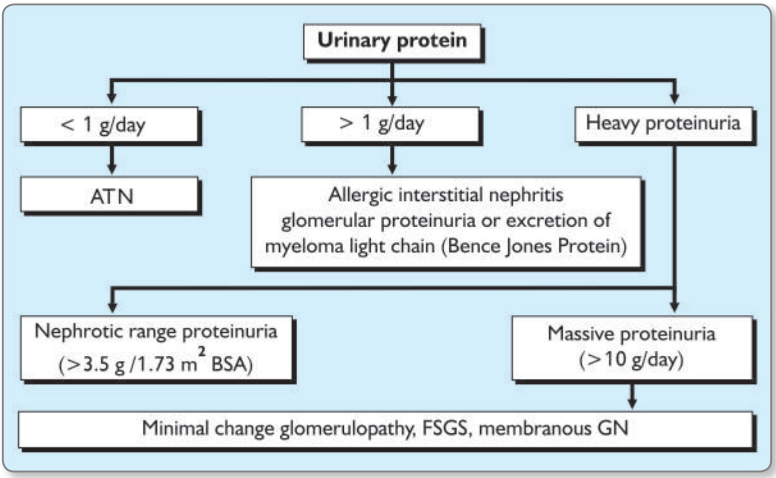
Detection of Biochemical Abnormalities Common in AKI

	Non-hypercatabolic	*Hypercatabolic*
1. Daily rise in BUN	10-20 mg/dL	20-100 mg/dL
2. Daily rise in serum creatinine	0.5-1.0 mg/dL	> 2 mg/dL
3. Daily rise in serum potassium	< 0.5 mEq/L	≥ 2 mEq/L
4. Daily rise in serum HCO_3-	< 1 mEq/L	> 2 mEq/L

B. **Urine Analysis and Renal Failure Indices Charts**







Examination of Urine

Chemical Analysis of Urine

Diagnostic index			Prerenal	Intrinsic
A.	*Concentration*			
	1.	Specific gravity	> 1.020	< 1.010
	2.	Uosm (mosm/Kg H_2O)	> 500	< 350
	3.	Uosm/Posm	> 1.3	< 1.1
	4.	Free water clearance (mL/min)	< (-20)	> (-1)
B.	*GFR and Tubule Reabsorptions*			
	1.	U/P Urea	> 8	< 3
	2.	U/P creatinine	> 40	< 20
	3.	Creatinine clearance (mL/min)	> 20	< 20
	4.	BUN/Plasma creatinine	> 20	~ 10
C.	*Tubule Handling of Solute*			
	1.	UNa (mEq/L)	< 20	> 40
	2.	FeNa (%)	< 1	> 1
	3.	Renal Failure Index	< 1	> 1
D.	*Urinary Markers of Tubule Damage*			
	Beta$_2$ microglobulin (mg/24 h)		< 1.0	> 50

AIRF = Acute Intrinsic Renal Failure

Utility: (a) To differentiate CRF from ARF by demonstrating kidney size
(b) To diagnose obstructive uropathy
(c) To estimate patency of renal vessel

Plain film abdomen
(i) Shrunken kidney → CRF
(ii) Enlarged kidney → obstructive, infiltrative disease, inflammation
(iii) Extensive calcification of renal artery → renovascular ds
(iv) Stippled cortical calcification → renal cortical nerosis

USG

IVP →
Immediate appearance of dense nephrogram persistent for
> 24 hours— S/O ATN

Antegrade and retrograde pyelography
→ provide most reliable information on patency of ureter

Radionuclide study
(i) To define flow, tubule function and excretion (99 mTc) or leucocyte infiltration (gallium scan)
(ii) To diagnose acute rejection vs ATN vs cyclosporine nephrotoxicity in transplanted kidneys

Angiography
useful when acute reversible renovascular event suspected

CT scan
gives information regarding size, shape

NMR and positron scan
for better visualization of intrarenal pathophysiology in ARF

Consideration for Kidney Biopsy

Indication: (Required in only 20% patients)

- Equivocal case history.
- Renal sign suggestive of glomerular, vascular or interstitial lesion.
- Patient with extrarenal manifestation.
- Prolonged renal failure (beyond 6 weeks).
- To confirm diagnosis of drug induced interstitial nephritis by diffuse inflammatory infiltrate with prominent component of eosinophil and plasma cell.
- When urine sediment contains red cell cast.

Novel Biomarkers

Biomarkers are needed:

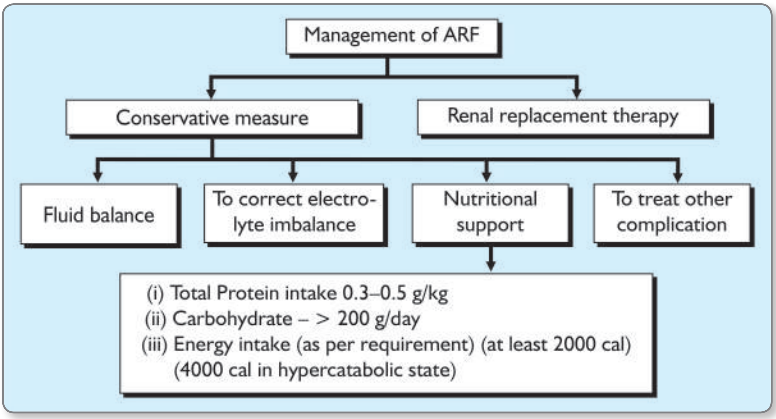
- Differentiate type of AKI
- To identify etiology
- Early diagnosis
- Predict severity
- Monitoring course and response to therapy.

The various AKI biomarkers are:

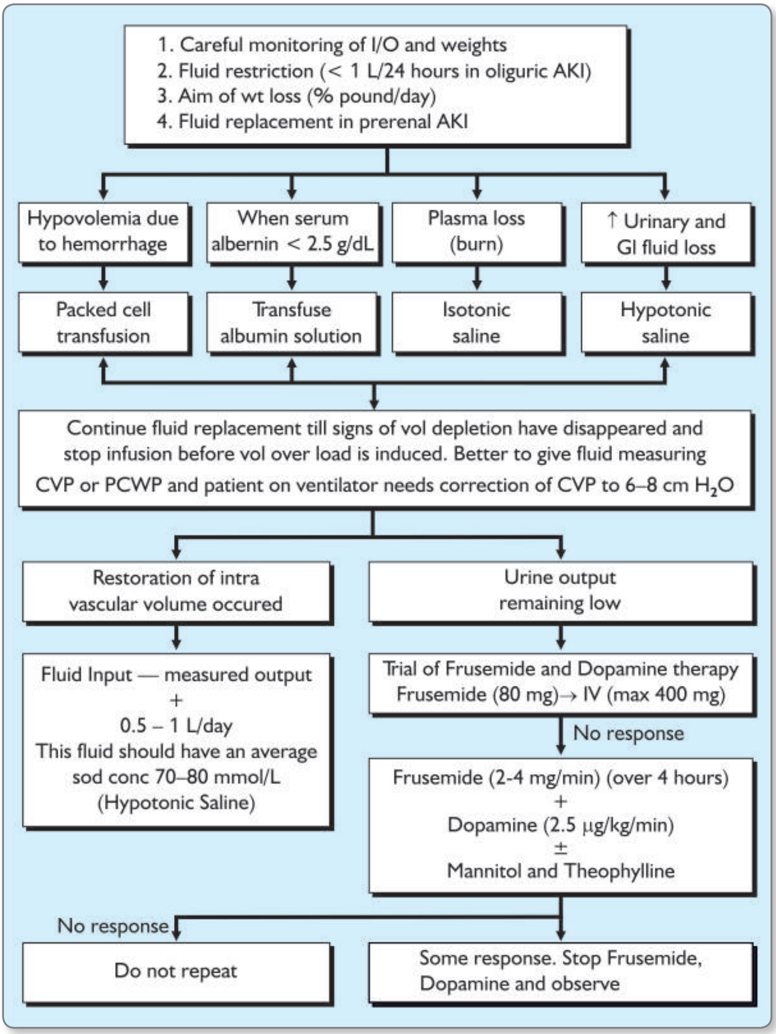
	Sample	Cardiac surgery	Contrast Nephropathy	Kidney transplant
NGAL	Plasma	Early	Early	Early
Cystatin C	Plasma	Intermediate	Intermediate	Intrermediate
NGAL	Urine	Early	Early	Early
IL-18	Urine	Intermediate	Absent	Intermediate
KIM-1	Urine	Intermediate		

NGAL = N neutrophil gelatin associated lipocalin
KIM1 = Kidney Injury molecule

Cystatin C – 13Kd cysteine protein that is a potential alternative to serum creatinine in measurement of GFR. It is filtered solely by glomerulus, well-secreted in tubules; completely reabsorbed by the tubules and generated at a constant rate by all cells in body which serve a reasonable basis for GFR calculation. It is increased about 1 to 2 days earlier than serum creatinine in AKI patients. It also has a prognostic value with regard to need for kidney transplant and in-hospital mortality.



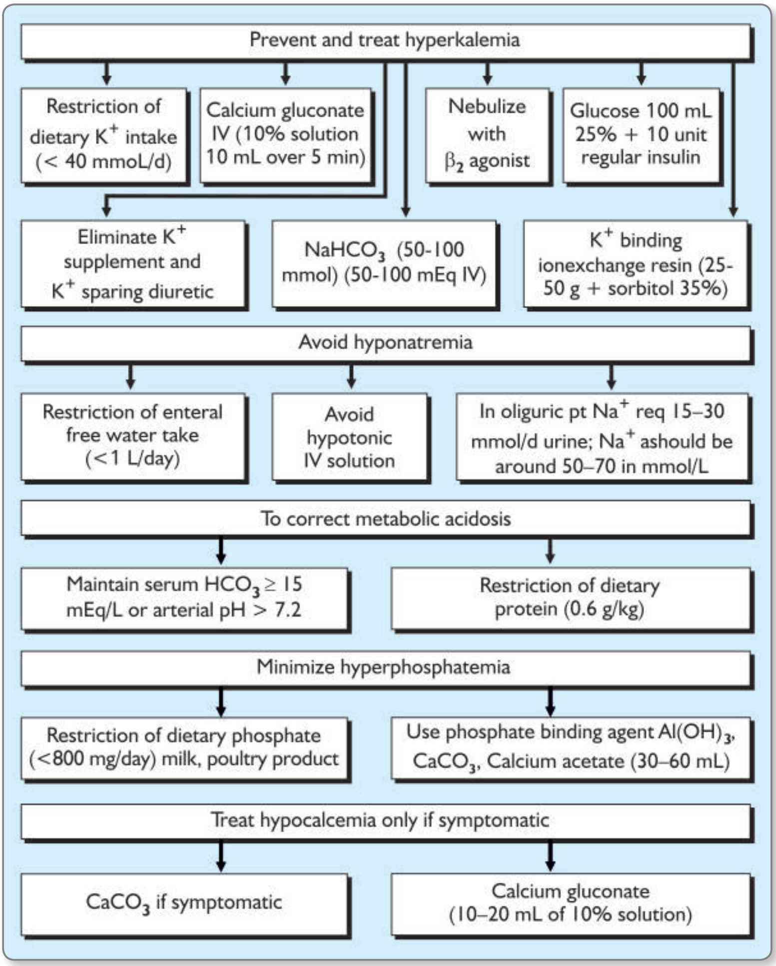
Fluid Balance



To Correct Electrolyte Imbalance

Salient Features

- Prevent and treat hyperkalemia.
- Avoid hyponatremia.
- To correct metabolic acidosis.
- Minimize hyperphosphatemia.
- Treat hypocalcemia only if symptomatic.



Nutrition

Goals

- To prevent protein energy wasting
- To preserve lean body mass and nutritional status
- To avoid complications
- Improve immune status and wound healing
- Improve antioxidant and endothelial function
- Reduce mortality.

Nutritional requirement

- Total energy intake should be 20 to 30 Kcal/kg/day in stage of AKI
- Energy:
  - Non-protein calories – 25 Kcal/kg/day
  - Carbohydrate – 5g/kg/day
  - Fat: 0.8 – 1.2 g/kg/day
- Protein:
  Conservative therapy (mild catabolism) – 0.8 g/Kg/day
  Extra-corporeal therapy, moderate catabolism : 1 – 1.5 g/Kg/day
  CRRT or SLED, severe catabolism : 1.5 – 2 g/Kg/day
- Enterally provided nutrition is preferred

To Treat Other Complication

Septicemia (51-89%)
(i) Regular examination of chest and abdomen for evidence of septic focus
(ii) Unused IV line and urinary catheter should be removed
(iii) Proven infection should be treated with appropriate antibiotic

→ Adjust doses and frequency of antibiotics according to severity of renal failure
→ Avoid nephrotoxic antibiotic

CVS Complication
(i) Pulmonary edema (most serious) →Hemo or peritoneal dialysis, venesection of 100–200 mL blood
(ii) Uraemic cardiomyopathy
(iii) Coronary artery disease
(iv) Aortic valve calcification
(v) MI
(vi) LVH

Bleeding
(i) Exclude possibility of Heparin use
(ii) Blood transfusion to obtain Hematocrit > 30%
(iii) Cryoprecipitate (10 bags)
(iv) Desmopressin (0.3 μg/kg/IV)
(v) Conjugated estrogen (0.6 mg/kg/day for 5 days – In angiodysplasia of colon)

Anemia
(i) May need Blood transfusion if severe
(ii) Erythropoietin — rarely used in ARF

Renal Replacement Therapy (RRT)

Classification

A. Intermittent therapy
   - Intermittent hemodialysis (IHD)
   - Sustained low efficiency dialysis (SLED) / Extended daily dialysis (EDD)

B. Continuous therapy
   - Slow continuous ultrafiltration (SCUF)
   - Continuous arterio-venous hemofiltration (CAVH)
   - Continuous arterio-venous hemodialysis (CAVH)
   - Continuous veno-venous hemodialysis (CVVHD)
   - Continuous veno-venous hemofiltration (CVVH)
   - Continuous arterio-venous hemodiafilteration (CAVHDF)
   - Continuous veno-venous hemofiltration (CVVHDF)

Comparison of Renal Replacement Therapy Modalities

	IHD	SLED	SCUF	CVVH	CVVHD	CVV HDF	PD
Blood flow (mL/min)	250-400	100-200	<100	200-300	100-200	100-200	-
Dialysate flow (mL/min)	500-800	100-200	0	0	16.7-33.4	16.7-33.4	0.4
FIlterate (L/day)	0-4	0-4	0-4	24-96	0	24-48	2.4
Replacement fluid (L/day)	0	0	0	21.6-90	4.8	23-44	0
Dialysate buffer	Bicarbonate	Bicarbonate	–	–	Lactate bicarbonate none (Titrate)	Lactate bicarbonate none (Titrate)	Lactate bicarbonate
Replacement fluid buffer	–	–	–	Lactate bicarbonate	–	Lactate bicarbonate	–
Mechanism of clearance	Diffusion	Diffusion	Convection	Convection	Diffusion	Both	Both
Urea clearance (mL/min)	180-340	75-90	1.7	16.7-67	21.7	30-60	8.5
Duration (hrs)	3-4	8-12	Variable	> 24	> 24	> 24	

Indications of RRT

Biochemical Indications

1. Refractory hyperkalemia > 6.5 mmol/L
2. Serum urea >25-30 mmol/L
3. Refractory metabolic acidosis pH < 7.15

4. Refractory electrolyte abnormalities : hyponatremia, hypernatremia or hypercalcemia. Tumor lysis syndrome with hyperuricemia and hyperphosphatemia. Urea cycle defects, and organic acidosis resulting in hyperammonemia

Clinical Indications

- Urine output <0.3 mL/Kg for 24 hours or complete anuria for 12 hours
- AKI with multiple organ failure
- Refractory volume overload
- End organ involvement: pericarditis, encephalopathy, neuropathy, myopathy, uraemic bleeding
- Severe poisoning or drug over dose

Types					
Hemodialysis		*Peritoneal dialysis*		*Hemofiltration (CAVH and CVVH)*	
Indication		Indication		Continuous process so that 1 lit of plasma ultrafiltrate is removed per hour (12-18 lit/24 hr); rate of ultrafiltration maintained 7-15 mL/min	
1.	Catabolic pt	1.	Noncatabolic pt		
2.	Hemodynamically stable	2.	Hemodynamically unstable pt.		
3.	Non-hypotensive	3.	Poor vascular access		
4.	Diagnosed intra abdominal ds	4.	Active hemorrhage		
5.	Recent abdominal surgery				
Disadvantage		Disadvantage		Disadvantage	
1.	Can impose substantial hemodynamic stress not tolerated by patient	1.	Not useful in patient of ARF following abd surgery since it needs intact peritoneum	1.	Anticoagulation reqd for very extended interval of time with risk of bleeding
2.	CVS abnormality	2.	Pain (56%), hemorrhage (30%) leakage (14%), restricted ability to clear fluid and uraemic waste (39%) peritoneal infection. Difficulty making dialysate flow, protein loss limit its use	2.	Needs to accurately control quite large input and output volume ↓ Not recommended for routine management of ARF; used only for patient with refractory fluid overload, complicated ARF, acid base and electrolyte derangement
		3.	Poor metabolic control		
		4.	Hyperglycemia		

*In hepatic failure acetatedialysis is contraindicated

There is no consensus as to which modality is superior, each having its own strengths and weaknesses; by and large, continuous therapies are used in hemodynamically unstable patients. The use of peritoneal dialysis in acute kidney injury is decreasing primarily because of the widespread availability of dialysis machines. However, PD has its unique advantages which includes the capacity to be performed anywhere.

Prevention of AKI

- Early recognition of "at risk" patients
- Maintaining adequate hydration to achieve effective circulatory volume
- Avoid nephrotoxic agent
- Recognise and treat sepsis promptly
- Follow contrast nephropathy guidelines in CKD.

Suggested Reading

1. Devarajan P. Emerging biomarkers of acute kidney injury. Contrib Nephrol. 2007;156:203-12.
2. Han JS, Kim YS, Chin HJ, et al. Temporal changes and reversibility of carbanylated Hb in renal failure. Am J Kidney Dis 1997;30:36.
3. Joannidis M, A Metnitz B, Baver P, et al. Acute Kidney Injury in critically ill patients classified by AKIN versus RIFLE using SAPS3 data base. Intensive Care Med 2009;35:1692-702.
4. Lewington AJP, Kanagasundaran NS. Clinical Practice Guidelines for Acute Kidney Injury [cited 24 January 2011]; available from http://www.renal.org/clinical/guidelines.
5. Lewington AJP, Kanayasundarum NS. Clinical Practice Guidelines for Acute Kidney Injury [cited 24th January 2011]; Available from : http://www.renal.org/clinical/guidelines section/acute kidney injury aspx; 2010.
6. Mehta RL, Kulum JA, Shah SV, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
7. O'Rilly P, Tolwani A. Renal Replacement Therapy 111; IHD, CRRT, SLED. Crit Care Clin 2005;21:367-78.
8. Shin J, Shaykh M, Anwar F, et al. Factors determining Hb carbanylation in renal failure. 1995;48:1605.

chapter 23

Endocrine Emergencies

Sudipto Chatterjee, Sujoy Ghosh

Endocrine emergencies are dealt by internists more than endocrinologists, so a thorough knowledge of handling these patients is mandatory for all emergency physicians and internists.

ADRENAL CRISIS

(Acute Adrenal Insufficiency)

Primary Adrenal Crisis

- Autoimmune polyglandular syndrome (1 Autoimmune polyglandular syndrome 2 Isolated autoimmune adrenalitis, congenital adrenal hyperplasia, adrenoleuko-dystrophy, familial glucocorticoid deficiency), Kearns Sayre syndrome (external opthalmoplegia, retinal degeneration, cardiac conduction defect, general failure), Smith-Lemli Opitz syndrome (mental retardation, growth failure, craniofacial malformation). Adrenal infection—tuberculosis, HIV, cytomegalovirus, cryptococcosis. Adrenal infiltration—metastasis, lymphoma, sarcoidosis, amyloidosis, hemochromatosis, adrenal hemorrhage - *Meningococcus Sepsis* (Waterhouse Frederickson Syndrome), primary antiphospholipid syndrome.
- Drug induced— ketokonazole, trilostane, itomedate, aminoglutethemide, bilateral adrenalectomy

Secondary Adrenal Insufficiency

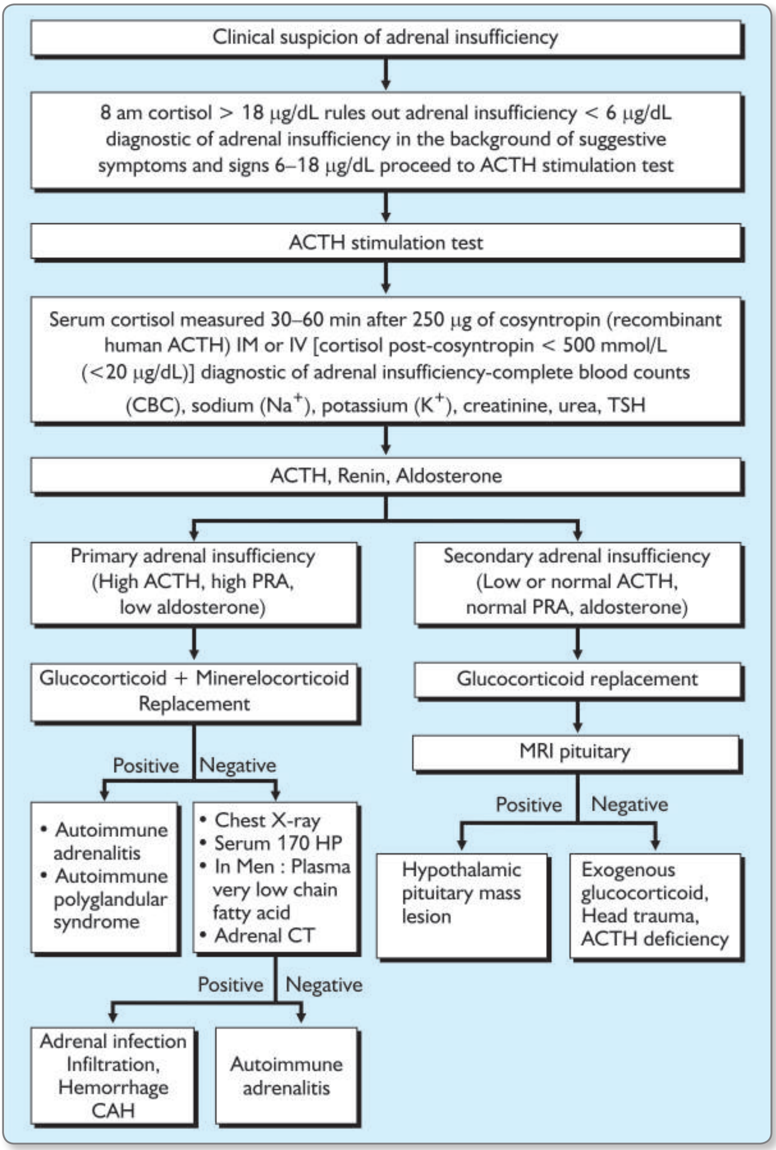
Pituitary tumor, mass lesion affecting hypothalamic pituitary region, pituitary irradiation, autoimmune hypophysitis, pituitary apoplexy, pituitary infiltration, combined pituitary hormone deficiency, congenital ACTH deficiency.

Sign and Symptoms

Glucocorticoid Deficiency: Fatigue, lack of energy, myalgia, joint pain, fever, anemia, lymphocytosis, eosinophilia, ↑ TSH, hypoglycemia, postural hypotension, hyponatremia.

Mineralocorticoid Deficiency: Abdominal pain, nausea, vomiting, dizziness, postural hypotension.

Adrenal Androgen Deficiency: Lack of energy, dry and itchy skin, loss of libido, loss of axilliary and pubic hair.



Treatment: Acute adrenal insufficiency

- Hydration (Normal Saline ~ 1 litre/h)
- Inj hydrocortisone 100 mg IV followed by 50 to 100 mg every 6 hourly.

Mineralocorticoid replacement initiated when hydrocortisone dose reduced < 50 mg/day as higher dose of hydrocortisone stimulates mineralocorticoid receptors. Mineralocorticoid—100 to 150 μg fludrocortisone/day.

HPA Suppression

- Alternate day Glucocorticoid therapy.
- Tapering Glucocorticoids.
- ACTH stimulation test

Pituitary Apoplexy

Pituitary apoplexy is characterized by sudden onset of headache, mental obtundation, visual symptoms, opthalmoplegia and resulting in multiple pituitary hormone deficiency.

It is due to acute hemorrhage or inflammation of pituitary gland. Vascular supply of anterior pituitary gland is derived from the branches of the internal carotid arteries (superior and inferior hypophyseal arteries) which forms the hypophyseal portal passing through the pituitary stalk. Apoplexy is believed to be due to compression of this portal system by enlarging pituitary resulting in compromised blood supply.

History and Clinical Features

Patient usually presents with headache, nausea, vomiting, diminished visual acuity or visual field defects, (diplopia and ptosis) due to cavernous sinus involvement (third, fourth, ophthalmic and maxillary division of fifth and sixth cranial nerves).

Headache occurs in >90 percent of patients often retro-orbital

Vomiting occurs in about 70 percent of patients simultaneously with headache

Visual acuity and field defects occur in 50 to 60 percent of patients and according to level of compression on optic nerve, chiasma or tract.

- If the optic chiasma is compressed the defect is bitemporal superior quadrantic defect most common.
- Optic tract involvement may occur if the chiasma is prefixed and result in contralateral homonymous hemianopia. (common).
- When the optic chiasma is postfixed, the pituitary may compress optic nerve with ipsilateral visual acuity loss and a central scotoma on visual field testing.

Extraocular muscle paresis is common (80%) and usually result from compression of cranial nerves in the cavernous sinus, which gives symptoms and signs of ptosis, diplopia and strabismus.

  - Involvement of third cranial nerve most common results in eye ball deviated down and out (Exotropia), ptosis and dilated pupil.

- Involvement of IV cranial nerve-less common. Cranial nerve IV cycloducts and infraducts the eye, i.e the trochlear nerve allows a person to view the tip of the nose. So an isolated right cranial nerve IV palsy will result in exotropia to right double vision that increases on looking to left and head tilt to right.
- Involvement of VI cranial nerve-least common. Isolated paralysis results in esotropia and inability to abduct the eye on the side of lesion. Patient complains of double vision on horizontal gaze only often called horizontal homonymous diplopia.
- Involvement of cranial nerve V. This may produce facial pain and sensory loss over the face. The area depends on which division of V nerve is affected. The other neighboring structures may be compressed giving rise to varying clinical presentation.

- Carotid artery: May be compressed leading to stroke. Blood in subarachnoid space may cause spasm of cerebral arteries, meningismus, stupor and coma.
- Sympathetic nerves: May be compressed leading to Horner's syndrome.
- Hypothalamus: Involvement of hypothalamus may alter thermal regulation.
- Posterior pituitary: Destruction of posterior pituitary tissue may lead to endocrine deficiency syndrome.

Precipitating Cause

- Endocrine stimulation test: TRH induced vasospasm.
- Bromocriptine treatment.
- Head trauma: Pituitary stalk injury.
- Pregnancy: Temporary enlargement of pituitary which compromises blood supply.
- Pituitary irradiation.
- Sheehan syndrome is postpartum pituitary necrosis of a nontumerous gland due to postpartum arterial spasm, often due to postpartum hemorrhage.

In Sheehan's syndrome inability to lactate after delivery due to prolactin deficiency and amenorrhea is secondary to gonadotrophin deficiency. Shaved pubic hair fails to grow. Hypothyroidism and hypoadrenalizm are observed. On MRI, pituitary appear hyperintense in T1 weighted images and is enlarged.

Treatment

Medical

- Glucocorticoids are required if corticotrophs are damaged—Hydrocortisone 15 mg morning, 10 mg afternoon. It has been suggested to keep the hydrocortisone tablets and a glass of water next to the bed while going to sleep in the night, so that the morning dose can be

consumed immediately on waking up and patients are advised to get out of the bed half an hour later.
- Thyroid hormone replacement for secondary hypothyroidism 100 to 200 μg/day oral.
- Sex hormone replacement in gonadotropin deficiency. Testosterone 50 to 400 mg IM every 4 week. Estrogen 0.3 to 0.625 mg/day.
- Growth hormone replacement is done usually in children unless patient is too symptomatic.

Surgical

Surgical decompression may rarely be life saving in pituitary apoplexy in a patient with raised intracranial tension along with imaging evidence of compression of neighboring structures.

Pheochromocytoma and Hypertensive Crisis

Crisis

Pheochromocytoma is an endocrinologist's curiosity but it is often a nightmare for anesthesists and obstetricians. An undiagnosed or improperly treated pheochromocytoma can cause severe morbidity or even mortality.

Hypertensive crisis may be defined as a clinical condition associated with blood pressure elevation and progressive or impending target organ damage.

Hypertensive crisis in pheochromocytoma is an hypertensive emergency. The criteria to be fulfilled before operation are:
- Blood pressure not more than 160/90 mm of Hg (normalization of blood pressure is preferable).
- Postural or orthostatic hypotension not exceeding 80/45 mm of Hg.
- No more than one ventricular extrasystole every 5 minutes.
- ECG without nonspecific ST segment elevation or depression and T wave inversion.

Treatment

- Phenoxybenzamine, an α-adrenoceptor blocker is mostly used for pre-operative control of blood pressure.
  The dose is 10-20 mg twice daily for 2 weeks before surgery.
- Alternative to phenoxybenzamine are selective α_1 adrenocepter blocking agents such as doxazosin and terazosin and calcium channel blockers.
- Beta(β) blockers are often used to control arrhythmias. But, a beta blocker should never be used before first blocking α-adrenoceptor mediated vasoconstriction by an α-blocker, because loss of β adrenoceptor mediated vasoconstriction and unopposed α-adrenoceptor mediated vasoconstriction may precipitate hypertensive crisis.
- Phentolamine may be used to treat hypertensive crisis. It can be given by:

- – IV boluses of 2.5 to 5 mg at the rate of 1mg/min; it can be repeated every 5 minutes until desired effect is reached.
- – IV continuous infusion by dissolving 100 mg of phentolamine in 500 mg of 5 percent dextrose and infusion rate is adjusted according to blood pressure response.

- Sodium nitroprusside-IV sodium nitroprusside could be infused alternatively at the rate of 0.5 to 0 µg/kg per minute.
- Metyrosine (Methyl-para-tyrosine) a competitive inhibitor of tyrosine hydroxylase is used if blood pressure is not controlled by α and β blockers. Dose 250 mg 2 to 4 times a day.

Postoperative Period

The two common problems are hypotension and hypoglycemia in the immediate postoperative period.

Hypotension-generous administration of IV fluids.

Hypoglycaemia-5 percent dextrose infusion.

Thyroid Storm/Thyrotoxic Crisis

Thyrotoxic crisis is an acute, life threatening, hypermetabolic state induced by iatrogenic or spontaneous release of thyroid hormones in a patient with uncontrolled thyrotoxicosis. Rarely thyroid hormones storm may be the initial presentation of thyrotoxicosis. The morbidity rate in undiagnosed and untreated case is 90 percent which could be reduced to less than 20 percent by early diagnosis and treatment.

Thyroid storm can be triggered by many different events usually in patients with underlying Grave's disease and toxic multinodular goitre.

- Infection
- Surgery
- Cardiac events
- Toxemia of pregnancy
- Diabetic ketoacidosis
- Radioactive iodine
- Sudden stoppage of antithyroid drugs
- Vigorous palpation of thyroid gland.

Though these patients are not able to give history but following history from a family member may help in the diagnosis.

- Weight loss (15%)
- Palpitation
- Chest pain
- Psychosis
- Menstrual irregularities
- Disorientation
- Tremor

- Nervousness, anxiety, emotional lability.
- Heat intolerance
- Proximal muscle weakness
- Dyspnea
- Bowel movements hyperactivity.

Clinical Examination Shows

- Fever
- Relative tachycardia
- Profuse sweating
- Dehydration
- Warm, moist skin
- Widened pulse pressure
- Congestive cardiac failure
- Atrial fibrillation
- Exophthamos
- Thyromegaly
- Fine tremor
- Thyroid bruit.

Laboratory Confirmation

Thyroid storm is a clinical diagnosis. Treatment should be started immediately without waiting for the reports. Several laboratory features may be associated with thyroid storm such as:

- Hyperglycemia
- Hypercalcemia
- Leukocytosis
- Hypokalemia
- Low serum cortisol
- Liver function abnormalities.
- Both T_4 and T_3 are elevated.
  ECG-sinus tachycardia, atrial fibrillation and complete heart block
  Chest X-ray show CCF or infection.

Treatment

- Once thyroid storm is suspected, treatment should not be delayed.
- Patient should be intubated, if level of consciousness is profoundly altered.
- Supplemental oxygen to maintain oxygen saturation.
- Aggressive fluid replacement according to electrolyte levels.
- Appropriate electrolyte replacement according to electrolytes levels.
- Fever is controlled with cooling measures and paracetamol. Aspirin should be avoided as it interferes with thyroid hormone binding with the circulating proteins resulting in increased free T_3 and T_4.

- Intravenous dexamethasone 2 mg every 6 hours inhibits hormone production, decrease peripheral conversion of T_4 to T_3 and also corrects adrenal insufficiency if associated.
- Antithyroid drugs-propylthiouracil (PTU) or carbimazole/methimazole are administrated orally or through nasogastric tube. Both drugs inhibit organification of tyrosine residues. PTU has the advantage of inhibiting peripheral conversion of T_4 and T_3 at higher doses of > 600 mg/day. Clinical effects starts one hour after administration.
  Dose
  – Propylthiouracil—600 to 1200 mg loading dose followed by 200 mg 6 hourly.
  – Methimazole—20 mg orally 4 hourly.
- **Iodine:** Iodine has the added benefit of inhibiting the release of thyroid hormones from the gland not observed with PTU or carbimazole. However, iodine should not be administered at least one hour after PTU/AMI is given, lest this iodine is utilized to synthesize more hormones. Lithium may be used in those with iodine allergy.
  Dose
  – Saturated solution of potassium iodide (SSKI) contain 36 mg of iodine per drop: 1 to 5 drops per oral thrice daily.
  – Lugol's solution contain 8 mg of iodine per drop: 5 to 10 drops per oral thrice daily.
  – Iopanoic acid: 1gm via slow IV drip 8 hourly for first 24 hours. Then 500 mg IV 12 hourly. The added advantage of iodinated contrast agents is that they prevent the peripheral conversion of T_4 to T_3.
- **Propranolol:** β adrenergic blocking agents blocks the sympathetic overdrive. Propranolol has additional advantage of inhibition of peripheral conversion of T_4 and T_3.
  Dose
  1. Oral: 20 to 80 mg, 4 hourly
  2. Intravenous: 1 to 2 mg slow IV.
- **Aggressively treat infections or any other precipitant:** Iodide should not be used in pregnancy with thyroid storm as it can lead to goitre in fetus. PTU should be preferred in pregnancy on in the first trimester. Carbimazole/methimazole is preferred in the second/third trimester.

Myxedema Coma

Cause

Precipitating factors are:
- Hypothermia
- Infections especially pneumonia
- Myocardial infarction or congestive heart failure
- Cerebrovascular accident

- Respiratory depression due to drugs (e.g. anesthetics, sedatives, tranquilizers)
- Trauma or gastrointestinal blood loss.

Clinical Features

Three main features are:

i. Altered mental state ranging from poor cognitive function through psychosis to coma.
ii. Hypothermia (as low as 23°C).
iii. Absence of fever inspite of severe infection.

Other Features

- Respiratory depression
- Bradycardia
- Hypotension
- Low voltage on ECG
- Hyponatremia
- Hypoglycemia
- Anemia
- Raised CPK, LDH.

Thyroid Function Test

Thyroid function test (TSH) values may only be modestly raised (and will be normal or low in secondary hypothyroidism) but free T_4 levels are usually very low.

Treatment

Rapid replacement of thyroid hormones is needed but there is no agreement on whether it should be "high dose" or "low dose".

"High dose" Regimen

If intravenous thyroxine is available, this can be given as a bolus of 300 to 500 μg followed by 50 to 100 μg daily. Oral thyroxine in similar doses can be given (usually by nasogastric tube) but absorption is uncertain. In view of impaired conversion of T_4 to T_3 in this condition, use of tri-iodothyromine (T_3) is also advocated, e.g. 10-20 μg initially (intravenous) followed by 10 μg every 4 hours for 24 hours, then 10 μg every 6 hours. However, adverse cardiac effects may occur with rapid administration. Alternatively, combination of 200 μg thyroxine (T_4) with 10 μg tri-iodothyronine (T_3) initially followed by tri-iodothyronine 10 μg every 12 hours and thyroxine 100 μg every 24 hours can be given till patient recovers to take thyroxine orally.

"Low dose" Regimen

25 μg of throxine daily for a week or 5 μg of tri-iodothyronine twice daily with a gradually increasing dose.

Other Aspects of Management

- Most patients require ventilatory support for 1 to 2 days
- Space-blankets for hypothermia
- Intravenous saline for volume expansion
- Hypertonic saline if sodium is < 120 mmol/L
- Intravenous hydrocortisone 50 to 100 mg 8 hourly.

Diabetic Emergencies

Diabetic Ketoacidosis

Introduction

It is characterized by the biochemical triad of:

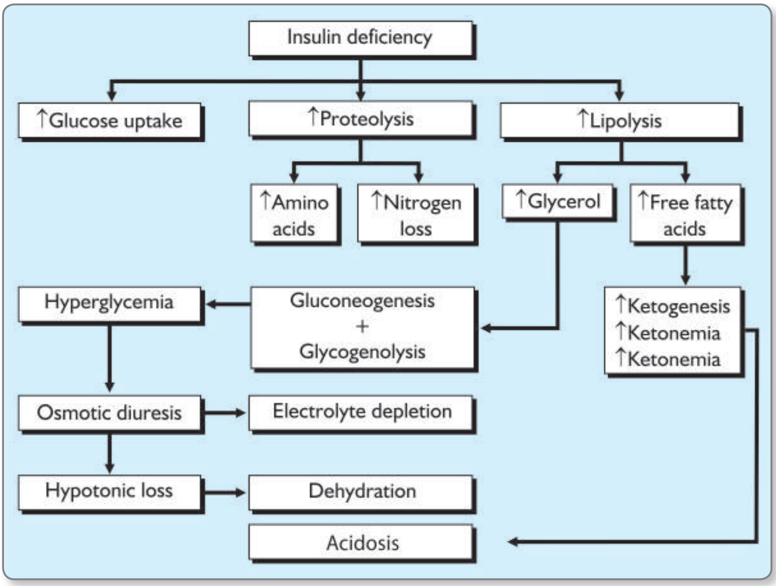
- Hyperglycemia
- Ketosis
- Acidosis.

Diabetic Ketoacidosis

Mortality rate < 1 to 10 percent, most common in Type 1 Diabetes.

Cause: Lack of endogenus or exogenus insulin, increased requirement of insulin secondary to infection, vascular disorder (myocardial infarction, cerebrovascular accident). Endocrine disorders (Hyperthyroidism, Cushing's syndrome, acromegaly) trauma, pregnancy—(increased secretion of counter regulatory hormones), stress.

Pathophysiology



Role of Counter Regulatory Hormones: Hypersecretion of epinephrine, glucagon, cortisol, growth hormone—Inhibit insulin mediated Glucose uptake of muscle, activating glycogenolysis, neoglucogenesis, activating lipolysis.

History and Clinical Features

History—onset of symptoms < 24 hours

Patients generally give an history of diabetes with irregular treatment (20% - of DKA may present without any history of diabetes).

A h/o the common event that may precipitate DKA are:

- Stoppage of insulin or inadequate and irregular insulin therapy is the most common cause (33%).
- The history of infection (pneumonia and UTI—30 to 50 percent of the illnesses that lead to DKA)
- Alcohol abuse
- Trauma
- AMI
- Pulmonary embolism
- Drug abuse—Corticosteriods, sympathomimetic agents; pentamidine, excessive use of diuretics in elderly
- Pancreatitis.

Symptoms of DKA

- Nausea, vomiting
- Thirst, polyuria, polydipsia, weight loss
- Abdominal pain
- Shortness of breath
- Altered mental status
- Fatigue.

Signs

A thorough physical examination with emphasis on the following must be done:

- Presence of any infection
- Patency of airway
- Cardiovascular + respiratory status.

Important Signs are:

- Fruity odor of breath
- Signs of dehydration
  - Loss of skin turgor
  - Dry mucous membrane
  - Tachycardia
  - Hypotension

- Tachypnea—Rapid and deep respiration (Kussmaul respiration)
- Abdominal tenderness
- Sensorium—Alert to drowsy to comatose (10 - 15%)
- When serum osmolality exceeds 340 mosmol/Kg
- Temperature—Normal to hypothermic.

Bedside Assessment

- Determination of capillary blood glucose.
- Qualitative assessment of urine + blood glucose, ketones, nitrites using reagent stick.

Where to Manage?

- If patient is alert to mildly drowsy with moderate dehydration — manage in ward.
- Patient comatose with or without features of hypovolemic shock → manage in intensive care unit.

Initial Investigations

(After Transfer to ITU)

- Blood gas analysis — Immediate
- Blood glucose
- Urea, creatinine
- Electrolytes
- Urine and/or serum ketones
- Blood count DC
- Cultures of blood, urine and other body fluids.
- Chest X-ray
- ECG
- Serum osmolality
- Other investigations to establish source of infection and eliminate associated conditions like
  - Pancreatitis
  - Myocardial infarction
  - Pulmonary embolism, etc.

Classification of Diabetic Ketoacidosis

	Mild	Moderate	Severe
Plasma Glucose	> 250 mg/dL	> 250 mg/dL	> 250 mg/dL
Urine and Serum Ketones	+ve	+ve	+ve
Serum Osmolality	Variable	Variable	Variable
$[Na^+]$ in mEq/L] + glucose/18 + BUN/2.8 $\left(\frac{\uparrow \text{ Normal}}{290 \pm 5}\right)$			
ANION GAP	10 – 12	> 12	> 12
$Na^+ - (Cl^- + HCO_3)$ $\left(\frac{\uparrow \text{ Normal}}{7 - 9\text{mEq}}\right)$			
Arterial pH	7.25 – 7.3	7.0 – < 7.24	< 7.0
Sensorium	Alert	Alert—Drowsy	Drowsy—Comatose

Treatment—Fluid therapy

a. 1L (0.9%) normal saline in the first hour,
b. Then 0.9 percent N or 0.45 percent N saline -250 to 500 mL/h depending on sodium (Na) concentration.
c. When blood glucose < 200 mg/dL. change fluid to 5 percent dextrose or 5 percent dextrose normal saline.

As water loss is more than salt loss ideal replacement fluid is half NS. But it causes further contraction of blood volume and cellular edema. So, NS is ideal fluid. Excess of saline infusion causes danger as:

- previous loss is not iso-osmotic,
- water loss > salt loss,
- hyperchloremic.

Acidosis (Caused by Chloride in NS): For this reason NS is replaced by 5 percent Dextrose after 4 to 6 hours because it provides calorie and prevents hypoglycemia, provides free water once glucose is metabolized, prevents excessive Na and Cl load.

Potassium Therapy: If K^+ >5 mEq/L then no replacement. If K^+ between 4 to 5 mEq/L then replacement 20 meq/L to each litre of NS. If K^+ between 3-4 mEq/L then 40 mEq/L to each liter of NS. If K^+ < 3 mEq/L then 10 to 20 mEq/hr. K^+ drops within 4 to 6 hours of hydration and insulin therapy. With glucose utilization potassium migrates from extracellular to intracellular fluid. When alkali is administered potassium drop is aggravated by the intracellular shift.

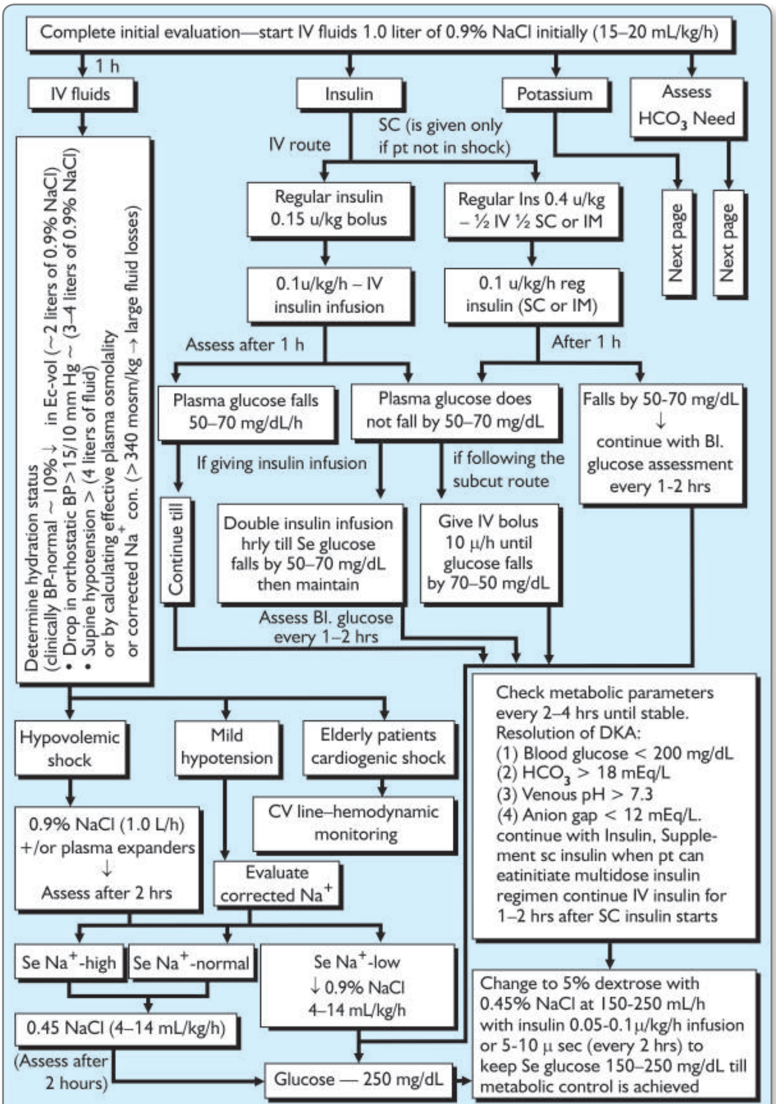
Bicarbonate Therapy: If pH <7 and bicarbonate < 5 mEq/L then 50 mEq of $NaHCO_3$ with 200 mL of water transfused over 1 hour until pH>7. If pH <6.9, 100 mEq of Bicarbonate and 20 mEq of KCL in 400 ml of water is transfused. Alkalosis of DKA grows over 2-3 days so correction should be in the same pace. Rapid correction of peripheral acidosis aggravates intracerebral acidosis. Oxygen dissociation and delivery to tissue is better in acidic state, hence sudden correction can jeopardize brain oxygenation. Elimination of ketone through kidneys better in acidic state. $NaHCO_3$ generates carbondioxide resulting in intracellular acidosis.

Magnesium and Phosphate: Profound unexplained weakness may be caused by hypomagnesemia which causes decreased parathormone level and hypocalcemia. Magnesium replacement, Inj MgSO4 2 ml of 50 percent solution IM. If Phosphate <1 mg/dL, 20 to 30 mmol of potassium phosphate to be given over 24 hours.

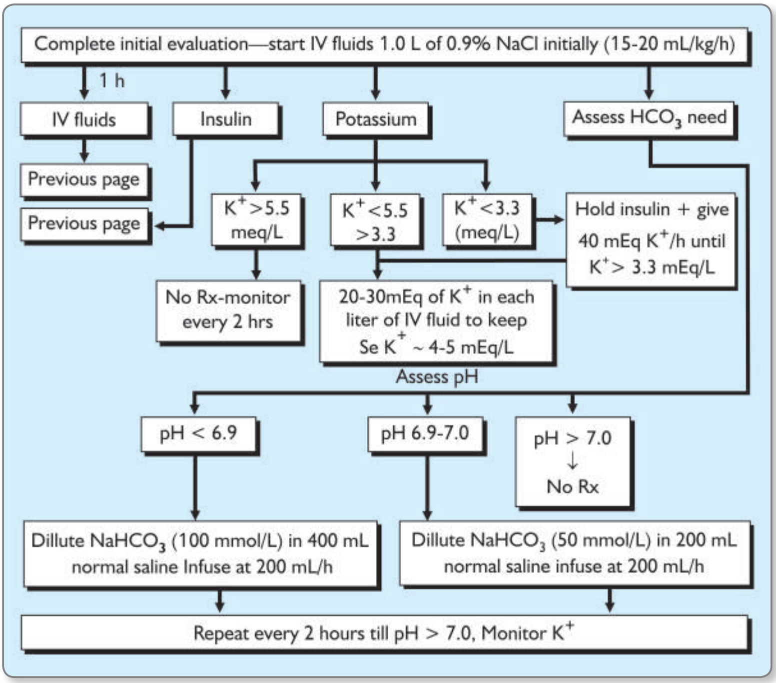
Insulin:
- IV Bolus 10 to 20 unit (0.1 U/Kg),
- IV 5 to 10U/h till blood glucose 250-300.
- IV 2 to 5U/h till blood glucose above 200 mg/dL,
- IV 1 to 2U/h + 6 to12 SC TDS when oral feed and IV fluid are continued.
- SC 6 to 12 U Stat 1 hr before stoppage of IV Insulin Infusion.
- SC 3 dose regime when IV fluid are discontinued.

Complication: Hypoglycemia, Hypocalemia, cerebral edema.

Management — (ICU or Ward)



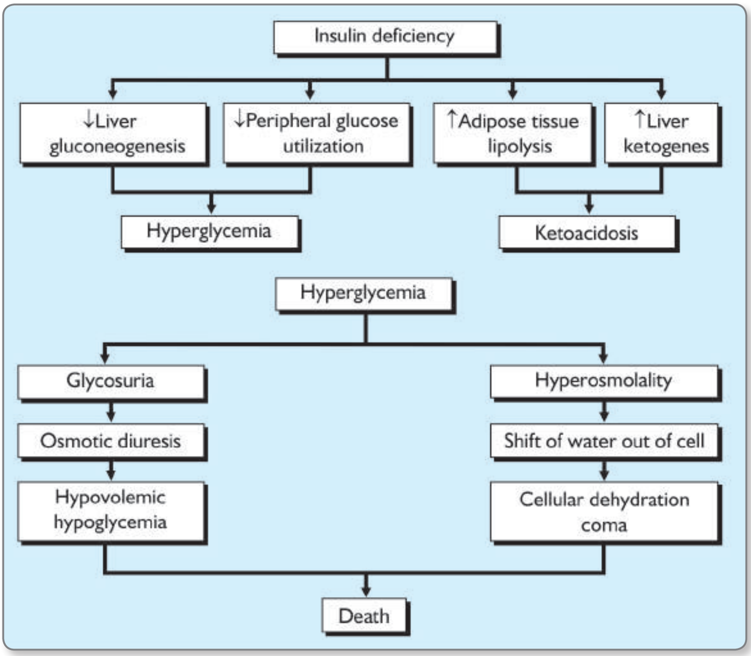
Note: Corrected Na^+ → for EACH 100 mg/dL glucose > 100 mg/dL add 1.6 to measured Na^+ concentration for corrected Na^+ value



Hyperglycemic hyperosmolar state

Diagnostic criteria		Clinical features	
1.	Plasma glucose > 600 mg/dL	1.	Symptoms develop insidiously
2.	pH > 7.3	2.	Polyuria; polydipsia; weight loss — can persist for several days before admission.
3.	Serum HCO_3^- > 15 mEq/L	3.	Signs of dehydration - prominent (total water deficit ~ 9 litres (100-200 mL/kg)
4.	Urinary and/or Plasma Ketones → small amounts	4.	Mental obtundation + coma are more frequent. - (Focal neurological signs - hemiparesis or hemianopia + seizures)
5.	Plasma Osmolality > 320	5.	Concomitant signs of any existing illness may be present
6.	Anion Gap < 12	6.	Bedside evaluation of blood glucose + Urine Ketones should be done.
7.	Mental State – comatose		

Hyperglycemic Hyperosmolar Nonketotic State Pathophysiology



Precipitating Factor: Too little insulin, infection, severe stress, hypokalemia, renal failure, old age, infancy, drug-cortisone, thiazide, beta-blocker, calcium channel blockers.

Sign and Symptom: Hyperosmolar coma, dehydration, increased temperature, convulsion, Kussmaul's breathing, abdominal pain-30 percent, vomiting-50 to 60 percent.

Laboratory Abnormalities:

- Blood Glucose > 700 mg/dL.
- Serum osmolality > 320 mOsm/L.
- Serum bicarbonate > 15 mEq/L.
- pH > 7.3
- Urine ketone - absent
- Sodium- low-normal-high.
- Leukocytes counts: 15000-40000.

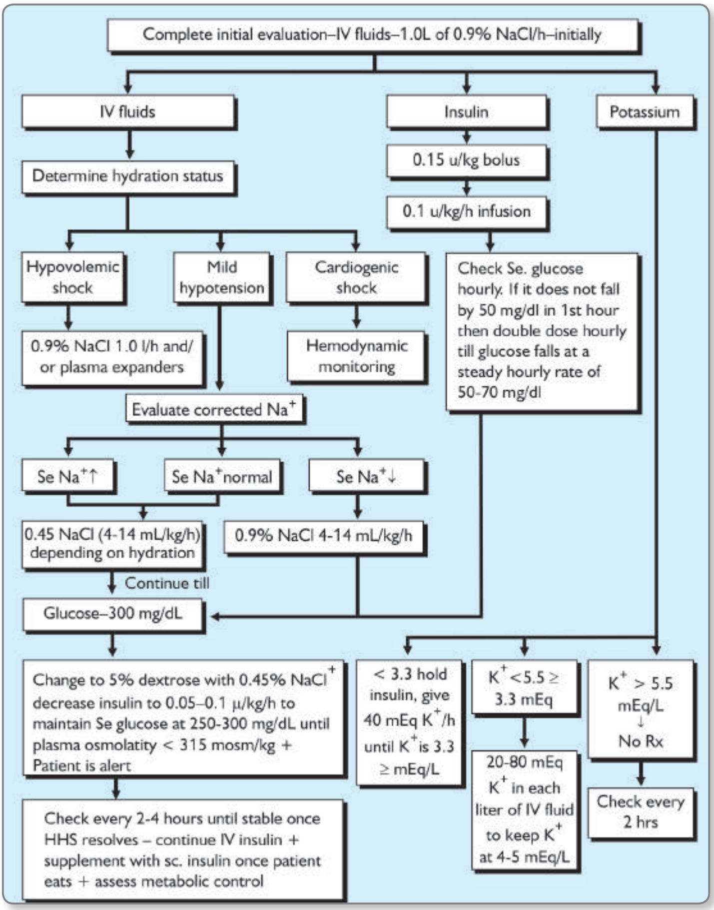
Treatment: Fluid replacement, estimated water loss-10 percent of body weight. Replace 50 percent of deficit in first 5 hours. Infuse normal saline if hypotension and sodium < 140 mEq/L. Infuse ½ NS if Na^+ >145 mEq/L and patient normotensive.

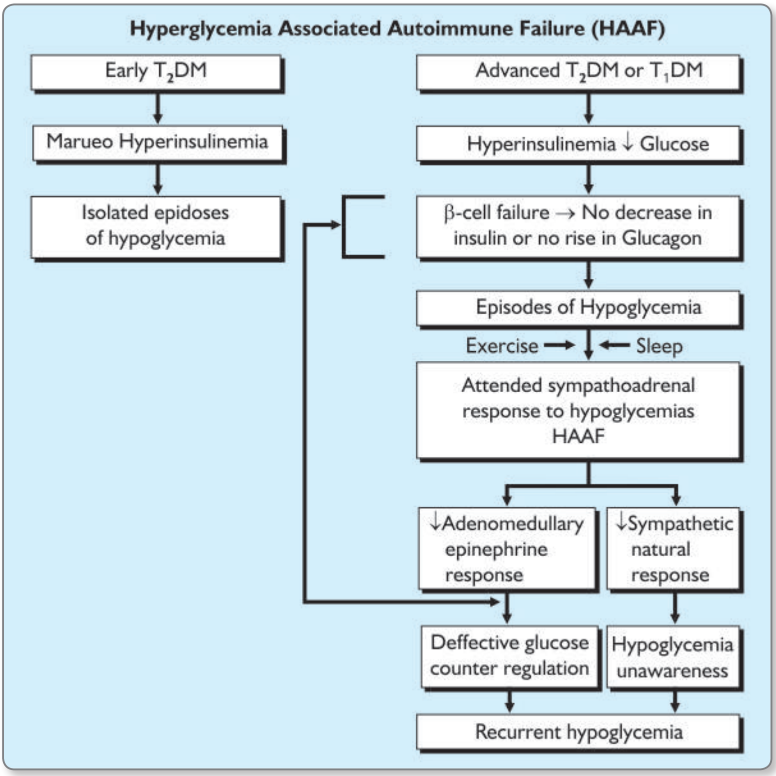
HOURS	**VOL**
½ to 1	1 L

2	1L
3	500 ml to 1L
4	500 ml to 1L
5	500 ml to 1L
First 5 hrs	3.5 to 5L
6-12 hrs	250 to 500 mL/hr
Insulin—same as DKA	

Complications: Infection, disseminated intravascular coagulation (DIC), deep-venous thrombosis (DVT), acute myocardial infarction (AMI), cerebrovascular accident (CVA), hypoglycemia, hypokalemia.

Management Ideally in ICU





Treatment: Initial dose — IV 50 percent dextrose@ 0.5 mL/kg, 25 percent dextrose—1mL/kg, 10 percent dextrose—2 to 5 mL/kg, SC or IM Glucagon 1 mg.

Hypoglycemia

Whipple's Triad: Symptoms of hypoglycemia, low plasma glucose concentration, relief of symptoms with glucose.

Under-production

a. **Hormone deficiency—**hypopituitarism, adrenal insufficiency, catecholamine deficiency,
b. **Enzyme deficiency—**G-6 Phosphatase, liver phosphorylase, pyruvate carboxylase,
c. **Substrate deficiency—**ketotic hypoglycemia of infancy, severe malnutrition, late pregnancy,

d. **Acquired liver disease**—Hepatic congestion, cirrhosis, hepatitis,
e. **Drugs**—Alcohol, propranolol, salicylate.

Over-utilization

a. **Hyperinsulism**—Insulinoma, beta-cell disorder, exogenus insulin overdose, sulfonylurea over dose,
b. **Inappropriate insulin level**—Extrapancreatic tumor.

Fed State Hypoglycemia (Reactive Hypoglycemia)

a. **Early (2-3 hour after meal)**—alimentary hyperinsulinism, post-gastrectomy, functional fructose Intolerance, galactosemia,
b. **Late (3-5 hour after meal)**—counter-regulatory deficiency of growth hormone, Glucagon, Cortisone, Epinephrine.

Pseudohypoglycemia–chronic leukemia—when leukocyte count is markedly elevated, and there is utilization of glucose by leukocyte. Such hypoglycemia is not associated with symptoms.

Physiologic response to hypoglycemia—decreased insulin, increase glucagon, increase epinephrine, increased cortisol and growth hormone.

Symptoms: Autonomic failure - (adrenergic)—palpitation, sweating, anxiety-tremor, tachycardia, (parasympathetic)—hyperactivity, nausea, hunger (Neuroglycopenia)—headache, fatigue, mental dullness, dizziness, blurring of vision, confusion, amnesia, seizure, unconsciousness.

	Hypoglycemic coma	Hyperglycemia coma
Pulse rate	Increased	Increased
Pulse volume	Full	Weak
Temperature	Decreased	Decreased
Respiration	Shallow	Rapid and deep
Blood pressure	Normal	Raised
Skin	Sweating	Dry
Tongue	Moist	Dry
Tissue Turgor	Normal	Decreased
Eye ball tension	Normal	Low
Breath	Normal	Fruity odor
Reflex	Brisk	Normal
Urine glucose	Negative	+
Plasma glucose	Low	Increased
Bicarbonate	Normal	Low
pH	Normal	< 7.3

No definite level of blood glucose to define hypoglycaemia

< 4.2 mmol/L (75.6 mg)	Endogenous insulin production by pancreas suppressed
< 3.8 mmol/L (68.4 mg)	Secretion of counter-regulatory hormones-glucagon, epinephrine, cortisol, growth hormones
< 3.2 mmol/L (57.6 mg)	Secretion of hormones causes autonomic symptoms sweating tremor tachycardia anxiety hunger nausea tingling
< 2.5 mmol/L (45 mg)	Signs and symptoms of neuroglycopenia appear dizziness headache clouding of vision blunted mental acuity confusion loss of fine motor skill abnormal behaviour convulsions loss of consciousness

Grades of hypoglycemia; detection + therapy

Grade		Detection	Therapy
1.	Asymptomatic	Lab or glucose meter	Adjust daily regimen
2.	Mild	Autonomic symptoms	Oral CHO-Self therapy
3.	Moderate	Neuroglycopenic + autonomic symptoms	Oral CHO-Self therapy
4.	Severe	Neuroglycopenic + autonomic symptoms	Oral/Parenteral assistance needed
5.	Unawareness	Coma, seizures, neuroglycopenic + autonomic signs detected by someone else (CHO = Carbohydrate)	Parenteral CHO

Oral Treatment

The 10 to 20 g of rapidly digested CHO; monitor after 10 mins.; repeat dose if required.

Parenteral Rx:

- **IV Glucose:**
  - if 50 percent Dextrose given then 0.5 mL/kg required to raise blood. Glucose by 5-8 mmol/dL
  - 25 percent Dextrose - 1 mL/kg of fluid needed

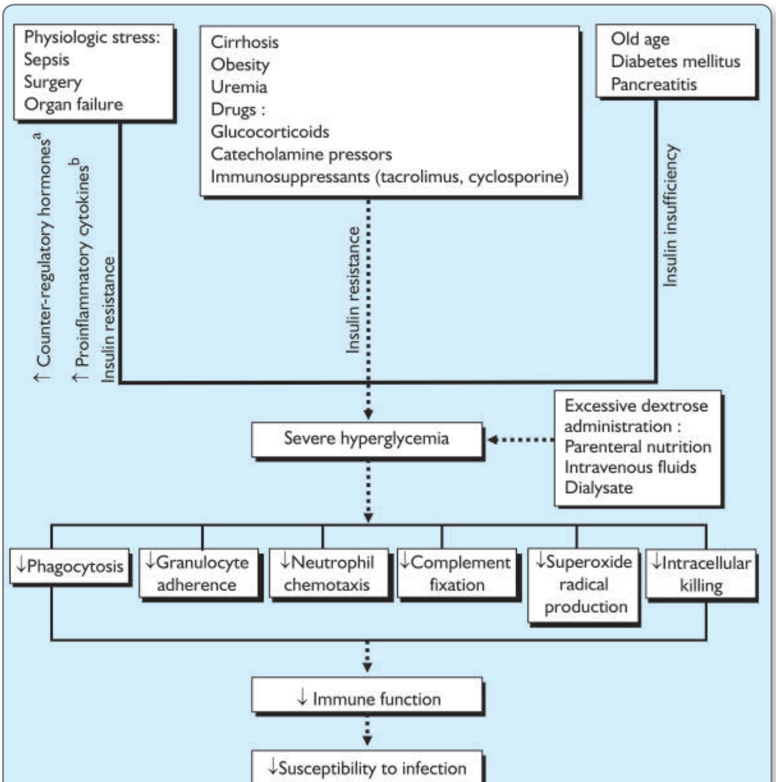
– 10 percent Dextrose - 2.5 mL/kg required

Monitor Capillary Glucose till hypoglycaemia corrected then 5-10 percent Dextrose to be given IV continuously for approximately 48 hrs.

- Parenteral Glucagon for Age > 5 yrs 1.0 mg - SC or IM (Repeat after 10 min if required).

Glucagon is contraindicated in sulfonylurea induced hypoglycemia and hypoglycemia secondary to chronic alcoholism.

Hyperglycemia : Its Impact on Infections in the ICU Patient



[a] Counter-regulatory hormones are glucagon, catecholamines, cortisol and growth hormone

[b] Proinflammatory cytokines are tumor necrosis factor-♋, interleukin(IL)-1, and IL-6

Complications of Hyperglycemia in the ICU Patient

- Osmotic diuresis
- Fluid and electrolyte imbalances
- Hyperosmolar nonketotic coma
- Worsening skeletal muscle catabolism
- Impaired wound healing
- Changes in coagulability and increased CV risk
- Impaired immune function
- Increased susceptibility to infections and increased risk of sepsis.
- Death in certain surgical patients (Butler SO, et al)

Glycemic Control in ICU

- Initiate resuscitation and check blood glucose.
- Assess glycemic risk: coronary artery disease, renal disease, liver disease, pancreatitis, obesity.
- Frequency of blood glucose (CBG) check – Hemodynamically unstable patient – hourly CBG check. After stabilization – prolong the interval. Any change in condition or nutrition delivery regimen – more frequent check.
- Target blood glucose: 140 to 180 mg/dL.
- Insulin delivery route: OHA or long acting insulin should be stopped. Intravenous regular insulin is treatment of choice. Step down from IV to SC route.
- Avoid hypoglycemia (blood glucose < 70 mg/dL) → Risk group – Renal failure, dialysis, liver failure, adrenal insufficiency. Check CBG every 15 minutes.
- Avoid large variation in glucose concentration.
- Switch over to S/C Insulin (short-acting along with long acting before discharge).

Acute Hypercalcemia

Cause

The most common cause is malignancy via either extensive bony involvement or by ectopic production of a PTH-like hormone.

- Hyperparathyroidism, either primary or secondary (associated with renal failure) — second most common cause.
- Others: Vitamin D toxicity
Sarcoidosis
Myeloma
Thiazides
Paget's disease of bone.

Manifestations

- Lethargy and mental status changes
- Vomiting
- Polyuria, polydipsia (Nephrogenic Diabetes Inspidus)
- Renal insufficiency
- Ectopic calcification
- Short QT interval on ECG.

Treatment

Severe hypercalcemia (corrected serum calcium > 3.0 mmol/L) requires urgent treatment.

- Volume repletion with intravenous normal saline (4 liters in first 24 hours)
- Loop diuretics (e.g. frusemide) which has calciuretic effects, should be given after initial volume expansion.
- Intravenous biphosphonates, such as sodium pamidronate at a dose of 30 to 90 mg are extremely effective in treatment of hypercalcemia of malignancy.
- If sarcoidosis or vitamin A or D intoxication are considered, corticosteroids (prednisolone 30 to 60 mg/day) are the drugs of choice.

Hypocalcemia

Hypocalcemia must be interpreted relative to plasma albumin concentration; a useful approximation is for every 1.0 mg/dL that the albumin is below 4.0, the calcium is lowered by about 0.6 mg/dL (Normal Ca^{2+} range: 8.4-10.2 mg/dL or 2.1 to 2.55 mmol/L). Alkalemia will cause more calcium to bind to albumin and will drop ionized calcium further. It is the free or ionized calcium that is physiologically relevant. (Ca^{2+} range: 2.24 to 2.60 mEq/L or 1.12 to 1.30 mmol/L).

Cause

- Vitamin D deficiency (poor sunlight or malnutrition malabsorption, phenytoin therapy, renal failure, etc.)
- Hypoparathyroidism (idiopathic or post surgical)
- Severe pancreatitis
- Severe sepsis
- Rhabdomyolysis.

Manifestations

- Tetany including laryngospasm
- Mental status changes
- Seizures
- QT prolongation → Arrhythmias (Torsade de pointes).

Treatment

Since calcium administration in the critically ill can cause hypoxic cell damage, so calcium should be corrected in this setting only if patient is symptomatic. Two intravenous ampoules of 10 percent calcium gluconate with frequent monitoring of serum levels should be done along with correction of underlying cause. It is also crucial that hypomagnesemia is corrected, since this may potentiate tendency to tetany and arrhythmias.

Suggested Reading

1. Delancy MF, et al. Diabetic ketoacidosis and hyperglycemic hyperosmolar non-ketotic syndrome. Endocrinol Metab Clin North Am. 2000;29:683.
2. Kearney T, Dang C. Diabetic and Endocrine Emergencies. Postgrad Med J 2007;83:79-86.
3. Kitabchi AE, et al. Management of hyperglycemic crises in patients with diabetes. Diabetes Care. 2001;24:131.
4. Matz R: Management of the hyperosmolar, hyperglycemic, syndrome. Am Fam Physician. 1999;60:1468.
5. Savage MW, Mah PM, Weetman AP, et al. Endocrine emergencies. Postgrade. Med J. 2004; 80: 506-15.
6. Van den Berghe G. Insulin therapy for the critically ill. Clin. Cornerstone. 2003;5:56-63.
7. Yee AH, Rabinstein AA. Neurologic presentations of acid-base imbalance, electrolyte abnormalities, and endocrine emergencies. Neurology Clinics 2010, 28(1):1-16.

Rheumatological Emergencies

chapter 24

Arghya Chattopadhyay, Samar Ranjan Pal

Emergencies in rheumatological diseases present to physicians as multisystem problems in various combinations and in a catastrophic manner with significant morbidity and mortality.

They may be divided into two broad categories:

A. **Disease related emergencies:**
   - Rheumatoid arthritis (RA):
     - Atlanto-axial dislocation
     - Scleromalacia perforans
     - Vasculitis
     - Infections
     - Disease flare
   - Systemic lupus erythematosus (SLE):
     - CNS Lupus
     - Cardiac involvement in the form of peri, myo and endocarditis
     - Lung involvement in the form of pneumonia, ARDS
     - Vasculitis
     - Pancreatitis
     - Infections
     - Pregnancy and neonatal lupus
   - Antiphospholipid antibody (APLA):
     - Catastrophic APLA
     - Thromboembolic events in the form of AMI; Retinal vessel thrombosis, PE
     - Thrombotic thrombocytopenic purpura (TTP)/microangiopathic presentation of APLA
   - Spondyloarthoathy:
     - Iridocyclitis
   - Vasculitis:
     - Cerebral vasculitis
     - Mesenteric vasculitis
     - Uveitis and optic neuritis
     - Acute nephritis
     - Hypertensive crisis
     - Visual loss in giant cell arteritis

- Systemic sclerosis:
  - Scleroderma renal crisis (SRC)
- Inflammatory myositis:
  - Respiratory failure
- Crystal induced arthopathies:
  - Acute gout
  - Acute interstitial nephritis
- Infection related arthritis:
  - Septic arthritis
  - Reactive arthritis
- Osteoporosis:
  - Fracture
- Miscellaneous:
  - Macrophage activation syndrome (MAS)
  - Pulmonary renal syndrome
  - SPG: Symmetric peripheral gangrene

B. **Drug related emergencies:**
- NSAIDs:
  - GI bleeding
  - Interstitial nephritis
- Steroids:
  - Addisonian crisis due to withdrawal
  - Psychosis
  - Infections
- DMARDs:
  - Bone marrow suppression
  - Hepatic failure
  - Steven Johnson Syndrome (SJC)
- Biologic response modifiers:
  - Infusion reactions
  - Infections.

Approach to a Rheumatologic Emergency

Detailed history taking of present and past illness; search of related physical signs, laboratory investigations and disease activity calculation will help to diagnose the specific cause of underlying emergency.

Lab investigation has to be done for:

Diagnose the underlying main disease (If not a diagnosed case)

Nature, precipitating cause, organ involvement and extent of disease and damage of underlying emergency

Rule out mimikers in appropriate settings

Laboratory Work-up

1. **Clinical pathology, microbiology and biochemistry:**
   - Hb%, TC, DC, Platelet, ESR, CRP, Reticulocyte count, PBS, LDH Coombs' test (DCT)
   - Na^+, K^+ Urea, Creatinine, Uric acid, LFT, Triglycerides (Tg), Ferritin, Blood Sugar, PT, APTT, INR, FDP, D-dimer, Fibrinogen, Urine R/E, ME, 24 hr urinary protein, 24 hr urinary uric acid.

     Cryoglobulin screening, Lupus anticoagulant
   - Synovial fluid aspiration for crystals , C/S,
2. **Immunology:**
   - ANF by hep. 2 cell
   - RF
   - c-and-p ANCA against PR3 and MPO
   - Anti GBM antibody
   - Anti Ro, La
   - Anti RNA Polymerase III
   - dsDNA
   - β2 glycoprotein [Anticardiolipin (IgG and IgM) antibodies]
3. **Serology:** HBsAg, Anti-HCV and HIV (IandII)
4. **Radiology:**
   - Chest X-ray
   - USG (Whole Abdomen)
   - HRCT – Thorax
   - CT – PNS and Brain
   - MRI Brain
   - Echo – 2D, M-mode with Doppler

Treatment: It is designed according to underlying disease process. Aim is to save life and prevent irreversible organ damage. Basic organ support therapy is common to all disease.

Before starting aggressive therapy with glucocorticoid infection must be ruled out in each and every case. Comorbidities should also be considered during therapy.

Individual Entities

Lupus Flare

High dose steroid therapy indicated for life-threatening SLE like – vasculitis, CNS lupus, diffuse proliferative glumerulonephritis (DPGN), Lupus pneumonia, myocarditis, hemolytic anemia.
There are three regimens as follows:

Regimen 1: Daily oral short-acting, prednisolone 1-2 mg/kg, daily in divided doses — controls disease rapidly: 5 to 10 days for hematologic or CNS diseases, serositis or vasculitis; 2 to 10 weeks for glomerulonephritis.

Regimen 2: IV methylprednisolone 500 to 1000 mg every day for 3 to 5 days then 1 to 1.5 mg/kg/day of oral glucocorticoid. Controls disease rapidly. A few non-responders to regimen 1 respond to regimen 2.

Regimen 3: Combination of regimen 1 or 2 with cyclophosphamide. (CPM) Many experts believe that it should be included in initial therapeutic regimens in most SLE patients with severe nephritis or other rapidly progressive, life threatening organ involvement. When cyclophosphamide is given IV once a month for 6 months and then discontinued, 50 to 80 percent patients can be expected to improve. That improvement is lost in more than half during subsequent 6 months. In contrast, if 6 monthly pulses are given at longer intervals for an additional 12 to 24 months, number of disease flares and preservation of renal function are better than in groups treated with glucocorticoids alone.

Catastrophic Antiphospholipid Syndrome

Diagnostic criteria

i. Clinical evidence of new thrombosis in ≥ 3 organs, systems and tissue
ii. Manifestations develop simultaneously or in less than one week
iii. Histopathological evidence of small vessel occlusion in at least one organ or tissue
iv. Laboratory confirmation of antiphospholipid antibodies (LA, ACL/β2 gp)

Definite: Presence of all 4 criteria:

Probable:

- All 4 criteria with the involvement of only 2 organs, systems and tissue
- Criteria except for the absence of laboratory confirmation 6 weeks apart due to early death of a patient never previously tested for antiphospholipid antibody
- (i), (ii) and (iv)
- (i), (iii) and (iv)and development of a third event in more than a week but less than a month despite anticoagulation.

Treatment

- **Anticoagulation** with heparin/LMWH following by oral anticoagulant warfarin to keep INR 2.5 for venous thrombosis and 3.5 for arterial thrombosis.
- **Corticosteroid:** Pulse therapy for 3 days followed by oral prednisolone as daily dose of 1 to 2 mg/kg. The postulated benefit of steroids may relate to inhibition of the systemic inflammatory response. However, steroids may simply be an ancilliary agent since, the recovery rate when used in isolation, was not significant.
- **Plasma exchange (PEX):** Theoretical benefit as it removes antibodies from circulation; however no control trials have been shown to prove

this. PEX can be done with fresh frozen plasma (FFP)/4% human albumin solutions. However, FFP can increase the level of procoagulant factors and theoretically may reduce the effectiveness of anticoagulation, as supported by Bortolati et al. who reported two patients with CAPS who worsened with FFP but improved once albumin solution was used in the replacement fluid.

- IVIg 400 mg/kg qd. for 5 days
- Rituximab 375 mg/m^2/week × 4 weeks
- Heparin / LMWH or factor Xa inhibitor
- Fondaparinux 7.5 mg S/c
- Rivaroxaban 10 mg OD per oral

Scleroderma Renal Crisis (SRC)

Occurs in 5 to 10 percent of systemic sclerosis (SSc) patients.

- **Risk factors include:**
  - Early diffuse SSc
  - Rapidly progressive skin disease
  - Anti-RNA polymerase III, Topoisomerase I and U3 RNP positivity
  - Corticosteroid use, [Steem and Medsger observed recent history of high dose, e.g. prednisolone/equivalent at >15 mg/day precede SRC diagnosis]
  - Anemia
  - Hormone replacement therpay
  - Pericardial effusion, cardiac insufficiency, new cardiac event
  - High skin score (modified Rodnan skin score)
  - Large joint contracture
- **Clinical Features:** New onset of significant systemic hypertension >150/85 mm Hg and decrease renal function [≥30% reduction in eGFR]

  Minority of the patient may be normotensive, 20 percent of the patients diagnosis of SRC may preceed diagnosis of SSc.

Treatment

- Aggressive treatment of hypertension in SRC patients is essential to prevent the occurrence of irreversible vascular injury.
- ACE inhibitors are the main stay of treatment. ACEI also helpful in normotensive SRC.
- Addition of CCB may be beneficial for patients with inadequate blood pressure control on ACE inhibitors.
- I/V Iloprost may also help to reverse microvascular changes.
- Additional oral hypotensive agents (e.g. Labetalol) together with nitrate infusion if there is pulmonary edema can be used.
- Plasma exchange is considered if there is substantial thrombotic microangiopathy.

- Renal function is supported by intermittent hemodialysis/continuous venous-venous hemofiltration.
- Renal function following SRC may become normal up to 2 years, so final decision regarding transplant should not be made until at least 2 years after SRC.
- Immunosuppressive, plasmapherosis and corticosteroids have no role in management.

Macrophage Activation Syndrome/Hemophagocytic Syndrome

MAS has been the most well studied and dreaded complication of systemic onset. Juvenile Idiopathic Arthritis (SOJIA). Other disease associated are SLE, Behcet's syndrome, Sjögren's syndrome, Kawasaki disease, MCTD, Sarcoidosis.

- **Clinical Features:** MAS should be suspected when a triad of hectic fevers; hepatosplenomegaly and cytopenias occurs.
- **Diagnostic Criteria:**
  - Molecular diagnosis of genetic defect – usually present in primary hemophagocytic syndrome.
  - Clinical and laboratory findings (5 out of 8 criteria required).
  - Fever > 7 days
  - Splenomegaly
  - Cytopenia affecting 2 out of 3 cell lines
    Hb <9, Plt. <1 lacs, nutrophil count <1 thousand
  - Hypertriglyceridemia >265 mg/dl
  - Hypofibrinogenemia < 1.5 gm/L
  - Low or absent NK cell activity
  - Ferritin level > 500 microgram/L
  - Soluble CD25 >2400 units/ml
- **Histological criteria:** Hemophagocytosis demonstrated in reticuloendothelial tissue.

Treatment

- Corticosteroid
- IVIg
- Plasmapheresis
- Anti-TNF therapy
- Stem cell transplantation.

Pulmonary Renal Syndrome

Causes

- **ANCA associated vasculitis:**
  - Granulomatosis with polyangitis (Wegener's granulomatosis)
  - Microscopic polyangiitis
  - Churg-strauss syndrome

- **ANCA negative vasculitis:**
  - HSP
  - Mixed cryoglobulinemia
  - Behcet's disease
  - SLE
  - Scleroderma (ANCA +ve)
  - RA
  - MCTD

Treatment

- Pulse methylprednisolone (1 gm) given daily for 3-5 days followed by oral corticosteroids starting at 1 to 1.5 mg/kg/day.
- Cyclophosphamide can be given either orally (1.5 – 2.5 mg/kg/day) or as monthly pulses of 0.5 to 1 gm/m2.
- Plasmapheresis in patients with very severe renal disease defined by a serum creatinine >5 mg/d or in patients with severe alveolar hemorrhage.
- Other therapies are Rituximab (Anti-CD20) and MMF.

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is a very serious condition in SLE with mortality ranging from 50 to 90 percent. It often mimic clinically and radiologically as severe pneumonia or ARDS. The characteristics presentation is abrupt onset of dyspnea, cough, fever, infiltrates and a dramatic fall in hemoglobin. Hemoptysis present in only 50 percent cases.

Treatment

- High dose steroid, with either cyclophosphamide or azathroprine
- Plasmapheresis
- Rituximals (ant CD20) shown to be effective in different trials.

Neonatal Lupus

Complete heart block (CHB) can be fatal. Those who survive develop cardiomyopathy or complete heart block.

- PRIDE study evaluate role in early diagnosis and treatment during pregnancy of Anti-Ro antibody exposed fetuses.
- Conclusion of this study was that first degree block is no more common than third degree block but unlike the latter may be reversible with dexamethasone in rare cases.
- In a study comprise of eight pregnancies in mothers with anti-SSA/Ro antibodies and previous children CHB treated with 1 gm/kg of IVIg at the 14th and 18th week of gestation prevented CHB in seven cases.

Acute Onset Digital Gangrene in the Context of CREST, Scleroderma or MCTD

Treated with intra-arterial prostacycline receptor antagonist.

Septic Arthritis

Aspiration/drainage + Antibiotics

Synovial Rupture

Aspiration + Intra-articular steroids

Atlantoaxial Dislocation

Fusion ± Decompression

Conclusion

Proper knowledge of natural history of the disease, its complications, good clinical judgement for early symptoms recognition and solving the dilemma between infection vs. inflammation and prompt institution of proper available therapy will save multiple lives. Most of the lives that are lost are due to non-recognition of exact underlying cause by the physician. Newer modalities of therapy also hold good promise in controlling these emergencies.

Suggested Reading

1. Kumar A, Marwaka V, Grover R. Emergencies in Rheumatology. J Indian Med Assoc 2003 Sept; 101(9):520-524.
2. Rao URK, Shantaram V. Rheumatological Emergencies. Supplement to JAPI, 2006. Vol. 54.
3. Rheumatological emergencies. Chapter 11. Oxford Handbook of Acute Medicine. DOI: 10.1093/med/97801992-30921.003.11

Antimicrobial Therapy Including Management of Septic Shock

chapter
25

Susanta Chakraborty, Yashesh Paliwal

The proper use of antibiotics can result in favorable therapeutic results. However, indiscriminate or inappropriate use will not only result in failure of therapy but also in the emergence of resistant organisms. In addition, antibiotics are associated with serious adverse reactions. Thus, the decision to use these drugs should be based on evidence that a treatable infection is present. Antimicrobial Stewardship program will help in streamlining the antibiotic usage in any hospital and limiting growth of multiresistant organisms.

General Principles of Antimicrobial Therapy

- ***Best guess:*** All appropriate microbiological samples should be taken before starting antibiotics. An immediate Gram stained report may provide clue to right antibiotic to be used. Alternatively, a 'best guess' choice is made depending on the clinical situation. Based on the organ system involved, the organism causing infection can usually be predicted as best guess.
  - Other factors as—site of sepsis, community versus hospital associated infections, recent antibiotic usage, local data regarding organisms and their sensitivity, etc.
- Blood cultures should be taken with adequate asepsis and from a vene-puncture site. Two separate sets (20 mL each) should be taken.
- Antibiotics should be given without any delay once the decision is made.
- ***Clinical response:*** Most serious nosocomial infections mandates initial broad spectrum antibiotics in combination, until culture—results are back, at which time de-escalation should be done if appropriate. Improper and/or delayed usage of correct antibiotic in ICU has been shown to impact morbidity and mortality. The clinical response to treatment already started should always be considered, when culture-results suggest a change in antibiotics. If the specimen was obtained from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural fluid, joint fluid), recovery of a microorganism in significant amounts is a meaningful finding even if the organism recovered is different from the clinically suspected agent and this may force a change in treatment. On the other hand, isolation of unexpected microorganisms from the respiratory tract, gastrointestinal tract, or surface lesions (sites that have a complex flora) may represent

colonization or contamination and cultures must be critically evaluated before drugs are abandoned that were judiciously selected on a "best guess" basis.

- ***Drug susceptibility tests:*** Some microorganisms are fairly uniformly susceptible to certain drugs; if such organisms are isolated, they need not be tested for drug susceptibility (e.g. most group A hemolytic streptococci and clostridia respond predictably well to penicillin). On the other hand, some organisms (e.g. enteric gram-negative rods) are variably susceptible and require drug-susceptibility testing whenever they are isolated.
- ***Promptness of response:*** Response depends on a number of factors, including the host, the site of infection, the pathogen and the duration of illness. Thus, depending on the clinical situation, persistent fever and leukocytosis several days after initiation of therapy may not indicate improper choice of antibiotics but may be due to the natural history of the disease being treated.
- ***Duration of antimicrobial therapy:*** A standard two week course of antibiotics is unnecessary and likely to be harmful. Shorter course of 7 to 10 days for pneumonia is usually adequate. However, varying periods of treatment may be required for cure, key factors include (1) The type of infecting organism (Non-fermenting Gram-negative bacterias, fungal and mycobacterial, etc.), (2) The location of the process (e.g. endocarditis and osteomyelitis require prolonged therapy) and (3) The immunocompetence of the patient. It is noteworthy that very few studies have examined appropriate length of treatment to effect a cure and duration of therapy is often arbitrary.
- ***Monotherapy vs Combination therapy:*** Monotherapy with an effective agent aims to decrease the drug antagonism, reaction or toxicity.There is no clear evidence that combination therapy prevents mortality and decreases emergence of resistance. However, combination therapy is usually suggested for endocarditis and *Pseudomonas* or *Acinetobacter* infections. When combination therapy is used, two different class of antibiotics from amongst classes that act synergistically are to be chosen.
- *Adverse reactions and toxicity:* These include—
  - Hypersensitivity reactions (e.g. fever, rashes, anaphylaxis)
  - Direct adverse effect or toxicity (e.g. diarrhea, vomiting, impairment of renal or hepatic function, neurotoxicity),
  - Superinfection by drug-resistant microorganisms or drug interactions such as the increased INR associated with trimethoprim-sulfamethoxazole added to warfarin.

If the infection is life-threatening and treatment cannot be stopped, the reactions may be managed symptomatically (especially if mild) or another drug may be chosen that does not cross react with the offending one.

If the infection is less severe, it may be possible to stop all antimicrobials and follow the patient carefully.

- ***Microbiologist consultation:*** For serious and multiresistant infections, it is vital to liaise with microbiologist regarding antibiotic minimum inhibitory concentration (MIC), antibiotic assay, serum bactericidal activity and synergy of different agents.
- ***Route of administration:*** Parenteral therapy is preferred for acute ill patients with serious infections (e.g. endocarditis, meningitis, sepsis, severe pneumonia) when high levels of antibiotics are required for successful therapy. Certain drugs (e.g. fluconazole, rifampicin, metronidazole and fluoroquinolones) are so well absorbed that they can be administered orally even in seriously ill patients. Food does not significantly influence the bioavailability of most oral antimicrobial agents. Exceptions include tetracyclines, quinolones, azithromycin.

  In the evaluation of a patient with fever who is receiving intravenous therapy, the catheter must always be considered as a potential source. Evidence suggests that there is no benefit of routinely replacing peripheral catheters at 48 to 72 hours versus removal. It should be removed if not needed or not working or if there is any redness and discharge around the catheter site. Antimicrobial-coated central venous catheters (minocycline and rifampicin, chlorhexidine and sulfadiazine) have been associated with a decreased incidence of catheter related infections. To avoid catheter related bloodstream infection it is not important that asepsis is maintained during insertion as well as during its usage. Peripherally inserted central catheters (PICC) are very good option in patients who need long-term venous access.
- **Cost of antibiotics:** Because of widespread use of antibiotics, the cost of these agents can be substantial both to institutions and to individuals. One must also consider the costs of monitoring for toxicity. Although, cost should not be the only determinant in choosing antibiotics, if several drugs with equal efficacy and toxicity are available, one should choose the least expensive.

Sepsis and Septic Shock

Sepsis is not a disease but a syndrome whose evaluation should prompt the doctor to look for a treatable cause. Causes of systemic inflammatory response syndrome (SIRS) are extensive but infection is common and generally treatable. For this reason, it should be considered first. However, other causes must be considered, e.g. tissue ischemia, injury, pancreatitis, SLE, drugs, etc.

Table 25.1 Sepsis definitions

Systemic inflammatory response syndrome (SIRS)	At least two among the following: Temperature < 36°C or > 38°C Heart rate > 90 beats/minute Respiratory rate >20 breaths/minute or $PaCO_2$ < 32 mm Hg or mechanically ventilated Leukocyte count <4000/µL or >12000/µL or > 10% immature band forms
Sepsis	SIRS + confirmed or presumed infection
Severe sepsis	Sepsis + organ hypoperfusion or dysfunction
Septic shock	Sepsis with refractory hypotension (systolic arterial blood pressure < 90 mm Hg, mean arterial pressure < 70 mm Hg) or vasopressor dependency after adequate volume resuscitation

Table 25.2 Diagnosis of sepsis associated organ dysfunction

Cardiovascular	Systolic arterial blood pressure < 90 mm Hg Decrease in systolic blood pressure >40 mm Hg Men arterial blood pressure < 70 mm Hg Decrease capillary refill or mottling
Respiratory	PaO_2/ FiO_2 <300
Renal	Creatinine increase > 60 µmol/L from baseline Creatinine increase > 60 µmol/L within last 24 hours Urine output < 0.5 mL/kg per hour for 2 hours Despite fluid resuscitation
Coagulation	Activated partial thromboplastin time > 60 seconds International normalized ratio > 1.5 Platelets < 100 000/µL
Liver	Bilirubin > 70 mmol/L
Acid-base	Lactate > 2.1 mmol/L

The early recognition of sepsis is not primarily, the diagnosis of a specific disease but the recognition that a patient is ill and in danger of acute deterioration and that immediate intervention is needed to:

- Restore hemodynamic stability and tissue perfusion.
- Determine cause (source) and source control (surgical intervention/ drainage) if appropriate.
- Institute appropriate organ support to prevent further organ damage.

Table 25.3 The predisposition, infection, response and organ failure (PIRO) sepsis staging system

Predisposition	Previous illness with reduced probability of short-term survival Age Genetic polymorphisms in components of inflammatory response
Insult/infection	Culture and sensitivity of infecting pathogens Disease amenable to source control Gene transcript profiles
Response	Systemic inflammatory response syndrome (SIRS) Sepsis Severe sepsis Septic shock Markers of activated inflammation (C-reactive protein, procalcitonin, interleukin-6) Markers of impaired host responsiveness human leukocyte antigen (HLA)- DR Detection of therapy target (protein C, tumor necrosis factor, platelet- activating factor)
Organ dysfunction	Number of failing organs Composite scores

Control of the Septic Focus

Source control is the critical, targeted intervention in the treatment of sepsis and septic shock, whereas most other therapies are purely supportive.

Identification of the Septic Focus

All patients with suspected sepsis should be evaluated for the possible focus of infection amenable to treatment by source control measures. Source of sepsis can be rapidly identified by integrating history, examination, results of focused diagnostic tests and imaging (chest X-ray, ultrasound, CT scan and MRI scan). Gram's stain of suspicious fluids may give early clues to the etiology of infection while cultures are incubating. As examples, urine should be routinely Gram's stained and cultured, sputum should be examined in a patient with a productive cough.

Blood should be taken from two distinct venipuncture sites and inoculated into standard blood culture media. Blood cultures should be incubated both aerobically and anaerobically. There is no single test that immediately confirms the diagnosis of severe sepsis or septic shock. However, several biomarkers have been studied as diagnostic markers of active bacterial infection. Commonly used clinically biomarkers are C-reactive protein (CRP), procalcitonin (PCT), presepsin (soluble CD14 subtype) and heparin binding protein (HBP).

Procalcitonin

Elevated serum procalcitonin levels are associated with bacterial infection and sepsis. Procalcitonin (PCT) levels tend to be low in viral infections. However, meta-analysis (Tang et al.) of 18 studies found that procalcitonin distinguished sepsis from nonseptic systemic inflammation poorly (sensitivity 71% and specificity 71%). Procalcitonin is useful in diagnosis, prognosis and antibiotic guidance. A decrease of 30 percent in PCT levels between day 2 and day 3 appears to be good prognostic indicator of effective antibiotic therapy and associated with better survival. As compared to CRP it allows earlier diagnosis with better diagnostic accuracy. However, raised PCT (in absence of infection) has been reported in other conditions associated with inflammatory response, e.g. trauma, major surgery, cardiac surgery, etc.

C-Reactive Protein

It is frequently used due to wider availability. Elevated concentration of serum CRP levels are correlated with an increased risk of organ failure and death. The study of CRP trends may be helpful to evaluate the response to therapy in septic patients.

Presepsin

In early studies, it was found to be better in predicting mortality as compared to acute physiology and chronic health evaluation (APACHE) 2 and PCT.

Heparin Binding Protein

It is an early marker of circulatory failure in sepsis. In one study, it was found to be more sensitive and specific in diagnosing severe sepsis when compared with PCT, CRP and others.

Combination of PCT, CRP, WCC and lactate levels may be more useful than any biomarker individually.

The plasma concentration of soluble TREM-1 (Triggering receptor expressed on myeloid cells) a member of immunoglobulin superfamily is specifically myoregulated in the presence of bacterial products is increased in patients with sepsis. A small trial by Gibot et al reported that increased TREM-1 levels were both sensitive and specific for diagnosis of bacterial sepsis (96% and 89% respectively). However, a subsequent prospective cohort study again by Gobot et al found that increased TREM-1 levels predicted sepsis with a sensitivity and specificity of only 53 and 86 percent respectively. Serial monitoring of TREM-1 may provide additional prognostic information in patients with established sepsis.

Increased expression of CD64 on polymorphonuclear leukocytes indicates cellular activation and has been shown to occur in patients with sepsis. In a prospective cohort of 300 critically ill patients by Gibot et al, increased CD64 expression predicted sepsis with a sensitivity of 84 percent and specificity of 95 percent, and these figures exceeded those of procalcitonin and TREM-1 in this study.

The combination of procalcitonin levels. TREM-1 levels and CD64 expression were superior to use of any of these markers alone. However, until additional investigational data become available, routine use of these biomarkers for identification of sepsis is not recommended at present.

Eradication of Infection

Source control includes removal of foreign bodies (vascular catheters and grafts etc.), incision and drainage of abscesses or fluid collections and debridement of infected necrotic tissues. For patients with necrotizing fascitis, outcome is directly related to the promptness of surgical intervention.

One should choose source control measure with maximum efficacy and minimum physiologic upset.

Table 25.4 Evaluation of sources of sepsis

Evaluation of common sources of sepsis		
Suspected site	*Symptoms/signs*	*Microbiological evaluation*
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Fever, urgency, dysuria, loin pain	Urine: microscopy reveals >50 WBC/hpf plus >100,000 cfu/mL; (2) Catheter urine >100,000 cfu/mL; (3) Suprapubic aspirate >1000 cfu/mL
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram's stain and culture of draining pus, wound, culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissues aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF microscopy, protein, glucose, culture, bacterial antigen test
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for *Salmonella*, *Shigella*, and *Campylobacter*
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) infections genital tract	Cloudy PD fluid, abdominal pain, fever low abdominal pain, vaginal discharge	Cell count and culture of PD fluid, endocervical and high vaginal swabs onto selective media

Resuscitation and Hemodynamic Support of the Septic Patient

The most immediate threat in septic patient is tissue hypoxia secondary to in adequate O_2 delivery (DO_2) in the development and course of septic shock, defined by sepsis with hypotension. Four key factors contributing to it are:

1. *Vasodilation:* Vasodilation results in quicker passage of blood through the capillary beds and therefore decrease in the time available for passive unloading of oxygen from oxygenated red blood cells.
2. *Loss of endothelial barrier function:* This results in loss of proteins and fluids into the interstitium. This further decreases the effective intravascular volume and increases the distance that oxygen must diffuse to reach the cell.
3. *Occlusion of capillaries:* It leads to impaired perfusion and oxygenated blood bypass these occluded capillaries (shunt). This results in increased total tissue oxygen deficit.
4. *Impaired myocardial contractility:* Cause of impaired myocardial contractility in septic patients is demonstrable but poorly understood. Its significance is uncertain, as cardiac output in sepsis is characteristically increased and clinical evidence of impaired cardiac output commonly reflects inadequate fluid resuscitation.

Net result of these changes is classical hemodynamic profile of resuscitated sepsis—tachycardia, peripheral edema, hyperdynamic circulation, warm extremities and hypoperfusion.

The main stay of cardiovascular support in septic shock is the rapid infusions of IV fluids with the goal of restoring hemodynamic stability. Adequate IV access is established and crystalloid solution is rapidly administered with the goal of giving a liter or more of fluid within first 30 minutes. Initial assessment of the response to resuscitation entails monitoring of vital signs, urine output and correction of base deficit and chance of raised lactate levels.

Restoration of blood pressure, heart rate, adequate urine output, lactate clearance, mental state/restlessness suggest that initial resuscitative measures have been successful. But if they are not stabilizing then more invasive strategy must be needed to optimize tissue perfusion. The best validated strategy is early goal directed therapy (EGDT) of River et al adopted by Surviving Sepsis Campaign (SSC) 2008.

Most patients will respond to the measures shown in EGDT; those who do not respond pose a challenge to ICU team and one for which approach must be systemically clinical and empirical. Moreover their risk of death is high. A reasoned approach is to consider any diagnostic or iatrogenic error.

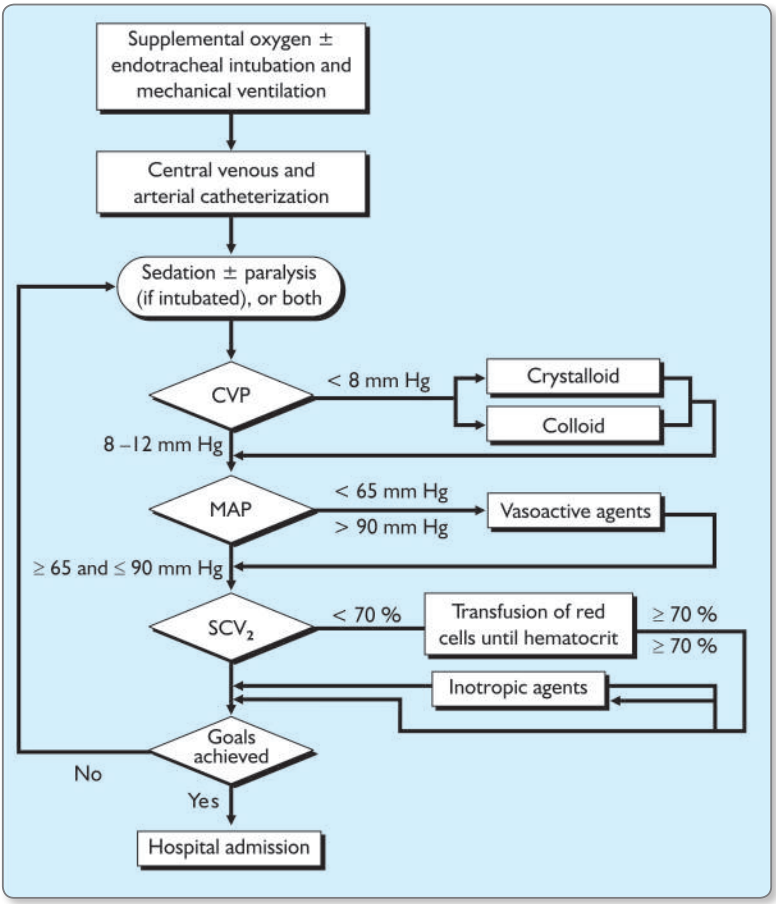
First, re-evaluate the clinical situation. If the failure to respond the function of refractory septic shock or has another unrecognized complication occurred, e.g. tension pneumothorax after central line, pulmonary edema due to aggressive fluid resuscitation, inappropriate or inadequate antimicrobial therapy or acute myocardial infarction with cardiogenic shock.

If all attempts to increase blood pressure fail, consider further fluid challenge if oxygenation is acceptable even if CVP is high. To re-evaluate the situation and consider accepting lower mean arterial pressure (MAP- 55 or 50 mm Hg). Remember, goal is to achieve adequate perfusion, not pressure.

Early hemodynamic resuscitation goals (first 6 hours) suggested by SSC includes:

- Central venous pressure 8 to 12 mmHg
- Mean arterial pressure ≥ 65 mmHg
- Urine output ≥ 0.5 mL/kg per hour
- Lactate clearance
- Central venous (superior vena cava) oxygen saturation ≥ 70 percent or mixed venous ≥ 65 percent

Flow chart 25.1 Early goal directed therapy (EGDT) (first 6 hours) in the treatment of severe sepsis and septic shock



Fluid Therapy

Choice of Fluid Crystalloid Versus Colloid

Crystalloids are certainly better than colloid as with use of crystalloids coagulopathy does not alter coagulation cascade. Starch in sepsis increase mortality by worsening acute kidney injury induced by sepsis as shown by more number of sepsis patient treated with starch needing renal replacement therapy (VISEP trial, CHEST trial, etc.). Albumin is safe in this regard but not cost effective (SAFE trial).

- There should be balance in giving crystalloid and colloid. Give crystalloids adequately first, if there is risk of fluid overload and significant positive fluid balance then, use colloid judiciously.
- Individualize the target of fluids resuscitation based on patient comorbid status, i.e. history of cardiac failure, chronic renal failure, cirrhosis, etc.

Vasopressor and Inotropes

When organ perfusion is inadequate inspite of adequate fluid resuscitation, vasoactive agents should be administered. Both noradrenaline and dopamine has been advocated as first line agents in case of sepsis. Debaker trial, recently proved that norepinephrine is preferred over dopamine. Due to less tachycardia and arrhythmogenicity, norepinephrine is likely to be better agent in patient with ischemic heart disease. The combination of noradrenaline and low dose dobutamine has been shown to prevent gastric mucosal erosin in comparision with adrenaline and dopamine.

Inotropes (dobutamine) may be helpful in sepsis induced myocardial depression. In refractory shock, exogenous vasopressin in limited dose may act synergistically with other vasopressor agents (VASST trial). Also there are few small studies which have shown that levosimendan may be useful in reversing sepsis—induced myocardial depression. But the evidence is small and early and levosimendan for this usage can not be recommended at present.

Regardless of the specific vasopressor selected, the main management principle is that excessive peripheral vasodilation in sepsis may require treatment with vasoconstrictors, and the clinician must monitor end points of therapy on a continuous basis to determine the appropriateness of the intervention chosen.

Antimicrobial Regimen

In order to maximize the efficacy of antimicrobial therapy it should be appropriate (susceptibility and timing), adequate (penetration) and optimal (pk/pd driven dosage).

Intravenous antibiotic therapy should be initiated immediately after obtaining appropriate cultures. In his landmark study, Kumar and colleagues have shown that there is progressive increase in mortality rate with increasing delay in initiation of effective antimicrobial therapy after onset of hypotension in septic patients.

He also published a study of 5717 patients in ICU with septic shock, showing that mortality rate was higher when empirical antimicrobial therapy was inappropriate (52%) than when appropriate (10.3%).

The choice of antibiotics can be complex and should consider the patient's history, comorbidities, clinical syndrome, Gram's stain data, and local resistance patterns, previous antimicrobial use, presence of invasive devices, length of hospital stay, admission category and presence of colonization by resistant pathogens, etc.

In Indian context, if a patient is presenting with severe sepsis or with septic shock and source of sepsis is not obvious immediately), one must cover Gram-negative bacteria and Gram-positive bacteria. Appropriate choices would be beta-lactam/beta-lactamase inhibitor (piperacillin/tazobactam) or cefoperazone/sulbactam or carbapenems with vancomycin/teichnoplanin/linezolid. In case of nosocomial septic shock with appropriate setting , *Candida* cover (azoles or echinocandins) should be added until microbiological data is available and patient is improving clinically.

One must also consider possibility of nonfermenters (*Pseudomonas*, acinetobacter, etc.) and methicillin resistant *Staphylococcus aureus* and antimicrobial selection should cover these organisms. Dual antipseudomonial cover (beta-lactam/beta-lactamase inhibitor, antipseudomonial carbapenems, quinolones, aminoglycosides and monobactam) may be considered until microbiological data is available. Selection of two agents from the same class should be avoided. Local susceptibility pattern is the key in choosing appropriate empirical cover.

Staphylococcus aureus is associated with significant morbidity if not treated early in the course of infection. There is growing recognition that methicillin-resistant *S. aureus* (MRSA) is a cause of sepsis not only in hospitalized patients, but also in community dwelling individuals without recent hospitalization. Severely ill patients presenting with sepsis of unclear etiology are treated with intravenous vancomycin (adjusted for renal function) until the possibility of MRSA sepsis has been excluded. Though it may be common practice in the West, incidence of MRSA is comparatively much less in this part of the globe and empiric use of anti-MRSA antibiotic may not be warranted in all patients of severe sepsis of undefined source.

After culture results and antimicrobial susceptibility data return, therapy should be pathogen-directed, even if there has been clinical improvement while on the initial antimicrobial regimen. Gram-negative pathogens have historically been covered with two agents from different antibiotic classes. However, several clinical trials and two meta-analyses have failed to demonstrate superior overall efficacy of combination therapy compared to monotherapy with a third generation cephalosporin or a carbapenem. Furthermore, one meta-analysis found double coverage was associated with an increased incidence of adverse events. For this reason, use of a single agent with proven efficacy and the least possible toxicity is recommended, except in patients with known or suspected *Pseudomonas* bacteremia or neutropenia.

Regardless of the antibiotic regimen selected, patients should be observed closely for toxicity, evidence of response, and the development of nosocomial superinfection. The duration of therapy should be determined by the clinical response of the patient, the identity of the pathogen, and the source and extent of infection. In patients who are neutropenic, antibiotic treatment should continue until the neutropenia has resolved. If infection is thoroughly excluded, antibiotics should be discontinued to minimize colonization or infection with drug-resistant microorganisms and superinfection with other pathogens.

Recombinant Activated Protein C [Drotrecogin Alfa Activated (DrotAA)]

It is no longer recommended in severe sepsis based on the findings of recent PROWESS SHOCK trial. It showed no difference in primary end-point of 28 days all cause mortality in 223 (26.4%) of 846 patients treated with drotrecogin alfa versus 202 (24.2%) of 834 in those given placebo for a relative risk of 1.09. The absolute difference between two groups in all-cause mortality at 28 days and 90 days were 2.2 and 1.4 percentage points, respectively with both trends slightly favoring placebo over DrotAA. Eli Lilly on October 25, 2011 announced the voluntarily withdrawal from market of drotrecogin alfa (activated) known as Xigris, a drug licenced for treatment of severe sepsis.

Corticosteroids

Surviving sepsis guidelines 2008 recommends to consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors. ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (CORTICUS trial). Hydrocortisone is preferred over dexamethasone. Steroid therapy may be weaned off once vasopressors are no longer required. Hydrocortisone dose should be less than 300 mg/day. Corticosteroid should not be used to treat sepsis in the absence of shock unless the patient's endocrine status or previous corticosteroid history warrants it.

Nutrition

Adequate nutritional support is essential for optimal immune function, and appears beneficial in both the prevention and the treatment of sepsis. The ideal composition and route of nutritional support remain to be defined, but several observations have been made:

- Early nutritional support improves wound healing and decreases the susceptibility of critically ill patients to infection.

- Early enteral nutrition may offer more benefit in preventing sepsis than parenteral nutrition, particularly when formulas which are fortified with immune-enhancing nutrients and antioxidants, including arginine and glutamine, are used. Such enteral formulas may favorably affect the resistance of the gut to bacterial translocation or exert direct effects on the behavior of intraluminal bacteria.
- Once sepsis is established, nutritional support results in higher lymphocyte counts and higher serum albumin levels, which have been used as surrogate markers of immune competence. Nutritional supplements rich in branched-chain amino acids may confer additional benefit and have been associated with improved survival in small randomized trials.

Glucose Control

Hyperglycemia and insulin resistance are common in critically ill patients, independent of a history of diabetes mellitus. Following initial stabilization of patients with sepsis, blood sugar should be maintained between 6 to 10 mmol/L preferably by insulin infusion. NICE study has revealed that tighter control of blood sugar level increases the risk of hypoglycemia and mortality.

Deep vein thrombosis prevention: Unfractionated heparin or low molecular weight heparin subcutaneously can be used to achieve this. Continuous use of pneumatic compression stockings can be used in cases of coagulopathy.

Gastric ulcer prophylaxis: This may be accomplished with sucralfate, an H_2 receptor blocker or a proton pump inhibitor.

Blood transfusion: Though EGDT recommends to transfuse packed red blood cell up to hematocrit (Hct) of 30 percent to achieve the target BP, CVP and $ScvO_2$. Hematocrit should be kept between 27 to 30 percent in patients with decreased cardiorespiratory reserve while more restrictive strategy should be adopted in other patients.

Ventilation strategy: The landmark ARDS network study has shown the benefits of ventilation with low tidal volumes with plateau pressure maintained at <30 cm H_2O. One of the recent trial demonstrated this lung protective ventilation strategy to be beneficial in patients who do not have acute lung injury or acute respiratory distress syndrome.

Mimics of Sepsis

Non-infective causes of SIRS

Cause	**Example**
Injury	Multi-trauma, hemorrhage, burns, ventilator induced lung injury
Ischemia/reperfusion	Limbs ischemia, opening the abdomen as therapy for abdomen compartment syndrome
Sterile inflammation	Acute pancreatitis

Immune mediated disease	Collagen vascular disease
	Systemic lupus erythematosus
	Transplant rejection
	Graft vs host disease
Idiopathic illness	Wegner's granulomatosis
	Thrombotic thrombocytopenic purpura
	Toxic epidermal necrolysis
Endocrinopathy	DKA, hypothyroidism, Addison's disease
Intoxication	Acetylsalicylic acid overdose
Iatrogenic	Drug reaction
	Transfusion reaction

Evaluation of Sources of Sepsis

Tips for blood culture:

- Two sets of 20 mL each should be drawn 1 hour apart, preferably from a peripheral site rather than through a central vascular catheter.
- Ten milliliter from each blood sample drawn is inoculated into an aerobic bottle and 10 mL into an anaerobic bottle. Cultures are held 4 days before being reported as negative.
- A single positive culture of these organisms suggests contamination especially with. *Bacillus* sp., coagulase negative staphylococci, diphtheroids, Propionibacterium acnes, viridans streptococci.
- An isolator tube of 10 mL of blood should be drawn if any of the following are suspected. *Bartonella*, *Bordetella*, *Francisella*, *Histoplasma capsulatam*, *Legionella*, *Mycobacterium* sp. These will be incubated for longer than 4 days before being considered negative.

Source Control in Sepsis

Source control methods for common ICU infections:

Site	Interventions
Sinusitis	Surgical decompression of the sinuses
Pneumonia	Chest physiotherapy, suctioning
Empyema thoracis	Drainage, decortication
Mediastinitis	Drainage, debridement, diversion
Peritonitis	Resection, repair, or diversion of ongoing sources of contamination, drainage of abscesses, debridement of necrotic tissue
Cholangitis	Bile duct decompression
Pancreatic infection	Drainage or debridement
Urinary tract	Drainage of abscesses, relief of obstruction, removal or changing of infected catheters

Catheter-related bacteremia	Removal of catheter
Endocarditis	Valve replacement
Septic arthritis	Joint drainage and debridement
Soft tissue infection	Debridement of necrotic tissue and drainage of discrete abscesses
Prosthetic device infection	Device removal

Special Infective Diseases in the ICU

Antibiotic Resistance in the ICU

Penicillin and steptomycin were introduced about 65 years ago as the first antibiotics available to treat bacterial infections. The phenomenon of antibiotic resistance emerged at the same time. There are at least six basic mechanisms by which bacteria can develop resistance to antimicrobial agents:

1. Enzymatic inactivation
2. Alteration of the antimicrobial binding site
3. Active efflux
4. Alterations in membrane permeability to prevent antimicrobial entry
5. Alterations in enzymatic pathways so that the targeted enzyme is no longer essential for organism survival
6. Overproduction of antimicrobial targets.

In addition, slow rates of growth as seen in small colony variants or in organisms growing in biofilms may also contribute to resistance *in vivo* that is not detected readily *in vitro* using standard susceptibility test methods.

Another important factor in understanding bacterial resistance is to appreciate that multiple mechanisms may act in concert, resulting in drug resistance. Extended spectrum beta-lactamase (ESBL) inhibitors are common in not only nosocomial infections but also in community making the empiric antibiotic choice difficult.

The most common type A *beta-lactamases* are TEM and SHV. These *beta-lactamases* degrade penicillin G, ampicillin, antipseudomonal penicillins, and narrow-spectrum cephalosporins such as cefazolin and cephalothin. Mutations can expand their spectra (ESBLs) so that they can hydrolyze aztreonam and third-generation cephalosporins such as cefotaxime and ceftazidime. Clavulanic acid continues to inhibit these enzymes and these organisms are still susceptible to cephamycins (cefoxitin) and carbapenems (imipenem). Genes encoding ESBLs are frequently found on large plasmids, which can also encode resistance to other antimicrobial agents such as aminoglycosides and fluoroquinolones. SHV and TEM-type extended-spectrum β-lactamases (ESBLs) are most frequently observed in *E. coli, Proteus mirabilis*, *K. pneumoniae and Pseudomonas aeruginosa*. Patients with bloodstream infection due to ESBL-producing Enterobacteriaceae have significantly increased morbidity and mortality. Various types of ESBLs inhibitors exist and key points about them are as follows:

- Another important class A ESBL is CTX-M. As with the TEM and SHV enzymes, organisms expressing this enzyme are resistant to all classes of penicillin, aztreonam, and first-, second-, and third-generation cephalosporins. Isolates expressing this enzyme remain susceptible to cephamycins and carbapenems, and like other type A ESBLs, this enzyme is inhibited by clavulanic acid and tazobactam.
- The KPC enzymes are ESBLs associated most closely with *Klebsiella pneumoniae* and also found in other Enterobacteriaceae. They are an unusual class A ESBL because they can degrade carbapenems such as imipenem in addition to penicillins, aztreonam, cephalosporins and aminoglycosides, fluoroquinolones, leaving few therapeutic options. KPC-type *beta-lactamases* are inhibited by clavulanic acid and tazobactam, but can be resistant to *them* due to other resistance mechanisms encoded by the KPC-containing plasmid.
- All class B *beta-lactamases* degrade imipenem and are inhibited by chelating agents such as ethylenediaminetetraacetic acid but not by clavulanic acid. They are seen with *Stenotrophomonas maltophilia,* or can be transferred by plasmids or transposons. The most commonly encountered transferable metallo-*beta-lactamases* are IMP and VIM. Metallo-*beta*-lactamase positive isolates are frequently also resistant to fluoroquinolones and aminoglycosides. IMP is most commonly found in *P. aeruginosa* and *Acinetobacter baumanii* and also in few Enterobacteriaceae. Only aztreonam among the *beta*-lactams may demonstrate activity against isolates expressing VIM or IMP.
- The Ambler class C *beta*-lactamase (Bush-Jacoby-Medeiros group 1) is referred to as AmpC. AmpC is chromosomally mediated in *Enterobacter* spp., making this genus intrinsically resistant to ampicillin, cefazolin, and cefoxitin. AmpC plasmid-encoded *beta-lactamases* have been found in a number of Enterobacteriaceae, most frequently in *K. pneumoniae.*
- Ambler type D OXA enzymes are resistant to *beta*-lactamase inhibitors. Plasmid-encoded ESBL OXA enzymes have been found in *P. aeruginosa.* These organisms are resistant to penicillins, first-, second-, and third-generation cephalosporins, and cefepime. Like other organisms with plasmid-mediated ESBLs, these isolates are resistant to aminoglycosides and fluoroquinolones.

Staphylococcal resistance to methicillin occurs due to an altered penicillin binding protein, which has low affinity for all β lactam agents. It is linked to a mecA gene. This gene does not develop readily and spread of methicillin resistance is by vector transmission, not by de novo production of resistance.

Commonly Prevalent Resistant Bacteria in the ICU

- ***Staphylococcus aureus:*** It is frequently isolated pathogen in the ICU; the incidence of infections caused by methicillin-resistant *Staphylococ-*

cus aureus (MRSA) is increasing. Prevalence of MRSA amongst strains of *S. aureus* in North American and European ICUs ranges from 20 to 55 percent.

The standard treatment for MRSA is vancomycin. However, resistance to vancomycin (intermediate/full) is being reported. Linezolid, teicoplanin and quinupristin/dalfopristin are currently the treatments of choice for patients infected with vancomycin resistant *Staph aureus* (VRSA).

- *Coagulase negative staphylococci (CoNS): CoNS* are the cause of 15 to 20 percent of ICU-acquired infections and the most frequent isolates in intravenous catheter related bacteremias. *S. epidermidis* is the species most commonly isolated in humans. Vancomycin is the drug of choice for this organism; however, although uncommon, resistance to vancomycin is being reported.
- *Enterococcus faecalis and Enterococcus faecium: Enterococcus faecalis* and *Enterococcus faecium* are also common isolates in ICU patients. Enterococci are intrinsically resistant to a number of antibiotics, including cephalosporins and fluoroquinolones and can develop acquired resistance to other antibiotics like vancomycin, aminoglycosides and beta-lactam antibiotics. Incidence of vancomycin resistant Enterococci (VRE) has risen from 0.4 to 37.5 percent among enterococci isolated in USA ICUs from 1990 through 2002. The antibiotics of choice for VRE are linezolid and quinupristin/dalfopristin; the latter is active only against *E. faecium* whereas linezolid is active against both species. Linezolid resistance in VRE has been reported.
- **Pseudomonas aeruginosa:** It is a common pathogen in hospital and ICU-acquired infections but rarely cause disease in healthy people. Rates of colonization increase following hospital admission; within 7 days of admission, 23 percent of patients are colonized and within 14 days, about 60 percent are colonized. *P. aeruginosa* is the most common cause of ventilator associated pneumonia. ARDS, antibiotic exposure and prolonged mechanical ventilation are the major risk factors for *P. aeruginosa* pneumonia. Combination therapy with two of the most active agents against *P. aeruginosa* (carbapenems, piperacillin, cefepime, ceftazidime, ciprofloxacin, amikacin and tobramycin) is commonly used for infections caused by these highly-resistant organisms. However, efficacy of such an approach is unknown.
- **Acinetobacter baumannii:** It is a gram-negative coccobacillus or rod common in environment (water, soil) and hospital (catheter, lotions, ventilation equipment). It is an increasingly important and very common global pan-resistant nosocomial pathogen. Isolation is often meaningless (representing colonization) unless from normally sterile sites, found as dominant pathogen in moderate or heavy growth from potentially contaminated sites or part of an outbreak. Usual sites of infection are

ventilator associated pneumonia, wounds, burns or as nosocomial infection. Also, it can rarely present as meningitis, brain abscess, liver abscess, endocarditis and urinary tract infections.

Antibiotic selection is guided by *in vitro* sensitivity report. No RCT data are available as guide. Treatment options are carbapenems, aminoglycosides, sulbactum, polymyxins, and tigecyclin. As a last resort, high dose sulbactam may also be used even in cases resistant to sulbactam. Due to high prevalence of resistance, combination therapy (imipenem/meropenem + colistin, sulbacatam + colistin, etc.) is being used commonly.

Polymyxins (Colistin and Polymyxin B)

Polymyxins are increasingly being used either as a single agent or as a part of combination therapy to treat multiresistant organisms. It can be given intrathecally and via inhalation (use immediately after reconstitution to avoid drug breakdown products precipitating ARDS like reaction). Polymyxins have serious renal and neurological side effects therefore one needs to monitor the same. A number of bacteria are intrinsically resistant to colistin (polymyxin E), including all gram-positive organisms, all anaerobic bacteria, and selected gram-negative bacilli, including *Burkholderia cepacia, Proteus, Providencia,* and *Serratia* spp.

Fungal Infections in the ICU

The incidence of fungal infections has increased dramatically over a 20 years period by 207 percent. Five percent of all cases of sepsis are caused by fungal infections. The mortality associated with systemic fungal infections remain very high (40-60%).

The diagnosis of a systemic fungal infection is very difficult, particularly in nonneutropenic surgical patients. In case of a septic syndrome which shows no response to a broad spectrum antibiotic therapy, a disseminated fungal infection must be taken into consideration. In these cases, normal colonization serves as an endogenous source for infection, e.g. *Candida esophagitis*, pneumonia (very rare in non-neutropenic patients), peritonitis. Many ICU patients have multiple risk factors (prolonged ICU stay, broad spectrum antibiotic use, invasive lines and catheters, TPN, abdominal surgery, diabetes etc) and therefore at risk of developing fungal infections. Infact, Candidemia is the most common fungal infection in ICU and it is the fourth most common cause of bloodstream infection. *Candida albicans* is most common species but there is increasing shift to nonalbicans *Candida*. This differentiation (albicans versus nonalbicans) is important from treatment point of view as most albicans are azole sensitive. Most common nonalbicans species isolated is *Candida tropicalis* which is usually fluconazole sensitive. With increasing resistance, this boundary between albicans and nonalbicans is blurring. Echinocandins should be used if patient is in shock and have been on azoles in the past and de-escalate after culture reports. In less sick patients fluconazole may be used. Candiduria should only be treated in symptomatic patient with high risk factors such as neutropenia, urological surgery, etc. For candiduria, fluconazole should be considered if species is susceptible. Echinocandins should not be used for candiduria. *Candida* in respiratory tract should not be treated in immunocompetent patient.

Molds, like *Aspergillus* species are ubiquitous in the surroundings, especially in soil and water. They are acquired exogenously, most by inhalation and less frequently, through damaged mucocutaneous surfaces (e.g. following surgery, contaminated equipment). Risk factors are immunocompromised state, homologous stem cell transplant and structural lung diseases. Apart from clinical and radiological findings, galactomannan assay may help in early diagnosis of invasive pulmonary aspergillosis. Voriconazole is drug of choice for invasive aspergillosis and caspofungin or amphotericin B can be added in refractory cases.

Antifungal Agents

1.a. Amphotericin B deoxycholate	Parenteral dose: 0.5-1.5 mg/h in 1 to 6 hours Elimination route: Renal
b. Liposomal Amphotericin B	Parenteral dose: 3 to 6 mg/kg in 0.5 to 1 hour Elimination route: ?
2. Flucytosine	Parenteral dose: 100 mg/kg every 6 hours Elimination route: Renal
3. Fluconazole	Loading dose: 10 to 12 mg/kg day 1 Parenteral dose: 400 to 800 mg per day or 5 to 6 mg/kg Enteral dose: 100 to 400 mg/day
4. Itraconazole	Loading dose: 200 mg twice a day for 2 days Parenteral dose: 200 to 400 mg per day Enteral dose: 200 mg per day
5. Voriconazole	Loading dose: a. Parenteral: 6 mg/kg twice a day b. Oral: $\geq$ 40 kg: 2 $\times$ 400 mg < 40 kg: 2 $\times$ 200 mg Maintenance dose: a. *Parenteral:* 4 mg/kg twice a day b. *Oral:* $\geq$ 40 kg: 2 $\times$ 200 mg < 40 kg: 2 $\times$ 100 mg

Table 25.5 Sensitivity of various fungi drugs

	Flucona-zole	Itracona-zole	Voricona-zole	Posacona-zole	Flucyto-sine	Amphote-ricin B
Yeasts						
Candida species						
C. albicans	S	S	S	S	S	S
C. glabrata	SDD-R	SDD-R	S-1	S-1	S	S-1
C. parapsilosis	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. krusei	R	SDD-R	S-1	S-1	1-R	S-1
C. lusitaniae	S	S	S	S	S	S-R
Cryptococcus neoformans	S	S	S	S	S	S
Molds						
Aspergillus species						
A. flavus	R	S	S	S	1-R	SDD-R
A. fumigatus	R	S	S	S	1-R	S
A. terreus	R	S	S	S	1-R	SDD-R
Zygomycetes						
Mucor spp.	R	R	R	S	R	S
Rhizopus spp.	R	R	R	S	R	S
Fusarium spp.	R	R	S	S	R	SDD-R
Scedosporium	R	R	S	S	R	SDD-R
Pneumocystis jiroveci	R	R	R	R	R	R

I: Intermediately resistant, R: Resistant, S: Susceptible, SDD: Susceptible dose/delivery dependent

Tropical Infections in the ICU

Some infections are more common in the tropics due to climatic conditions which favor arthropod vectors like mosquitoes or to expoure to contaminated water. Certain well defined syndromes should point towards presence of these tropical infections. These are:

- Fever and thrombocytopenia:
  - Dengue fever
  - Malaria (usually falciparum but also vivax)
  - Leptospirosis
  - Rickettsial infections
  - Viral infections

- Fever with hepatorenal dysfunction:
  - Falciparum malaria (oliguric renal failure)
  - Leptospirosis (non-oliguric renal failure)
  - Scrub typhus
  - Hepatitis E or A (with fulminant hepatic failure)
- Fever with pulmonary-renal syndrome:
  - Falciparum malaria acute respiratory distress syndrome (ARDS)
  - Leptospirosis (ARDS or alveolar hemorrhage)
  - Hantavirus infection
  - Scrub typhus
  - Severe pneumonias (due to *Legionella*/*Pneumococcus*)
- Fever with altered sensorium:
  - Cerebral malaria
  - Encephalitis
  - Meningitis
  - Typhoid fever
  - Septic encephalopathy

Table 25.6 Tropical infections in the ICU

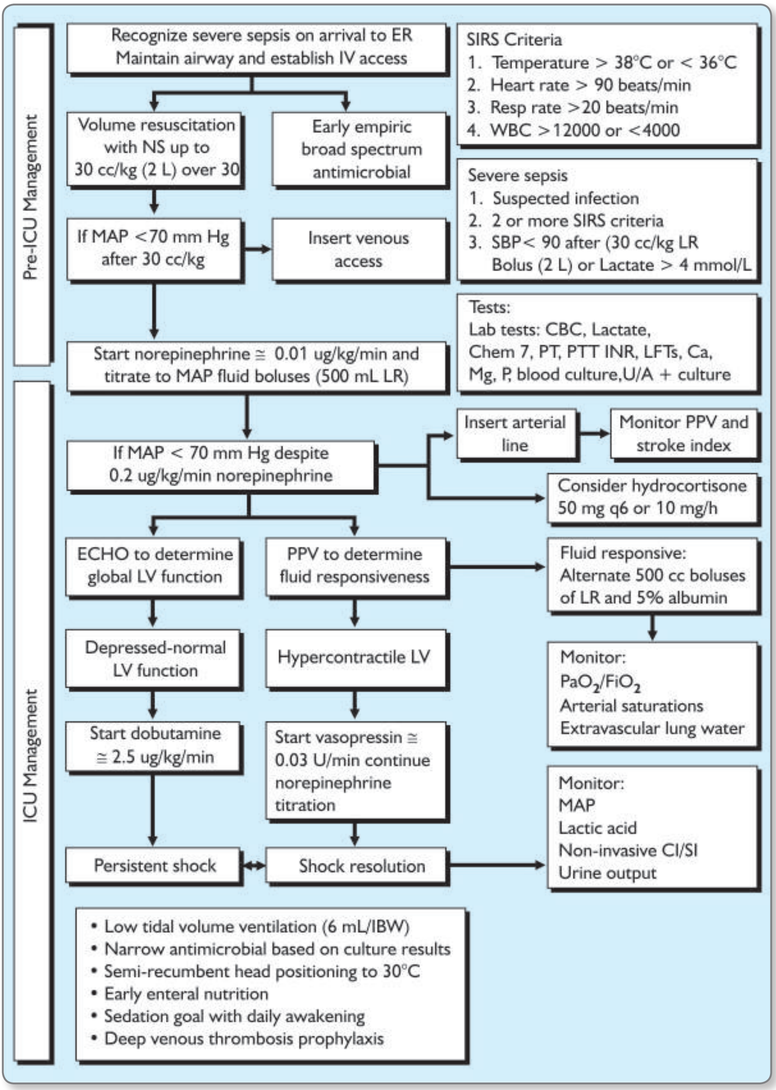
Disease	Clinical features	Commonly used diagnostic tests	Treatment
Malaria	Incubation: 10-14 days Regular fever spikes Splenomegaly Hepatorenal dysfunction ARDS Thrombocytopenia	Thick and thin smears Monocolonal antibody Dipstick tests for antigens	• IV quinine 10 mg/kg q 8 hourly • IV artesunate 2.4 mg/kg IV stat then 1.2 mg/kg at 12 and 24 hours. Then 1.2 mg/kg daily × 7 days • Doxycyline may be added as an adjunct if resistance to quinine or artemether is suspected • CRRT (continuous renal replacement therapy) in case of oliguric renal failure
Leptospirosis	Incubation: 8-14 days Fever, mylagias Conjunctival hemorrhages, Hepatorenal dysfunction, Pulmonary hemorrhages, Thrombocytopenia	Dridot test for IgM antibody Serum IgM and IgG antibodies Proteinuria, Hematuria pyuria	Crystalline penicillin 1.5 mu q 6-hour ceftriaxone 1g IVq 12 h doxycycline 100 mg/ PO or IV q 12-hour

Contd…

Contd...

Disease	**Clinical features**	**Commonly used diagnostic tests**	**Treatment**
Dengue	Incubation: 4-7 days Fever, severe myalgias headache, rash, periorbital edema, pleural and peritoneal effusions, shock, hemoconcentration, thrombocytopenia, leukopenia	ELISA for IgM and IgG antibodies	• No specific therapy • Crystalloids for shock; colloids if shock is severe • Platelet transfusion for symptomatic thrombocytopenia
Scrub typhus	Incubation: 7-10 days Fever with myalgias, rash, eschar, lymphadenopathy, thrombocytopenia, hepatorenal dysfunction, vasculitic manifestations	ELISA for IgM and IgG antibodies	• Doxycyline • Azithromycin • Chloramphenicol
Hantavirus infection	Incubation: 3 weeks Fever with pulmonary edema, hemorrhagic manifestations, acute thrombocytopenia, renal failure, shock, thrombocytopenia, leukocytosis (up to 90,000/mm^3)	ELISA for IgM and IgG antibodies	• No specific therapy • Possibly ribavirin in hemorrhagic fever with renal syndrome
Japanese B encephalitis	Altered sensorium, seizures, abnormal posturing (i.e. opisthotonus, choreoathetosis myoclonic jerks, opsoclonus) 'Locked-in' state in case of severe brainstem injury. Initial leukocytosis followed by leukopenia	• IgM capture ELISA • Reverse transcriptase PCR of blood or CSF • CSF may show a pleocytosis • Characteristic lesions in thalamus and basal ganglia on MRI	• No specific treatment is available

Flow chart 25.2 Management of sepsis in ICU



Suggested Reading

1. Adam Lindler, et al. Heparin binding protein- an early marker of circulatory failure in sepsis. Clinical Infectious Disease 2009;49:1044-50.
2. ARDS Network. Ventilation withlower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory syndrome. NEJM 2000;342:1301-8.
3. Charles L Sprung and CORTICUS group. Hydrocortisone therapy for patients with septic shock. NEJM 2008;358:111-24.
4. Charles PE, et al. Kinetics within the first days of sepsis: relatoionships with the appropriateness of antibiotic therapy and the outcome. Critical Care 2009:13;16-20.
5. Daniel De Baker, et al. Comparison of dopamine and norepinephrine in the treatment of shock. SOAP2 NEJM 2010.
6. Frank M Bounkhorst VISEP study. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. NEJM 2008;358:125-39.
7. Henry Paw, Rob Shulman Handbook of drugs in Intensive Care. An A – Z Guide, 4th edition, Reprin 2012, page 216.
8. Hotchkigs RS. The pathophysiology and treatment of sepsis. N Engl J Med 2003; 348:138.
9. JAMA patient page. Antibiotic resistance. JAMA 1998;280:1288.
10. James A Russell and VASST investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. NEJM 2008;358:877-87.
11. John G, Bartiett MD, Johns Hopkins Antibiotic Guide: Acinetobacter baumannii.
12. Jorgensen JH. Antimicrobial susceptibility testing: general principles and contemporary practices. Clin Infect Dis 1998;26:973.
13. Kothari VM, Karnad DR, Bichile LS. Tropical Infections in the ICU. JAPI 2006;54:291-8.
14. Kumar A, et al. Initiation of inappropriate antimicrobial therapy results in a five fold reduction of survival in human septic shock. Chest 2009;136(5):1237-48.
15. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589.
16. Lampiris HW, Maddix DS. Clinical use of antimicrobial agents. In: Katzung BG (Ed). Basis and Clinical Pharmacology (8th edn). Lange Medical Books/McGraw Hill, 2000.
17. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta lactam aminoglycoside antibiotic treatment for gram negative bacteraemia, A prospective, observational study; Antimicrob Agents Chemother 1997;41:1127
18. Lila Bouadma, et al. Use of procalcitonin to reduce patients exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. Lancet 2010;375:463-74.

19. Lim SM, Webb SA. Nosocomial bacterial infections in the Intensive Care Units I: Organisms and mechanisms of antibiotic resistance. Anaesthesia 2005;60:887-902.
20. Management of severe sepsis and septic shock in adults. Wolters Klwer Health Official reprint up to date © 2012 upto date.
21. Mermel LA. Prevention of catheter-associated infection. Ann Intern Med 2000; 132:391.
22. Michalopoulos and Falagas. Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Annals of Intensive Care 2011, 1:30.
23. NICE Sugar study investigators. Intensive versus conventional glucose control in critically ill patients. NEJM 2009;360:1283-97.
24. Phillip Dellinger R, et al. Surviving sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 Critical Care Medicine 2008;vol 36:No.1.
25. Ranieri VM, Thompson BT, Barie PS, et al (for the PROWESS-SHOCK group). Drotrecogin Alga (Activated) in adults with Septic Shock. N Engl J Med. 2012;366:2055-64.
26. Rivers E, Nguyen B, Havstad S, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. NEJM 2001;345:1368.
27. SAFEstudy-A comparison of albumin and saline for fluid resuscitation in ICU. NEJM 2004;350:2247-56.
28. Shozushima T, et al. Presepsin(sCD14-st) as new diagnostic biomarker of sepsis: development of diagnostic tools using whole blood. Critical Care 2011;15(suppl 3): P3.
29. Tang BMP et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: A systematic review and meta-analysis. Lancet Infectious disease 2007;7:210-7.
30. The Lancet Infectious Diseases No.12, issue 2, page 89, February 2012. For sepsis the drugs don't work.
31. Zones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs. central oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 2010; 203:739.

Cardiac Surgery: Postoperative Care

chapter
26

Kayapanda M Mandana

The chapter is intended to provide the basis for patient care postoperatively in the cardiac surgical unit.

The guidelines contained within are appropriate to this situation though they should not be regarded as fixed dogma. As far as possible specific differences in the regimens expected by different surgical consultants have been minimised; however where these exist they have been outlined and should be adhered to. Departures from the guidelines contained within are always best discussed with a more senior member of the surgical team rather than being implemented unilaterally.

Cardiac surgery involves the active participation of a large number of different specialists, including anesthesiolgists, cardiologists and the surgical team. It is the primary role of the surgical team to integrate and coordinate the various contributions allowing decisions regarding patient management to be taken together rather than in isolation.

The junior staff are immediately responsible for the care of the patients under the direction and the supervision of the Consultants.

It is also the responsibility of the junior staff to maintain accurate and regular clinical notes detailing any changes in the overall condition or treatment of postoperative patients.

Postoperative Care

1. General principles
2. Reception from operating theater
3. Routine care during early postoperative period
   a. Fluid replacement
   b. Potassium
   c. Ventilation
   d. Sedation and analgesia
   e. Antibiotics
   f. Urine output
   g. Chest radiography
4. Special problems in the early postoperative period
   a. Excessive blood loss
   b. Tamponade

   c. Low output states: Inotropes/IABP
   d. Hypertension
   e. Cardiac arrest
   f. Postoperative arrhythmias
   g. Neurological complications
   h. Renal failure
   i. Nutrition
   j. Acid base balance
5. Routine care in the postoperative ward
   a. Removal of IV lines/drains
   b. Anticoagulants/diuretics/digoxin/antiplatelets/beta blockers
   c. Physiotherapy/Chest radiographs/Routine blood tests.

Department of Cardiac Surgery

Postoperative Care

General Principles

The primary object of our postoperative care is to maintain an adequate cardiac output. The satisfactory performance of other sub-systems, e.g. renal function, normal consciousness, etc. is dependent on this. Though, the primary role of the open heart surgery is to improve the function of the heart and the hemodynamic situation, this may not be so in the early postoperative period for two reasons:

i. Transient but appreciable damage is done to the heart during any operation by ischemia, cardiotomy, cooling, etc.
ii. The period of perfusion imposes an insult to the entire organism. Documented physiological changes after bypass include:
   a. High extracellular (extravascular) water
   b. High extravascular total lung water
   c. Low circulating red cell mass
   d. Low total body potassium
   e. Increased endogenous catecholamines.

To be able to maintain an adequate cardiac output there are four basic mechanisms which can be adjusted:

i. Heart rate
ii. Filling pressure (Preload)
iii. Peripheral resistance (After load)
iv. Ventricular contractility

Cardiac output is determined by the product of heart rate and stroke volume ($CO = HR \times SV$).

The maintenance of stroke volume is central to the maintenance of cardiac output and is determined by Starling's Law (Force of contraction is proportional to initial fiber length). In other works, the fuller the ventricle at the end of diastole (within limits) the more forcefully it will eject its contents in systole.

i. **Heart Rate:** A heart rate of 60 to 100 beats per minute usually optimizes cardiac output. If lower than this, despite an adequate stroke volume cardiac output will be suboptimal. Above this, the ventricular filling time is reduced such that stroke volume and hence cardiac output is reduced.
ii. **Filling Pressure:** The left atrial pressure is the best measure of left ventricular filling pressure and either direct left atrial pressure measurements or *Mean* Pulmonary Capillary Wedge pressure (which approximate the LAP) are used as a guide to transfusion requirements. CVP (right atrial pressure) is only a very crude guide to transfusion requirements. The normal left atrial pressure is 1 to 4 mm Hg in healthy individuals. There is seldom any advantage in increasing the mean LAP to greater than 20 mm Hg in postoperative surgical patients.
iii. **Ventricular Contractility:** Ventricular contractility can be improved by a variety of inotropic agents if cardiac output is inadequate. (See Inotropes).
iv. **Peripheral Resistance (Afterload):** Under certain circumstances cardiac output may be increased by a reduction in afterload (peripheral resistance) by the use of vasodilator drugs. Mechanical devices such as IABP may also reduce afterload and increase cardiac output.

In our Intensive Care Unit, cardiac output was monitored in certain patients by thermodilution techniques using Swan Ganz Catheter and a computer. Cardiac output, cardiac index and pulmonary and systemic vascular resistances may be calculated by this method. The normal cardiac output for a healthy adult male is 5 to 6 liters per minute. The normal cardiac index (CI = CO/sqm of body surface area) is about 3 liters/min/m^2 but in the early postoperative period a figure of 2 liters\min\m^2 would be regarded as acceptable. Nowadays in our unit Swan Ganz is rarely used but TEE (Trans esophageal echo)is extensively used in assessing the heart and its output in cardiac ITU settings.

Reception from the Operating Theater

i. Inform the duty house-officer and nurses of the operation, any problems, monitoring lines, inotropic support, pacing etc.
ii. The anesthetist will attach the patient to the ventilator.
iii. Make base-line observations of heart rate, rhythm, arterial pressure, etc.
iv. The labeled chest drains are secured , made sure they are functioning and initial drainage is strictly measured for the first few hours to look for surgical bleedings.
v. Attach monitors and check zero and calibration. Zero is at the junction of the mid axillary line and the fourth intercostal space. (Remember

– maladjustment of the monitoring equipment is often the cause of an apparent change in the condition of the patient, e.g. deteriorating arterial pressure and should always be double checked).

vi. Order drugs and fluids on the ITU drug charts and specify guidelines for colloid and crystalloid transfusion.

vii. Order initial tests: Complete blood count
Urea and electrolytes
Blood gases
Blood sugar/calcium/albumin
Urinary electrolytes
Coagulation screen (only if necessary)
Chest X-ray

viii. Connect pacemaker wires.

ix. Position the patient with 15° of head up – unless bp is low.

x. Ensure a brief operation note is recorded in the notes detailing any specific problems encountered in the operation or immediate post bypass period. RA and LA pressures to act as a guide to the early intensive care management.

Routine Care during the Early Postoperative Period

Fluid Replacement: Blood or colloid transfusion is required after cardiopulmonary bypass because:

i. There is bleeding via the chest drains.
ii. Following operation the circulating volume is low.

The object of colloid replacement is to prevent depletion of intravascular volume and to provide an LVEDP (measured as LA) sufficient to maintain an adequate stroke volume (rarely > 17-20 mm Hg).

The colloids available for transfusion may be:

1. Blood
2. Single donor plasma (SDP) or FFP if there is a clotting problem
3. Human albumin solution (HPPF) – limited availability
4. Hespan (Heta-Starch) – synthetic starch solution with 24 hour half life. (Avoid in large volumes).

Our present policy is to transfuse blood only if the hemoglobin is 9.5 g/dl or less in the early postoperative period, otherwise colloids are given.

A relatively low hemoglobin in the postbypass period has the theoretical advantage of reducing plasma viscosity and is particularly relevant since a low viscosity favors high graft flow after coronary artery bypass surgery. Hemoglobin rises anyway in the day following surgery as the relative hemodilution following bypass corrects itself. Unless blood loss via chest drain continues, colloid transfusion is continued until the morning following surgery.

Cardiac Output and its Determinants

The cardiac index in normally recovering adults in the intensive care is often 2.5 to 3.5L/min/m^2 after cardiac surgery performed with modern methods of myocardial management. It is generally higher 4 to 6 hours after operation than it is in the operating room and still higher the next day, although exceptions occur.

Risk factors for low cardiac output seem primarily to be those that affect cardiac output in the OT, which in turn is strongly correlated with cardiac output 4 to 6 hours later and next day. Cardiac output after operations using cardiopulmonary bypass (CPB) is usually correlated with age of the patient, cardiac condition, functional state of the patient just before operation (NYHA), the duration of the CPB and duration of global myocardial ischemia. During the early postoperative period , a heart rate within usual ranges correlates directly with cardiac output, and arterial blood pressure within usual ranges correlates inversely with it.

Determinants of cardiac output are ventricular preload, afterload, myocardial contractility, and heart rate.

Causes of Acute Dysfunction (Low Cardiac Output) After Cardiac Surgery

i. Inadequate operation
ii. Myocardial dysfunction
iii. Increased ventricular afterload
iv. Reduced preload
   1. *Hypovolemia:* The most common cause of reduced preload is overlooked hypovolemia. This may be a relative intravascular loss secondary to vasodilatation, bleeding into undrained cavities, or uncharted or blocked chest tube drains. Occasionally, excessive diuresis leads to relative hypovolemia and lowering of cardiac output.
   2. *Diastolic Dysfunction:* In the presence of LV hypertrophy, fibrosis, or myocardial edema, filling pressures do not reflect ventricular volume. Doing an echocardiography in the SICU will help. The picture will reflect in a small ventricular chamber in the presence of high filling pressure, tachycardia, small stroke volume, low arterial blood pressure, and low cardiac output. Appropriate interventions should be aimed at decreasing heart rate, initiating beta-blockade, and subsequent volume infusion. Some inotropic agents may be detrimental in this situation.

Acute Cardiac Tamponade

Acute pericardial tamponade (with its resultant acute decrease in ventricular preload in the face of elevated atrial pressures) must always be considered when low cardiac output is present early postoperatively.

Undrained intrapericardial bleeding may cause acute cardiac tamponade. It may also occur as a result of marked myocardial edema and chamber dilatation inside the closed chest, because at times the pericardium can be constricting even when it is not resutured.

After an early period of adequate and stable cardiac output , cardiac tamponade is a likely cause of rapid deterioration that cannot be easily explained otherwise.

It is usually associated with rapidly rising right and left atrial pressures. Often drainage from chest tubes is initially brisk and then ceases, and serial chest X-rays show progressive widening of the cardiac and superior mediastinum silhouette. Arterial pressure falls, urine output falls, and pulse pressures narrows.

Therefore, when the diagnosis of cardiac tamponade is considered as a possible etiology of low cardiac output that does not promptly respond to nonsurgical intervention, emergent reoperation is indicated (Bedside sternal reopening, specially in infants).

Treatment of Low Cardiac Output

Experience shows that it is worthwhile to intensively treat patients with low or inadequate cardiac output early after cardiac surgery, because cardiac performance often improves after 1 or 2 days, followed by good recovery.

Cardiac tamponade has to be ruled out as the first cause for low cardiac output. When excluded, treatment is directed at increasing CO by manipulating preload, afterload, contractile state, heart rate and improving tissue oxygen levels. Noninvasive methods of improving cardiac output with inotropic supports is mentioned in the 'Protocol section'.

When these measures fail, Invasive methods with devices to support the circulation must be considered, i.e. 'Intra-aortic balloon pump' and 'Temporary ventricular assistance' devices.

1. Protocol for reducing Arterial Blood Pressure and Afterload

Sodium nitroprusside is administered intravenously (IV) continuously or intermittently as required. It acts directly on arterial (and to a lesser extent, venous) smooth muscle and thus decreases systemic and pulmonary vascular resistance and systemic venous tone. Its onset and end of action are immediate. The dose is 1 to 10 μg kg^{-1} min^{-1}(doses larger than this are not used), regulated in the most cases to maintain a mean arterial blood pressure 10 percent above the normal value for the patient's age. Toxicity is treated by

IV infusion over 15 minutes of 150 μg. kg^{-1} of a 25 percent solution of sodium thiosulfate (10 μg kg^{-1} min^{-1})

Nitroglycerin decreases venous tone but also decreases coronary resistance. It is therefore particularly useful when myocardial ischemia is present. Infusion rate of 0.5 to 3 μg kg^{-1} min^{-1} are recommended. Nitroglycerin is absorbed into polyvinyl tubing used for IV infusions, and the concentration reaching the patient is less than planned until the tubing becomes saturated. Nitroglycerin is not as effective as nitroprusside in lowering arterial pressure.

Phenoxybenzamine is a noncompetitive blocker of alpha-receptors with a prolonged (12-24 hour) effect and a delayed (30- 60 min.) onset. It acts on both arterial and venous vessels and has no important side effects. It is administered IV in a dose of 1 mg.kg^{-1}, with the solution diluted in 20 to 50 mL of normal saline solution and infused slowly over about 15 minutes.

2. Standard Infusion rates of Inotropic Agents

Standard rates of infusion
Dopamine 10 μg .kg^{-1} .min^{-1}
Dobutamine 10 μg. kg^{-1} .min^{-1}
Isoproterenol 0.05 μg .kg^{-1} .min^{-1}
Epinephrine (Adr.) 0.1 μg .kg^{-1} . min^{-1}
Norepinephrine (Nor-adr) 0.1 μg .kg^{-1} . min^{-1}

3. Protocol for managing some aspects of Ventricular Electrical Instability

Early interventions for ventricular electrical instability

1. Give lidocaine (xylocard) as an intravenous bolus injection (the dose is 1 mg kg^{-1} for adults and children, although in adults the usual dose is 50 mg) if the arrhythmia is premature ventricular contraction (PVC) or ventricular tachycardia (VT) with a good hemodynamic state. If there is VT and reduction of cardiac output, use immediate DC cardioversion (100 and then 200 J).
2. Draw a blood sample for determination of serum K^+ (potassium); when the result is available, treat Hypokalemia (K^+ concentration < 4.0 mEq .L^{-1}) if present.
   i. Administer 5 mEq K^+ as an slow IV bolus
   ii. Administer 20 mEq K^+ in 50 ml of 5 % dextrose over 1 hour; then obtain repeat serum K^+ level measurement and repeat treatment until serum level is satisfactory (preferably ≥ 4.0 mEq. L^{-1})
   iii. Double the IV maintainance K^+ dose. (oral potassium supplement as 20% KCl, 10 ml twice daily can be given)
3. If the ventricular rate is < 80 to 90 beats/min, initiate pacing (Atrial pacing). When cardiac rhythm is other than sinus, AV junctional, or atrial pacing fails, use ventricular pacing.

4. If the arrthymia recurs promptly or is not controlled by these simple measures, begin continous IV lidocaine infusion in a dose of 20 to 50 μg . kg^{-1} min^{-1}

4. Protocols for Acute Management of Postoperative Atrial Fibrillation

i. In hemodynamically stable adult patients, intravenous Verapamil, Esmolol, Propranolol, or Amiodarone are effective alternative therapies. *Verapamil:* 5 to 10 mg IV bolus, may be repeated after 15 min.
ii. *Amiodarone:* 150 mg IV over 10 minutes or 300 mg over one hour and can be given as a maintainance dose (600 to 900 mg) for the next 23 hrs depending on the body weight.
iii. In unstable hemodynamics digoxin has been classically recommended, but it may be slow to act (3-8 hrs) and relatively ineffective at decreasing heart rate in postoperative patients with increased sympathetic activity. Dosage used in adult is 0.25 mg IV slowly over 10 min . after checking serum K^+. in adults and can be repeated after 6 hrs with a smaller dose (0.125 mg IV Slow).
iv. Amiodarone infusion is started, if digoxin not responding.
v. Lastly, DC cardioversion can be attempted.

5. Protocol for Oliguria

Urine output in the early postoperative period of < 0.5 to 1.0 mL/kg/hour in children and infants and <0.5 mL/kg/hour (30-35 mL) in adults.

Rationale: To reverse, the universal occurrence of fluid retention following cardiopulmonary bypass.

Treatment

1. Exclude low cardiac output as the cause of the oliguria.
2. Administer a diuretic.
   i. *Furosemide:* 1 mg/kg for infants and children and for adults 20 to 40 mg administered IV as a bolus. However, doses up to 180 to 240 mg may be necessary in patients with chronic heart failure, cirrhosis and nephrotic syndrome.
   ii. *Torsemide:* 10-20 mg IV as a bolus.
   iii. A continous intravenous infusion of the diuretic just mentioned may be safer and more effective in some patients. Furosemide is usually given at an initial infusion rate of 5 mg per hour, increasing up to 20 mg per hour, if necessary, till the diuretic phase is reached. (Torsemide: 5 -10 mg per hour).

6. Protocol for Hyperkalemia serum K level > 5.5 mEq from AKI (Acute Kidney Injury)

i. Give Glucose insulin solution IV for adults. For adults, mix 20 units of regular insulin in 50 mL of 50 percent dextrose and give IV over 10 min.

For children, mix 0.5 mL of regular insulin per kg of body weight in 2 mL of 25 percent dextrose per kg and give IV over 10 min.

ii. Administer a sodium polystyrene sulfonate enema.

iii. Give 1meq/kg sodium bicarbonate IV for infants and children and for adults give 44 mEq IV slowly.

If these measures do not result in the serum K level <5.5 mEq, nephrology consultation should be obtained.

7. Protocol for Intravenous Fluids

5% dextrose or Normal saline (adults and children)

On day of surgery: 1 ml per kg body weight per hour.
Day 1 following surgery: 1.5 ml per kg bodyweight per hour.
Day 2 following surgery: 2 ml per kg per hour and encourage oral intake.

8. Protocol for Metabolic Acidosis

Indication: Metabolic acidosis exists if the base deficit is >2 m/Eq per liter and pH is <7.35 or $PaCO_2$ is <30 mm Hg.

Rationale: Treatment is directed only at the extracellular fluid, and a conservative dose of $NaHCO_3$ (Soda bicarb.) is given initially because more can easily be administered if needed.
Extracellular fluid volume = 30 percent bodyweight (Kg)
Base deficit (mEq per liter) × 0.3 bodyweight (kg) = total extracellular base deficit.

Treatment: Administer Sodabicarb so that the amount of Na (mEq) equals half the total extracellular base deficit.

Remeasure base deficit in 30 to 60 minutes and repeat treatment if indicated.

Suggested Reading

1. Cardiac Surgery: Kirklin/Barratt-Boyes, Fourth edition 2013 Published by Elsevier.
2. Gleen Textbook of Thoracic and Cardiovascular Surgery : Fifth edition. Appleton-Lange 1990.
3. Manual of Perioperative care in Adult Cardiac Surgery : Robert M. Bojar. Fifth edition. John Wiley and Sons 2011.

Drugs Used in Cardiovascular Emergency

chapter 27

Soumitra Kumar

Adenosine

Indication: Termination of sinus node reentrant tachycardia.
Termination of AV nodal reentrant tachycardia.
Termination of AV reentrant tachycardia (using accessory pathway).

Dosage: 6 mg IV bolus over 1 to 2 seconds.
If needed, a 12 mg IV bolus after 1 to 2 minutes, followed by another 12 mg IV bolus 1 to 2 minutes after second dose.
[Each IV dose should be followed with a rapid saline flush].

Contraindications: Drug-induced tachycardias
Wide QRS tachycardias of unknown origin
Patients taking dipyridamole.

Side-effect: Transient dysrhythmias, facial flushing, dyspnea, chest pressure, hypotension, headache, bronchospasm.

Amiodarone

Indication: *Labeled:* Ventricular arrhythmias
Unlabeled: Atrial arrhythmias.

Dosage: *Intravenous:* Cardiac arrest (VF or pulseless VT)—300 mg IV bolus over > 3 mins can repeat 150 mg bolus as needed upto a total maximum dose of 2.1 gm in 24 hours.
Other situations: 150 mg IV infusion over no less than 10 mins. This may be followed by an infusion of 1 mg/min × 6 hours, then a maintenance infusion of 0.5 mg/min × 18 hours or until switch to oral amiodarone can be made. Additional 150 mg bolus over no less than 10 minutes can be made for breakthrough events.
Oral: Loading dose: 200 mg q8h × 1 week
(upto 800-1600 mg/day × 1-3 weeks)
followed by
200 mg bid × 1 week
followed by
maintenance dose of ≤ 200 mg/day.

Contraindications: Severe sinus node dysfunction
Second or third degree AV block
Symptomatic bradyarrhythmias without a pacemaker backup
With caution in renal failure
With caution in patients on drugs that prolong QT interval.

Side-effect: Bradycardia
Heart block
Hypotension
Hyper/hypothyroidism
Chemical hepatitis
Pulmonary fibrosis
Corneal microdeposits
Photosensitivity
Blue/gray skin discoloration
Peripheral neuropathy/Tremor
Proarrhythmia (Torsade de pointes).

Alprostadil (Prostaglandin E1)

Indication: To maintain the patency of the ductus arteriosus in neonates who have congenital heart defects and depend on a patent ductus arteriosus for survival, till corrective or palliative surgery can be done.

Dosage: The desired pharmacological effect is obtained with an initial dosage of 0.01 mg/kg/min IV or intra-arterial (umbilical artery) can be increased upto 0.1 mg/kg/min. Higher doses do not offer added benefit. Alprostadil is most effective when given within 96 hours after birth since post-natally, ductus rapidly loses its responsiveness.

Contraindications: Cyanotic infants with persistent fetal circulation.
Neonates with total anomalous pulmonary venous return below the dipaphragm.
Neonates with polysplenia or asplenia in whom pulmonary atresia is combined with anomalous pulmonary venous return.

Caution: Neonates with suspected bleeding tendencies.
Neonates with respiratory distress syndrome.

Side-effect: *CVS:* Flushing, bradycardia, hypotension, cardiac arrest
CNS: Fever, Seizures
Respiratory: Apnea
Gastrointestinal: Diarrhea
Hematological: Disseminated intravascular coagulation.

Atropine

Indication: Ventricular asystole/pulseless electrical activity (PEA)
Symptomatic sinus bradycardia or intranodal (Mobitz type I) AV block
Nausea and vomiting caused by morphine.

Dosage: *Asystole/PEA:* 1 mg IV push
Others: 0.5-1.0 mg IV
May be repeated upto total dose of 3 mg
Tracheal dose/route: 1 to 2.5 mg in 10 to 25 cc normal saline.

Contraindication:

- Use with caution in ACS (increased heart rate can provoke myocardial ischemia, acute MI, and rarely VT/VF)
- Can worsen Infranodal (Mobitz type II) second-degree AV block.

Side-effects: Anti-cholinergic effects
Low dosage (< 0.5 mg) can cause paradoxic slowing of heart rate.

Beta-blockers for Acute Indications

Indications: All ACS patients (unless contraindicated); start IV in high-risk patients (e.g. acute MI, ongoing pain, dynamic electrocardiogram (ECG) changes).

Dosage:
Metoprolol: 5 mg (IV) over 1 to 2 minutes, repeated every 5 minutes for a total intial dose of 15 mg. Follow in 15 minutes with 50 mg (PO)q12h × 24 hrs then 100 mg (PO)q12h, as tolerated. Initial dose can be reduced to 1-2 mg if a conservative regime is desired.
Atenolol: 5 mg (IV) over 5 minutes, repeated 5 minutes later × 1. Follow in 10 minutes, if tolerated, with 50 mg (PO)q12h.
Esmolol: In addition to ACS, can also be used for

- Rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative or postoperative or other emergent circumstances.
- In non-compensatory sinus tachycardia
- Intra-operative or postoperative tachycardia and/or hypertension especially during induction and tracheal intubation.

Dosage schedule: For H/R, BP control during surgery
80 mg bolus over 15 to 30 sec
followed by 150 to 300 mcg/kg/min
For SVTs and AMI
500 mcg/kg/min bolus over 1 min
followed by 50 to 300 mcg/kg/min (Tables 27.1 and 27.2)
For tracheal intubation-induction sequence
60 to 100 mg bolus (6 to 10 mL) and if needed follow by an infusion.

Table 27.1 Bolus dose 500 mcg/kg/min

Body weight (Kg)	50	60	70	80	90	100
mL/min*	2.5	3.0	3.5	4.0	4.5	5.0
* Using a 100 mg vial (10 mg/mL concentration)						

Table 27.2 Maintenance infusion (mL/min)

Body weight (Kg)	50	60	70	80	90	100
50 mcg/kg/min	0.25	0.30	0.35	0.40	0.45	0.50
100 mcg/kg/min	0.50	0.60	0.70	0.80	0.90	1.00
150 mcg/kg/min	0.75	0.90	1.05	1.20	1.35	1.50

Contraindications: Systolic BP< 100 mm Hg
HR < 50 bpm
Severe decompensated HF
PR interval > 0.24 seconds
Second or third degree AV block
Sick Sinus Syndrome
Clinically important bronchospasm.

Adverse-effects: Hypotension
Bradycardia/Heart Block/Sinus pause
Syncope/Dizziness
Pulmonary edema
Confusion, headache, depression
Bronchospasm
Nasal congestion.

Caution: Concurrent use of verapamil/diltiazem.

Digoxin for Acute Indications

Indication: Heart Failure

Slowing of ventricular response in patients with atrial fibrillation/flutter/paroxysmal atrial tachycardia.

Dosage: IV Load: 10 to 15 mg/kg: 50 percent given initially then 25 percent after 6 hours and further 25 percent 6 hours after second dose

(Lower dose in elderly or uremic patients).

Maintenance (Oral): 0.0625 to 0.5 mg daily dependent on renal function and patient size.

Side-effects: Bradycardia/AV block

Anorexia/nausea/diarrhea/abdominal pain/blurred vision/Yellow-green halo around light/proarrhythmia.

[For acute overdose, 20 vials of digoxin immune Fab (each vial 38-40 mg) and for life-threatening toxicity during chronic therapy, 6 vials are recommended].

Diltiazem (IV)

Indication: Supraventricular tachycardia (AV nodal reentry tachycardias)

Control of ventricular rate in atrial fibrillation or flutter.

Dosage: IV Loading dose: 0.25 mg/kg over 2 min

If no response in 5 to 10 min, then repeat loading dose with 0.35 mg/kg.

IV maintenance dose: 5 to 15 mg/hour.

Contraindication: Avoid in patients with WPW and atrial fibrillation

Consider reduced doses in patients with hepatic dysfunction.

Side-effect: Negative inotropic

Headache

Flushing

Dizziness

Bradycardia

AV block

Hypotension.

Dobutamine

Indication: Acute heart failure without shock

Hemodynamically significant RV infarction not responding to volume loading.

Dosage: 2 to 20 mcg/kg/min IV infusion

(Doses upto 40 mcg/kg/min have been used)

Use lowest effective dose, as tachycardia is more likely to develop at higher doses. Titrate infusion so that heart rate dose not increase > 10 percent. Taper gradually upon discontinuation. Tolerance can occur with prolonged (> 24 hours) use, requiring an increase in dose [Vide infusion chart].

Contraindications: Avoid in cardiogenic shock (dobutamine is an inotrope with mild peripheral vasodilating effects)

Severe aortic stenosis

Hypertrophic obstructive cardiomyopathy

Sulfite allergy (possible anaphylaxis).

Side-effects: Tachycardia
Hypo-/hypertension
Ventricular arrhythmias
Nausea
Headache
Myocardial ischemia.

Dopamine

Indication: Hypotension/shock secondary to cardiac origin, septicemia and trauma.

Dosage: 1 to 3 mg/kg/min: primarily dopamine effects
5 to 10 mg/kg/min: primarily β effects
10 to 20 mg/kg/min: primarily α effects.
(IV infusion through central line)
Use lowest effective dose, as tachycardia and systemic/splanchnic vasoconstriction are more likely to develop at higher doses. Taper gradually upon discontinuation; additional IV fluids may be required during taper. Tachyphylaxis can occur with prolonged use, requiring an increase in dose. (Vide Infusion chart).

Contraindication: Avoid in patients with pheochromocytoma, VF, sulfite allergy (possible anaphylaxis). Skin necrosis may occur with extravasation (Treated by infiltration with phentolamine).

Side-effect: Tachycardia
Ventricular arrhythmias
Hypertension
Headache
Nausea.

Epinephrine (Adrenaline)

Indications: Asystole
Pulseless electrical activity
Ventricular fibrillation or Pulseless ventricular tachycardia (resistant to defibrillation)
Severe hypotension
Symptomatic bradycardia after atropine.

Dosage: *Cardiac arrest:* 1 mg (10 cc of 1:10,000 solution) IV bolus or 2 mg (diluted in 10 cc normal saline) via endotracheal tube. May be repeated every 3 to 5 minutes. Higher doses (upto 0.2 mg/kg) are not routinely recommended but can be considered if the initial doses are ineffective. Each IV dose should be followed by a saline flush (20 cc) (use central line for IV infusion).
Profound bradycardia or hypotension: 2 to 10 mcg/min IV infusion.

Side-effects: Tachycardia
Flushing
Hypertension
Restlessness
Exacerbation of narrow angle glaucoma
Ventricular arrhythmias.

Fibrinolytic Agents

(Vide chapter on ST-elevation MI)
Chapter 1, (Table 1.4)

GPIIb/IIIa Inhibitors

(Abciximab, Eptifibatide, Tirofiban)
[Vide chapter on Non ST-elevation ACS and infusion charts]
Chapter 2, (Table 2.3).

Heparin (Unfractionated and Low Molecular Weight Heparin)

(Vide chapter on Non-ST-elevation ACS)
Chapter 2, (Tables 2.4 and 2.5)

Isoprenaline (Isoproterenol)

Indication:
- Acute Stokes Adams attacks before temporary pacing can be initiated
- Severe bradycardia precipitated by beta-adrenergic antagonist
- Torsade-de pointes.

Dosage: 2 to 20 mg/min IV infusion. Start at lowest dosage and increase gradually while carefully monitoring the patients (Vide infusion chart).

Contraindications: Acute coronary syndrome
Patients who are prone to VT/VF.

Side-effects: Tachycardia
Ventricular arrhythmias
Hypotension
Myocardia ischemia
Tremor/flushing.

Levosimendan

Indication: For short-term treatment of acutely decompensated severe chronic heart failure.

Dosage: *Loading dose:* 12 to 24 mcg/kg over 10 minutes.
Infusion: 0.1 mcg/kg/min – if the response is deemed excessive i.e. hypotension and tachycardia, than the rate can be decreased to 0.05 mcg/kg/min or discontinued. If the initial dose is tolerated and an increased hemodynamic effect is required than the rate can be increased to 0.2 mcg/kg/min.

Duration of infusion is normally 24 hours.

Preparation of 0.05 mg/mL is done as following:

Infusion: Mix 10 mL of Levosimendan 2.5 mg/mL concentrate for solution for infusion with 500 mL 5 percent Glucose solution.
Route: Peripheral or central intravenous.
Precautions: Used cautiously in hypotensive tachycardia, atrial fibrillation or patients with a rapid ventricular response.

Contraindications: Patients with severe renal and hepatic failure.

Adverse reactions: Headache, hypotension

Rarely – atrial and ventricular arrhythmias.

Lignocaine (Lidocaine)

Indication: VF or pulseless VT resistant to defibrillation and epinephrine

Hemodynamically-stable VT

Hemodynamically-unstable VPCs.

Dosage: A single IV bolus of 1.5 mg/kg is acceptable for cardiac arrest Tracheal administration: 2 to 4 mg/Kg.

i. Normal LV function and no hepatic impairment: Loading dose of 75 mg IV followed by 50 mg IV every 5 minutes × 3 (total dose 225 mg); maintenance infusion of 2 mg/min.
ii. Moderate decrease in LV function: Loading dose of 75 mg IV followed by 50 mg IV every 5 minutes × 1 (total dose 125 mg); maintenance infusion of 1 mg/min.
iii. Severe decrease in LV function or significant hepatic impairment: Loading dose of 50 to 75 mg IV × 1; maintenance infusion of 0.5 mg/min.

Contraindication: Prophylactic lignocaine for acute MI is not indicated (increased risk of death primarily from asystole).

Side-effect: Drowsiness, slurred speech (Perioral numbness)

Confusion/Coma

Seizures

Paraesthesias/Tinnitus

Proarrhythmia

Cardiac depression (with high levels)

Bradycardia/asystole.

Magnesium Sulfate

Indications: Cardiac arrest due to Torsade de pointes
Torsade de pointes (not in cardiac arrest)
VT refractory to lidocaine/amiodarone
Life-threatening ventricular arhythmias due to digitalis toxicity.
* Not routinely recommended for acute MI unless magnesium deficiency is documented.

Dosage: 1 to 2 gm in 50 to 100 cc dextrose over 5 to 60 mins consider an addtional 2 gm IV over the next several hours. Regimens vary.

Contraindications: Renal disease, Heart block, Hypermagnesemia.

Side-effect: Hypotension, asystole, cardiac arrest, respiratory and CNS depression, flushing, sweating.

Milrinone

Indication: Short-term management of congestive heart failure; may be useful in patients with β-blocker overdose to increase contractility.

Dosage: *Loading dose:* 50 mg/kg
Maintenance infusion: 0.375 to 7.5 mg/kg/min.

Contraindications: Hypersensitivity to the drug
No clinical studies have been conducted in patients in the acute phase of myocardial infarction.

Side-effect: Hypotension
Ventricular arrhythmias
Supraventricular arrhythmias
Angina
Headache
Thrombocytopenia (rare).

Morphine Sulfate

Indication: Ischemic chest pain
Acute pulmonary edema associated with LV dysfunction.

Dosage: 2 to 4 mg IV over 1 to 5 minutes
2 to 8 mg repeated every 5 to 15 minutes as needed.

Contraindications: Use with caution in:
- Severe, chronic lung disease (increased risk of respiratory depression)
- RV infarction (risk of hypotension)
- Volume depleted patients (risk of hypotension).

Side-effect: Hypoventilation (Treat with naloxone 0.4-2.0 mg IV)
Hypotension (Treat by elevating legs and IV saline 200-500 cc bolus)
Nausea/vomiting and bradycardia (Treat with atropine)
[Overdose may be reversed with naloxone 2 mg IV, IM, SQ, ET (upto total dose 10 mg)].

Nitroglycerin (Acute)

Indication:
- Acute coronary syndromes to control ongoing ischemic pain
- Severe hypertension
- Acute heart failure
- Recurrent ischemia.

Dosage:
On initial presentation: Sublingual nitroglycerin tablets (0.4 mg) or aerosol spray every 5 mins × 3 (do not shake aerosol spray as it affects metered dose)
IV nitroglycerin: Initial IV bolus of 10 to 20 mcg if systolic BP > 100 mm Hg then infusion of 10 to 20 mcg/min. The infusion can be increased by 5 to 10 mcg/min every 5 to 10 min until ischemia is relieved, mean arterial pressure falls by 10 percent (or 30% if hypertensive), heart rate increases by 10 bpm or pulmonary artery end-diastolic pressure decrease by 10-30 percent. Do not allow SBP to fall below 90 mm Hg or heart rate to exceed 110 bpm. Doses in excess of 200 mcg/min are generally not recommended. [Vide infusion chart].

Contraindications: Systolic BP< 90 mm Hg
Severe bradycardia (< 50 bpm) or tachycardia
RV infarction
Severe hypovolemia
[Avoid if sildenafil or vardenafil is used within 24 hours or tadafil is used within 48 hours].

Adverse effects:
- Common are headache and hypotension
- Can worsen V/Q mismatch and cause hypoxemia in COPD
- Tolerance can occur after one day of continuous therapy (Increase dose or provide a nitrate-free interval = 12 hours)
- Can reduce sensitivity to heparin, i.e. higher heparin doses needed during nitrate administration.

Nitroprusside

Indications:
- Hypertensive emergencies
- Acute heart failure
- After load reduction for acute mitral or aortic regurgitation.

Dosage: IV infusion of 0.3 to 0.5 mcg/kg/min, titrated every 3 to 5 minutes to desired effect (usual dose 0.5 to 8.0 mcg/kg/min). Use lowest effective dose. Maximum dose of 10 mcg/kg/min IV should not be used for longer than 10 minutes. Taper gradually upon discontinuation [vide infusion chart].

Contraindication:
- Pre-existing hypotension (systolic < 90 mmHg, diastolic < 60 mmHg)
- Severe obstructive valvular heart disease
- AMI is not a contraindication, provided that excess hypotension and tachycardia is avoided.

Adverse effects:
- Headache, nausea, vomiting, abdominal discomfort
- Can worsen V/Q mismatch and cause hypoxemia in COPD
- Thiocyanate toxicity (tinnitus, blurred vision, mental status changes, abdominal pain, seizures) is uncommon, but is more likely to occur with higher (>2 mcg/kg/min) doses, prolonged (> 2 day) infusions or renal failure (Treated with 3% sodium nitrite followed immediately by sodium thiosulfate) [Use infusion pump, protect from light with aluminium foil].

Norepinephrine

Indication: Hypotension

Norepinephrine is most effective in a shock-like state accompanied by peripheral vasodilation ("warm shock") It is also effective in hypovolemia and cardiogenic shock.

Dosage: 0.1 to 3.5 mg/kg/min IV infusion (central line) or 2 to 12 mg/min IV infusion.

[5% dextrose or 5% dextrose and sodium chloride solution should be used as a diluent. Administration in saline solution alone is not recommended. Whole blood or plasma if indicated to increase blood volume should be administered simultaneously. In case of extravasation, area should be infiltrated immediately with 10 to 15 mL of saline solution containing 5 to 10 mg of phentolamine].

Contraindication: Pre-existing excess vasoconstriction
Late pregnancy (Risk of inducing uterine contraction).

Side-effects: Hypertension
Tachycardia
Ventricular arrhythmias
Headache.

Phenoxybenzamine

Indication: To control the hypotension caused by pheochromocytoma during the preoperative period and in patients whose tumors are inoperable. A beta, blocker must also be given after alpha-blockade is established.

Dosage: *IV:* 1 mg/kg in 200 mL of saline infused over atleast 2 hours
Oral: 10 mg once or twice daily by mouth.

Contraindications: Acute porphyria
Use with caution in CHF, coronary or cerebrovascular or renal insufficiency.

Side-effect: Postural hypotension
Dizziness
Reflex tachycardia
Nasal congestion
Miosis.

Phenylephrine

Indication: Maintenance of an adequate level of blood pressure during spinal and inhalation anesthesia and for treatment of vascular failure in shock, shock like states and drug induced hypotension or hypersensitivity.

Dosage: 5 mg subcutaneous or intramuscular injection followed by supplementary doses of 1 to 10 mg if necessary. Alternatively, 5 to 20 mg may be given in 500 mL of normal saline injection or 5 percent dextrose by slow IV infusion (central line) (0.5-15 mg/kg/min).

Contraindications: Severe hypertension
Ventricular tachycardia (No beta effects, hence quite rare)
Concurrent use with MAO inhibitors.

Side-effects: Bradycardia
Hypertension
Myocardial ischemia.

Verapamil (Intravenous)

Indications: Supraventricular tachyarrhymias (AV nodal re-entry tachycardia)
Control of rapid ventricular rate in atrial flutter or fibrillation.

Dosage: *IV:* 2.5 to 10 mg given over 2 minutes, may repeat 10 mg dose at 30 min (Maximum: 20 mg)
Maintenance infusion (IV): 5-10 mg/hour.

Contraindications: Avoid in patients with WPW and atrial fibrillation
Consider reduced doses in patients with hepatic dysfunction.

Side-effects: Negative inotropic
Constipation
Hypotension
Bradycardia
AV block.

Vasopressin

Indications: Cardiac arrest (in ACLS)
Vasodilatory shock
Control of esophageal varices
Diabetes insipidus.

Dosage: *For ventricular fibrillation in ACLS:* 40 u IV bolus followed by 300 to 360J DC shock
For vasodilatory shock: 0.02-0.1 u/min IV
For esophageal bleeding: 0.2-0.9 u/min IV infusion
For diabetes insipidus: 5-10 u IM or SC two or three times daily.

Contraindications: Known hypersensitivity to vasopression or its components.

Side-effects: Arrhythmias, angina, peripheral vasoconstriction, abdominal cramps, nausea and vomiting, tremor, vertigo, bronchoconstriction.

Epinephrine and Isoproterenol

Epinephrine Mix 1 mg in 250 mL (4 mcg/mL)		Isoproterenol Mix 1 mg in 250 mL (4 mcg/mL)	
Dose (mcg/min)	*Infusion rate (mL/hr)*	*Dose infusion (mcg/min)*	*Rate (mL/hr)*
1	15	0.5	8
2	30	1	15
3	45	2	30
4	60	3	45
5	75	4	60
6	90	5	75
7	105	6	90
8	120	7	105
9	135	8	120
10	150	9	135
15	225	10	150
20	300	15	225
25	375	20	300
30	450	25	375
35	525	30	450
40	600		

Nitroglycerin (Determine the infusion rate in mL/hr using the ordered dose and the concentration of the drug solution)

Dose (mcg/min)	25 mg/250 mL (100 mcg/mL)	50 mg/250 mL (200 mcg/mL)	100 mg/250 mL (400 mcg/mL)
5	3	2	1
10	6	3	2
20	12	6	3
30	18	9	5
40	24	12	6
50	30	15	8
60	36	18	9
70	42	21	10
80	48	24	12
90	54	27	14
100	60	30	15
150	90	45	23
200	120	60	30

Dobutamine [Mix 250 mg in 250 mL of D_5W (1,000 mcg/mL). Determine the infusion rate in mL/hr, using the ordered dose and the patient's weight in pounds or kilograms]

Dose	Patient's weight														
(mcg/ kg/	lb 88	99	110	121	132	143	154	165	176	187	198	209	220	231	242
min	kg 40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
2.5	6	7	8	8	9	10	11	11	12	13	14	14	15	16	17
5	12	14	15	17	18	20	21	23	24	26	27	29	30	32	33
7.5	18	20	23	25	27	29	32	34	36	38	41	43	45	47	50
10	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
12.5	30	34	38	41	45	49	53	45	60	64	68	71	75	7	83
15	36	41	45	50	54	59	63	68	72	77	81	86	90	95	99
20	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132
25	60	68	75	83	90	98	105	113	120	128	135	143	150	158	165
30	72	81	90	99	108	117	126	135	144	153	162	171	780	189	198
35	84	95	105	116	126	137	147	158	168	179	189	200	210	221	231
40	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264

Dopamine [Mix 400 mg in 250 mL of D_5W (1,000 mcg/mL). Determine the infusion rate in mL/hr, using the ordered dose and the patient's weight in pounds or kilograms]

Dose	Patient's weight													
(mcg/ kg/	lb 88	99	110	121	132	143	154	165	176	187	198	209	220	231
min	kg 40	45	50	55	60	65	70	75	80	85	90	95	100	105
2.5	4	4	5	5	6	6	7	7	8	8	8	9	9	10
5	8	8	9	10	11	12	13	14	15	16	17	18	19	20
7.5	11	13	14	15	17	18	20	21	23	24	25	27	28	30
10	15	17	19	21	23	24	26	28	30	32	34	36	38	39
12.5	19	21	23	26	28	30	33	35	38	40	42	45	47	49
15	23	25	27	31	34	37	39	42	45	48	51	53	56	59
20	30	34	38	41	45	49	53	56	60	64	68	71	75	79
25	38	42	47	52	56	61	66	70	75	80	84	89	94	98
30	45	51	56	62	67	73	79	84	90	96	101	1078	113	118
35	53	59	66	72	79	85	92	98	105	112	118	125	131	138
40	60	68	75	83	90	98	105	113	120	128	135	143	150	158
45	68	76	84	93	101	110	118	127	135	143	152	160	169	177
50	75	84	94	103	113	122	131	141	150	159	169	178	188	197

Nitroprusside [Mix 50 mg in 250 mL of D_5W (200 mcg/mL). Determine the infusion rate in mL/hr using the ordered dose and the patient's weight in pounds or kilograms]

Dose	Patient's weight														
(mcg/ kg/	lb 88	99	110	121	132	143	154	165	176	187	198	209	220	231	242
min	kg 40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
0.3	4	4	5	5	5	6	6	7	7	8	8	9	9	9	10
0.5	6	7	8	8	9	10	11	11	12	13	14	14	15	16	17
1	12	14	15	17	18	20	21	23	24	26	27	29	30	32	33
1.5	18	20	23	25	27	29	32	34	36	38	41	43	45	47	50
2	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66
3	36	41	45	50	54	59	63	68	72	77	81	86	90	95	99
4	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132
5	60	68	75	83	90	98	105	113	120	128	135	143	150	158	165
6	72	81	90	9	108	117	126	135	144	153	162	171	180	189	198
7	84	95	105	116	126	137	147	158	168	179	189	200	210	221	231
8	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264
9	108	122	135	149	162	176	189	203	216	230	243	257	270	284	297
10	120	135	150	65	180	195	210	225	240	255	270	285	300	315	330

Norepinephrine [Mix 4 mg in 250 mL D_5W (16 µg/mL) and run at]

Dose in (mcg/min)	mL/hr	Dose in (mcg/min)	mL/hr
0.5	2	9	34
1	4	10	38
2	8	11	41
3	11	12	45
4	15	13	49
5	19	14	53
6	23	15	56
7	26	16	60
8	30		

Tirofiban for ACS in ICCU

Most patients							Severe renal insufficiency Creatinine clearance < 30 mL/min					
30 min loading infusion rate (0.4 mcg/kg/min)			*Maintenance infusion rate (0.1 mcg/kg/min) for 48 hrs*			*30 min loading infusion rate (0.2 mcg/kg/min)*				*Maintenance infusion rate (0.05 mcg/kg/min) for 48 hrs*		
Patient weight (kg)	mL/hr	mL/min	Micro drops/min	mL/hr	mL/min	Micro drops/min	mL/hr	mL/min	Micro drops/min	mL/hr	mL/min	Micro drops/min
30-37	16	0.27	16	4	0.07	4	8	0.13	8	2	0.03	2
38-45	20	0.33	20	5	0.08	5	10	0.17	10	2.5	0.04	2
46-54	24	0.40	24	6	0.10	6	12	0.20	12	3	0.05	3
55-62	28	0.47	28	7	0.12	7	14	0.23	14	3.5	0.06	4
63-70	32	0.53	32	8	0.13	8	16	0.27	16	4	0.07	4
71-79	36	0.60	36	9	0.15	9	18	0.30	18	4.5	0.08	5
80-87	40	0.67	40	10	0.17	10	20	0.33	20	5	0.08	5
88-95	44	0.73	44	11	0.18	11	22	0.37	22	5.5	0.09	5
96-104	48	0.80	48	12	0.20	12	24	0.40	24	6	0.10	6
105-112	52	0.87	52	13	0.22	13	26	0.43	26	6.5	0.11	7
113-120	56	0.93	56	14	0.23	14	28	0.47	28	7	0.12	7
121-128	60	1.00	60	15	0.25	15	30	0.50	30	7.5	0.12	7
129-137	64	1.07	64	16	0.27	16	32	0.53	32	8	0.13	8
138-145	68	1.13	68	17	0.28	17	34	0.57	34	8.5	0.14	8
146-153	72	1.20	72	18	0.30	18	36	0.60	36	9	0.15	9

Tirofiban in ACS with PCI

Most patients					Several renal insufficiency Creatinine clearance < 30 mL/min			
3 min loading infusion rate (25 mcg/kg)		*Maintenance infusion rate (0.15 mcg/kg/min) upto 16-18 hrs*			*3 min loading infusion rate (12.5 mcg/kg)*		*Maintenance infusion rate (0.075 mcg/kg/min) upto 16-18 hrs*	
Patient weight (kg)	mL/3 min	mL/hr	mL/min	Micro-drops/min	mL/3 min	mL/hr	mL/min	Micro-drops/min
30-37	16.8	6	0.10	6	8.4	3	0.05	3
38-45	20.8	7	0.12	7	10.4	4	0.06	4
46-54	25.0	9	0.15	9	12.5	5	0.08	5
55-62	29.3	11	0.18	11	16.4	5	0.09	5
63-70	33.3	12	0.20	12	16.6	6	0.10	6
71-79	37.5	14	0.23	14	18.8	7	0.11	7
80-87	41.8	15	0.25	15	20.9	8	0.13	8
88-95	45.8	16	0.27	16	22.9	8	0.14	8
96-104	50.0	18	0.30	18	25.0	9	0.15	9
105-112	54.3	20	0.33	20	27.1	10	0.16	10
113-120	58.3	21	0.35	21	29.1	10	0.17	10
121-128	62.3	22	0.37	22	31.1	11	0.19	11
129-137	66.5	24	0.40	24	33.1	12	0.20	12
138-145	70.8	25	0.42	25	35.4	13	0.21	13
146-153	74.8	27	0.45	27	37.4	13	0.22	13

Eptifibatide in percutaneous coronary intervention (*1 bolus is given followed by a second bolus at an interval of 10 minutes. The volume of bolus is given as below according to the weight*)

Kg	180 µg/kg volume mL	2 µg/kg/min Bolus infusion for 24 hrs mL	Number of Bolus	Number of Infusions
43-47	4.05	172.8	2	2
48-52	4.50	192.0	2	2
53-57	4.95	211.0	2	3
58-62	5.40	230.2	2	3
63-67	5.85	249.6	2	3
68-72	6.30	268.8	2	3
73-77	6.75	288.0	2	3
78-82	7.20	307.2	2	4
83-87	7.65	326.0	2	4
88-92	8.00	345.0	2	4
93-97	8.55	364.0	2	4
98-102	9.00	384.0	2	4
103-107	9.45	403.0	2	5
108-112	9.90	422.0	2	5
113-117	10.35	441.0	2	5

Eptifibatide in Acute Coronary Syndrome

Kg	180 µg/Kg volume mL	2 µg/kg/min Bolus infusion for 24 hrs mL	Number of Bolus	Number of Infusions
43-47	4.05	172.8	1	
48-52	4.50	192.0	1	2
53-57	4.95	211.0	1	3
58-62	5.40	230.2	1	3
63-67	5.85	249.6	1	3
68-72	6.30	268.8	1	3
73-77	6.75	288.0	1	3
78-82	7.20	307.2	1	4
83-87	7.65	326.0	1	4
88-92	8.00	345.0	1	4
93-97	8.55	364.0	1	4
98-102	9.00	384.0	1	4
103-107	9.45	403.0	1	5
108-112	9.90	422.0	1	5
113-117	10.35	441.0	2	5

Guideline Chart for Eptifibatide dosing in Mild and Moderate Renal Dysfunction

Procedure	**PCI**				**ASC**
Weight (kg)	*< = 121 kg*		*> 121 kg*		*Any*
Serum creatinine (mg/dL)	< 2	2-4	< 2	2-4	2-4
Bolus 1	180 µg/kg	180 µg/kg	22.6 mg (Maximum)	22.6 mg (Maximum)	180 µg/kg
Bolus 2	180 µg/kg	180 µg/kg	None	None	None
Infusion	2 µg/kg/min	1 µg/kg/min	15 mg/hr (Maximum	7.5 mg/hr (Maximum)	1 µg/kg/min

Guidelines for Antimicrobial dosing in Adult

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Acyclovir	IV/PO	>50 25-50 10-25 0-10	5-10 mg/kg q8h 5-10 mg/kg q12h 5-10 mg/kg q24h 2.5-5 mg/kg q24h	Yes	–
Amikacin	IV/IM	>30 <30	5-9 mg/kg q8-24h depending on age 11 mg/kg one dose	Yes	Yes
Amoxicillin	PO	>50 10-50 <10	250-500 mg q8h 250-500 mg q8-12h 250-500 mg q12h	Yes	No
Amoxicillin/clavulanate	PO	>30 10-30 <10	875 mg q12h OR 250-500 mg q8h 250-500 mg q12h 250-500 mg q24h	Yes	No
Ampicillin	IV	>50 10-50 <10	1-2 g q4-6h 1-2 g q6-12h 1-2 g q8-12h	Yes	No
Ampicillin/sulbactam	IV	>30 15-30 <15	1.5-3 g q6-8h 1.5-3 g q12h 1.5-3 g q24h	Yes	–
Azithromycin	IV	No renal dose adjustment necessary	500 mg q24h	No	No
	PO	No renal dose adjustment necessary	250-500 mg q24h	No	No
Aztreonam	IV	>30 10-30 <10	1 g q8h 500 mg q8h 250 mg q8h	Yes	Yes
Cefazolin	IV	>55 35-54 11-34 <10	1 g q8h 1 g q8-12h 500 mg-1g q12h 500 mg-1g q24h	Yes	No

Contd…

Contd…

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Cefdinir	PO	>30 <30	300 mg q12h or 600 mg q24h 300 mg q24h	Yes	–
Cefixime	PO	>60 21-59 <20	400 mg q24h 300 mg q24h 200 mg q24h	Yes	–
Cefpodoxime	PO	>30 10-29 <10	100-400 mg q12h 100-400 mg q24h 100-400 mg 3x/wk	No	–
Cefepime	IV	>60 30-60 11-29 <11	500 mg-2g q12h 500 mg-2g q24h 500 mg-1g q24h 250 mg-500 mg q24h	–	–
Cefoperazone + Sulbactam	IV/IM	>30 15-30 <15	1-2 g q12h 1 g q12h 0.5 g q12h		
Ceftazidime	IV	>50 31-50 16-30 <15	1 g q8h 1 g q12h 1 g q24h 500 mg-1g q24h	Yes	Yes
Ceftizoxime	IV	>80 50-79 5-49 <5	1 g q8-12h 0.5-1 g q8-12h 500 mg-1g q12-24h 500 mg q24h	Yes	–
Ceftriaxone	IM/IV	No renal dose adjustment necessary	1g q24h		
Cefuroxime	IV	>20 10-20 <10	750 mg-1.5 g q8-12h 750 mg q12h 750 mg q24h	Yes	No
Cephalexin	PO	>40 10-40 <10	250-500 mg q6h 250-500 mg q8-12h 250 mg q12-24h	Yes	Yes

Contd…

Contd...

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Chloramphenicol	IV	No renal dose adjustment necessary	0.5-1g q6h	No	No
Ciprofloxacin	IV	>30 <30	400 mg q12h 400 mg q24h	No	–
Clarithromycin	PO	>30 <30	250-500 mg q12h 250-500 mg q24h	–	–
Clindamycin	IV	No renal dose adjustment necessary	600-900 mg q8h	No	No
	PO	No renal dose adjustment necessary	150-450 mg q6h	No	No
Colistin	IV/IM	> 50 20-50 10-20 <10	2 million units q 8h or 2.5-5 mg/kg/day in 3 divided dose 1-2 million units q 8 h 1 million units q 12-18 h 1 million units q 18-24 h	–	Yes
Doxycycline	IV/PO	>10 <10	100 mg q12h 100 mg q24h	No No	– –
Erythromycin	IV	>10 <10	0.5-1 g q6h 250-500 mg q6h	No	No
	PO	No renal dose adjustment necessary	250-500 mg q6h	No	No
Ganciclovir	IV	>80 50-79 25-49 <25	5 mg/kg q12h 2.5 mg/kg q12h 2.5 mg/kg q24h 1.25 mg/kg q24h	Yes	–
Gatifloxacin	IV/PO	>40 <40	400 mg q24h 400 mg first dose then 200-500 mg q24h	–	–
Gentamicin	IM/IV	>30 <30	1.5-2.5 mg/kg q8-24h depending on age 3 mg/kg one dose	Yes	Yes
Imipenem	IV	>70 30-70 20-30 <20	500 mg q6h 500 mg q8h 500 mg q12h 250 mg q12h		

Contd…

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Imipenem	IV	>70 30-70 20-30 <20	500 mg q6h 500 mg q8h 500 mg q12h 250 mg q12h		
Levofloxacin	IV/PO	>50 20-50 10-19 <10	250-500 mg q24h 250-500 mg first dose then 125-250 mg q24h 250-500 mg first dose then 125 mg q24h 250-500 mg first dose then 125 mg q24-48h	–	–
Linezolid	IV/PO	No renal dose adjustment necessary	600 mg q12h		
Meropenem	IV	>50 26-50 10-25 <10	0.5-1.0 g q8h 2 g q8h (in meningitis) One unit dose every 12 hours One half unit dose every 12 hours One half unit dose every 24 hours	Yes	–
		Unit doses of 500 mg, 1 g, 2 g; 500 mg indicated inpneumonia, UTI, gynecological, skin and skin structure infections; 1 g indicated in nosocomial pneumonitis, peritonitis, presumed infections in neutropenic patients, septicemias 2 g indicated in meningitis]			
Penicillin G	IV	>50 10-50 <10	2-4 million units q2-4h 1-2 million units q4-6h 1-2 million units q8-12h or 0.5-1 million units q4-6h	Yes	–
Pentamidine	IV	>50 10-50 <10	4 mg/kg q24h 4 mg/kg q24-36 4 mg/kg q48h	–	–

Contd…

Contd…

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Imipenem	IV	>70 30–70 20–30 <20	500 mg q6h 500 mg q8h 500 mg q8h 250 mg q12h		
Piperacillin/ tazobactam	IV	>40 20-40 <20	3.375 g q6h 3.375 g q8h 3.375 g q12h	Yes	–
Tetracycline	PO	>50 10-50 <10	250-500 mg q6-12h 250-500 mg q12-24h 250-500 mg q24h	No	No
Teicoplanin	IV/IM	>60 40-60 <40	200 mg q24h (Moderate infection) 400 mg q24h (severe infection) Dose adjustment from 4th day 400 ml q48h or 200 mg q24h 400 mg IV loading dose - 20 mg/l per bag 1st week - 20 mg/l in alternate bags in alternate bags in 2nd week - 20 mg/l in overnight dwell bag in 3rd week	400 mg IV 400 mg q12h × 3 doses 400 mg q72h	 Yes
Tobramycin	IV/IM	>30 <30	1.5-2.5 mg/kg q8-24h depending on age 3 mg/kg one dose	Yes	Yes
Trimethoprim/ sulfamethoxazole	IV	>30 15-30 <15	5 mg/kg q6-8h 2.5-5 mg/kg q12h 2.5-5 mg/kg q24h (All doses based on trimethoprim)	Yes	No
	PO	>30 <30	1DS q12h 1DS q24h 1DS = 160 mg of trimethoprim	Yes	No

Contd…

Contd…

Drug	Admin route	CrCl (mL/min)	Suggested dosage regimen	Supplement for dialysis	
				H/D[1]	*P/D*
Vancomycin	PO	(for psendo membranous colitis)	125 mg q6h No renal dose adjustment necessary		
	IV	 >50 30-50 <30	750 mg-1500 mg (depending on body weight) q12h q24h q12h × 2 (followed by random levels)	–	–

Calculation of Creatinine Clearance (CrCl):

$$\text{CrCl Male} = \frac{(140 - \text{aged})(\text{body weight})}{72 \times \text{serum creatinine}}$$

$$\text{CrCl Female} = \text{Male CrCl value} \times 0.85$$

Variables Included in Severity-of-illness Scoring Systems in Clinical Use

	APACHE II	APACHE III	MPM II_0 ADM	MPM II_{24}, 24 Hours	SAPS II
Age	x	x	x	x	x
Prior treatment location		x			
Type of admission	x	x	x	x	x
CPR prior to ICU admission			x		
Mechanical Ventilation			x	x	
Vasoactive drug therapy				x	
Acute Diagnoses					
Acute renal failure			x		
Cardiac dysrhythmias			x		
Cerebrovascular incident			x		
Gastrointestinal bleeding			x		
Confirmed infection				x	
Intracranial mass effect			x	x	

Contd…

Contd...

	APACHE II	APACHE III	MPM II_0 ADM	MPM II_{24}, 24 Hours	SAPS II
Acute Diagnoses					
Select one of 50 diagnoses	x				
Select one of 78 diagnoses		x			
Physiology					
Temperature	x	x			x
Heart rate	x	x	x		x
Respiratory rate	x	x			
Blood pressure	x	x	x		x
Hematocrit	x	x			
White blood cell count	x	x			x
Albumin		x			
Bilirubin		x			x
Glucose		x			
Serum sodium	x	x			x
Serum potassium	x				x
Serum bicarbonate					x
Blood urea nitrogen		x			x
Creatinine	x	x		x	
Urine output		x		x	x
PaO_2 or (A-a) DO_2 or FiO_2	x	x		x	x
pH and PCO_2	x	x			
Prothrombin time				x	
GCS or modified GCS score	x	x			x
Coma or deep stupor			x	x	
Chronic Health Status					
AIDS	x	x			x
Immunosuppression	x	x			x
Lymphoma*	x	x			x
Leukemia/multiple myeloma*	x	x			
Metastatic cancer		x	x	x	x

Contd...

Contd…

	APACHE II	APACHE III	MPM II_0 ADM	MPM II_{24}, 24 Hours	SAPS II
Chronic Health Status					
Hepatic failure	x	x			
Cirrhosis	x	x	x	x	
Chronic renal insufficiency	x		x		
Chronic heart insufficiency	x				
Chronic respiratory insufficiency	x				

* In SAPS II, these two criteria are grouped into one entity called hematologic malignancy.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; APACHE III, Acute Physiology and Chronic Health Evaluation III; MPM IIo, Mortality Probability Models II, assessment at ICU admission; MPM II_{24}, Mortality Probablity Models II, assessment 24 hours after ICU admission; SAPS II, Simplified Acute Physiology Score II; CPR, cardiopulmonary resuscitation; (A-a) DO_2, alveolar-arterial oxygen difference; FiO_2, Fraction of inspired oxygen; GCS, Glasgow Coma Scale; AIDS, acquired immunodeficiency syndrome, multiple myeloma, multiple myeloma.

Index

B

N