Quick Management Guide in Emergency Medicine

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Foreword

It has been exactly 20 years since I sat in the library of the Seremban Hospital and drafted the first edition of this book “Emergencies in Internal Medicine” by hand. My wife typed out the final draft on a mechanical typewriter. Hence, I am so happy that two decades later, a second edition with multi contributors will arrive in full digital format.

I am greatly honoured to have tutored Dr Lee Say Fatt two decades ago when he was a student in University Malaya. When he approached me to ask for permission to create a completely revised version in which specialists in their own field will each review and contribute a chapter, I was gratefully happy. More than a year has since passed and Dr Lee is finally ready to deliver this new baby! I am sure it will serve doctors as well as the original “Little Red Book” did.

The "Little Red Book" was written as a NON-PROFIT venture. It was sold at RM5, which was the cost price of the book. The spirit of sharing of knowledge and helping the young house-officers and medical officers prevails in this new edition. I congratulate the team on this effort.

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Preface

The primary intent of this book is to provide the busy doctor with a simple but adequate management guide in treatment of various medical emergencies. How did this book get started? It all started in 1988 when Dr Wong Yin Onn first published a small guidebook called “Emergencies in Internal Medicine”. This small book has served many young doctors at that time and I personally found it to be a great help in managing various medical emergencies. Somehow, no further edition was printed and the book was then forgotten. Fortunately, I found my old copy two years ago and felt that it is a waste to let it go. Therefore, I have contacted Dr Wong for his permission to update this book and published it as an ebook. In updating the book for this edition, I found that there were some sections which needed very little revision, yet other sections needed major rewrites. In certain instances, I have added entirely new chapters.

This ebook is not meant to compete with other much better emergency medicine guides, but to ensure that the doctors encountering medical emergencies will have at
least a simple, quick and adequate guidebook to enable them to manage their patient safely. There are numerous excellent medical textbooks out there, but these will become useless if one has no access to them to guide them managed their patient in the ward at 2 o’clock in the morning. This ebook has many appeals, particularly the superior search facilities, their instant accessibility, speedy availability and a whole host of other useful features. If you have a PDA phone, you will be able to access it anytime and anywhere.

We do not expect everyone to agree with the recommendations presented here. Such a disagreement is unavoidable, for medicine is not an exact science. We welcome feedbacks, questions or criticisms from the medical community so that we can improve in the future edition. We are open to contributions as well, so that we hope this ebook will grow in terms of the content and usefulness for the future generations of doctors working in the frontline of medical care. This ebook will not be restricted to Internal Medicine specialities but may include topics from other areas of medicine such as psychiatry, ophthalmology and other surgical disciplines. Therefore, we invite doctors to contribute contents to make it better and to participate in this ebook project. Let’s make it our project. In view of the widen scope of coverage, I have decided to change the name of this book from Emergencies in Internal Medicine (the first edition title) to Quick Management Guide in Emergency Medicine so that we can include all the other area of specialities in medicine in the future edition. Ultimately, we hope that this book will benefit our patients and ensure that they get the best care possible.

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October 2010

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This book would not have been possible without the generous support of many people. I was fortunate to know many doctors who are expert in their own respective fields in internal medicine and have been kind enough to contribute to the various chapters in this book. My sincere thanks and appreciation to all of them.

We are particularly grateful to the following persons for their contributions:

- Staffs of Merck Sdn Bhd and Dr Alex Leow Hwong Ruey – for converting the old edition into the Word document.
- Dr Tan Swee Looi – for script reading.
- Miss Wu Chin Huei (Chief Operating Officer) and Miss Leana Petrina Pelly (Legal Adviser) of Sime Darby Medical Centre Subang Jaya – for support and advise on copyright issues.
- Continence Foundation of Malaysia, particularly Dr Peter Ng for his assistance during the final stage of the project.
- Alex Toh for his artistic design of the cover
We would also like to thank Sanofi Aventis for their support and educational grant in helping us convert the whole content in Word Document into the ebook format.

Disclaimer

 Whilst appreciable care has been taken in the preparation of this ebook, it is not our intention to declare that this ebook contains the latest information on medical treatment in the field of emergency medicine. While attempts are made to be as accurate as possible, it should not be relied upon as being 100 % comprehensive or error-free. The copyright holder, all the contributors, developers, sponsors or anyone else connected to this ebook offer no warranty whatsoever that the contents of this ebook are suitable for the management of all patients and that the facts are current and up to date. As treatment is unique to each individual, the recommendations presented here may not be suitable for all patients. Any action on your part in response to the information provided in this ebook is at the reader's discretion. Readers should refer to other sources of information such as journals for detailed clinical guidelines and updates if in doubt. The user assumes all responsibility and risks for the use of this ebook. Under no circumstances, including negligence, shall anyone involved in creating or maintaining this ebook be liable for any direct, indirect, incidental, special or consequential damages, or lost profits that result from the use of this ebook in whatsoever way.

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About this release
Version 1.0 - All the contributors listed either edited or wrote the individual chapter in this version.

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   4.1 Acute Cardiogenic Pulmonary Edema
   4.2 Cardiogenic Shock
5. Management of Arrhythmias
6. Management of Severe Hypertension
7. Management of Anaphylactic Shock

Refer to these guidelines produced by the Ministry of Health, National Heart Association of Malaysia, Malaysian Society of Hypertension and Academy of Medicine, Malaysia.

- Clinical Practice Guidelines on UA / NSTEM 2002
- Clinical Practice Guidelines on STEMI 2007
- Clinical Practice Guidelines on Heart Failure 2007
- Clinical Practice Guidelines on Hypertension 2008

Download these guidelines from http://www.moh.gov.my or http://acadmed.org.my

1. Acute Coronary Syndromes (ACS)

Clinical definition

Acute coronary syndrome (ACS) is a clinical spectrum of ischaemic heart disease ranging from unstable angina (UA), Non-ST-Elevation Myocardial Infarction (NSTEMI) to ST-Elevation Myocardial Infarction (STEMI) depending upon the degree and acuteness of coronary occlusion.(refer Figure 1) The pathogenesis of UA, NSTEMI and STEMI are similar.

Patients presenting with ACS may be classified based on the presence of ST elevation in the resting ECG and / or the presence of elevated cardiac biomarkers into:

- **Unstable Angina (UA)**
  - ST segment is not elevated in the resting ECG
  - cardiac biomarkers are not elevated

- **Non ST Elevation Myocardial Infarction (NSTEMI, formerly known as NQMI)**
  - ST segment is not elevated in the resting ECG
  - presence of elevated cardiac biomarkers but generally not to that high levels

- **ST Elevation Myocardial Infarction (STEMI, formerly known as QwMI)**
  - ST Elevation seen in the resting ECG
  - presence of elevated cardiac biomarkers, usually at high levels

The clinical presentation of patients with UA, NSTEMI and STEMI are similar. The severity of the symptoms however varies, patients with UA having the mildest symptoms and those with STEMI having the most severe.
Adapted with modification from Antman EM, Anbe DT, Armstrong PW et al. “ACC/AHA Guidelines for the management of patients with ST Elevation Myocardial Infarction” at www.acc.org

Figure 1: Diagnosis of Acute Coronary Syndromes (ACS)
Chest pain

**History**

Concomitant initial management includes:

- Prop up patient
- Two i.v. lines, blood samples taken for cardiac biomarkers, FBC, renal function, sugar, lipid profile
- Sublingual GTN
- Give oxygen
- Continuous ECG monitoring
- Aspirin (300 mg stat)
- Clopidogrel (300 mg stat)
- i.v morphine

**ECG**
- Cardiac Biomarkers (troponins, CK, CKMB)

**Specific therapy**

- Aspirin (75-150mg daily)
- Clopidogrel (75 mg daily)
- β - Blockers
- ACEI / ARB
- Statins
- Nitrates
- *Calcium antagonists
- *Aldosterone antagonists

* when clinically indicated

**Flow chart 1: Management of patients presenting with Acute Coronary Syndrome.**
Management of Unstable Angina / Non ST Elevation Myocardial Infarction (UA/NSTEMI)

2.1 Clinical diagnosis of UA / NSTEMI

**History**
- Patients with UA and NSTEMI present with:
  - Chest pain – typically retrosternal, central or in the left chest, may radiate to the jaws or down the left upper limb, often described as crushing, pressing or burning in nature.
  - Atypical presentations include unexplained fatigue, shortness of breath, epigastric discomfort, nausea or vomiting.
  - Some may present in acute left ventricular failure.

**ECG Changes**
- The resting ECG may be completely normal.
- An ECG done during an episode of chest pain is most valuable.
- There may be ST segment depression and / or T wave inversion.

**Cardiac Biomarkers**
- In UA the cardiac biomarkers are not elevated whereas in NSTEMI they are raised but their levels are not high.
- Cardiac troponins are the primary cardiac biomarkers for UA and NSTEMI. These may not rise till about 3-8 hours after a myocardial infarction (MI). Thus, too early a measurement may result in a misleadingly low level. (refer Figure 2)

![Figure 2: Time Course of Elevation of Serum Cardiac Biomarkers after a Myocardial Infarction](image)

2.2 Risk Stratification

Patients with UA / NSTEMI have an increased risk of death, recurrent MI, recurrent symptomatic ischaemia, serious arrhythmias, heart failure and stroke.

All patients should be risk stratified at presentation. This risk should be continuously reassessed during the patient's hospital stay since it may change over time as the disease progresses. Risk stratification will help guide appropriate therapy such as the use of glycoprotein IIb / IIIa antagonists and the need for an early invasive strategy in high risk individuals.

**A. Patients with UA / NSTEMI who at HIGH RISK for death or MI:**

- Patients with severe symptoms:
  - recurrent ischaemia (either with accelerating tempo of ischaemic symptoms in preceding 48 hours or prolonged ongoing [> 20 min] rest pain)
  - rest angina which is not relieved with nitrates
  - early post infarction angina
  - previous or prior revascularisation (coronary artery bypass graft, percutaneous coronary intervention)
  - prior aspirin therapy of less than 7 days

- Patients with haemodynamic instability within the observation period:
  - pulmonary oedema
  - new or worsening mitral regurgitation
  - hypotension, bradycardia or tachycardia

- Patients with ECG abnormalities:
  - dynamic ST segment changes > 0.5mV, particularly ST segment depression
  - transient ST segment elevation
  - T wave inversion > 0.2mV
  - pathological Q waves
  - bundle branch block, new or presumed new
  - sustained ventricular tachycardia

- Patients with elevated troponin levels

- Patients with left ventricular dysfunction and left ventricular ejection fraction (LVEF) < 40%

**B. Patients at LOW RISK for death or MI:**

- Patients with no recurrence of chest pain within the observation period.
- Patients without ST segment depression or elevation but rather negative T waves, flat T waves or normal ECG.
- Patients without elevation of troponin levels or other cardiac biomarkers.

Patients may also be risk stratified using the TIMI risk score. This is determined by the sum of the presence of 7 variables at admission - 1 point is given for each of the following variables:

- Age 65 y or older
- At least 3 risk factors for coronary artery disease (family history of premature coronary artery disease)
hypertension, elevated cholesterol, active smoker, diabetes
Known CAD (coronary stenosis of > 50%)
Use of aspirin in prior 7 days
ST-segment deviation (>0.5mm) on ECG
At least 2 anginal episodes in prior 24 hours
Elevated serum cardiac biomarkers

Total Score = 7 points
Low Risk : < 2 point; Moderate Risk: 3-4 points ; High Risk : >5 points

2.3 Management

Management of patients presenting with UA / NSTEMI is as outlined in Flowchart 1 and Flowchart 2.

A. General Measures
- High risks patients should be monitored in the Critical Care Unit / High Dependency Unit looking for signs of ongoing ischaemia, arrhythmias and heart failure.

B. Concomitant Therapy
I. Oxygen
- Oxygen is indicated in the presence of hypoxemia.
- Oxygen, via nasal prongs, at 2 - 4 litres/min is usually adequate. One should aim to maintain the oxygen saturation above 95%.

II. Morphine
- Morphine is recommended for patients with persistent or recurrent symptoms despite anti-anginal therapy.
- The dose is 2-5 mg administered intravenously every 5-15 minutes until pain is relieved. Watch for evidence of toxicity – hypotension and respiratory depression. Anti-emetics (i.v. metoclopromide 10mg or promethazine 25 mg) should be given.

III. Anti platelet Agents
Aspirin
- Aspirin is indicated in all patients at diagnosis and should be continued indefinitely unless contraindicated.
- The initial dose of 300 mg should be followed by a maintenance dose of 75 – 150 mg daily.

Clopidogrel
- Clopidogrel should be initiated at the time of diagnosis if there are no contraindications.
- A loading dose of 300 mg should be given followed by a maintenance dose of 75 mg daily.
- It should be continued for at least a month and ideally for at least a year.

Ticlopidine
This may be used as an alternative to clopidogrel at a dose of 250 mg b.d.

Ticlopidine is associated with neutropenia in 2.4% of patients. Blood counts should be checked periodically during the first 3 months. If neutropenia (<1500 neutrophils/mm) or thrombocytopenia (<100,000 platelets/mm) develops, the drug should be withdrawn.

### IV. Anti thrombotic Agents

The antithrombotic agents that have been studied in UA / NSTEMI are:

- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
- Synthetic pentasaccharide – fondaparinux
- Unfractionated heparin (UFH) or low molecular weight heparin should be given for 2-7 days or until hospital discharge. Refer Table 1 for dosages.

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Dosage</th>
<th>Target aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enoxaparin</strong>*(LMWH)*</td>
<td>Age &lt; 75 years 30 mg i.v. bolus, s.c 1.0 mg/kg b.d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≥ 75 years No bolus, s.c 0.75 mg/kg b.d</td>
<td></td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong>(UFH)</td>
<td>60 U/kg bolus (max 4000 U)</td>
<td>aPTT should be 1.5 - 2 X normal or approximately 60 - 80 seconds.</td>
</tr>
<tr>
<td></td>
<td>Infusion 12 U/kg/h (max 1000 U/h)</td>
<td></td>
</tr>
<tr>
<td><strong>Fondaparinux</strong>**</td>
<td>s.c 2.5 mg/kg daily</td>
<td></td>
</tr>
</tbody>
</table>

* Reduce dose in renal impairment  
** Avoid if creatinine clearance is < 30 ml/minute

**Table 1: Recommended dosages of Anti Thrombotic Agents in UA / NSTEMI**

### V. Platelet Glycoprotein (GP) IIb / IIIa Receptor Antagonists

- These block the GP IIb / IIIa receptor which is involved in the final step of platelet aggregation.
- The benefit associated with the use of these agents was seen mainly in patients with on-going ischaemia or with other high risks features such as an elevated troponin level.
- Abciximab is most useful as part of an early revascularisation strategy (ie early invasive strategy, refer section C).
- Eptifibatide and Tirofiban have been shown to reduce death or MI if started several days prior to angiography. (“upstream” use)
- Refer Table 2 for dosages.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abciximab</strong></td>
<td><strong>Upstream Use</strong></td>
</tr>
<tr>
<td>(Reopro)</td>
<td>i.v. bolus: 0.25 mg/kg for 18-24 hours before the procedure</td>
</tr>
<tr>
<td></td>
<td>Followed by continuous infusion of 0.125 ug/kg/min (max 10 ug/min) for 12 hours</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>i.v. bolus: 0.25 mg/kg for 10-60 minutes before the start of PCI</td>
</tr>
<tr>
<td></td>
<td>Followed by continuous infusion of -0.125 ug/kg/min (max 10ug/min) for 12 hours</td>
</tr>
<tr>
<td><strong>Eptifibatide</strong></td>
<td><strong>Upstream Use</strong></td>
</tr>
<tr>
<td>(Integrilin)</td>
<td>i.v. bolus: 180 ug/kg</td>
</tr>
<tr>
<td></td>
<td>*Followed by infusion of 2 ug/kg/min for 72 hours or hospital discharge</td>
</tr>
<tr>
<td></td>
<td>In the case of PCI, infusion continued for 96 hours</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>i.v. bolus: 180 ug/kg</td>
</tr>
<tr>
<td></td>
<td>Followed by infusion 2 ug/kg/min</td>
</tr>
<tr>
<td></td>
<td>Then a second 180 ug/kg bolus after 10 minutes</td>
</tr>
<tr>
<td></td>
<td>*Infusion should be continued till hospital discharge, up to 18-24 hours</td>
</tr>
<tr>
<td><strong>Tirofiban</strong></td>
<td><strong>Upstream Use</strong></td>
</tr>
<tr>
<td>(Aggrastat)</td>
<td>i.v. bolus: 0.4 ug/kg/min for 30 minutes</td>
</tr>
<tr>
<td></td>
<td>**Followed by infusion 0.1ug/kg/min for 48-108 hours</td>
</tr>
<tr>
<td></td>
<td>In the case of PCI, the infusion should be continued for 12-24 hours after PCI</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td>i.v. bolus: 0.4 ug/kg/min over 30 minutes</td>
</tr>
<tr>
<td></td>
<td>**Followed by infusion of 0.1 ug/kg/min for 18-24 hours</td>
</tr>
</tbody>
</table>

* Reduce the infusion rate by 50% in the presence of creatinine clearance less than 50mL/min
** Reduce the infusion rate by 50% if the creatinine clearance is less than 30mL/min

**Table 2: Recommended dosages of GP IIb / IIIa Receptor Antagonists**

**VI. Nitrates**
- IV GTN should be used in patients who:
  - do not get symptomatic relief with three 0.5 mg sublingual GTN tablets
- have ECG evidence of myocardial ischaemia
- have concomitant heart failure
- In normotensive patients, the systolic blood pressure (SBP) should not fall below 110mmHg
- In hypertensive patients, the mean arterial BP should not drop by more than 25%
- Oral nitrates may be commenced after a pain free period of 12-24 hours
- Rebound angina may occur after abrupt cessation of nitrates
- Refer Table 3 for dosages

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dosage</th>
<th>Time of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine, Glyceryl trinitrate</td>
<td>Intravenous</td>
<td>5 - 200µg/min*</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>Sublingual</td>
<td>0.3 - 0.6mg, can repeat up to 3 times at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>GTN Spray</td>
<td>0.4 - 0.8mg per metered dose, no more than 3 sprays at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>0.2 - 0.8mg over 12 hours on, then 12 hours off</td>
<td>1 - 2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Intravenous</td>
<td>1.25 - 5mg / hour</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>2.5 - 10mg</td>
<td>3 - 4 minutes</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10 – 20mg, 2 – 3 times daily</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>20 - 30mg, 2 - 3 times daily, up to 120mg in divided doses</td>
<td>30 - 60 minutes</td>
</tr>
</tbody>
</table>

*The dose of IV nitrates should be titrated every 5 - 10 minutes until symptoms and / or ischaemia is relieved and the desired haemodynamic response is obtained

Table 3: Recommended doses of Nitrates in UA / NSTEMI

VII. β-blockers
- β-blockers should be used in all patients without specific contraindications.
- Contraindications to β – blockers are:
  - bradycardia < 60/minute
  - SBP < 100mmHg
- pulmonary congestion with crepitations beyond the lung bases
- signs of peripheral hypoperfusion
- second or third degree atrio-ventricular (AV) block
- asthma or chronic obstructive airway disease (COAD)
- severe peripheral vascular disease

- The target resting heart rate is 50-60/min
- Refer Table 4 for dosages

<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>25 mg b.d</td>
<td>100 mg b.d</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25 mg o.d</td>
<td>100 mg o.d</td>
</tr>
<tr>
<td>Propranolol</td>
<td>5 mg t.d.s</td>
<td>80 mg t.d.s</td>
</tr>
</tbody>
</table>

Table 4: Recommended dosages of β-blockers in UA / STEMI

VIII. Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)
- ACEI should be prescribed and continued indefinitely in all patients if there are no contraindications. (refer Table 5 for dosages)
- They are most beneficial in patients with:
  - heart failure
  - left ventricular dysfunction (LVEF< 40%)
  - hypertension
  - diabetes
- Patients who are intolerant of an ACEI, should be given an ARB if they have clinical or radiological signs of heart failure and LVEF < 40%.
- Contraindications to ACEI and ARB therapy:
  - SBP < 100mmHg
  - established contraindications e.g. bilateral renal artery stenosis, worsening renal function.
<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg b.d – t.d.s</td>
<td>25 – 50 mg t.d.s</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg b.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 – 5 mg o.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5 mg o.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg o.d</td>
<td>4 mg o.d</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80 mg o.d</td>
<td>160 mg o.d</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 mg o.d</td>
<td>100 mg o.d</td>
</tr>
</tbody>
</table>

Table 5: Recommended dosages of ACEI and ARB in UA / NSTEMI

IX. Calcium Antagonists
- These agents may be used in patients with continuing or recurrent angina who are already on adequate doses of nitrates and β-blockers or those who are unable to tolerate nitrates and / or β-blockers. Refer Table 6 for dosages.
- Prinzmetal’s angina (variant angina)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Immediate release: 30-120 mg t.d.s</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Slow release: 100-360 mg od</td>
<td>Long</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release: 40-160 mg t.d.s</td>
<td>Short</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-480 mg o.d</td>
<td>Long</td>
</tr>
</tbody>
</table>

Table 6: Recommended dosages of Calcium Antagonists in UA / STEMI

X. Statins
- Statins are beneficial in UA / NSTEMI and should be started early irrespective of the serum lipid levels.

XI. Aldosterone antagonists
- Aldosterone antagonists (spironolactone, epleronone) should be given to patients with:
  - symptomatic heart failure
  - LVEF < 40%
They should be used with caution in patients with:
- significant renal dysfunction (creatinine clearance less than 30mL/min)
- hyperkalemia (potassium should be less than or equal to 5 mEq/L)

C. Revascularisation

- There are 2 management strategies in patients presenting with UA / NSTEMI:
  - Early conservative strategy – coronary angiogram is reserved for patients with evidence of ischemia despite optimal medical therapy
  - Early invasive strategy – all patients without specific contraindications are subjected to coronary angiography and revascularization as indicated
- An early invasive strategy is recommended in high risk patients with UA / NSTEMI.
- An early invasive strategy is not recommended in patients with extensive co-morbidities and low risk individuals.
- The final decision on which strategy is most appropriate for the patient should however be individualized.

If an early conservative strategy is adopted, then the following should be assessed during the hospital stay and follow up:

- left ventricular function - by clinical, chest X-ray, echocardiogram, radionuclide studies or cardiac MRI
- presence of myocardial ischaemia by -
  - clinical (recurrent angina)
  - exercise stress testing in asymptomatic patients
  - for those who cannot exercise, consider dobutamine stress echocardiogram, radionuclide perfusion studies or cardiac MRI
- presence of myocardial ischemia and / or depressed left ventricular function (LVEF < 40%) is an indication for coronary angiography and myocardial revascularisation as appropriate.

D. Post discharge therapy

Following discharge, patients should be:

- continued on the medications that were required to control their ischemia in hospital. This should include:
  - Aspirin
  - Clopidogrel or ticlopidine for at least a month and ideally for at least a year
  - β-blockers (try to maintain resting heart rate 50-60/min)
  - nitrates
  - ACEI or ARB
  - Statins
- instructed on the use of sublingual or spray GTN
- advised on the symptoms of recurrent or worsening ischemia and instructed to seek early medical attention
Chest pain

Initial Management

- UFH / LMWH
- Nitrates (i.v. or oral)
- β-blockers
- *GP IIb / IIIa Antagonists

UA / NSTEMI

ECG
Cardiac biomarkers

Concomitant therapy

Risk stratification

Low Risk
(TIMI risk score < 2)

Medium and High Risk
(TIMI risk score > 2)

Early Invasive Strategy

Early Conservative Strategy

spontaneous recurrent ischemia +/- LV failure

Yes

No

**Inducible ischaemia

Diagnostic coronary angiography

Yes

No

LVEF < 40%

Yes

No

Revascularisation as indicated

Medications on discharge (refer Flowchart 1)

* when clinically indicated

** by exercise stress test, dobutamine stress echocardiogram or cardiac MRI

Flow chart 2: Management of patients presenting with UA / NSTEMI
3. MANAGEMENT OF ACUTE ST ELEVATION MYOCARDIAL INFARCTION (STEMI)

3.1 Clinical diagnosis of STEMI

It is diagnosed by:
- clinical history of ischaemic type chest pain
- ECG changes – The following are integral to the diagnosis of STEMI:
  - New onset ST-segment elevation of:
    - $\geq 0.1$ mV in 2 contiguous limb leads, or V4 to V6 and/or
    - $\geq 0.2$ mV in 2 contiguous precordial leads V1 to V3 OR, presumed new left-bundle branch block
  - evidence of myocardial injury or necrosis as indicated by elevated serum cardiac biomarkers.

History

- Chest pain of STEMI is typically retrosternal, severe, crushing, squeezing or pressing in nature, lasting more than 30 minutes, associated with profuse sweating, nausea, vomiting and shortness of breath.
- Diabetics, the elderly and females may not present with typical chest pains. Common presenting symptoms in these patients are dyspnoea and atypical chest pains.

Electrocardiographic changes

- The evolving ECG changes of STEMI are:
  - hyperacute changes of a tall peaked T-wave,
  - ST segment elevation,
  - followed by the development of Q-waves,
  - return of the ST segment to isoelectric and
  - T-wave inversion.
- However in some cases, the ECG may be normal or equivocal. If the clinical index of suspicion of STEMI is high, 12 lead ECG tracings repeated at close intervals of at least 15 minutes might show evolving changes.
- In patients with an inferior infarct, one should look for associated posterior, lateral and RV infarct. The latter requires right sided chest leads for diagnosis.
- For localization of infarct refer Table 7.

Serum Cardiac Biomarkers

- A rise and fall in the levels of serum cardiac biomarkers support the diagnosis of STEMI. One should not, however, wait for the results of these biomarkers before initiating reperfusion therapy. These cardiac biomarkers include:
  - cardiac troponins (cTnT and cTnI)
  - creatine kinase-myocardial band (CK-MB)
  - creatine kinase (CK)
  - myoglobin
  - fatty acid binding proteins
For the relative timing, rate of rise, peak value, duration of elevation and properties of these cardiac biomarkers following STEMI, refer to Figure 2.

<table>
<thead>
<tr>
<th>Location</th>
<th>Leads</th>
<th>ECG findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteroseptal</td>
<td>V1 – V3</td>
<td>ST elevation, Q wave</td>
</tr>
<tr>
<td>Extensive anterior</td>
<td>V1 – V6</td>
<td>ST elevation, Q wave</td>
</tr>
<tr>
<td>Posterior</td>
<td>V7 – V8</td>
<td>ST elevation, Q wave</td>
</tr>
<tr>
<td>Posterior</td>
<td>V1 – V2</td>
<td>ST depression, R wave</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>I, AVL, V5 – V6</td>
<td>ST elevation, Q wave</td>
</tr>
<tr>
<td>Inferior</td>
<td>II, III, AVF</td>
<td>ST elevation, Q wave</td>
</tr>
<tr>
<td>Right Ventricular</td>
<td>V4R, V5R</td>
<td>ST elevation, Q wave</td>
</tr>
</tbody>
</table>

Table 7: ECG patterns of various STEMI locations

3.2 Management of STEMI

3.2.1 Immediate therapy

The following should be done immediately and concomitantly in the emergency department (refer to Flowchart 3):

- Assessment and stabilization of the patient's haemodynamics
- Sublingual GTN if chest pain persists (unless SBP < 90 mmHg)
- Continuous ECG monitoring
- 300 mg of aspirin chewed and swallowed if not given earlier
- Clopidogrel at a dose of 300 mg should be given if not given earlier
- Oxygen by nasal prongs / facemask
- Venous access established and blood taken for cardiac biomarkers, full blood count, renal profile, glucose and lipid profile. Preferably 2 intravenous lines should be set up.
- Pain relief - morphine should be administered intravenously at 2 to 5 mg every 5-15 minutes until pain is relieved. Watch for evidence of toxicity – hypotension and respiratory depression. Anti-emetics (i.v. metoclopramide 10 mg or promethazine 25 mg) should be given.
- Intramuscular injections should be avoided
- Assessment for reperfusion strategy – Primary Percutaneous Coronary Intervention (PCI) or fibrinolytic therapy

3.2.2 Reperfusion Strategies

- Early and prompt reperfusion is crucial as TIME LOST is equivalent to MYOCARDIUM LOST.
Most studies indicate that primary PCI is superior to fibrinolytic therapy as a reperfusion strategy.

However in patients who present within 3 hours of symptom onset and are at low risk, both treatment strategies appear to have similar benefits.

The best reperfusion strategy will depend upon:

A. Time from onset of symptoms
B. Contraindications to fibrinolytic therapy
C. High risk patients
   - These include patients with:
     - large infarcts
     - anterior infarcts
     - cardiogenic shock
     - elderly patients
     - post revascularization (post CABG and post PCI)
     - post infarct angina

Primary PCI is the preferred strategy in these high risk patients.

The goals of time to reperfusion therapy should be within:

- 30 minutes door to needle time for thrombolytic therapy
- 90 minutes door to balloon time for Primary PCI

I. Fibrinolytic Therapy

a. Indications - Fibrinolytic therapy should only be given to patients with STEMI.

b. Contraindications

**Absolute contraindications**

*Risk of Intracranial haemorrhage*
- any history of intracranial haemorrhage
- ischaemic stroke within 3 months
- known structural cerebral vascular lesion (e.g. arteriovenous malformation)
- known intracranial neoplasm

*Risk of bleeding*
- active bleeding or bleeding diathesis (excluding menses)
- significant head trauma within 3 months
- suspected aortic dissection

**Relative contraindications**

*Risk of intracranial haemorrhage*
- severe uncontrolled hypertension at presentation (BP > 180/110 mm Hg)*
- ischaemic stroke more than 3 months ago
- history of chronic, severe uncontrolled hypertension

*Risk of Bleeding*
- current use of anticoagulation in therapeutic doses (INR > 2)
- recent major surgery < 3 weeks
- traumatic or prolonged CPR >10 minutes
- recent internal bleeding (e.g. gastrointestinal or urinary tract haemorrhage) within 4 weeks
- non-compressible vascular puncture
- active peptic ulcer

Others
- pregnancy
- prior exposure (>5 days of first usage) to streptokinase (if planning to use same agent)

*The blood pressure should be reduced prior to institution of fibrinolytic therapy.*

c. Choice of Fibrinolytic Agent
Presently the agents available in Malaysia are:

- Streptokinase - 1.5 mega units in 100 ml normal saline or 5% dextrose over 1 hour.
- Alteplase
  - For patients > 65 kg - 15 mg bolus; then 50 mg over 30 minutes and 35 mg over the next 60 minutes.
  - For patients < 65 kg - 15 mg bolus; then 0.75 mg/kg over 30 minutes and 0.5 mg/kg over the next 60 minutes.
- Tenecteplase
  - Single i.v. bolus
    - 30 mg if < 60kg
    - 35 mg if 60 to < 70kg
    - 40 mg if 70 to < 80kg
    - 45 mg if 80 to < 90kg
    - 50 mg if > 90kg

Heparin needs to be given for at least 48 hours following the administration of alteplase and tenecteplase.

d. Indicators of successful reperfusion
Some useful guides are:
- resolution of chest pain (may be confounded by the use of narcotic analgesics)
- early return of ST segment elevation to isoelectric line or a decrease in the height of the ST elevation by 50% within 60 - 90 minutes of initiation of fibrinolytic therapy
- early peaking of CK and CK-MB levels
- restoration and / or maintenance of haemodynamic and / or electrical stability

e. Failed fibrinolysis
- This is manifested as continuing chest pain, persistent ST segment elevation and haemodynamic instability. These patients are more likely to develop complications such as heart failure and arrhythmias.
- The treatment of choice for these patients is rescue PCI.

II. Percutaneous Coronary Intervention (PCI)
a. Primary PCI - This is the reperfusion strategy of choice.

b. Facilitated PCI - This is not recommended.

c. Rescue PCI – This may be considered in patients who have failed fibrinolytic therapy or have recurrent chest pain and / or ischaemic complications. Those who may benefit are patients with:
   - ongoing chest pains
   - haemodynamic and electrical instability
   - cardiogenic shock in patient < 75 years old, within 36 hours of STEMI and <18 hours of shock whose coronary anatomy is suitable for revascularisation
   - heart failure and onset of chest pain within 12 hours

   This strategy is associated with high mortality and morbidity rates. As such, patients should be individually evaluated.

d. Delayed PCI (> 72 hours after fibrinolytic therapy) - routine angiography and PCI in asymptomatic and stable patients post fibrinolytic therapy is controversial.

3.3 Concomitant Therapy

I Oxygen

II Anti-platelet agents
   a. Aspirin - The initial dose of 300 mg should be followed by a maintenance dose of 75 to 150 mg daily.
   b. Clopidogrel - A loading dose of 300 mg should be given followed by a maintenance dose of 75 mg daily.
   - Dual anti-platelet therapy is recommended for at least 1 month after fibrinolytic therapy.
   - Following PCI, a longer period of dual anti-platelet therapy is necessary particularly when drug-eluting stents are used.

III β-blockers
   - Oral β-blockers should be used early in all patients without specific contraindications. (refer Table 8 for dosages)
   - Contraindications to β - blockers:
     - bradycardia < 60/minute
     - SBP < 100 mmHg
     - pulmonary congestion with crepitations beyond the lung bases
     - signs of peripheral hypoperfusion
     - second or third degree atrio-ventricular (AV) block
     - asthma or chronic obstructive airway disease ( COAD)
     - severe peripheral vascular disease
<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>25 mg b.d</td>
<td>100 mg b.d</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25 mg o.d</td>
<td>100 mg o.d</td>
</tr>
<tr>
<td>Propranolol</td>
<td>5 mg t.d.s</td>
<td>80 mg t.d.s</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg b.d</td>
<td>25 mg b.d</td>
</tr>
</tbody>
</table>

Table 8: Recommended dosages of β-blockers in STEMI

IV Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)

- Early use of ACEI (within 24 hours) following STEMI has been shown to improve survival. (refer Table 9 for dosages)
- ACEI should be started when the blood pressure is stable and SBP remains above 100 mmHg.
- In patients who cannot tolerate ACEI, the ARB, Valsartan, has been shown to have a similar survival benefit.
- Contraindications to ACEI and ARB therapy:
  - SBP < 100 mmHg
  - established contraindications e.g. bilateral renal artery stenosis, worsening renal function.

<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg b.d –t.d.s</td>
<td>25 – 50 mg t.d.s</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg b.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 – 5 mg o.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5 mg o.d</td>
<td>10 mg o.d</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg o.d</td>
<td>4 mg o.d</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80 mg o.d</td>
<td>160 mg b.d</td>
</tr>
</tbody>
</table>

Table 9: Recommended dosages of ACEI and ARB in STEMI

V Nitrates

- The routine use of nitrates has not been shown to have a survival benefit.
- Nitrates can be considered in patients with:
  - continuing chest pain and / or ischaemia
  - heart failure
  - hypertension
- In the acute stage, i.v nitrates are recommended. After the first 48 hours, oral or topical nitrates may be continued in patients with persisting ischaemia and / or heart failure. (refer Table 10 for dosages)
- Contraindications to nitrate therapy:
  - hypotension (SBP< 90vmmHg)
  - Right ventricular infarction
  - history of phospho-diesterase 5 inhibitors ingestion depending upon the half-life of the agent.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dosage</th>
<th>Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine, Glyceryl trinitrate</td>
<td>Intravenous</td>
<td>5 – 200 µg/min*</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>Sublingual</td>
<td>0.3 - 0.6 mg, can repeat up to 3 times at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>GTN Spray</td>
<td>0.4 - 0.8 mg per metered dose, no more than 3 sprays at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>0.2 - 0.8 mg over 12 hours on, then 12 hours off</td>
<td>1 - 2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Intravenous</td>
<td>1.25 – 5 mg / hour</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>2.5 – 10 mg</td>
<td>3 - 4 minutes</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10 – 20 mg, 2 – 3 times daily</td>
<td>30-60 minutes</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>20 – 30 mg, 2 - 3 times daily, up to 120 mg in divided doses</td>
<td>30 - 60 minutes</td>
</tr>
</tbody>
</table>

*The dose of IV nitrates should be titrated every 5 - 10 minutes until symptoms and / or ischaemia is relieved and the desired haemodynamic response is obtained

Table 10: Recommended doses of Nitrates in STEMI

VI  Calcium Channel Blockers
There is no data to support the routine use of calcium channel blockers post STEMI. However they may be used as adjunctive therapy in patients with hypertension and / or on-going ischaemia despite β-blockers and nitrates.

VII Antithrombotic Agents

The antithrombotic agents that have been studied in STEMI (see Table 11 for dosages) are:

- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
- Synthetic pentasaccharide (fondaparinux)

Heparin is indicated in patients with:

- post infarct angina
- atrial fibrillation
- mural thrombus
- extensive anterior infarction
- post fibrin-specific fibrinolytic agent

a. Unfractionated heparin (UFH)
   Unfractionated heparin is administered as a bolus of 60 units/kg (maximum 4000 units) followed by an infusion rate of 12 units/kg/hour (maximum 1000 units/hour) adjusting the dose to maintain the aPTT (activated partial thromboplastin time) of 1.5 to 2.5 times control.

b. Low molecular weight heparin (LMWH)
   Low molecular weight heparin (LMWH) – it is given subcutaneously twice a day. In patients >75 years of age and with renal impairment (serum creatinine > 200 umol/L in women and >250 umol/L in men), UFH is preferable to LMWH.

c. Synthetic pentasaccharide (fondaparinux)
   Synthetic pentasaccharide (fondaparinux) - fondaparinux is given at a dose of 2.5 mg/kg per day for 8 days, or the duration of index hospitalization. In patients who were given fibrinolytic agents or who were not reperfused, it was shown to be beneficial.
<table>
<thead>
<tr>
<th>Heparin</th>
<th>Dosage</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>&lt; 75 year: i.v bolus 30 mg, s.c 1 mg/kg b.d</td>
<td>Until hospital discharge</td>
</tr>
<tr>
<td></td>
<td>≥ 75 year: No bolus, s.c 0.75 mg/kg b.d</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>60 U/kg bolus (max 4000 U)</td>
<td>≥ 48 hours</td>
</tr>
<tr>
<td></td>
<td>Infusion 12 U/kg/h (max 1000 U/hour)</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>s.c 2.5 mg/kg daily</td>
<td></td>
</tr>
</tbody>
</table>

* Reduce dose in renal impairment  
** Avoid if creatinine clearance is < 30 ml/minute

Table 11: Recommended dosages of Anti thrombotic Agents in STEMI

VIII Glycoprotein (GP) IIb / IIIa Receptor Antagonists - Glycoprotein IIb / IIIa receptor inhibitors are used mainly in the setting of primary PCI.

IX Statins - recent data has shown that statins started within 24 hours of admission or continued after admission leads to a reduction in major adverse cardiac events.

X Aldosterone Antagonists - Eplerenone, a selective aldosterone receptor antagonist, when added to β-blockers and ACEI, has been shown to be reduce mortality and hospitalizations. It is given to patients post MI with impaired LV function and with mild heart failure.
Complications of STEMI
These are:

3.4.1 arrhythmias
3.4.2 left ventricular dysfunction and shock
3.4.3 mechanical complications
3.4.4 right ventricular infarction
3.4.5 others e.g. pericarditis
3.4.1 Arrhythmias (see section on Management of Arrhythmias)

These include:

A. Tachyarrhythmias

I  Pulseless ventricular tachyarrhythmias.
   → This includes pulseless ventricular tachycardia and ventricular fibrillation.
   → Defibrillate immediately.
   → Early ventricular fibrillations (VF) occurs within the first 48 hours and is due to electrical instability.
   → Late VF is associated with large infarcts and poor pump function and carries a poor prognosis (refer to section on Arrhythmias - algorithm 1).
   → [Shockable waves refers to the presence of recognizable organized or disorganized cardiac rhythms on continuous ECG monitoring while non shockable waves refers to the absence of any heart rhythm on ECG monitoring]

II  Stable Ventricular Tachycardia (VT).
   → Ventricular tachycardia in the setting of STEMI may arise from either ischaemia or from myocardial scar resulting from the infarct.
   → Treatment of ischaemia may result in the termination of the tachycardia. (refer to section on Arrhythmias - algorithm 2).

III Ventricular Premature Contractions (VPC).
   → These are often benign and do not require treatment.
   → Correct underlying ischaemia, hypoxia and electrolyte disturbances.

IV Accelerated Idioventricular Rhythm (AIVR).
   → These do not require any treatment.
   → This is a sign suggestive of successful reperfusion.

V Atrial fibrillation (AF).
   → This is more commonly seen in the elderly and is associated with large infarcts and atrial infarcts.
   → It denotes a poorer prognosis and carries an increased risk of thromboembolism. (refer to section on Arrhythmias - algorithm 3).

B. Bradyarrhythmias

These are:

I  Sinus bradycardia.
   → This does not require treatment unless associated with symptoms and / or hypotension.

II Atrio-ventricular Block (AV Block).
First degree and second degree type 1 (Mobitz 1) do not need treatment.

Patients with second degree type 2 (Mobitz 2) and complete AV block may not require treatment if haemodynamically stable.

In patients who are haemodynamically unstable, arrangements must be made for urgent temporary pacing. Atropine may be given in the interim. (maximum 3 mg) (refer to section on Arrhythmias - algorithm 4)

In patients with anterior infarct, second degree and complete AV block carry a worse prognosis. They may require urgent temporary pacing (refer to section on Arrhythmias - algorithm 4)

III Asystole / Pulseless Electrical Activity

Asystole / Pulseless electrical activity can be differentiated from pulseless ventricular tachyarrythmias by the presence of shockable waves on ECG monitoring. (refer to section on Arrhythmias - algorithm 4)

3.4.2 Left Ventricular Dysfunction and Shock

A. Presentation:

The clinical manifestation of left ventricular dysfunction varies from asymptomatic to cardiogenic shock.

An important prognostic indicator is left ventricular (LV) function which can be assessed objectively using echocardiography.

A useful clinical classification is the Killip's Classification (refer to table 12)

<table>
<thead>
<tr>
<th>KILLIP CLASS</th>
<th>Clinical features</th>
<th>Approximate proportion of patients with AMI (%)</th>
<th>30 day - Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No signs of LV failure</td>
<td>71.0</td>
<td>7.0</td>
</tr>
<tr>
<td>II</td>
<td>S3 gallop, bibasal crackles</td>
<td>23.0</td>
<td>20.0</td>
</tr>
<tr>
<td>III</td>
<td>Acute pulmonary oedema</td>
<td>3.7</td>
<td>39.0</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiogenic shock</td>
<td>2.4</td>
<td>70.0</td>
</tr>
</tbody>
</table>

Table 12: Clinical and Haemodynamic Subsets in AMI

B. Differential diagnoses of LV dysfunction and shock

Differential diagnoses are:

- pump failure due to extensive myocardial infarction
→ mechanical complications
→ right Ventricular infarction
→ hypovolemia
→ arrhythmias
→ drugs
→ aortic root dissection.

C. Investigations
Investigations that may be helpful in making the diagnosis and in the management includes:
→ chest radiograph
→ ECG
→ echocardiography
→ arterial blood gases
→ pulmonary artery catheter

D. Management
➢ Heart Failure- see section on Acute Heart Failure
➢ Cardiogenic shock – see section on Acute Heart Failure
→ Cardiogenic shock is defined as a SBP of < 90 mmHg associated with signs of tissue hypoperfusion, and central filling pressure (PCWP) is > 20 mmHg or cardiac index is < 1.8L/min/m².
→ This condition is associated with a very high mortality rate.
→ Emergency Percutaneous Coronary Intervention (PCI) may be life-saving and should be considered early. Intra-aortic balloon pump may be useful.
→ When cardiogenic shock is due to a mechanical defect, urgent surgical repair is indicated.
→ Pre-operative coronary angiography and subsequent coronary artery bypass graft (CABG) surgery in these patients remain an issue of debate. The decision must be individualized.

3.4.3 Mechanical complications
• These include the following:
  ➢ free wall rupture
  ➢ ventricular septal rupture
  ➢ papillary muscle rupture
• The diagnosis should be suspected in patients with sudden clinical deterioration and suggested by the presence of new murmurs or diminished heart sounds.
• The diagnosis can be confirmed by echocardiography.
• In these patients early surgery should be considered.

3.4.4 Right Ventricular Infarction (RVI)
• Patients with RVI may have varying clinical presentation, from asymptomatic to cardiogenic shock.
• Haemodynamically significant RVI complicates approximately 5-10% of all STEMI.
• It occurs in 30 – 50% of patients with infero-posterior STEMI and is associated with a significantly higher mortality.
• RVI can also occur in patients with extensive anterior STEMI.

A. Clinical Diagnosis
  ➢ The presence of RVI should be sought in all patients with inferior STEMI.
  ➢ The clinical triad of hypotension, clear lung fields and elevated jugular venous pressure in the setting of inferior STEMI is suggestive of RVI.
  ➢ ST elevation in the right precordial leads (V4R) is the most specific finding in diagnosing RVI. However, this ECG finding may be transient, often resolving within 8-10 hours.

B. Management
  ➢ Treatment strategies depend on the severity of peripheral hypoperfusion and the degree of co-existing LV dysfunction.
  ➢ Drugs that reduce the preload, such as nitrates and diuretics should be avoided.
  ➢ Management includes:
    - optimization of intravenous fluid (saline or colloids)
    - inotropes
  ➢ Failure to respond to these measures usually indicates concomitant LV dysfunction.
  ➢ These patients require more aggressive management with afterload reducing agents such as nitroprusside and intra-aortic balloon pump.

3.4.5 Others

A. Chest pain post STEMI
• Chest pain post STEMI may be due to reinfarction, ischaemia or pericarditis.
• Non-cardiac causes must also be considered.

I Reinfarction
  ➢ Reinfarction occurs in about 3-4% of patients who had undergone fibrinolytic therapy and received aspirin.
  ➢ Reinfarction may be diagnosed by:
    - recurrence of ischaemic type chest pain
    - recurrence of ST segment elevation of at least 0.1mV in at least 2 contiguous leads and / or
    - re-elevation of serum cardiac biomarkers especially CK
  ➢ Death, severe heart failure and arrhythmias are more common in these patients.
  ➢ They should be considered for rescue PCI.

II Post-infarct angina
  ➢ Early recurrent angina, especially after successful reperfusion may occur in up to 20% of patients.
The ECG in these patients may show ST segment changes or pseudo-normalisation of inverted T-waves. These patients should be sent for early coronary angiography with a view to revascularization.

### III Pericarditis

- Pericarditis secondary to STEMI may produce pain as early as the first day and as late as 6 weeks.
- The pain classically becomes worse on deep inspiration and may be relieved when the patient sits up and leans forward.
- A pericardial rub may be detected.
- Dressler's syndrome (post MI syndrome) usually occurs 2-10 weeks after STEMI. This is immunologically mediated. It is treated with aspirin 600 mg 3-4 times a day. Steroids and NSAIDS are best avoided in the first 4 weeks of STEMI.

### B. LV Thrombus and Arterial Embolism

- LV mural thrombus has been identified in about 20-40% of patients with STEMI.
- The majority of these occur following anterior or large infarcts.
- Anticoagulation therapy with warfarin for a minimum of 3-6 months is advocated in these patients.

### C. Deep Venous Thrombosis (DVT)

- In high risk patients (prolonged bed rest, heart failure, unable to mobilize), prophylactic anti-coagulation therapy (subcutaneous heparin 5000 units bd, LMWH – e.g. enoxaparin given s.c 40mg daily) may be considered until the patient is ambulant.

### 3.5 Risk Stratification Post-STEMI

- Risk stratification serves to prognosticate and identify appropriate treatment strategies. Risk stratification starts from admission and is a continuing process.
- Poor prognostic indicators include:
  - older persons ( > 65 years)
  - female gender
  - previous MI
  - anterior MI
  - inferior MI with RV involvement
  - diabetes mellitus
  - ECG changes in multiple leads
  - persistent or recurrent ischaemia as manifested by post-infarction angina or ST segment depression at rest
  - hypotension
  - heart failure
  - atrial fibrillation and late (after 48 hours) ventricular arrhythmias
  - presumably new left bundle branch block (LBBB)
- The above high risk patients should be considered for early coronary angiography.
• All other patients should be risk stratified early. This may be done by assessing:
  - left ventricular function by clinical evaluation, chest X-ray, echocardiogram, radionuclide studies or cardiac MRI
  - presence of myocardial ischaemia by clinical evaluation (recurrent angina) and exercise stress testing in asymptomatic patients.
  - presence of malignant ventricular arrhythmias.
• The presence of angina, an abnormal stress test or late ventricular arrhythmias necessitates early coronary angiography with a view to revascularization.
• In patients with poor LV function, myocardial viability studies (dobutamine stress echocardiogram, radionuclide perfusion studies or cardiac magnetic resonance imaging) would help to differentiate scarred from viable ischaemic myocardium. The latter patients would benefit from revascularization.
• Patients with palpitations, near faints and syncope require comprehensive evaluation. This includes:
  - serum electrolytes
  - resting ECG
  - 24 hour ambulatory ECG recording
  - evaluation of LV function
  - assessment for reversible myocardial ischaemia
  - coronary angiography
• In these patients, reversible causes such as electrolyte disturbances and ischaemia should be corrected.
• The following medications have been shown to reduce the incidence of sudden death:
  - β-blockers
  - ACEI
  - Aldosterone antagonist, eplerenone
  - Statins
• The following patients should be considered for an Implantable Cardioverter defibrillator (ICD):
  - Secondary prevention in patients with resuscitated sudden cardiac death
  - Primary prevention in patients with LV dysfunction (LVEF < 30%). The ICD should be implanted 30 days post STEMI and 3 months post revascularisation

3.6 Cardiac Rehabilitation in STEMI
• All patients post STEMI (including those post PCI or CABG surgery) should undergo comprehensive cardiac rehabilitation. This programme aims at:
  - improving the long-term prognosis
  - optimizing the physical, psychological and social well-being of the patient.
• It comprises prescribed exercise training and education, counseling, risk factor modification and behavioural interventions.
Cardiac rehabilitation should start in the cardiac care unit, continue to outpatient settings and extend to community care.

3.7 Check lists for follow-up visit

- Delineate the presence or absence of cardiac symptoms and determine the functional class of the patients.
- Evaluate patients psychosocial (anxiety & depression) status and the social integration and support network.
- Review pre discharge risk assessment and planned workup
  - evaluation for further cardiac ischaemia
  - LV function
- Re-evaluate the list of all current medications and optimize their doses.
- Actively review the following issues with the patient and family members
  - principles of secondary prevention
  - CPR training
  - a plan for appropriate recognition and response to a potential acute cardiac event
- Treat to target.
  - blood pressure: <130/80 mmHg
  - lipids: LDL- C < 2.6 mmol/L, optional target < 1.8 mmol/L in high risk patients
  - diabetic control: Fasting blood glucose < 6.0mmol/L and HbA1C < 6.5%
  - achieve and maintain ideal body weight and waist circumference

4. Management of Acute Heart Failure (AHF)

4.1 Acute Cardiogenic Pulmonary Edema

- Acute Heart Failure may present de novo or as acute decompensation of Chronic Heart Failure (CHF).
- The clinical manifestations may vary from mild decompensation to Acute Cardiogenic Pulmonary Oedema and Cardiogenic Shock.
- Myocardial Infarction / Ischaemia is an important and common cause of AHF. The other causes are as listed in Table 13.
- Investigations are as listed in Table 14.
The most common underlying causes of HF in adults are:

- Coronary heart disease
- Hypertension

Slightly less common causes include:

- Idiopathic dilated cardiomyopathy
- Valvular heart disease
- Diabetic cardiomyopathy

Other causes of HF are:

- Congenital heart disease
- Cor pulmonale
- Pericardial disease: constrictive pericarditis, cardiac tamponade
- Hypertrophic cardiomyopathy
- Viral myocarditis
- Acute rheumatic fever
- Toxic: Alcohol, adriamycin, cyclophosphamide
- Endocrine and metabolic: thyroid disease, acromegaly, phaeochromocytoma
- Collagen vascular disease: systemic lupus erythematosus, polymyositis, polyarteritis nodosa
- Tachycardia induced cardiomyopathy
- Miscellaneous
  - severe anaemia
  - peripartum cardiomyopathy
  - large A-V shunts

Table 13: Aetiology of Heart Failure

- The principles of management are:
  - rapid recognition of the condition
  - stabilization of haemodynamics
  - improvement in clinical symptoms and signs
  - identification and treatment of the underlying cause and the precipitating / aggravating factors.
- After initial clinical assessment of vital signs, treatment of AHF should be instituted as outlined in Flowchart 4.
- For dosages see Table 15
Essential Investigations:
- ECG
- Chest X-ray
- Blood Investigations: Haemoglobin, serum electrolytes, urea, creatinine,
- serum cardiac biomarkers, arterial blood gases
- Echocardiography

Special Investigations:
- Cardiac catheterization/coronary angiography when acute intervention for acute myocardial ischaemia or infarction/valvular disease is anticipated.
- Swan Ganz catheter placement (Flowchart 4)

Table 14: Investigations in Acute Cardiogenic Pulmonary Oedema

4.1.1 Therapy

- The initial management includes a combination of the following first line therapy:
  - **Oxygen**
    - 5 to 6 litres / minute by mask, with the aim of achieving oxygen saturation of more than 95%.
    - Elective ventilation using non invasive positive pressure ventilation (Continuous Positive Airway Pressure [CPAP] or Bi-level Positive Airway Pressure [BiPAP]) should be considered early if necessary.
    - Should the oxygen saturation be inadequate or the patient develops respiratory muscle fatigue, then endotracheal intubation and mechanical ventilation is necessary.

- **Frusemide**
  - Intravenous (i.v.) frusemide 40 – 100 mg.
  - Dose should be individualized depending on the severity of the clinical condition.
  - Administration of a loading dose followed by a continuous infusion has been shown to be more effective than repeated bolus injections alone.
  - The dose should be titrated according to clinical response and renal function.

- **Morphine sulphate**
  - i.v. 3 - 5 mg bolus (repeated if necessary, up to a total maximum of 10mg).
  - It reduces pulmonary venous congestion and sympathetic drive.
  - It is most useful in patients who are dyspnoeic and restless.
  - Intravenous anti-emetics (metoclopramide 10mg or prochlorperazine 12.5 mg) should be administered concomitantly.
  - Care must be exercised in patients with chronic respiratory diseases.

- **Nitrates**
If the BP is adequate (SBP > 100 mmHg), nitrates are indicated as first line therapy in acute heart failure (AHF).

It should be administered sublingually or intravenously.

Studies have shown that the combination of i.v. nitrate and low dose frusemide is more efficacious than high dose diuretic treatment alone.

Extreme caution should be exercised in patients with aortic and mitral stenosis. Nitrates are contraindicated in severe valvular stenosis.

- An attempt should be made to identify the underlying cause e.g. acute myocardial infarction / myocardial ischaemia, valvular heart disease and hypertension. This would enable the appropriate treatment to be instituted early.
- Response to drug therapy should be assessed continuously. Parameters to assess during treatment includes:
  - Symptoms and signs
    - Vital signs
      - oxygen saturation
      - heart rate
      - blood pressure
      - respiratory rate
      - urine output
      - body weight
  - Investigations
    - renal function tests
    - Invasive haemodynamic monitoring (if necessary)
    - pulmonary capillary wedge pressure, cardiac index
- An adequate response would be reflected by an improvement in the patient’s clinical condition, decrease in his heart rate and an improvement in his oxygen saturation. Generally, a SBP ≥ 90mmHg would be considered adequate if the patient feels well and has good tissue perfusion as shown by the absence of giddiness, warm skin and stable renal function with good urine flow.
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Route of Admin</th>
<th>Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide</td>
<td>IV</td>
<td>40 mg -100 mg</td>
</tr>
<tr>
<td></td>
<td>Infusion</td>
<td>5 - 40 mg/hour (better than very high bolus doses)</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Infusion</td>
<td>0.2 – 10 ug/kg/minute</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Infusion</td>
<td>0.1 – 5 ug/kg/minute</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Infusion</td>
<td>2 – 20 ug/kg/minute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 2 - 3 ug/kg/minute renal arterial vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 - 5 ug/kg/minute inotropic doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 - 15 ug/kg/minute peripheral vasoconstriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion</td>
<td>0.02 – 1 ug/kg/minute till desired blood pressure is attained</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline</td>
<td>Infusion</td>
<td>0.1 – 1 ug/kg/minute</td>
</tr>
<tr>
<td>Phosphodiesterase-3- Inhibitors</td>
<td>Infusion</td>
<td>25 - 75 ug/kg bolus then 0.25 - 0.75 ug/kg/minute</td>
</tr>
</tbody>
</table>

Table 15: Drugs Commonly Used in AHF

- In most cases of mild to moderate acute heart failure (AHF) the following measures would suffice. If the patient fails to respond to the above therapy, further management would depend upon the blood pressure and tissue perfusion.

A. In the presence of an adequate blood pressure:
   - Frusemide
     - i.v. frusemide infusion 5 – 40 mg/hour.
     - Combination of a loop diuretic at low doses with nitrates is superior to high dose diuretic therapy alone.
     - Combination with dobutamine or dopamine is also more effective than increasing the dose of diuretic alone.
     - Alternatively one could consider adding an oral thiazide diuretic.
   - Inotropes
Dopamine: Low dose at < 2 - 3 ug/kg/min to improve renal flow and promote diuresis

Dobutamine infusion: Started at 2 – 5 mg/kg/minute and titrated by 1 - 2 mg/kg/minute increments at 30 minute intervals until the desired clinical and haemodynamic response is attained.

Milrinone: This agent improves symptoms and haemodynamics in AHF.

Vasodilators

Sodium Nitroprusside would be useful in patients not responsive to nitrates.

This drug is particularly useful in cases of uncontrolled hypertension, acute mitral or aortic regurgitation.

Continuous intra-arterial monitoring is necessary as acute changes in blood pressure with hypotension can occur.

Infusion should not be continued beyond 3 days because of the danger of cyanide poisoning.

Infusion should be for shorter periods in patients with hepatic and renal impairment.

B. If the blood pressure is low at initial presentation (SBP < 100mmHg) or drops during treatment:

Dopamine infusion

Noradrenaline infusion or in its absence, adrenaline infusion

Avoid vasodilators (nitrates, nitroprusside) and morphine until the blood pressure has stabilized

Over diuresis or hypovolaemia - correct accordingly.

In Right Ventricular (RV) Infarction, the hypotension may respond to volume loading.

Other Measures

Intubation and mechanical ventilation

should the oxygen saturation be inadequate or the patient develops respiratory muscle fatigue, then endotracheal intubation and mechanical ventilation is necessary.

Correction of acidosis

Invasive haemodynamic monitoring

if available, would be useful in patients not responsive to medical therapy and are hypotensive.

this can include arterial pressure line, central venous pressure line and pulmonary artery catheter.

this would allow a more accurate assessment of the fluid status of the patient and allow better titration of medications.

Intra-aortic balloon counterpulsation (IABP)

would be useful in patients who are not responding optimally to medical therapy as a bridge to definitive treatment. IABP would be particularly useful in patients with intractable myocardial ischaemia or acute mitral regurgitation.

it is contraindicated in patients with aortic regurgitation or aortic dissection.
Ventricular Assist Devices (VAD) - this would be useful as a bridge in patients for whom recovery from acute heart failure (AHF) is expected or for whom heart transplantation is an option.

- Following adequate response to intravenous therapy, the patient should be converted to optimal oral medications. (refer to Flowchart 5). The initial dose of oral diuretics required is generally higher than the intravenous dose.

4.1.2 Special Situations

- Myocardial Ischaemia / Infarction:
  - Reversible myocardial ischaemia causing AHF needs early recognition, rapid stabilization and referral for urgent coronary angiography.
  - In acute myocardial infarction, reperfusion therapy by fibrinolytic or primary Percutaneous Coronary Intervention (PCI) may significantly improve or prevent AHF.
  - Long term management strategy should include adequate coronary revascularization, anti platelet therapy, ACEI and / or ARB, β-blockers and statins.

- Hypertension: (refer to section on Management of Severe Hypertension)
  - Typically presenting as “flash pulmonary oedema” with hypertensive crisis.
  - Systolic LV function tends to be normal.
  - The blood pressure needs to be reduced relatively quickly.
  - It is generally suggested that the systolic blood pressure (SBP) be reduced by 25% over 3 to 12 hours.
  - This is best achieved with parenteral drugs such as intravenous nitrates or nitroprusside.
  - No attempt should be made to restore “normal” values of BP as this may cause deterioration of organ perfusion.
  - Look for secondary causes of hypertension such as renal artery stenosis and phaeochromocytoma.

- Valvular Heart Disease
  - AHF can be caused by valvular conditions such as acute mitral or aortic valve incompetence or stenosis, bacterial endocarditis, aortic dissection and prosthetic valve thrombosis.
  - Vasodilator therapy would be beneficial in acute valvular regurgitation, but is contraindicated in severe valvular stenosis.
  - Early access to echocardiography is crucial for the diagnosis and management.
  - Percutaneous intervention such as mitral valve commissurotomy can be life saving in patients with severe mitral stenosis.

- Arrhythmias (refer to section on Management of Arrhythmias)
→ tachyarrhythmias particularly atrial fibrillation / atrial flutter with fast ventricular rates need to be identified and treated appropriately e.g. electrical or pharmacological cardioversion.

- Renal Failure
  → AHF and renal failure can co-exist and either may give rise to the other.
  → Renal failure influences the response to drug therapy.
  → In these patients with refractory fluid retention, continuous ultrafiltration may be helpful.

- Decompensation in a previously stable patient with heart failure
  → precipitating causes should be identified and treated appropriately (Table 16).

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Cardiac causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• non compliance to medications</td>
<td>• superimposed myocardial ischaemia or infarction</td>
</tr>
<tr>
<td>• dietary indiscretion especially salt and fluid intake</td>
<td>(often asymptomatic)</td>
</tr>
<tr>
<td>• inappropriate medications e.g. NSAIDS</td>
<td>• uncontrolled hypertension</td>
</tr>
<tr>
<td>• alcohol consumption</td>
<td>• arrhythmias</td>
</tr>
<tr>
<td></td>
<td>• pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>• secondary mitral or tricuspid regurgitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• superimposed infections</td>
<td></td>
</tr>
<tr>
<td>• anaemia</td>
<td></td>
</tr>
<tr>
<td>• thyroid disease</td>
<td></td>
</tr>
<tr>
<td>• electrolyte disturbances</td>
<td></td>
</tr>
<tr>
<td>• worsening renal disease</td>
<td></td>
</tr>
</tbody>
</table>

Table 16: Factors Contributing to Decompensation in a Patient with Stable HF

- Following stabilization of the AHF - the patient should be started on optimal anti failure therapy as outlined in Flowchart 5. This should include:
  - Diuretics (Furosemide, thiazides, aldosterone antagonists alone or in combination)
  - ACEI and / or ARB
  - β-Blockers
ACUTE CARDIOGENIC PULMONARY EDEMA

Oxygen, i.v diuretics

BLOOD PRESSURE*

SBP \geq 100 \text{ mm Hg} 

? ARRHYTHMIA

SBP < 100 \text{ mm Hg}

- Nitrates (caution in valvular stenosis)
- Morphine

IMPROVED

NO IMPROVEMENT

** Oral Medications

SBP \geq 100 \text{ mm Hg}

- \uparrow \text{ Diuretics, continuous infusions} +
  combination of diuretics
- \uparrow \text{ Nitrates}
- low dose dopamine
- dobutamine

IMPROVED

NO IMPROVEMENT

** Oral Medications

SBP < 100 \text{ mm Hg}

- dopamine 1\textsuperscript{st}
- noradrenaline 2\textsuperscript{nd}
- correct hypoxia/acidosis

NOTE: * It is important to look for tissue hypoperfusion - cool peripheries, sweating, low volume pulse, decreasing urine output. ** Flow Chart 5.

From onset, evaluate to identify correctable / reversible lesions.

Special situations: Myocardial ischaemia / infarction: Treat accordingly
Hypertension: Control BP quickly
Valvular heart disease: Corrective surgery / balloon valvuloplasty

Please refer to CPG on Management of Heart Failure 2007 (2nd Edition) for details OR download this guidelines from http://www.moh.gov.my or http://acadmed.org.my

Flowchart 4: Management of Acute Cardiogenic Pulmonary Oedema
Flowchart 5: Optimizing Drug Therapy in CHF

Please refer to CPG on Management of Heart Failure 2007 (2nd Edition) for details OR download this guidelines from http://www.moh.gov.my or http://acadmed.org.my
I  Diuretics
- Diuretics are indicated in all patients with AHF.
- Diuretic therapy must be used with care because over diuresis can produce:
  - severe intravascular dehydration
  - deteriorating renal function
  - hypokalaemia. Oral potassium supplementation is usually necessary.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Route of Administration</th>
<th>Usual Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusemide</td>
<td>IV / Oral</td>
<td>20 – 80 mg</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>IV / Oral</td>
<td>0.5 – 2 mg</td>
</tr>
<tr>
<td>Thiazides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Oral</td>
<td>25 – 50 mg</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>Oral</td>
<td>250 – 500 mg</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Oral</td>
<td>12.5 mg – 50 mg</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Oral</td>
<td>25 mg – 50 mg</td>
</tr>
</tbody>
</table>

Table 17: Diuretics Used In Heart Failure

II  Angiotensin Converting Enzyme Inhibitors (ACE-I)
- ACE-I improves survival and quality of life in all classes of HF.
- In the initiation of ACE-I, the following steps are recommended:
  - Care should be exercised in the following patients for whom referral to a specialist may be considered.
    - SBP <100mmHg
    - Creatinine > 250 µmol/L
  - Avoid excessive diuresis before treatment. If patients are on large doses of diuretics, the blood pressure and renal function should be monitored.
  - Start with a low dose. The dose should be increased gradually to the target dose (Table 18) or maximum tolerated dose.
  - Monitor blood urea, creatinine and serum potassium at 7-14 days, especially in patients with impaired renal function. If the rise in serum creatinine level is > 20% compared to baseline, then ACE-I therapy may need to be stopped.
  - Avoid potassium sparing diuretics during initiation of therapy.
  - Avoid non steroidal anti-inflammatory drugs

A number of different ACEI are available. The dose should be titrated up to the maintenance level as shown in Table 18.
<table>
<thead>
<tr>
<th>Drugs (ACE-I)</th>
<th>Initiating Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg t.d.s</td>
<td>50 mg t.d.s</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg b.d</td>
<td>10 mg b.d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 mg daily</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>2.5-5 mg daily</td>
<td>20 mg b.d</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg daily</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10 mg daily</td>
<td>20 mg daily</td>
</tr>
</tbody>
</table>

**Table 18: Recommended doses of ACEI used in HF**

- Major adverse effects of ACEI, which are:
  - cough
  - hypotension
  - renal insufficiency
  - hyperkalaemia
  - angioedema

### III Angiotensin II Receptor Blockers (ARB)
- In patients intolerant to ACEI, ARB should be considered.
- In patients post MI with impaired LV function, the ARB, Valsartan was found to be as effective as captopril. *(Table 19)*

<table>
<thead>
<tr>
<th>Drugs (ARB)</th>
<th>Initiating Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>25 mg daily</td>
<td>50-100 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg daily</td>
<td>80-160 mg bid</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 mg daily</td>
<td>16-32 mg daily</td>
</tr>
</tbody>
</table>

**Table 19: Recommended doses of ARB in HF**

### IV β- Blockers
- Large clinical trials have shown that β-blockers reduce morbidity and mortality in patients with HF.
• β-blocker therapy should be initiated when pulmonary congestion is absent and the patient is clinically stable.
• In initiating β-blocker therapy the following should be considered:
  ➢ The initial dose should be small (Table 20).
  ➢ The dose should be slowly titrated upwards till target dose or maximum tolerated dose is achieved.
  ➢ Contraindications include the following:
    → acute HF
    → bronchial asthma or severe chronic obstructive airway disease
    → symptomatic bradycardia or hypotension
    → second or third degree heart block without a pacemaker
    → a requirement for beta agonist therapy or positive inotropic support

<table>
<thead>
<tr>
<th>Drugs (β-Blockers)</th>
<th>Initiating Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125 mg daily</td>
<td>25 mg bid</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate CR*</td>
<td>12.5 – 25 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

Table 20: Recommended doses of β-Blockers used in HF
*Currently only metoprolol tartrate is available in Malaysia

V Aldosterone Receptor Antagonists
• The addition of spironolactone to ACE-I, loop diuretics and digoxin in patients with severe HF reduces mortality and rehospitalization.
• Care should be exercised in patients with renal impairment. Serum potassium should be monitored regularly. Potassium supplements may need to be reduced or stopped. If hyperkalemia persists, then aldosterone receptor antagonists should be stopped.

VI Digoxin
• Digoxin is indicated in patients with HF and atrial fibrillation.
• In patients with HF and normal sinus rhythm, digoxin may be added if symptoms persist despite diuretics, ACEI, β-blockers and low dose spironolactone.
• Digoxin has no effect on mortality but reduces hospitalization. The usual maintenance dose of digoxin is 0.125 mg to 0.25 mg daily. Lower doses should be used in the elderly and in patients with impaired renal function.

VII Anti-Coagulation Therapy
Heart failure patients with the following risk factors for thromboembolism should be anti-coagulated with warfarin (unless there are contraindications):
- atrial fibrillation
- intracardiac thrombus (except for organized mural thrombus)
- past history of thromboembolic episode(s)

VIII  Other Concurrent Therapies
- Calcium channel blockers are not recommended for the treatment of HF due to systolic dysfunction.
- Second generation dihydropyridines calcium channel blockers such as amlodipine or felodipine may be considered for the treatment of concurrent hypertension and angina.

IX  Anti–arrhythmic Drug Therapy
- Arrhythmias are common in HF. The more common ones are:
  - atrial fibrillation
  - ventricular tachyarrhythmias
  - bradyarrhythmias
- Atrial fibrillation is a common problem among patients with HF.
- All patients with atrial fibrillation should be anti-coagulated with warfarin unless contraindicated.
- These patients can be managed by either rate control or rhythm control.
  - Rate control can be achieved by using either:
    - β-blockers and/or
    - digoxin.
  - Rhythm control can be achieved by elective cardioversion after a period of anticoagulation.
- Sinus rhythm can be maintained by using amiodarone.
- Studies show that 40-50% of deaths in heart failure are sudden, the risk increasing with the severity of HF. This is most often due to either sustained ventricular tachycardia (VT) or ventricular fibrillation (VF)
- The following medications have been shown to reduce the incidence of sudden death:
  - β-blockers
  - Aldosterone antagonist, eplerenone:
  - ACEI
  - Statins
- In addition to the above, in patients with ventricular tachyarrhythmias, the following are important:
  - Identify contributing factors such as electrolyte disturbances, ischemia and drugs.
  - Implantable cardioverter defibrillator (ICD) can be considered in selected patients. These have been found to improve survival both as secondary prevention and as primary prevention in selected patients.
Anti-arrhythmic drug therapy with amiodarone can be considered as adjunctive therapy in patients with ICD.

Patients with significant bradyarrhythmias, trifascicular blocks and high-degree AV blocks should be considered for pacemaker therapy.

Please refer to CPG on Management of Heart Failure 2007 (2nd Edition) for details OR download this guideline from http://www.moh.gov.my or http://acadmed.org.my

4.2 Cardiogenic Shock

Management of Cardiogenic Shock

- Cardiogenic shock carries a very high mortality rate. Features include:
  - Systolic BP < 90mmHg not improved with fluid administration
  - Signs of hypoperfusion - cold extremities, altered mental status, restlessness
  - Reduced urine output (< 20 ml/hour)
  - Cardiac index of < 2.2 L/min/m2

- It is important to establish the aetiology and institute appropriate resuscitative therapy immediately.
- An ECG should be obtained and continuous monitoring begun.
- Venous access should be secured, preferably via central venous cannulation (subclavian or internal jugular).
- Important considerations are:
  - Ventricular Function - echocardiography would allow rapid determination of LV function and mechanical causes (e.g. acute valve regurgitation, acute septal rupture, cardiac tamponade) of cardiogenic shock. In the presence of preserved LV systolic function, other causes of shock such as sepsis and intravascular volume depletion should be considered.
  - Intra Vascular Volume Status - an absolute or relative reduction in left ventricular filling pressures may be present. This may be due to excessive diuretic or vasodilator therapy, concomitant GI bleed or RV infarction. In the absence of signs of LV failure, fluid challenge with normal saline should be administered (usual recommended volume: 200 – 500 mls). Invasive haemodynamic monitoring would be useful to guide fluid therapy.
  - Arrhythmias - should be identified and appropriate treatment such as cardioversion or pacing instituted. Resistant arrhythmias would require additional anti-arrhythmic drug therapy.

- In the presence of cardiogenic shock or near shock (hypoperfusion with adequate blood pressure) treatment would include the following:
Inotropic support: High dose dopamine and/or noradrenaline. If blood pressure is adequate in the setting of near shock, dobutamine may be used.

Mechanical device support: Intra-aortic balloon pump or LV assist device

Identifying correctable causes - this includes myocardial ischaemia / infarction. Cardiogenic shock in this setting could be due to:

- pump failure - these patients should be identified early and treated aggressively with prompt revascularization by PCI. Often they would require ventilatory support and intra-aortic balloon counterpulsation (IABP).
- mechanical complications such as ventricular septal rupture and acute mitral regurgitation. Echocardiography will be useful in the diagnosis. Urgent surgery is beneficial but carries a high mortality.

Following Stabilization of the Cardiogenic Shock, the patient should be started on optimal anti failure therapy as outlined in Flowchart 5. This should include:

- Diuretics
- ACEI and/or ARB
- β-Blockers

5. Management of Arrhythmias

These include:

A. Tachyarrhythmias

- Pulseless ventricular tachyarrhythmias (refer to algorithm 1)

[Shockable waves refers to the presence of recognizable organized or disorganized cardiac rhythms on continuous ECG monitoring while non shockable waves refers to the absence of any heart rhythm on ECG monitoring]

- Stable Ventricular Tachycardia (VT) (refer to algorithm 2).
- Ventricular Premature Contractions (VPC) - these are often benign and do not require treatment. Correct underlying ischaemia, hypoxia and electrolyte disturbances.
- Atrial fibrillation (AF) (refer to algorithm 3) - these patients should be considered for long term anticoagulation with warfarin. This is especially important in patients with:
  - congestive cardiac failure
  - hypertension
  - age more than 75 years
  - diabetes
  - stroke or previous TIA

B. Bradyarrhythmias - these are:

- Sinus bradycardia - This does not require treatment unless associated with symptoms and/or hypotension.
- Atrio-ventricular Block (AV Block) (refer to algorithm 4)
- Asystole / Pulseless Electrical Activity - asystole/ pulseless electrical activity can be differentiated from pulseless ventricular tachyarrhythmias by the presence of shockable waves on ECG monitoring (refer algorithm 1).

Algorithm 2: Stable Ventricular Tachycardia

- Assess and support ABCs
- Give oxygen
- Monitor ECG

Haemodynamically stable

Monomorphic VT
- i.v amiodarone 150 mg over 10 minutes
- Repeat as needed up to 2.2 gm/24hours

- Successful cardioversion
  - Oral amiodarone

- Failed medical cardioversion
  - Electrical cardioversion

Polymorphic VT
- Check electrolytes and correct accordingly
- Stop all anti-arrhythmics drugs (if any)
- i.v magnesium
- Overdrive pacing
- i.v isoprenaline

- Electrical cardioversion
Search and treat identifiable underlying causes

Haemodynamically stability

Stable

Unstable

Normal LV function

Rate or rhythm control

- Rate control
  - blockers
  - Calcium blockers
- Rhythm control
  - i.v amiodarone followed by oral amiodarone
- Anticoagulation
  - If persistent after 48 hours or if cardioversion is contemplated

Impaired LV function

- Rhythm control preferably with i.v amiodarone followed by oral amiodarone
- Anticoagulation
- Cardioversion

Electrical cardioversion

Successful cardioversion

Oral amiodarone

Unsuccessful cardioversion

i.v amiodarone

Algorithm 3: Atrial fibrillation
**Bradycardia**
- Slow (absolute bradycardia) = $< 60 \text{ bpm}$
  - OR
- Relatively slow (rate less than expected relative to the underlying condition/cause)

- Assess ABCD
- Vital signs monitoring
- Search for underlying reversible causes e.g. electrolytes, drugs and treat accordingly

**Serious symptoms due to bradycardia?**

**No**
- Type II 2\textsuperscript{nd} degree AV block OR 3\textsuperscript{rd} degree AV block?
  - **No**
  - **Yes**
    - Observe

**Yes**
- Intervention sequence
  - Atropine 0.5 to 1 mg
  - Dopamine 5 to 20 mcg/kg/min
  - Epinephrine 2 to 20 mcg/kg/min
  - Transcutaneous pacing if available

- Transcutaneous pacing
6. Management of Severe Hypertension

6.1 Clinical Definition

- Stage IV (severe) hypertension is defined as BP > 180 / 110 mmHg.
- These patients may present in the following manner:
  - incidental finding/asymptomatic
  - non-specific symptoms like headache, dizziness, lethargy
  - symptoms and signs of target organ complications. These include heart failure, stroke, acute coronary syndromes, acute renal failure, dissecting aneurysm and hypertensive encephalopathy.
- Management of these patients depends on the clinical presentation and laboratory investigations.
- The evaluation of these patients is as in any other patient with hypertension should include a thorough history and physical examination, particularly looking for signs of acute target organ damage and causes of secondary hypertension.
- Further investigations to look for secondary causes is necessary (refer to Table 21)

<table>
<thead>
<tr>
<th>Causes</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchyma</td>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>Primary glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>Tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Systemic disorders with renal involvement</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td></td>
<td>Vasculitides</td>
</tr>
<tr>
<td>Renovascular</td>
<td>Atherosclerotic disease</td>
</tr>
<tr>
<td></td>
<td>Fibromuscular dysplasia</td>
</tr>
<tr>
<td></td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Conn syndrome (primary hyperaldosteronism)</td>
</tr>
<tr>
<td></td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Drugs</td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td></td>
<td>Cyclosporin</td>
</tr>
<tr>
<td></td>
<td>Clonidine withdrawal</td>
</tr>
<tr>
<td></td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>Coarctation of Aorta</td>
<td>-</td>
</tr>
<tr>
<td>Pre-eclampsia / eclampsia</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 21. Common causes of Severe Hypertension*

* The most common cause of severe hypertension is still long-standing poorly controlled essential hypertension.
After this initial assessment, patients can then be categorized as:

I  **Severe asymptomatic hypertension**
II  **Hypertensive Urgency**
III  **Hypertensive Emergency**
IV  (II) and (III) are also referred to as "hypertensive crisis".

### 6.2 Management

**I  Severe asymptomatic hypertension**

- Admission may be necessary in those who are newly diagnosed or where non-compliance is suspected.
- Patients already on treatment need to be reviewed and appropriate measures taken. This includes optimizing treatment by using effective combination therapy.

**II  Hypertensive Urgencies**

- These include patients who have grade III and IV retinal changes, proteinuria and symptoms which may suggest organ failure.
- These patients need to be admitted.
- Blood pressure measurement should be repeated after 30 minutes of bed rest.
- Initial treatment should aim for about 25% reduction in blood pressure over 24 hours but not lower than 160/90mmHg.
- Oral drugs shown to be effective in clinical trials are as in Table 22.
- Combination therapy is often necessary. This does not necessarily mean that these drugs should be routinely used in all cases of hypertensive urgencies.

**III  Hypertensive Emergencies**

- These are complications of severe hypertension such as acute left ventricular failure, dissecting aneurysm, acute coronary syndromes, hypertensive encephalopathy, subarachnoid haemorrhage, haemorrhagic stroke, acute renal failure and eclampsia.
- These may occur in patients with BP < 180/110 mmHg, particularly if the BP has risen rapidly.
- All these patients must be admitted.
- The blood pressure needs to be reduced relatively quickly.
- It is generally suggested that the BP be reduced by 25% over 3 to 12 hours but not lower than 160/90mmHg.
- This is best achieved with parenteral drugs (Table 23)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Onset of action (hours)</th>
<th>Duration of action (hours)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>25 mg</td>
<td>0.5</td>
<td>6</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10-20 mg</td>
<td>0.5</td>
<td>3-5</td>
<td>1-2 hours</td>
</tr>
<tr>
<td>Labetolol</td>
<td>200-400 mg</td>
<td>2</td>
<td>6</td>
<td>4 hours</td>
</tr>
</tbody>
</table>

Table 22: Oral treatment for Hypertensive Urgencies

- Dangers of rapid reduction in blood pressure - rapid reduction of BP (within minutes to hours) in an asymptomatic severe hypertension or hypertensive urgencies is best avoided as it may precipitate ischaemic events
  - Oral or sublingual drugs with rapid onset of action can result in an uncontrolled drop in blood pressure leading to stroke, myocardial ischaemia and even death.
  - Several serious side effects have been reported with the administration of sublingual fast-acting nifedipine.
  - Therefore, its routine use to lower blood pressure rapidly in the general adult population is no longer recommended.
- Following stabilization of the patient's BP, subsequent management is tailored towards achieving optimal control using a combination of medications.
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Onset of action</th>
<th>Duration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25 – 10 µg /kg/min</td>
<td>seconds</td>
<td>1 – 5 minutes</td>
<td>Caution in renal failure</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>i.v. bolus 50 mg (over at least 1 minute) repeating if necessary at 5 minute intervals to a max of 200 mg then 2 mg/min i.v.</td>
<td>≤ 5 min</td>
<td>3 – 6 hours</td>
<td>Caution in heart failure</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5 – 100 µg /min</td>
<td>2 – 5 min</td>
<td>3 – 5 minutes</td>
<td>Preferred in acute coronary syndromes and acute pulmonary oedema</td>
</tr>
<tr>
<td>Hydralazine*</td>
<td>i.v. 5 – 10 mg maybe repeated after 20-30 minutes i.v. 200-300 mcg/ min initially. Maintenance 50-150 µg /min</td>
<td>10 – 20 min 20 – 30 min</td>
<td>3 – 8 hours</td>
<td>Caution in acute coronary syndromes, cerebrovascular accidents and dissecting aneurysm</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>i.v. bolus 10-30 mcg/ kg over 1 minute i.v. 2 – 10 µg /kg/min</td>
<td>5 – 10 min</td>
<td>1 – 4 hours</td>
<td>Caution in acute heart failure and coronary ischaemia</td>
</tr>
<tr>
<td>Esmolol</td>
<td>i.v. bolus 250 – 500 µg /kg over 1 min i.v. 50 – 200 µg /kg/min for 4 min. May repeat sequence</td>
<td>1 – 2 min</td>
<td>3 – 10 minutes</td>
<td>Used in peri-operative situations and tachyarrhythmias</td>
</tr>
</tbody>
</table>

Table 23: Treatment options for Hypertensive Emergencies

# In pregnancy, 200 mg labetalol in 50 ml normal saline and start infusion at 4 ml/hour.
* In pregnancy, the initial dose is 25 mg/min IV infusion (25 mg in 500 ml normal saline at 30 ml/hour).
7 Management of Anaphylactic Shock

- **Aetiology**
  - This is a severe and potentially life threatening medical emergency.
  - It an immunologically mediated hypersensitivity reaction and involves prior sensitization to an allergen and then re-exposure.
  - Anaphylactoid reaction produces a similar clinical syndrome but is not immune-mediated.
  - Common allergens includes:
    → drugs such as penicillin, aspirin
    → i.v. radiological contrast medium
    → pollen
    → food such as peanuts, shellfish
    → insect stings

- **Pathophysiology**
  - In anaphylaxis, the allergen binds to the antigen specific immunoglobulin (Ig) E molecule attached to the sensitized basophils and mast cells.
  - This results in the release of mediators such as histamine, leukotriene C4, prostaglandin D2 and tryptase.
  - In an anaphylactoid reaction, exposure to an inciting substance causes direct release of the chemical mediators, a process that is not mediated by IgE. The manifestations and treatment are the same as that for anaphylaxis.
  - These mediators cause increased mucous secretion, bronchospasm as well as airway oedema - all these contribute to the respiratory symptoms observed in anaphylaxis.
  - Hypotension results from decreased vascular tone and capillary leakage.
  - Histamine release causes urticaria and itching.

- **Signs and symptoms - these include:**
  - urticaria and itching
  - acute angioedema and / or bronchospasm leading to respiratory distress
  - hypotension
  - cardiovascular collapse
  - nausea, vomiting or diarrhea
  - obtundation due to hypoxia and hypotension
  - death

- **Management:**
  - General measures includes:
    → assess airway and haemodynamics
    → monitor vital signs
    → give oxygen
    → large caliber IV access
  - Specific therapy (refer to Table 24) - the drugs of choice are adrenaline and antihistamines.
    → Adrenaline is the drug of choice for treating anaphylaxis. It may also be self administered with an auto injector (EpiPen and EpiPen Jr)
→ H1 Antihistamines for cutaneous manifestations of anaphylaxis. Continue for 2-5 days to prevent recurrence.
→ Inhaled β-agonists for bronchospasm.
→ Corticosteroids help prevent recurrence of symptoms that may occur after 6 to 8 hours (the biphasic reaction). May have a role in treating bronchospasm and cutaneous manifestations. Oral steroids are usually continued for 2 to 3 days.
→ Glucagon – for treating refractory hypotension in patients on β-blockers.

- Complications - these includes:
  - Laryngeal or oropharyngeal spasm:
    → Adrenaline rapidly reverses airway compromise.
    → Defer intubation attempts and ventilate with bag / mask while awaiting medications to take effect.
    → In extreme cases, cricothyrotomy may be necessary.
  - Bronchospasm - treatment includes:
    → adrenaline
    → inhaled β-agonists
    → intravenous aminophyline
  - Hypotension - the following should be given concurrently:
    → Adrenaline – repeated doses or a continuous infusion may be necessary.
    → Fluids (isotonic crystalloid solutions such as normal saline, Ringer’s lactate). Sometimes large volumes may be required.
    → If the hypotension still persists, noradrenaline or dopamine may be given.
    → Patients on β-blockers may be resistant to the effect of adrenaline. Larger than usual doses or glucagon may be necessary.
  - Urticaria - treat with repeated doses of antihistamines and / or adrenaline.

- Long Term care:
  → Identify the offending agent and avoid it.
  → If the inciting agent is not known, the patient should be referred for allergy testing and wherever appropriate, desensitization done.
  → The patient should be told that attacks may recur.
  → Patients with severe reactions should be taught to administer adrenaline with an auto injector (EpiPen or EpiPen Jr) at the earliest sign of an attack.
  → The EpiPen contains 0.3 mg of a 1:1000 adrenaline solution and the EpiPen Jr (for paediatric use) contains 0.15 mg of a 1:1000 solution.
  → Following administration of the auto injector, the patient must go to hospital because the effects of the adrenaline can wear off and there is a chance of a second reaction.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Route of administration</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>s.c, i.,m (usual routes)</td>
<td>0.3-0.5 ml 1:1000 sol s.c or i.m every 15 minutes</td>
<td>0.01 ml/kg (minimum 0.1 ml) 1:1000 sol s.c or i.m every 15 minutes</td>
</tr>
<tr>
<td></td>
<td>i.v. (when patient is in extremis)</td>
<td>1 ml 1:10,000 sol (diluted in 10 ml normal saline) i.v.; slow administration; repeat PRN</td>
<td>0.01 ml/kg (minimum 0.1 ml) 1:10,000 sol i.v, repeat prn</td>
</tr>
<tr>
<td></td>
<td>Sublingual (SL) or via ETT if there if no i.v. access.</td>
<td>0.3-0.5 ml 1:1000 sol SL every 15 min 1.0 ml 1:1000 sol ETT in approximately 10 ml normal saline</td>
<td>1:1000 sol SL every 15 min 0.01 ml/kg (minimum 0.1 ml) 1:1000 sol ETT in approximately 1-3 ml normal saline</td>
</tr>
<tr>
<td></td>
<td>Continuous infusion when shock is refractory</td>
<td>i.v. infusion: 0.1-1 mcg/kg/minutes</td>
<td>i.v. infusion: 0.1-1 mcg/kg/minutes</td>
</tr>
<tr>
<td>Inhaled β-agonists - Ventolin</td>
<td>nebulizer</td>
<td>0.5 ml 0.5% sol in 2.5 ml normal saline, nebulized every 15 minutes</td>
<td>0.03-0.05 ml/kg 0.5% sol in 2.5 ml of normal saline via nebulizer every 15 minutes</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>i.v. or i.m (usual route) Occasionally oral</td>
<td>25-50 mg i.v./i.m every 4-6 hours. 50 mg PO every 4-6 hours</td>
<td>1-2 mg/kg i.v./i.m every 4-6 hours. 2 mg/kg PO every 4-6 hours</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>i.v. or i.m oral</td>
<td>40-250 mg i.v./i.m every 6 hours 2-60 mg PO every 6 hours</td>
<td>1-2 mg/kg i.v./i.m every 6 hours 1 mg/kg PO every 6 hours</td>
</tr>
<tr>
<td>Glucagon</td>
<td>i.v. or i.m or s.c</td>
<td>1-10 mg i.v./i.m/s.c; typically 1-2 mg every 5 minutes to effect</td>
<td></td>
</tr>
</tbody>
</table>

Table 24: Drugs used in the treatment of Anaphylaxis
Chapter 2
Respiratory Emergencies

Table of contents
1. Severe Asthma
2. Spontaneous Pneumothorax
3. Haemoptysis
4. Deep Vein Thrombosis
5. Pulmonary Embolism

1. Severe Asthma

- Clinical presentation
  - A potentially fatal disease. The severity of the attack should be assessed by:
    - History taking
    - Physical examination
    - PEF (peak expiratory flow) measurement
    - Arterial blood gases (ABG)
  - Features to suggest a severe attack includes (DANGER SIGNALS):
    - Inability to talk or drink, breathless at rest, monosyllable answers.
    - Dehydrated, exhausted, confused, agitated or drowsy.
    - Respiratory rate > 30 / minute
    - Tachycardia > 120/min, bounding pulse, warm hands, pulsus paradoxus. Bradycardia or hypotension indicates very severe attack and imminent cardiorespiratory failure.
    - Loud or absent wheeze, cyanosis (late sign).
    - PEF (peak expiratory flow) < 60% of predicted or personal best. (or single PEF reading of < 100 l/min).
    - Arterial blood gases (ABG) showing acidosis and reduced Pa O2 (< 60 mmHg) with normal or elevated Pa CO2 (>45 mmHg).
  - Rule out pneumothorax, both clinically and with CXR.

- Management
  - Oxygen – high dose humidified oxygen (> 40%) by mask or by nasal catheter. Try to achieve oxygen saturation of 95%. In asthma associated with chronic obstructive pulmonary disease (COPD), high O2 flow rates may remove the hypoxic drive and lead to respiratory arrest. (oxygen mask at 24-28% is safe in this group of patients).
  - Inhaled bronchodilators - inhalation is the method of choice as the drug is delivered to the target site directly. The rapid acting β 2 agonists should be delivered directly to the target organ and best done via a nebuliser. A severely distressed patient will find an inhalational aid like a "Volumetric" or a "Nebuhaler" helpful if a nebuliser device is not available. Once the patient is stable, change therapy to metered dose inhaler.
    - Salbutamol 5 mg or terbutaline 5 -10 mg or fenoterol 5 mg via a nebuliser. Repeat according to response every half hourly (or even more frequently initially) to 6 hourly. Be careful of arrhythmias in elderly patients especially if given frequently.
    - Ipratropium bromide - effective in relieving bronchospasm associated with chronic bronchitis which fails to respond to beta2 agonists. It has
little side effects and is useful in elderly patients with associated heart disease. May be used in combination with beta 2 agonists. Dosage: 0.4 - 2 ml of 0.025% solution (= 250 μg/ml). May be given up to 4 times a day.

- Intravenous bronchodilators such as aminophylline, given at 5 mg/kg as a loading dose over 10 mins, followed by a maintenance dose of 0.5 - 0.9 mg/kg/hour. In patients on oral theophylline, the loading dose is not necessary. Aminophylline has a narrow therapeutic index and may be complicated by seizures, arrhythmias and emesis. IV salbutamol or terbutaline can be used as an alternative to aminophylline. The bolus dose is 250 μg, given over 10 minutes.
- Steroid therapy is started when moderate or severe asthma is diagnosed. Prednisolone is usually given at dose of 0.5 -1 mg/kg/day. In severely ill or unable to tolerate orally, give IV hydrocortisone 200 mg stat and then 6 hourly as an initial therapy. Prednisolone is given for a duration of 1 to 2 weeks in a tailing off dose.
- Correction of acidosis - correct only if sodium bicarbonate levels are dangerously low as anticipated in a collapsed patient or if arterial blood gases shows actual bicarbonate less than 10 mmol/L. Correction of bronchospasm will spontaneously correct the acidosis.
- Correct the dehydration and electrolyte imbalance.
- Antibiotic is given only if infection is suspected.
- Sedatives and narcotics are contraindicated unless patient is mechanically ventilated.
- Intubation/Tracheostomy and positive pressure respiration may be necessary if the patient does not respond to above measures. Indications:
  - Deteriorating PEF
  - Clouding of consciousness or coma
  - Profound exhaustion
  - Hypotension, respiratory arrest
  - Cardiac arrhythmias
  - PaO2 < 50 mmHg
  - PaCO2 > 50 mmHg
- Patients must be reviewed frequently. Clinical symptoms and signs of improvement or deterioration should be carefully looked for. Aids to monitoring include:
  - ABG
  - PEF measurement
  - Measurement of forced expiratory volume in 1 second (FEV1) / forced vital capacity (FVC).

2. Spontaneous Pneumothorax

- Causes: Rupture of subpleural bleb, bulla, lung cyst or abscess.
- Always rule out pneumothorax in a patient who presents with acute dyspnoea especially in an emphysematous lungs.
- Usually presents as
  - Sudden unilateral pleuritic pain
- Acute dyspnoea
  - In tension pneumothorax, the mediastinum is displaced to the opposite side, compressing the other lung and obstructing venous return. Death can occur from respiratory or cardiac failure.
- Clinical presentation of pneumothorax
  - Tachycardia, tachypnoea, ± cyanosis
  - Diminished expansion of the hemithorax
  - Deviation of the trachea away from the affected site
  - Reduced or absent breath sounds and hyper-resonant percussion note
  - Elevated jugular venous pressure (JVP)
- Hypotension
- Differential diagnosis
  - Pulmonary embolism
  - Myocardial Infarction
  - Asthma
- Investigations
  - Chest x-ray: typically shows a clear line of visceral pleura with absence of peripheral lung markings beyond it. There may be deviation of the trachea and mediastinum to the contralateral side. To calculate the size of a pneumothorax: a technique recommended by the British Thoracic Society (Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010) is to measure the distance between the pleural surface and the lung edge (taken at the level of the hilum – see Figure 3). If this is 2 cm or more it represents a pneumothorax of at least 50% of the hemithorax and is an indication for drainage. Depending on the measurement, “small” is therefore regarded as a pneumothorax of < 2 cm and “large” as a pneumothorax of ≥ 2 cm.

Figure 3: Measurement of the depth of pneumothorax (British Thoracic Society guidelines)
- Arterial blood gases (ABG): usually show hypoxia, with severity depending on the extent of the pneumothorax and any presence of underlying lung disease.
- CT scan: this is not done routinely. It is only used when differentiating from complex bullous disease, to indicate other pathology such as emphysema and when aberrant tube placement is suspected.

### Management:
- Immediate aspiration or intercostal drain insertion on clinical diagnosis of tension pneumothorax, in severely dyspnoeic patients or bilateral/haemodynamically unstable.
- In young patients with small pneumothorax and with no compromise on respiratory function, observe till lung re-expands. Usually takes 3-4 weeks. Those with size > 2 cm and/or breathless, initial aspiration (using 16 -18G needle) should be attempted. If this does not offer improvement, insertion of an intercostal drain should be performed.
- In patients with co-existent lung disease and little respiratory reserve, all degrees of pneumothorax should be treated with an intercostal drain. Aspiration may be performed in those with small pneumothorax and without respiratory compromise. Consider intercostal drain insertion if there is no significant improvement.
  - For insertion of intercostals drain, the 4th or 5th intercostal space at the mid-axillary line is chosen. A small incision is made after 1% lignocaine is given locally and a trocar/chest drain is then inserted. The trocar is withdrawn and the drain is left 6 - 8 cm inside the pleural cavity. The drain is kept in position by a suture. The other end of the drain is attached to an underwater seal.
    - **NB: Rapid re-expansion of lung is associated with:**
      - Intrapulmonary haemorrhage
      - Pulmonary oedema
  - Start on physiotherapy and balloon blowing to encourage passive re-expansion.
  - When the intercostals drain stops bubbling (usually after several days), the drain is clamped and a repeat CXR is done. If this shows full re-expansion, the drain is left clamped for another 24 hours and the CXR is repeated. Confirmation of no further leakage of air is followed by removal of the drain.
- Other measures that may be required are:
  - High flow oxygen (unless suspected oxygen sensitive)
  - Analgesic for pleuritic pain
  - Relief of cough
  - Antibiotics if an infection or empyema is present
  - Blood transfusion to replace a large haemothorax
  - Bronchodilators if required
  - Advise to stop smoking
  - In recurrent pneumothorax of the same side or history of previous pneumothorax in the other lung, chemical pleurodesis can be considered if a patient is either unwilling or unable to undergo surgery. This is done either by sterile talc or tetracycline (1gm) diluted in 50 ml of Dextrose 5% and with 5 ml of 2% lignocaine instilled into the pleural cavity via the chest tube once the pneumothorax has re-expanded.
3. Haemoptysis

- Common causes:
  - Upper respiratory tract infection
  - Chronic bronchitis, pneumonia
  - Bronchiectasis, lung abscess
  - Tuberculosis both active & from healed lesions
  - Cardiovascular causes eg. mitral stenosis, pulmonary embolism
  - Carcinoma of the lung
  - Aspergillosis
- The severity of haemoptysis has no correlation with the severity of the underlying disease.
- Investigations:
  - CXR
  - CT scan of the chest
  - Sputum for acid-fast bacilli (AFB) direct smear, malignant cells, fungi C+S
  - Bronchoscopy
  - Baseline coagulation profile
- Management
  - Bed rest, with or without oxygen. Be careful of oxygen therapy in patients with prolonged hypoxia as this may remove the hypoxic drive. 24-28% oxygen given via mask is safe.
  - Mild sedation with a benzodiazepine. The patient is often very frightened and reassurance is necessary. Massive haemoptysis is uncommon and haemoptysis is self-limiting in the majority of cases. Careful observation is still mandatory as death may occur from asphyxiation or sudden unexpected massive bleed.
  - Treat the underlying cause if known eg. antibiotics for bronchitis, pneumonia, tuberculosis.
  - Give i.v Vitamin K 10 mg every 8 hourly
  - Antifibrinolytics such as tranexamic acid are of doubtful value. The usual dosage is 250 to 500 mg t.d.s given orally or 1 – 2 ampoules given intravenously as 1 – 2 doses daily.
  - Suppress cough – linctus codeine is helpful.
  - Blood replacement, if necessary. Insert a large bore intravenous branula in all cases. Reserve at least 2 units of blood.
  - Occasionally, urgent bronchoscopy followed by surgical treatment may be necessary eg. massive bleeding from an old TB cavity or aspergillosis.
  - Consider angiogram and embolisation when indicated and where facilities are available.

4. Deep vein thrombosis

- To diagnose this condition, one must be aware and actively looking for it. The causes and associations are remembered by considering Virchow’s triad:
  - Stasis: Immobilised limb/patient, CCF, obesity, Pregnancy
  - Vessel wall trauma: surgery, soft tissue injury, fractures, malignant infiltration.
  - Blood hyperviscosity/ hypercoagulability: Post-trauma/, surgery/partum Polycythaemia, OCP, Malignancies (especially carcinoma of the pancreas) & thrombocytosis
In young patients with NO obvious cause of DVT, think of the followings (which are very rare):

- Antithrombin III deficiency
- Protein C deficiency
- Paroxysmal nocturnal haemoglobinuria
- Lupus anticoagulant
- F XIII deficiency

In the majority of patients, there is swelling and pain of the calf associated with oedema, warmth and distended superficial veins. Physical signs are highly unreliable and many DVT remain undiagnosed. Homan's sign should NOT be elicited as it may dislodge the clot.

Investigation for diagnosis includes:

- Doppler ultrasound
- Venogram

Management

- Bed rest with elevation of foot, elastic bandage application, analgesia.
- Urgent anticoagulation with s.c low molecular weight heparin in therapeutic doses:
  - Enoxaparin (Clexane) - single daily injection of 150 anti-Xa IU/kg or 100 anti-Xa IU/kg given b.d.
  - Tinzaparin (Innohep) - 175 anti-Xa IU / kg daily.
  - Nadroparin (Fraxiparine) - 2 daily injection, given as 12 hourly dose (≥100 kg 1.0 ml/inj; 90-99 kg 0.9 ml/inj; 80-89 kg 0.8 ml/inj; 70-79 kg 0.7 ml/inj; 60-69 kg 0.6 ml/inj; 50-59 kg 0.5 ml/inj; 40-49 kg 0.4 ml/inj)
- Oral anticoagulation, warfarin, is started about 3 days before the planned day of termination of s/c heparin. Onset of anticoagulation effect takes about 3 days. It's adequacy is monitored by PT aiming for 1.5 - 2 times the control. When this is achieved, the s/c heparin therapy is stopped.
- Oral anticoagulation is required for:
  - One single episode of DVT - 3 to 6 months
  - Two episodes of DVT - 6 months to 1 year
  - Three episodes of DVT - Indefinite
- Urgent reversal of oral anticoagulation is with fresh frozen plasma. Warfarin acts by interfering with Vitamin K metabolism. Give IV Vitamin K 10 - 30 mg. The anticoagulant effect is reversed in 24 hours. For transient reversal of anticoagulation, it is preferable to use FFP because reversal with Vitamin K will cause resistance to warfarin for up to 2 weeks.

Prevention - This is by far the most important.

- Leg exercises in post operation period.
- S.C low molecular heparin in prophylactic dose in high risk patients. Laboratory monitoring is usually not necessary. This does not cause primary or secondary haemorrhage.
  - Enoxaparin (Clexane) - 2000 anti-Xa IU (0.2 mL) or 4000 anti-Xa IU (0.4 mL) given once daily
  - Tinzaparin (Innohep) - 50 anti-Xa IU/kg given once daily
  - Nadroparin (Fraxiparine) - 0.3 ml daily given once daily
- TED stockings for lower limbs in non-ambulatory patients

5. Pulmonary thromboembolism
• 95% arise from emboli from the deep venous system of the lower limbs. The femoro-iliaic venous segment is the most common source.
• Sudden onset of dyspnoea is usually the only symptom. Pleuritic chest pain and haemoptysis occur only if infarction has occurred.
• Investigations:
  ➢ Arterial blood gases (ABG) - hypoxaemia, hypocarbia seen
  ➢ CXR - may be normal. Difficult to find the classic wedge shape shadow, elevated diaphragm, pleural effusion and diminished vasculature.
  ➢ ECG – right sided strain pattern (tall R in V1, Deep S in V6, Peak P) RAD, RBBB, ST depression in (R) sided leads, S1Q3T3 may be present.
  ➢ Ventilation/Perfusion scan - classic finding of “ventilation – perfusion mismatch”.
  ➢ Pulmonary angiography - the gold standard for localisation of primary site of clot.
• Management
  ➢ Treatment with anticoagulation may be started on CLINICAL grounds.
  ➢ The treatment is s/c heparin – same doses as in treatment of deep vein thrombosis. With massive embolisation, the patient is in critical condition. Circulatory and cardiac arrest requires resuscitation. External cardiac massage may break up the embolus. Pulmonary angiography followed by pulmonary embolectomy is the definitive treatment. Thrombolytic agents like streptokinase and plasminogen activators offer alternative treatment.
  ➢ Patients who remain critically ill with persistent hypoxia and hypotension require transfer to a centre where pulmonary angiography and embolectomy could be carried out.
  ➢ Thrombolytic agents has a higher success rate but is associated with a high risk of haemorrhage

Chapter 3
Neurological Emergencies

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1. The comatose patient

• Definition: A patient who fails to respond to call, often stuporose but may have verbal response or movement to pain stimuli. Glasgow Coma Scale is often used to assess the severity of comatose state.
Etiology
- trauma
- drugs/poisons eg. morphine, hypnotics, alcohol, organophosphates, paraquat
- stroke – including subarachnoid haemorrhage
- epilepsy
- shock – hypovolaemic shock from acute haemorrhage – both internal and external, diarrhoea, peritonitis, acute pancreatitis, anaphylaxis
- uraemia
- diabetic emergencies – hypo/hyperglycaemic coma
- respiratory failure – hypoxia and hypercarbia
- hepatic failure/encephalopathy
- myxoedema coma, Addison’s disease
- hypothermia/hyperthermia

Clinical presentation
- scalp/skull – injuries, bruises
- nose & ears – discharge of pus, blood, CSF
- tongue – dehydration/bitten/burnt by corrosives
- neck – rigidity, carotid pulse, bruit
- chest – rate, depth, rhythm of respiration
- abdomen – enlarged liver, spleen or kidneys, ascites
- urine – incontinence or retention, protein, sugar, acetone, output
- eyes - conjunctive-haemorrhage, jaundice, pupils-size, reaction to light → fundi for papilloedema, signs of diabetes or hypertension, subhyaloid haemorrhage → pinpoint pupils: narcotic abuse, pontine haemorrhage → dilated pupils: tricyclic abuse
- breath – uraemic, acetone, alcohol, organophosphates
- skin – cold, moist, dry flushed, cyanosis, sallow jaundice
- heart – abnormality of rhythm
- arms – BP, hemiplegia, injection marks
- hands – pulse rate, rhythm, volume, tremors
- legs – hemiplegia, plantar responses

Investigation
- CT scan brain (plain)
- EEG
- lumbar puncture if no contraindication (e.g normal CT scan brain)
- general blood screen
- toxicology screen

Immediate management:

A – Airway
B – Breathing
C – Circulation

- Airway must be kept clear. In comatose patients, an oropharyngeal airway is helpful to prevent the tongue from falling back and to assist suction.
- Check carotid pulse and respiration. If negative, initiate CPR.
- Control external haemorrhage.
- Secure a good IV line in case of need for resuscitation and for infusion of fluids and medication.
Examine pockets/handbag for medical cards, medical alert pendants.
Take blood for sugar, urea and serum electrolytes, toxicology studies. Use a test strip for immediate blood sugar value.
If pupils are pinpoint, give naloxone 0.4 mg stat and observe for response. A dramatic but short lived response is seen in narcotic overdose.
In alcohol abuse, provide 5% Dextrose as an infusion and give IV thiamine 100 mg.
Observations by Glasgow come scale and chart.
Determine the underlying cause of the coma and provide specific treatment.

**Tips on Neurological examination:**

- “Pin-point pupils” suggest pontine lesions, narcotic poisoning, miotics or organophosphorous poisoning.
- Fixed dilated pupils may be found after an epileptic fit or tricyclic poisoning.
- Raised intracranial pressure above the tentorium causes temporal lobe herniation with pressure on the oculomotor nerve (usually on the side of the lesion). The pupil contracts for a short while then dilates and does not respond to light. With further increase in pressure the other pupil is also affected. May be associated with up going plantar on the contralateral side.
- Skew deviation or dissociated rolling of the eye-balls indicates mid-brain damage.
- Fundoscopy – look for papilloedema. In subarachnoid haemorrhage, subhyaloid haemorrhage may be noted. DO NOT use mydriatics. You will lose a very valuable sign. Always check fundi for papilloedema before doing and lumbar puncture. NEVER do an lumbar puncture if a space occupying lesion is present. Main indications for lumbar puncture are:
  - to confirm meningitis and to identify with Gram’s stain, Indian ink and Ziehl-Neelsen stain, polymerase chain reaction (PCR) for tubercle bacillus (TB), cryptococcal antigen and to culture the organism.
  - confirm subarachnoid haemorrhage.
- Assess muscle tone. In acute cerebrovascular accident (CVA), the side affected is hypotonic and possibly areflexic.
- In recent cerebral insult, the head and eyes tend to turn to the damaged side. In brainstem lesions, they deviate to the contralateral side.
- In decerebrate rigidity the lower limbs are hyperextended and the upper limbs are extended, adducted and hyperpronated with fists clenched.
- In decorticate rigidity, the upper limbs are flexed at the elbow, adducted and flexed at the wrist.
- Any “crossed” signs indicate a brainstem lesion.
- A unilateral extensor plantar response points to damage of the opposite hemisphere provided spinal cord damage is excluded.
- Kernig’s sign should be elicited only if cervical cord injury is excluded.
- Always consider meningitis if there is headache, irritability or neck rigidity as it is treatable.

2. **Meningitis**

- Definition: Infection of the meninges of the brain by micro-organisms. Often there is presence of abnormal cerebrospinal fluids (CSF) findings.
- Etiology:
The common causative agents are: Streptococcus pneumonia, Haemophilus influenza, Neisseria meningitides
- Others – cryptococcal meningitis and tuberculous meningitis

- **Clinical presentation**
  - headache, drowsiness, coma, fits
  - neck stiffness
  - fever
  - photophobia
  - vomiting

- **Investigation**
  - CT scan brain (plain) - if normal to proceed to lumbar puncture
  - Lumbar puncture (LP) must be performed early and cerebrospinal fluids (CSF) sent for culture and sensitivity (C+S), microscopy, Gram Stain, Ziehl-Neelsen stain, Indian ink stain, cryptococcal antigen, polymerase chain reaction (PCR) for tubercle bacillus, cytology and biochemical analysis.
  - CSF opening pressure should be measured. Normal CSF is clear and colorless. Opening pressure is less than 25 cm H2O.

- **Diagnosis**
  - The diagnosis of meningitis is associated with raised white cell count in the cerebrospinal fluid (CSF). The CSF protein level is usually elevated and the sugar level can be either normal or low.
  - In viral meningitis or partially treated bacterial meningitis, the CSF showed moderate pleocytosis (increased cellular counts) and protein level is usually moderately elevated and sugar level is normal or mildly low.
  - In bacterial meningitis, white cell count is markedly raised, with predominantly neutrophils. The sugar level is low and the protein level is moderately high. However, in early cases of bacterial meningitis, the CSF findings may be normal.
  - In chronic infection of the meninges, predominantly tuberculosis and cryptococcus, the CSF sugar is very low and protein level is markedly elevated with pleocytosis.

- **Treatment:**
  - Antibiotics are started early on clinical suspicion without waiting for CSF analysis. Broad spectrum antibiotics that penetrate the blood brain barrier are used.
  - Antibiotic for bacterial or viral meningitis
    - i.v Ceftriaxone 3g daily in 100 ml normal saline infusion OR
    - i.v Cefotaxime 2 grams 6 hourly OR
    - i.v Meropenem 2 grams 8 hourly
  - Duration of treatment is from 7 to 14 days.
  - Use of steroids is best avoided unless there is evidence of progressive focal neurological signs or deterioration of level of consciousness.
  - Different antibiotics may required in specific conditions such as:
    - Non immunocompromised patients with cryptococcal meningitis - IV Amphotericin (Colloidal or Non Colloidal ) is given at 1-2 mg/kg per day to a cumulative dose of 2-4 grams.
    - Immunocompromised patients with cryptococcal meningitis - IV Fluconazole 200-400 mg daily for 4-6 weeks Or IV Amphotericin (Colloidal or Non Colloidal ) is given at 1-2 mg/kg per day to a cumulative dose of 2-4 grams.
→ Treatment for tuberculosis (TB) meningitis
  - Pyrazinamide 15-25 mg/kg/day (maximum 2 g/day)
  - Rifampicin 10-20 mg/kg/day (maximum 600 mg/day)
  - Isoniazid at 5 mg/kg/day (maximum 300 mg/day)
  - Pyridoxine 25 mg daily
  - (Ethambutol is best avoided as it may cause optic neuritis)

3. Stroke

- Definition: a sudden focal neurological deficit attributable to a specific vascular territory.
  - Transient Ischaemic Attacks (TIA) is a “mini” stroke that lasts for < 24 hours.
  - Cerebral infarction from thrombosis or embolism accounts for 85% of strokes. Cerebral haemorrhage account for the remainder.
    → Cerebral Infarcts: The mechanism of cerebral Infarcts may be due to in situ thrombosis or embolism. Embolism may be from a cardiac source or artery to artery emboli. Causes are due to risk factors for atherosclerosis.
    → Cerebral haemorrhage: Primary Intracerebral Haemorrhage is associated with rupture of Charcot-Bouchard aneurysms in patients who usually have hypertension.
  - All patients should have a CT scan brain done immediately. It is the only reliable investigation to exclude a cerebral bleed.
- Treatment:
  - General Measures
    → admit a patient to ICU or an acute stroke unit
    → coma nursing to prevent bed sores, hypostatic pneumonia, contractures, exposure keratitis
    → fluids: intravenously if unable to feed
    → reduce pyrexia.
    → maintain good glycaemic control
    → give oxygen if oxygenation is inadequate. Intubate patient if necessary.
    → maintain electrolytes within normal ranges.
    → maintain adequate caloric intake.
    → treatment of associated illnesses e.g pneumonia.
    → physiotherapy and speech therapy
  - Specific treatment
    → Hypertension - Mildly elevated BP may be the body’s response to the stroke and should be left alone. The ischaemic areas around the infarcted zone lose auto-regulation of cerebral blood flow and perfusion is dependent on the blood pressure. Rapid lowering of BP may be associated with decreased perfusion to these areas and is thus harmful. Gentle reduction of the BP is advised. Hypertensive encephalopathy warrants a more rapid reduction of BP. Treat if blood pressure is
      180 mm Hg systolic
      120 mm Hg diastolic
Cerebral oedema - often manifested with deteriorating level of consciousness. CT scan may show the massive mass effect and herniation of the brain. Dexamethasone is generally ineffective in strokes as cerebral edema is mostly cytopathic rather than vasogenic. Dehydrating agents e.g. mannitol and frusemide may be used with little benefit. In a young patient with massive cerebral edema due to an infarct in the non dominant cerebral hemisphere, a radical decompressive surgery may be performed. However, the patient’s relatives must be informed about the significant deficit that may occur after surgery.

Embolism - a source of emboli may be clinically found eg. mitral valve stenosis or atrial fibrillation. Cerebral infarcts from embolisation may undergo haemorrhagic transformation in 15% of cases. Hence it is important that a CT scan be performed before anticoagulation is started to avoid secondary haemorrhage. Furthermore, early anticoagulation may precipitate secondary haemorrhage and it is advisable to start anticoagulation only after one to two weeks in large artery territorial infarcts. Anti-platelet agents such as aspirin or clopidogrel may be given at the onset of acute cerebral infarcts. If the onset of cerebral infarct is less than 4.5 hours and the CT scan of brain is absolutely normal with no early infarct sign, then thrombolysis using recombinant tissue plasminogen activator (r-TPA) at a dose of 0.9mg/kg may be given. 10% of the calculated dose is given bolus then the remainder over one hour in an infusion pump. There must be no general contraindication for thrombolysis and the family must be aware of the risk of haemorrhagic transformation that may occur in up to 10% of cases. If symptomatic haemorrhagic transformation occurs, use of cryoprecipitate and neurosurgical referral is needed.

Intracerebral bleed – this is diagnosed on CT scan. Progression to coma and death is rapid due to brainstem compression. Suspect in patients who are rapidly deteriorating. Neurosurgery opinion is required.

Subarachnoid haemorrhage - Risk of re-bleeding is high with peak incidence at the 7 – 10 days. One third of cases re-bleed in the first one to two weeks. CT scan brain and angiography is needed to indicate the site of bleeding and other associated aneurysms. Surgical clipping of the aneurysm or intravascular coiling is the preferred definitive treatment.

Seizures - IV Diazepam 5 to 10mg is the drug of choice. Diazepam may be give per rectum at the same dose if an IV line could not be secured rapidly. Anticonvulsants should be given as soon as possible.

Prognosis - The prognosis from acute stroke depends on the subtype of stroke. Often there is a 10% annual risk of recurrent stroke.

Poor prognostic signs are:
- depressed level of consciousness on admission
- loss of papillary reflexes
- paralysis of conjugate eye movements
- bilateral extensor plantars
- respiratory abnormalities eg. Cheyne – Strokes respiration
4. Treatment of Intracranial Hypertension

- Neurosurgical intervention is possible treatment for large intracranial haematomas with mass effect and deterioration of neurological status.
- Medical treatment may be suitable for cerebral oedema associated with infections, malignant hypertension, anoxia following cardiac arrest and tumours. However, treatment of underlying cause is the mainstay of treatment.
  - Dehydration therapy – this is useful for short term management of intracranial hypertension. Watch for side-effects of dehydration and electrolyte imbalance
    → Agents which increase the osmotic pressure of the blood eg. 1.0 – 2.0 gm/kg of mannitol given over 30 minutes every 8-12 hours.
    → Frusemide 80 mg i.v. Takes 15 minutes to act and pressure is relieved for 4 – 6 hours.
  - Corticosteroids are less effective with slower onset of action. IV dexamethasone 8 mg is given 6 -8 hourly is useful for vasogenic cerebral edema associated with primary or secondary tumours. Cytopathic cerebral edema due to anoxia or infarction does not usually respond to steroids.
  - Hyperventilation - This will decrease the Pa CO2 and cause the intracranial blood vessels to undergo vasoconstriction. This reduces the intracranial volume of blood and decreases intracranial pressure. The Pa CO2 is reduced to 25 – 30mm Hg. Hence, elective ventilation may be needed.

5. Diagnosis of Brain Death

- Definition - means irreversible cessation of brain stem function. Need to exclude that this is not due to drugs, primary hypothermia, metabolic or endocrine causes because these cause reversible coma.
- If patient is on a ventilator, ensure that the effects of anaesthetic drugs are reversed before coming to the conclusion that there is no spontaneous respiration.
- Tests that are performed to assess brain death includes:
  - response to deep stimuli
  - pupillary reflex
  - cornea reflex
  - gag reflex
  - doll’s eye reflex
  - ice-water calorie test
  - respiratory response to an increased Pa CO2 to 60mm Hg.
- In brain death, there is no response to the above tests. If in doubt, re-establish mechanical ventilation. Repeat tests after 24 hours.

6. Status Epilepticus

- Definition: The condition where one seizure follows another without recovery of consciousness. It may be convulsive or non convulsive.
- Emergency evaluation of seizures:
  - History – look out for history of trauma, previous seizures, drugs or alcohol use, current medications.
  - Physical examination
vital signs such as pulse rate and rhythm (to rule out dangerous cardiac arrhythmia, cardiac arrest), blood pressure (rule out hypotension and shock), body temperature (rule out hyperthermia 41 – 42°C).

papilloedema, focal neurological signs

heart murmur

look for evidence of systemic disease

Laboratory and special investigations

- serum glucose: either hypoglycemia or hyperglycemia
- arterial blood gases: hypoxia, hypercapnia, acidosis
- ECG: cardiac arrhythmia
- serum electrolytes: hyponatremia or hypernatremia
- full blood count
- serum calcium and magnesium levels
- hepatic and renal function studies
- lumbar puncture
- CT scan brain
- blood and urine samples for toxicology studies (if indicated)

Treatment - therapeutic aims are towards rapid termination of seizures and the prevention and treatment of associated complications.

- Place an oropharyngeal airway (Guedel) to prevent the tongue from falling back and to facilitate suction. Do not force when fitting. Place it in between seizures.
- High flow oxygen to correct hypoxia. The un-coordinated respiratory efforts together with increased metabolism requires oxygen at high flow rates.
- Rule out hypoglycaemia. Use a test strip to determine the blood glucose.
- i.v diazepam 5mg/min. Pause at 10 mg and at each subsequent 5 mg to assess the effects. Maximum bolus dose is 20 mg. The dose may be repeated if necessary after 30 minutes. Risk of hypotension and respiratory depression with high doses. Be prepared for mechanical ventilation. Diazepam may be given per rectum if an IV line is not immediately available. IV diazepam infusion may be given without dilution at 2 to 4 mg per hour. Watch for respiratory depression. DO NOT give i.m diazepam as absorption is slow and erratic.
- Anticonvulsant agents
  - i.v phenytoin – to be given in saline of 100 ml at a loading dose of 10-15 mg/kg at a rate no faster than 50 mg/minute. IV maintenance at 100 mg every 8 hourly. Monitor the BP closely for hypotension. ECG monitoring is required.
  - i.v sodium valproate 1.2 gm is given bolus followed by maintenance dose of 400 mg every 8 hours.
  - i.v phenobarbitone is given at a loading dose of 200 mg over one hour. Further i.v doses of 100 – 200 mg can be given until the seizure stop and has to be titrated according to blood pressure measurement and respiratory rate
- Consider paralysis and mechanical ventilation if seizures persistent. It is important to continue with anticonvulsants as seizure activity may persist despite the paralysis. EEG monitoring is useful if available to assess the effectiveness of the anticonvulsants in inhibiting the abnormal cerebral discharge.
Monitor electrolytes - metabolic acidosis is likely with prolonged seizures. NaHCO3 may be required for correction. Amount of NaHCO3 (mmol/l) = 1/3 x BW (kg) x base deficit.

Acute renal failure may rarely result from rhabdomyolysis and myoglobinuria. If myoglobinuria is present treat with I/V fluids, mannitol or frusemide to establish good urine output and prevent acute renal failure.

Cerebral oedema may complicate prolonged seizures.

7. Tetanus

Definition - a potentially fatal disease caused by Clostridium tetani. The organism produces tetanospasmin which blocks the function of inhibitory neurons hence increasing reflex excitability of motor nerves.

The injury allowing the Clostridium tetani spores to enter the body may be trivial.

Incubation period – refers to time interval from injury to first symptom. This period varies greatly from one to three months. Generally, it is less than 14 days. The shorter the incubation period, the worse the prognosis.

Period of onset – it is the time interval between the first symptom and the first spasm. The shorter the interval, the worse the prognosis.

Clinical presentation
- rigidity – occurs in all cases. Ranges from "stiff" jaw muscles, risus sardonicus, neck stiffness, abdominal rigidity to opisthotonus in extreme cases.
- reflex spasms – these are sudden exacerbation of underlying rigidity. Whole groups of muscles suddenly contract and this will impede respiration. Spasms may be rapidly recurrent and this will seriously embarrass respiration.
- the patient is generally most severely ill in the first 6 weeks.
- coughing while drinking or eating or dysphagia is an important symptom which indicates serious disease. There is risk of laryngospasm and a tracheostomy is required.
- spontaneous recovery occurs from the tenth day onwards. Laryngeal spasms may occur suddenly and must be looked for.

The diagnosis is based on clinical features.

Complications - the principal problem is respiratory complications from spasms, aspiration and pneumonia. Severe cases may be complicated by:
- heart failure, pulmonary oedema
- autonomic dysfunction - tachy or bradycardia, sweating, ileus,
- hyperpyrexia
- deep vein thrombosis (DVT)
- syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH)

Treatment
- Passive immunization with human anti-tetanus immunoglobulin. Given as early as possible. It is effective only against circulating toxin. Toxin which has already reached the CNS is unaffected.
  → prophylactic dose: i.m 250 to 500 units
  → treatment dose: i.m 3000 to 6000 units (there is doubt about the efficiency of passive immunization in established tetanus. It is however routinely given).
- Wound - this is cleared and any narcotic tissue debrided.
- Antibiotics - Clostridium tetani is sensitive to:
i.v Benzyl Penicillin: 1 – 3 Mega every 6 hours.

- Erythromycin or tetracycline is given if allergic to penicillin

- Control spasms - infusion of diazepam at 1mg to 4 mg per hour with or without i.m chlorpromazine 50 mg 4 to 6 hourly is adequate to control most cases of mild tetanus. These patients should be nursed in a quiet darkened room to minimize external stimuli.

- Laryngospasm may be treated with i.v chlorpromazine 100 mg or with paralysis, intubation and mechanical ventilation. The use of tacheostomy circumvents this risk.

- Severe spasms and patients with respiratory embarrassment will require paralysis and mechanical ventilation. A tracheostomy is usually required. Patients are paralysed for at least 10-14 days. Most patients start to recover by the 3rd week of illness.

- Supportive measures – this is very important as patients die from complications of tetanus rather than from the spasms or rigidity.
  - chest physiotherapy and care of airway.
  - parenteral nutrition or feeding via a naso-gastric tube if airway is secured.
  - ensure normal arterial blood gases and electrolytes
  - autonomic dysfunction - sympathetic overactivity is treated with labetolol. Parasympathetic over activity is treated with atropine.
  - treat intercurrent infection.

- s.c low molecular weight heparin for deep vein thrombosis (DVT) prophylaxis.

- Active immunisation with anti-tetanus toxoid (ATT) - natural immunity does not occur after tetanus as immunizing dose is higher than the fatal dose of tetanus toxin. Active immunisation with 0.5 ml the toxoid must be given preferably at convalescence and then at 6 weeks and 6 months later. Immunity lasts for 5 years and booster doses are then required. If ATT is given during the acute illness, passive immunisation with immunoglobulins must be given at a different site.

8. Gullain Barre Syndrome (Acute Inflammatory Demyelinating Polyneuropathy)

- Definition: Post infectious auto immune disease due to the presence of antibodies to myelin and axons.
- Clinical presentation - progressive weakness of distal muscles of both upper and lower limbs, ascending numbness, autonomic changes, dysphagia, cranial neuropathy.
- Investigations
  - general blood screen (including HIV test) to exclude electrolyte imbalance
  - nerve conduction study
  - lumbar puncture to assess for raised protein levels and pleocytosis of cells.
- Treatment
  - General support
    - maintain airways, respiratory care with mechanical ventilation.
    - inotrope support for autonomic changes (for inotrope dose, see table 15)
feeding via naso gastric tube or IV parenteral feeds may be needed to keep good nutritional requirement.

- prophylactic anticoagulation to prevent deep vein thrombosis.
- i.v antibiotics to treat infection, if present.
- physiotherapy

Specific treatment
- i.v immunoglobulins at 0.5 g/kg/day for 5 days or plasmapharesis three times a week for 2-3 weeks.
- there is no evidence that corticosteroid use is effective.

9. Myasthenia Gravis

- Definition - Autoimmune disease characterized by weakness and fatigability of muscles.
- May be ocular or generalized involving the laryngeal and respiratory muscles.
- Treatment
  - Generalized measures
    - admit to ICU bed. Maintain airway and support circulation.
    - treat co-incidental infection.
    - intubation and mechanical ventilation if indicated eg patient has rising PCO2 levels or poor respiratory effort. Tracheostomy if long term ventilation is needed.
    - nasogastric feeding if dysphagia occurs. Need to maintain good caloric intake.
  - Specific therapy
    - pyridostigmine 60 mg every 8 hourly given oral or via NG tube
    - i.v immunoglobulins at 0.5 g/kg/day for 5 days or plasmapharesis three time a week for 2 - 3 weeks.
    - immunosuppression - oral prednisolone 40 to 50 mg daily and/or azathioprine 1 to 2 mg/kg/day. Both will take a few weeks to work.
    - thymectomy if needed.

Chapter 4
Metabolic / Endocrine Emergencies

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   B. Diabetes ketoacidosis
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   D. Lactic acidosis
2. Hypercalcaemia
3. Thyroid emergencies
   A. Myxoedema coma
   B. Thyrotoxic crisis

1. Diabetes mellitus emergencies
A. Hypoglycaemic Coma

- Always rule out this condition first in any comatose patient.
- Patients may be drowsy, comatose, having abnormal behavior or seizures. May be mistaken as being drunk. They may have focal neurological deficits such as hemiparesis and can be easily mistaken for a stroke.
- Bizarre and false positive localizing signs may be present. If prolonged, this may result in permanent brain damage.
- Beware of prolonged hypoglycaemia seen with long acting hypoglycaemic agents such as glibenclamide, long acting insulin or even traditional herbal medications that may contain glibenclamide in patients with renal or hepatic failure.
- Test-strips provide a rapid indicator of the blood sugar level and the level should be monitored regularly.
- Treatment:
  - Give 50 ml of 50% Dextrose intravenously and follow with a Dextrose 10% drip till patient is eating.
  - For patients with hypoglycaemia and reduced conscious level and intravenous access is not available, intamuscular (i.m) glucagons 1 mg should be used. Further action (such as feeding) is needed to prevent recurrent episodes.
  - Monitor blood sugar level (hourly to every 2 hours) till stable.
  - Look for precipitating or causal factors
  - To prevent further episodes of hypoglycaemia, the following should be done prior to discharge:
    - Dosage and timing adjustment of hypoglycaemic agents may be necessary.
    - Counseling regarding diet and physical activity. Patient and their relatives should be taught on how to correct impending hypoglycaemia with food or drinks rich in glucose or sugar.

B. Diabetic ketoacidosis (DKA)

- A serious condition characterized by:
  - hyperglycaemia
  - ketoacidosis
  - dehydration
  - electrolyte imbalance
- Associated precipitating factors:
  - acute myocardial infarction, strokes
  - infection: bladder, lungs, septicaemia, cellulitis and gangrene
  - trauma & surgery
  - sudden withdrawal of insulin in Type 1 diabetes mellitus. Type 2 diabetics may also develop DKA if there are precipitating factors causing an increase in insulin requirement.
- Onset is over days and patients are drowsy rather than comatose. It is very important to realize that DKA may present as epigastric pain.
- Investigations
  - full blood count - total white may be raised
  - blood glucose – significant hyperglycaemia, which may not necessarily correlate with severity
  - serum electrolytes – hyperkalemia with normal or reduced Na+.
- blood urea and creatinine – both usually raised due to dehydration or existing renal impairment
- arterial blood gases - acidic with low bicarbonate.
- urine microscopy – glycosuria, ketonuria, +/- cellular changes which may suggest infection
- infection screen – blood and urine cultures, CXR,
- others - ECG

Treatment:
- Recognition of precipitating factors and appropriate treatment given. This is an essential step, which must not be overlooked.
- Correct hypovolaemia/dehydration - an average of 6-8 litres of fluid is given over the first 24 hours. Adequate fluid replacement is crucial and patients must be examined frequently to look for signs of overloading or under hydration. Suggested regime:
  - 1 litre of normal saline in first 30 minutes
  - 1 litre of normal saline in next 1 hour
  - 1 litre of normal saline in next 2 hours,
  - 3 litres of normal saline over next 20 hours.
  - If initial serum Na⁺ level exceeds 150 mmol/l, use 0.45% NaCl.
  - The infusion is changed to D5% or D10% when the blood glucose level falls to 15 mmol/l. This is to avoid hypoglycaemia and to provide substrate for the Kreb’s cycle. This will correct the acidosis/ketosis as the acetoacetate is utilized. The patient must be monitored carefully to avoid overloading and pulmonary oedema especially in the elderly and those with congestive cardiac failure (CCF) or renal impairment. A central venous line (CVP) line is helpful.
- Give intravenous short acting regular insulin via the infusion pump at 0.1 – 0.15 unit/kg BW/hour. An intravenous loading dose of 10 units of insulin can be given prior to infusion. If no infusion pump is available, insulin is given via a burette or as hourly intramuscular injections. The blood glucose level should be made to fall at 3 to 6 mmol/hour. When the blood glucose falls to 15 mmol/l, the rate of insulin infusion is halved. In patients with serious infections, insulin resistance may occur and will pose a challenge in maintaining good blood sugar control.
- Two hourly blood glucose monitoring is necessary. Glucose test strip is a convenient and rapid way of monitoring.
- Give intravenous potassium chloride (KCl) – there is potassium deficiency, which is aggravated when insulin is started. Put 1gm KCl in each 0.5 litre of fluid. Monitor with blood urea and serum electrolytes twice daily and ECG monitoring in order to determine whether the replacement is adequate or excessive.
- Bicarbonate therapy – this should only be given when:
  - DKA is accompanied by shock or coma
  - pH < 7.0
  - serum HCO₃⁻ level < 10 mmol/l
  - severe hyperkalaemia present

The amount of bicarbonate (NaHCO₃) needed (mmol/l) is calculated from the formula = 1/3 X BW(kg) x Base deficit (24 – Actual HCO₃⁻ level).
Please note that the 8.4% NaHCO₃ is extremely hyperosmolar and therefore, must be infused slowly. Arterial blood gas monitoring is required. Additional potassium supplement is required whenever alkalis are given. Indiscriminate use of NaHCO₃ is associated with:
- shift of O₂ dissociated curve to the left.
- paradoxical CSF acidosis.
- hypokalaemia.
- sodium overload, sudden changes in osmolarity and pH, rebound alkalosis

Ketouria can persist after correction of acidosis, hence urine ketones have limited role in monitoring therapy. Measurement of anionic gap is a more reliable gauge of ketoacidosis. The formula is \( \text{anionic gap} = \text{Na}^+ + \text{K}^+ - (\text{Cl} + \text{HCO}_3^-) \). The normal value is < 20mmol/l

- Aspirate stomach contents with naso-gastric tube as gastroparesis is common.

C. Hyperglycaemic hyperosmolar non-ketotic coma

- Occurs predominantly in Type 2 diabetes mellitus, presenting with severe dehydration and hyperglycaemia, without ketoacidosis. This occurs usually in the setting of an elderly diabetic living alone who is ill from some other concurrent illness.
- Patients often present in coma, severely dehydrated and with underlying illness and with following features:
  - hyperglycaemia often > 33 mmol/l
  - serum sodium > 150 mmol/l
  - plasma osmolarity > 330 mmol/l. This can be calculated from formula \( = 2(\text{Na} + \text{K}) + \text{Glucose} + \text{Blood urea (SI units)} \). The normal range is 270 to 295 mmol/l
- Investigations – similar to those with DKA
- Treatment
  - Recognise and treat precipitating factors.
  - **Rehydrate** with 0.9% saline or 0.45% saline. If serum Na+ is > 150 mmol/l, 0.45% saline is used. Large quantities of fluid are needed for replacement but this must be infused slowly and with careful central venous pressure (CVP) monitoring. Overzealous and rapid infusion can result in cerebral oedema, disequilibrium syndrome and pulmonary oedema in these elderly patients. Correct deficit over 24 hours.
  - Intravenous insulin therapy: these patients are very sensitive to insulin hence only small doses should be used. The blood glucose is gradually lowered as in DKA because too rapid lowering will result in cerebral oedema / disequilibrium syndrome. Start at 1 to 3 units per hour. Monitor with glucose test strip 2 to 4 hourly in the first 24 hours.
  - **Give K+ supplement as in DKA**.
  - The risk of deep vein thrombosis (DVT) is high. Therefore, **appropriate dose of low molecular weight heparin is needed to prevent DVT**.

D. Lactic Acidosis
- Occurs in elderly diabetics, and often with a background of renal impairment or liver impairment e.g. cirrhosis.
- This may be precipitated by biguanides or alcohol, trauma and infection.
- These patients are severely acidotic. Blood sugar may be slightly raised or normal and there is little if any ketonuria. Blood lactic acid levels are raised and HCO$_3^-$ reduced. Suspect if a big anionic gap is seen (> 20 mmol/l).
- Treatment:
  - Recognize and treat precipitating factors
  - Intravenous insulin infusion, often in large doses because of insulin resistance.
  - Glucose, given i.v
  - NaHCO$_3$ in large doses, up to 2000 mmol/24 hour.
  - Dialysis is useful as it can remove the drug and lactic acid.
  - Consider nasogastric tube placement in those with reduced conscious level

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Urine</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sugar</td>
<td>Acetone</td>
</tr>
<tr>
<td>Hypolycemia</td>
<td>0</td>
<td>0 or +</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Non ketotic hyperglycemia</td>
<td>++++</td>
<td>0</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>0 or +</td>
<td>0 or +</td>
</tr>
</tbody>
</table>

Table 4.1: Laboratory diagnosis of diabetic emergencies

2. Hypercalcaemia

- Causes:
  - malignancy
  - primary hyperparathyroidism
  - immobilization
  - sarcoidosis
  - hypervitaminosis D
• **Clinical presentation**
  - gastrointestinal - anorexia, nausea, vomiting, abdominal pain, constipation
  - polyuria, dehydration
  - psychosis, coma

• **Treatment:**
  - Treat the underlying cause
  - Rehydration – this is the most important step. Saline infusion is useful for rehydration and to promote the excretion of Ca\(^{2+}\). Na\(^+\) competes with the renal tubular reabsorption of Ca\(^{2+}\). 0.9% NS and 0.45% NS is alternately infused at rates of 250 – 500 ml/hour. When patient is rehydrated, i.v frusemide in frequent small doses of 20 – 40mg every 2 hours is given to prevent overloading and to further promote Ca\(^{2+}\) excretion. Potassium supplements are needed. The fluid balance must be carefully monitored. This is a rapid and effective way of removing Ca\(^{2+}\) from the body. Central venous pressure (CVP) monitoring is required.
  - Calcitonin – this will decrease skeletal release of Ca\(^{2+}\) and increases renal clearance of Ca\(^{2+}\). The effect is rapid but only temporary in lowering the serum Ca\(^{2+}\). It becomes ineffective after a few days for unknown reason. It can be given by either via intramuscular (i.m) or subcutaneous (SC) route, usually at 4 to 8 units/kg every 6 to 8 hours.
  - Steroids – useful in hypercalcaemia due to malignancies. However, it is not useful in primary hyperparathyroidism. The onset is slow and requires several days for therapeutic effect. Dose : i.v hydrocortisone 200 – 400 mg every 6 to 8 hours is used initially followed by oral prednisolone 10 – 30 mg every 6 to 8 hours.
  - Intravenous biphosphonates – pamidronate 60 mg or zoledronic acid as i.v infusion.
  - Intravenous phosphate – very effective but employed only in extreme emergencies. It may cause shock, fatal hypocalcaemia and renal cortical necrosis. May be given orally or as an enema. Oral phosphate is given at 250 mg of PO\(_4^{3-}\) every 6 hourly. The use is limited to patients with hypophosphataemia (as in primary hyperparathyroidism) because of the risk of metastatic calcification.

3. **Thyroid emergencies**

A. **Myxoedema coma**

• A high index of suspicion is needed to diagnose this condition.
• Clinical presentation – hypothermia, altered conscious level, bradycardia, hypotension, delayed tendon reflexes
• Look for precipitating factors such as -
  - infections
  - surgery or trauma
  - acute myocardial infarct
  - stroke
  - hypothermia
  - sedative-hypnotic or narcotics drugs
• Investigations
  - Full blood count – macrocytic anaemia picture
- Blood glucose - hypoglycaemia
- Arterial blood gases – hypoxaemia
- Thyroid function tests – hypothyroid picture
- Serum electrolytes – low Na+
- Blood urea and serum creatinine
- Infections screen – blood and urine culture
- Others – CXR, ECG

Treatment:
- Treat the precipitating event.
- Thyroid hormone results are seldom available rapidly and treatment is often started on clinical grounds.
- Ensure proper coma nursing. It is important to keep the body temperature within normal with the use of blankets or warmer.
- Supportive measures
  - Give nasal oxygen (+/- mechanical ventilation may be necessary).
  - Correct electrolytes to normal.
  - Ensure adequate hydration. Central venous pressure (CVP) monitoring may be required.
  - Steroids – intravenous hydrocortisone is given as these patients have impaired response to stress due to impaired ACTH outflow, which can occurs in primary hypothyroidism or in those with Addison’s disease (adrenal insufficiency). Addison’s disease can be associated with Hashimoto’s disease. Myxoedema coma may also result from pituitary pathology with deficient ACTH and TSH.
  - Thyroid hormone replacement - there is controversy over whether T₄ or T₃ is better in the treatment of myxoedema coma. Both the oral or intravenous form of T₄ or T₃ can be used.

I. T₄ - a dose of 0.5 mg daily is given initially and then continue with daily maintenance doses of 0.1 mg – 0.2 mg one week later. A large dose is necessary in the setting of myxoedema coma because of tissue resistance to T₄. Clinical response is slow and often takes several days to see the effects. Initial low doses are recommended in the setting of uncomplicated hypothyroidism in the elderly because of the risk of ischaemic heart disease.

OR

II. T₃ - this is four times as potent as T₄. It has an earlier onset of action, which is 5 hours after dosage. It circumvents the reduced peripheral conversion of T₄ to T₃ in hypothyroidism. Therefore, low dose T₃ must be used in view of the above. T₃ is given at 20 micrograms every 12 hours. T₄ may be substituted for T₃ when the patient is improving.

B. Thyrotoxic Crisis

- It is a state of decompensated thyrotoxicosis, with failure of organs to cope with the additional metabolic demands. Death is frequently from congestive cardiac failure and bronchopneumonia.
- Clinical presentations:
- fever, sweating,
- altered mental state such as restlessness, delirium, coma,
- cardiac - arrhythmias, heart failure,
- gastrointestinal - diarrhea, abdominal pain,
- liver failure – jaundice
- myopathy.

- Look for the precipitating factors such as:
  - infections
  - surgery, trauma
  - pulmonary embolism
  - drugs eg. Amiodaron
  - acute myocardial infarct
  - diabetic ketoacidosis

- Investigations
  - Full blood count
  - blood glucose
  - thyroid function tests
  - serum electrolytes
  - blood urea and serum creatinine
  - infections screen – blood and urine culture
  - others (to look for causes) – CXR, ECG

- Treatment:
  - Treat the precipitating cause.
  - Give sedation such as intravenous midazolam (titrated accordingly at 1 to 2.5 mg). May need to continue with infusion and preferably be monitored in intensive care unit.
  - Supportive measures:
    - Oxygen
    - Ensure adequate hydration. Central venous pressure (CVP) monitoring is useful for this purpose.
    - Treat cardiac failure and arrhythmias.
    - Give vasopressors infusion (see Table 15 for dosage) if hypotensive.
    - Tepid sponging and paracetamol for fever. Aspirin is contraindicated as it displaces bound thyroxine from its carrier protein.
    - Give intravenous vitamin B complex.
  - Specific measures
    - Inhibition of thyroid hormone formation
      I. Propylthiouracil 150 - 300 mg given 6 hourly for first 24 hours and then reduce dosage to 100 – 200 mg 8 hourly. This has the added advantage of inhibitory effect on conversion of T4 to T3, hence this is the drug of choice
      OR
      II. Carbimazole 15 – 30 mg 6 hourly for first 24 hours and then reduce dosage to 10 – 20 mg 8 hourly.

    - Inhibition of thyroid hormone release - oral potassium iodide 100 mg given 6 hourly or intravenous sodium iodide 1 gm/24 hours by slow infusion or oral Lugol's iodine 20 drops 8 hourly. Iodine is only administered at least 2 hours after propylthiouracil or carbimazole has
been given. This is to ensure that the iodine given is not taken up by
the gland for further thyroid hormone synthesis and subsequent
release. Iodine normally only temporarily inhibits the thyroid hormone
release (the acute Wolff-Chaikoff effect, which lasts only for about 1-2
weeks). Therefore, the drug should be withdrawn over the subsequent
2 weeks.

→ Receptor blockade – intravenous propanolol 1 - 5 mg 6 hourly for 24
hours then 40-80 mg 6 hourly given orally. This is the drug of choice.
Caution in cardiac failure and obstructive airway disease.

→ Steroids – intravenous dexamethasone 2mg 6 hourly is given to
decrease the hormone release and inhibits peripheral conversion of
T₄ to T₃.

➢ If the above measures fail, peritoneal dialysis and exchange transfusion may
be done to reduce the circulating thyroxine.

Chapter 5
Haematological Emergencies

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- Specific Conditions
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  2. Immune Thrombocytopenic Purpura (ITP)
  3. Thrombotic Thrombocytopenic Purpura (TTP)
  4. Haemophilia
     I. Haemophilia A
     II. Haemophilia B
  5. Disseminated Intravascular Coagulation (DIC)
  6. Warfarin overdose

Introduction

- A bleeding disorder is characterized by spontaneous, excessive or delayed
  bleeding following trauma. Bleeding can result from diseases of vessels, platelets
  or coagulation factors.
- The cause of bleeding can usually be determined from the history and physical
  examination. A family history of bleeding provides a clue to haemophilia or Von
  Williebrand’s disease. Certain medications can also cause abnormal bleeding.
- Certain bleeding patterns may suggest the underlying pathology, such as
  ➢ The appearance of excessive or prolonged bleeding, haematoma or
    haemarthrosis hours after an injury suggests a coagulation factor deficiency.
  ➢ Prolonged bleeding from superficial wounds, ecchymoses at sites of minor
    trauma, petechiae and spontaneous gum bleeding suggests platelet
    deficiency or abnormality.
  ➢ Papular petechiae suggest an underlying vasculitic lesion.
  ➢ Bleeding from multiple sites such as the gastrointestinal tract, gums, urinary
    tract, from previous venepuncture sites and bruising suggests disseminated
    intravascular coagulation (DIC).
- Investigations
- Full blood count
- Coagulation profile – Prothrombin time (PT), Partial thromboplastin time (PTT), Thrombin time (TT).
- Peripheral blood smear
- Disseminated intravascular coagulation (DIC) screen (if clinically indicated)
- Platelet function tests (if clinically indicated)

<table>
<thead>
<tr>
<th>Coagulation profiles</th>
<th>Measured parameters</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time (BT)</td>
<td>Reflects platelet function</td>
<td>2.5 to 9.5 minutes</td>
</tr>
<tr>
<td>Clotting time (CT)</td>
<td>A crude measure of the intrinsic pathway</td>
<td>5 to 10 minutes</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>Measures the extrinsic pathway. Reflects deficiency of F VIII, F X, prothrombin.</td>
<td>Abnormal when more than 2 seconds longer than control</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>Measures the intrinsic pathway.</td>
<td>35 to 45 seconds. Abnormal when more than 10 seconds longer than the control</td>
</tr>
<tr>
<td>Thrombin time (TT)</td>
<td>Evaluates the last phase of coagulation. Fibrinogen deficiency will results in prolonged TT</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1 showing the coagulation profiles tests and the normal values
Prolonged | Mechanism | Disease State
--- | --- | ---
PT only | F VII | • F VII deficiency

PTT only | F VIII F IX | • Haemophilia A
• Haemophilia B
• Von Willebrand’s disease
• Circulating anti coagulant

PT & PTT (with normal thrombin time) | Both intrinsic & extrinsic pathways involved | • Liver disease
• Vitamin K deficiency
• Warfarin therapy
• Circulating anti coagulant

PT, PTT, Thrombin time | Both intrinsic & extrinsic pathways involved with impaired fibrin formation | • DIC
• Heparin therapy
• Hypofibrinogenaemia

| **Table 5.2 showing guide to interpretation of PT, PTT, TT** |

**Specific Condition**

1. **Thrombocytopenia**

- **Definition:** refers to a reduction in platelet counts below normal (less than 150,000 /µl).
  - A platelet count > 50,000/µl is not associated with significant bleeding.
  - Severe spontaneous bleeding is rare with platelet counts > 20,000/µl.
  - Risk of spontaneous bleeding is high with platelet counts < 10,000/µl.

- **Causes**
  - Reduced production
    - Marrow infiltration by leukaemias, myelofibrosis, myelomas.
    - Marrow hypoplasia induced by drugs (such as cytotoxics), radiation, benzene, aplastic anaemia.
    - Infections: following congenital rubella and other viral agents such as Ebstein-Barr, Varicella, etc.
    - Congenital amegakaryocytic thrombocytopenia
    - Vitamin B12 or folic acid deficiency
  - Decreased platelet survival
    - Drug induced - quinine, phenytoin, sulphonamides, aspirin
    - Immunologic - ITP, SLE, lymphoma, Post transfusion associated Purpura
Consumed
   → Microangiopathic haemolytic anaemia
   → Disseminated intravascular coagulation (DIC)
   → Haemangioma
   → Viral infections
   → Sequestration – Hypersplenism.

- Treatment:
  - It is important to remember that thrombocytopenia is only a manifestation of an underlying disorder. The treatment is directed towards the underlying cause.
  - Platelet transfusions are reserved for patients with or at serious risk of significant haemorrhage. In such cases, at least 6 units of platelets or apheresed platelets (SDPs) are transfused.
  - The life span of platelets is only about 7 days. In patients without consumptive coagulopathy or immunologic destruction of platelets, 1 unit of platelet concentrate raises the platelet count by 10,000/ul per m² body surface area.
  - Patient with Immune Thrombocytopaenic Purpura (ITP) produce auto-antibodies which react with all human platelets and derive little benefit from platelet transfusions.

2. Immune Thrombocytopaenic Purpura (ITP)

- ITP is characterized by thrombocytopenia, caused probably by auto-immune destruction.
- Diagnosis is made by exclusion since tests for anti-platelet antibodies are not routinely available. The bone marrow picture is supportive but not diagnostic.
- There are two clinical types:
  I. Acute self limited form, usually preceded by infection (often viral) such as Ebstein-barr virus, cytomegalovirus, hepatitis.
     → Latent period of 1-2 weeks
     → Resolves spontaneously in days to 6 months
     → Usually in children. Rare in adults
  II. Chronic recurrent type - associated with obvious initiating illness. Women aged 20-40 years are most commonly affected.
- Clinical presentations
  - symptoms range from petechiae, bruises, epistaxis menorrhagia and bleeding from the GIT, urinary tract, lungs and intracranial blood vessels.
  - splenomegaly is unusual and found in only 10% of cases. Presence of splenomegaly suggests other causes of thrombocytopaenia.
  - In the presence of an obviously low platelet count, DO NOT perform the Hess test – this will consume platelets and aggravate the condition.
- Investigations
  - Full blood count
  - Coagulation profiles - PT, PTT
  - Collagen screen - Anti-cardiolipin antibodies (ACA), anti-nuclear antibodies (ANF)
Full blood picture – to exclude platelet clumping (pseudo-thrombocytopaenia) and look for fragmented red cells (which suggests Thrombotic Thrombocytopaenic Purpura rather than ITP)

Bone marrow aspirate – megakaryocytes present in normal or increased numbers

Treatment

- Platelet transfusions are rarely indicated. The indications are:
  - Dangerously low platelet counts (< 10,000 μ/l), with significant bleeding.
  - Significant bleeding - fundus, gastrointestinal tract, urinary tract, lungs, cerebral
  - During splenectomy
- Blood transfusion is necessary in those presenting with severe haemorrhage.
- Steroids are needed for chronic or recurrent ITP.
  - The aim to fully suppress the clone of platelet antibody producing lymphocytes.
  - Prednisolone is given at dose of 1-2 mg/kg for 2-3 weeks, then reduced to 0.5mg/kg for 1 month and tail off over 2 months
  - During treatment with steroids, the platelets counts should start to rise after 2 weeks. It should return to normal levels.
  - If platelet counts fall on taking off the steroids, a relapse may be impending. Only 10-15% of patients achieve a complete remission. Steroid side effects may make long-term treatment unacceptable.

- Splenectomy is indicated for symptomatic patients, such as:
  - for second relapse
  - as an emergency measure to improve haemostasis when significant bleeding is present despite adequate steroid therapy
  - when patients are steroid dependent and side effects are unacceptable. These steroid responsive but steroid dependent patients respond well to splenectomy. About 80% will have a sustained remission.
- Immunosuppressives are reserved for patients who fail to respond to splenectomy or are not “fit” for splenectomy.
- Immunoglobulins – given to block the Fc receptors of the macrophages causing temporary phagocytic blockade and a rise in platelet count.
- The acute self-limiting type of ITP probably does not benefit from treatments.
- The patient is observed carefully and platelet counts monitored.
- Newer treatments (to be given only on advice of a haematologist):
  - Rituximab: Monoclonal antibody against CD20 expressing cells (B lymphocytes)
  - Eltrombopag: a new drug which is a thrombopoietin receptor agonist
- If a patient is not bleeding and maintains a platelets count of > 50,000/ul consistently, it is better to observe the patient regularly without the need for further treatment.

3. Thrombotic Thrombocytopaenic Purpura (TTP)
• Thrombotic Thrombocytopenic Purpura and HUS (Haemolytic Uraemic Syndrome) are now considered the same syndromes as the clinical features and pathophysiology are virtually identical.

• This is due to a deficiency of metalloproteinase, now called ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 repeats), which results in accumulation of large von Willebrand factor (vWF) multimers, platelet aggregation and clumpings.

• Causes
  ➢ Infections - E. Coli (O157:H7 or Shiga toxin producing), HIV, pneumococcus
  ➢ Drugs - ticlopidine, clopidogrel, cyclosporin, tacrolimus, quinine, mitomycin C & other cytotoxics
  ➢ Iatrogenic - cardiac surgery, allogeneic stem cell transplantation
  ➢ Autoimmune disease - SLE, antiphospholipid syndrome
  ➢ Pregnancy and combined oral contraceptives pills.

• Clinical presentation (clinical and laboratory)
  ➢ Neurological symptoms and signs such as focal neurological deficits or drowsiness or coma.
  ➢ Fever
  ➢ Microangiopathic blood picture - non-immune haemolysis with presence of fragmented red blood cells (schistocytes)
  ➢ Thrombocytopenia
  ➢ Renal dysfunction

• Treatment
  ➢ Stop any offending drug.
  ➢ Plasma exchange is the mainstay of therapy. Fresh frozen plasma (FFP) transfusions may be given but are less effective.
  ➢ Platelet transfusions are contraindicated as they may aggravate TTP.
  ➢ Other drugs used:
    → Corticosteroids
    → Vincristine
    → Intravenous Immunoglobulin
    → Rituximab
    → Defibrotide (for recurrent TTP)

4. Haemophilia

I. Haemophilia A

• Definition - bleeding tendencies due to a deficiency of Factor VIII or a dysfunction of Factor VIII. Most common inherited disorder of coagulation, which is X-link recessive.

• Clinical presentation
  ➢ Symptoms depend on degree of Factor VIII clot promoting activity left.
  ➢ Bleeding can occur hours or days after injury and may last for days or weeks.
  ➢ Large collections of partially clotted blood may put pressure on tissues and cause compartment syndrome.

• Treatment
- Symptoms often precede objective bleeding. When the patient complains of pain, start treatment as early treatment is more effective, less costly and can be lifesaving.
- Avoid intramuscular injections and aspirin.
- Minor cuts, abrasions and bruising usually do not require treatment.
- Minor soft tissue haemorrhage can be treated by raising Factor VIII activity to 15 to 20% by a single infusion of Factor VIII concentrate or cryoprecipitate.
- Haemarthrosis and large haematomas or haematomas in critical positions e.g. paratracheal, would require Factor VIII activity at 25-50% for at least 72 hours.
- Any life threatening bleeding into CNS or following major trauma or surgery requires Factor VIII. One unit of Factor VIII activity is the activity present in 1 ml of fresh normal plasma.
- The circulating half-life of Factor VIII is 8-12 hours only. Efficient replacement therapy requires serial transfusions every 8-12 hours.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Level of F VIII activity</th>
<th>Clinical picture</th>
<th>CT</th>
<th>PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>0.2%</td>
<td>Haemarthrosis, Severe spontaneous bleeding</td>
<td>Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Moderate</td>
<td>2-5%</td>
<td>Serious bleeding from trivial trauma.</td>
<td>N</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Mild</td>
<td>5 – 25%</td>
<td>Serious bleeding from trauma and surgery</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Subhaemophilic</td>
<td>25-50%</td>
<td>Moderate bleeding following major trauma</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 5.3 showing the relationship between the level of Factor VIII activity and the severity of clinical presentation.
### Blood products

<table>
<thead>
<tr>
<th>Blood products</th>
<th>Amount of Factor VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma</td>
<td>0.6 units per ml</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>3-5 units per ml (about 100 to 150 units per bag)</td>
</tr>
<tr>
<td>Freeze dried human Factor VIII</td>
<td>250 – 400 units per bottle</td>
</tr>
</tbody>
</table>

Table 5.4 showing the amount of Factor VIII in different blood products

**Calculation:**

The plasma volume of the body is 45 ml/kg BW. Since 1 ml of normal plasma contains 1 unit of Factor VIII activity, 45 units/kg BW must be infused to increase its level from zero to 100%.

A dose of 25-50 units/kg BW is generally given to raise the level to 50-100% of normal; the desired level depends on the severity of the bleed. This has to be repeated every 8-12 hourly to maintain the desired level.

An alternative formula is the 1 unit of Factor VIII activity per kg BW raises Factor VIII level about 1.8%.

### II. Haemophilia B

- Definition: bleeding tendencies due to a deficiency of Factor IX.
- Levels of Factor IX required to treat bleeding episodes are similar to Haemophilia A.
- Cryoprecipitate does not contain Factor IX and should not be given.
- Fresh frozen plasma (FFP) is used and if large volumes of FFP are needed to maintain an adequate Factor IX level, then Factor IX concentrates should be used.
- Factor IX has half life of about 24 hours, therefore replacement is given every 16-24 hours.

### 5. Disseminated Intravascular Coagulation (DIC)

- Definition - DIC is the consequence of the intravascular activation of both the coagulation and fibrinolytic systems. The diffuse intravascular clotting triggered by the underlying cause consumes clotting factors and platelets.
The micro-thrombosis or the trigger may also activate the fibrinolytic system and this results in fibrinogenolysis and fibrinolysis with resulting in increased fibrinogen-fibrin breakdown products.

Pathogenesis and clinical presentation – see flowchart 5.1

**Flowchart 5.1: Pathogenesis and clinical presentation of DIC**

- Release of endotoxins, Ab-Ag complexes & tissue factors, which act as coagulants, and damage endothelium
- Deposition of microthrombi with reduced capillary lumen
- Consumption of platelets and clotting factors
  - Fibrinolysis
  - Fibrinogenolysis
  - Depletion of Factor V, Factor VIII and prothrombin
  - Minor decrease in Factor XI and XIII
  - Thrombocytopaenia
  - Fibrinogen degradation products (FDP) may complex with fibrin monomers and cause further impairment of clotting
- Fragmented RBC seen on peripheral blood smear
- Fragmented RBC taken up by the liver and spleen
- Bleeding diathesis
- Ischaemic tissue damage
- Haemolytic anaemia
Acute

- Obstetric complications
- Abruptio placentae
- Incomplete or missed abortion
- Amniotic fluid embolism
- Infections - sepsicaemia especially Gram negative, meningococcal, staphylococcal and clostridium
- Surgery - especially of the heart, lungs and prostate
- Snake bite - Vipers
- Haemolytic transfusion reaction
- Pulmonary embolism
- Heat stroke
- Fat embolism
- Shock
- Massive trauma

Subacute

- Neoplasia
- Cancer prostate, lung breast, pancreas
- Acute leukaemia esp promyelocytic
- Systemic lupus erythematosus (SLE)
- Haemangioma

<table>
<thead>
<tr>
<th>Acute</th>
<th>Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric complications</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Abruptio placentae</td>
<td>Cancer prostate, lung breast, pancreas</td>
</tr>
<tr>
<td>Incomplete or missed abortion</td>
<td>Acute leukaemia esp promyelocytic</td>
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<tr>
<td>Amniotic fluid embolism</td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Infections - sepsicaemia especially Gram negative, meningococcal,</td>
<td></td>
</tr>
<tr>
<td>staphylococcal and clostridium</td>
<td></td>
</tr>
<tr>
<td>Surgery - especially of the heart, lungs and prostate</td>
<td></td>
</tr>
<tr>
<td>Snake bite - Vipers</td>
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<tr>
<td>Haemolytic transfusion reaction</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Heat stroke</td>
<td></td>
</tr>
<tr>
<td>Fat embolism</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td>Massive trauma</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.5 showing the various causes of DIC

- Clinical presentation
  - Bleeding from multiple sites and organs, from previous venepuncture sites and blood which does not clot.
  - Organ damage eg. renal failure
  - Features of the underlying cause.
  - Less often, acrocyanois, thrombosis and pregangrenous changes in digits where blood flow is reduced by microthrombi.

- Investigations
  - Full blood count – low haemoglobin, low platelets
  - PT, PTT,TT – prolonged clotting values
  - Peripheral blood film - Microangiopathic haemolysis
  - Fibrin – increased fibrinogen degradation products (FDP) / D-dimers
  - Low Factor II, V and VIII
  - Plasma fibrinogen level: correlates closely with bleeding.

- Treatment
  - Treatment of the underlying condition is the most important step. Unless serious haemorrhagic or thrombotic features are present, no further therapy is usually needed.
  - Both anticoagulant and factor replacement therapy are potentially dangerous and should be used with caution. Infused platelets may form aggregates and block microcirculation while infused fibrinogen may lead to further deposition and damage.
  - Replacement treatment is with the following:
    → Fresh-frozen plasma (FFP) – contains all the coagulation factors
    → Platelet concentrates
Cryoprecipitate if Factor VIII is depleted
Whole blood if blood loss is extensive

- Heparin may be needed to stop the clotting process.
  - It is contraindicated in fresh bleeding from open wounds or in cases with intracranial bleeding. It is usually used in cases with a subacute or chronic cause whereby the triggering factor persists or cannot be immediately removed. Heparin is also used in cases with predominant thrombotic features.
  - Heparin will not function if given by itself because the anti thrombin III is depleted in the body's attempt to stop the coagulation cascade.
  - Fresh frozen plasma must be simultaneously given to provide the anti thrombin III. (Heparin acts by increasing the natural anticoagulant activity of anti thrombin III).
  - Heparin is started at low doses e.g 500 units per hour via intravenous infusion.
  - The use of heparin in cases with active bleeding is controversial.

- Recombinant factor VIIa has been used in an off-label fashion for patients with severe bleeding including refractory DIC. DIC per se is not a contraindication for use of recombinant factor VIIa.

6. Warfarin overdose

- Warfarin overdose may be accidental or due to drug interaction, potentiating the action of warfarin.
- Patients who are more susceptible to warfarin overdose and bleeding include the elderly, diabetics, liver disease, uncontrolled hypertension, heart failure, thyroid dysfunction, those with bleeding lesions (gastrointestinal tract), prior stroke, concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and/or anti-platelet use.
- Loading doses of warfarin are no longer employed as they increase the risk of bleeding.
- Diagnosis - the diagnosis is made from the clinical history and the prolonged INR value.
- Management
  - INR prolongation without bleeding:
    → If INR modestly prolonged (between 5-8) but no bleeding, withhold warfarin. There is no need to give FFP or vitamin K. The patient can be closely followed up daily as an outpatient (unless logistically difficult). Try to identify the cause
    → If INR is > 8 but < 12 but no bleeding, admit the patient for further management. Withhold the warfarin and give i.v vitamin K 2mg stat. If INR > 12, give i.v vitamin K 5 mg stat. Repeat INR daily till < 5 and then restart warfarin at a lower maintenance dose.
  - INR prolonged with bleeding:
    → Admit the patient for further management. Give FFP 2-4 units and i.v vitamin K 2-5 mg (larger doses may make re-anticoagulation difficult). If INR within therapeutic range and patient is bleeding, look hard for a local cause of the bleeding e.g. peptic ulcer in gastrointestinal bleed.
Chapter 6
Management of Acute Transfusion Reaction

Table of contents
1. Introduction
2. Clinical Presentation (subtypes) and management of Acute Blood Transfusion Reactions
3. Management of blood transfusion reaction

1. Introduction

- Blood transfusion is potentially life-saving in appropriate setting but carries a small risk of acute or late adverse effects.
- Transfuse blood or blood products only if clinically indicated. Indications should be documented in the clinical notes.
- Inform patient of the potential side effects. Consent need to be taken for blood transfusion.
- Hospitals need to have standard operating procedure (SOP) for collection of pre transfused sample and blood administration.
- Close monitoring of patients receiving transfusion is essential and prompt response to transfusion reactions is critical to ensure favorable outcome.

2. Clinical Presentation (subtypes) and management of Acute Blood Transfusion Reactions

The most common immediate adverse reactions to transfusion are fever, chills and urticaria. The most potentially significant reactions include acute and delayed haemolytic transfusion reactions and bacterial contamination of blood products. During the early stages of a reaction it may be difficult to ascertain the cause.

A. Febrile (non-haemolytic) reactions
   - Common, but usually not serious.
   - Cause: Fever and chills due to contaminating white cells in blood products. Fever occurs more commonly with platelet transfusion (10-30%) than red cell transfusion (1-2%).
   - Investigation: Fever can be the initial sign in more severe transfusion reactions (haemolytic or bacterial sepsis) and should be taken seriously.
   - Management: Treatment is symptomatic only, including paracetamol.
   - Prevention: Use of white cell filter for red cell and platelet transfusion.

B. Urticarial (allergic) reactions
   - Common, not serious.
   - Cause: Seen in approximately 1% of recipients and caused by foreign plasma proteins.
   - Investigation: In those with urticarial reactions without other signs or symptoms, it is not necessary to submit blood specimens for investigation.
   - Management:
     → Administer antihistamine such as chlorpheniramine 10 mg, given either as slow intravenous over 1 minute, intramuscular or subcutaneously (maximum dosage is 40 mg in 24 hours)
→ Restart infusion at slower rate
→ Close monitoring.

C. Volume overload
- Fairly common and serious
- Cause: Patients with cardiopulmonary disease, elderly and infants are at risk of volume overload especially during rapid transfusion.
- Management:
  → Stop the transfusion immediately.
  → Administer oxygen and diuretics as required.
  → Prevention: Avoid unnecessary fluids and use appropriate infusion rates. May need to monitor the transfusion rates with central venous pressure in those at risks. Diuretics may need to be given with blood transfusion.

D. Severe allergic (Anaphylactic) reactions
- Uncommon but serious
- Clinical presentation:
  → Cardiovascular instability including hypotension, tachycardia, cardiac arrhythmia.
  → Respiratory - dyspnoea and stridor.
  → These may lead to cardiac arrest, shock and loss of consciousness.
- Cause: IgA deficiency patients with anti-IgA antibodies can have these reactions.
- Investigation: IgA levels and anti-IgA antibodies.
- Management:
  → Immediately stop transfusion.
  → Give supportive care including airway management such as nasal O2, with or without nebulizer sabutamol.
  → Adrenaline may need to be given as 0.5 ml of 1:1000 solution, either as subcutaneously, intramuscular or slow intravenous.
- Prevention: consult haematologist. Patient will need washed red blood cells and plasma products prepared from IgA deficient donors.

E. Acute haemolytic reactions
- Uncommon but can be fatal
- Causes:
  → The majority of haemolytic reactions are caused by transfusion of ABO incompatible blood, e.g group A, B or AB red cells to a group O patient.
  → Other causes include - antibody in recipient plasma reacting with minor red cell antigen or non-immune haemolysis of RBC due to inadvertent freezing or overheating, infection etc.
- Clinical presentations – Chills, fever, pain (along IV line, back, chest), hypotension, dark urine, uncontrolled bleeding due to DIC.
- Management:
  → Immediately stop the blood transfusion. Notify hospital blood bank urgently (another patient may also have been given the wrong blood!).
→ These patients usually require ICU support and therapy includes vigorous treatment of hypotension and maintenance of renal blood flow.

- **Prevention:** Usually arises due to clerical errors. Hence, it is of paramount importance to ensure the right blood goes to the right person at the right time for the right indication! Prevention of non-immune haemolysis requires adherence to proper handling, storage and administration of blood products.

### F. Bacterial contamination

- **Uncommon but serious**
- **Cause:** Bacteria may be introduced into the pack at the time of blood collection from sources such as donor skin, donor bacteraemia or equipment used during blood collection or processing. Platelets are more frequently implicated than red cells.
- **Clinical presentation:** Very high fever, rigors, profound hypotension, nausea and/or diarrhoea.
- **Management:**
  → Immediately stop the transfusion and notify the hospital blood bank.
  → After initial supportive care, blood cultures should be taken and broad-spectrum antimicrobials commenced.
- **Prevention:** Inspect blood products prior to transfusion. Some but not all bacterially contaminated products can be recognized (such as presence of clots, clumps, or abnormal colour). Maintain appropriate cold storage of red cells in a monitored blood bank refrigerator. Once removed from blood bank refrigerator, blood is to be immediately transfused and duration of transfusion of packed cells should not be more than 4 hours.

### G. Transfusion-related acute lung injury (TRALI)

- **Very uncommon but very serious**
- **TRALI** is a clinical diagnosis of exclusion. It is characterized by acute respiratory distress and bilaterally symmetrical pulmonary oedema with hypoxaemia developing within 2 to 8 hours after a transfusion. A CXR shows interstitial infiltrates when no cardiogenic or other cause of pulmonary oedema exists.
- **Cause:** Secondary to cytokines in the transfused product or from interaction between patient white cell antigens and donor antibodies (or vice versa).
- **Management:**
  → Symptomatic support for respiratory distress which includes 100% oxygen administration and may require intubation and mechanical ventilation.
  → Symptoms generally resolve over 24-48 hours.

### H. Hypothermia

- **Cause:** Due to rapid infusion of large volumes of stored blood. Infants are particularly at risk during exchange or massive transfusion.
- **Management and prevention:** Appropriately maintained blood warmers should be used during massive or exchange transfusion.
I. Citrate toxicity
- **Cause:** Rapid administration of large quantities of stored blood may cause hypocalcaemia and hypomagnesaemia when citrate binds to calcium and magnesium. This can result in myocardial depression or coagulopathy. Patients most at risk are those with liver dysfunction or neonates with immature liver function having rapid large volume transfusion.
- **Management:**
  - Slowing or temporarily stopping the transfusion allows citrate to be metabolized.
  - Replacement therapy may be required for symptomatic hypocalcaemia or hypomagnesaemia.

J. Potassium effects
- **Cause:** Stored red cells leak potassium proportionately throughout their storage life. Irradiation of red cells increases the rate of potassium leakage. Clinically significant hyperkalaemia can occur during rapid, large volume transfusion of older red cell units in small infants and children.
- **Prevention:** Blood less than 7 days old is generally used for rapid large volume transfusion in small infants in situations such as during cardiac surgery, extra corporeal membrane oxygenation (ECMO) or exchange transfusion.

3. Management of blood transfusion reaction
- Stop the transfusion immediately.
- Keep the intravenous branula and start running in normal saline.
- Check vital signs - temperature, pulse rate, respiratory rate, BP and oxygen saturation.
- Monitor urine output – continuous bladder drainage (CBD) may need to be inserted.
- Administer oxygen if breathless or hypoxic.
- Clinical examination: auscultate the lungs and heart, inspect skin for urticaria, and look for signs of bleeding.
- Depending on your assessment, blood may need to be sent for blood cultures, repeat GXM, full blood count, full blood picture, coagulation screen, Coomb's test, renal profile, liver function test and urinanalysis.
- Management will depend on the potential cause and the severity of presentation. Initiate definitive treatment based on the clinical evaluation.

I. Mild reactions:
- Present in those with febrile non haemolytic reactions or allergic reaction.
- Antihistamine such as chlorpheniramine 10 mg, given either as slow intravenous over 1 minute, intramuscular or subcutaneously (maximum dosage is 40 mg in 24 hours)
- Restart infusion at slower rate.
- Give paracetamol for fever.

II. Moderately severe reactions
- Symptoms include palpitations, tachycardia, dyspnea
Stop the transfusions immediately and maintain the i.v line with normal saline.
Clinical assessment should be done by a doctor.
Give symptomatic treatment.
Further management will depend on the evolution of symptoms and signs.

III. Severe reactions
- A life threatening reactions: Big problem!
- Stop the transfusion immediately and maintain the i.v line with normal saline.
- Need immediate medical attention. Call for help. Inform blood bank.
- Immediate treatment:
  - Infuse intravenous fluid for hypotension.
  - Give oxygen via nasal prong or mask.
  - Adrenaline for anaphylaxis, given as 0.5 ml of 1:1000 solution, either as subcutaneously, intramuscular or slow intravenous.
  - Give diuretic (intravenous frusemide 40 mg stat) if fluid/volume overload is present.
- Need to complete the transfusion reaction form and send the blood bag together with the appropriate blood samples from the recipient to blood bank.
- Further management will depend on the likely cause.

Chapter 7
Renal Emergencies

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1. Acute Renal Insufficiency (ARI)
2. Specific Syndromes
   2.1 Rhabdomyolysis
   2.2 Abdominal compartment syndrome
   2.3 Renal failure in patients with cirrhosis
   2.4 Radiocontrast nephropathy

1. Acute Renal Insufficiency (ARI)
   - Acute renal insufficiency (ARI) (previously known as acute renal failure) is defined as rapid decline in glomerular filtration rate (GFR) from hours to days, leading to metabolic derangement with or without anuria or oliguria.
   - For the purpose of management and diagnosis, ARI is divided into three major categories or processes:
     I. Pre-renal causes
        - Hypovolaemia from extracellular fluid loss- e.g haemorrhage
        - Gastrointestinal losses from vomiting and diarrhoea
        - Extravascular sequestration – burns and hypoalbuminaemia
        - Low cardiac output
        - Systemic vasodilatation - sepsis and anaphylaxis
II. Intrinsic (ARI)

- Renovascular obstruction - such as renal artery obstruction and thrombosis, renal vein thrombosis.
- Disease of renal glomeruli or vasculature such as glomerulonephritis/vasculitic, thrombotic microangiopathy due to malignant hypertension or collagen vascular disease
- Acute tubular necrosis (ATN)
  - Ischaemia
  - Toxins
    - contrast agents, antibiotics (amphotericin B, cisplatin, aminoglycosides)
    - Endogenous – haemolysis and rhabdomyolysis (pigment nephropathy)
  - infections with and without sepsis
- Interstitial nephritis - infections, inflammation (Sjogrens), drugs (NSAIDS, pencillins)
- Intratubular obstructions-
  - Endogenous -myeloma proteins, uric acid (tumour lysis syndrome)
  - Drugs - acylovir, gangcyclovir, methotrexate, indinavir

III. Post Renal

- Upper urinary tract obstruction - stone, tumours, retroperitoneal fibrosis, retroperitoneal or pelvic malignancies.
- Lower urinary tract obstruction - prostatic tumour (benign and malignant) , urethral stricture, neurogenic bladder.

- Clinical assessment
  - Pre-renal signs and symptoms
    - Thirst
    - Orthostatic giddiness
    - Orthostatic hypotension
    - Tachycardia
    - Reduced skin turgor
    - Dry mucus membranes
  - Intrinsic renal failure signs and symptoms
    - Evidence of fluid overload
    - Fever, arthralgia, rash - may suggest interstitial nephritis
    - Fever, rash, vasculitis - may suggest collagen vascular disease
    - Digital ischemia, livedo reticularis suggest cholesterol emboli
  - Post renal failure signs and symptoms
    - Flank pain radiating to the groin indicates ureteric obstruction
    - Definitive diagnosis of post renal ARI depends on radiological evaluation

See Table 7.1 for RIFLE criteria for assessment of progression and severity of ARI
<table>
<thead>
<tr>
<th>Progression of ARI</th>
<th>GFR</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>↑ creatinine by 1.5 times Or GFR ↓ 25%</td>
<td>Urine output &lt; 5ml/kg/hour x 6 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>↑ creatinine by 2 times Or GFR ↓ 50%</td>
<td>Urine output &lt; 5ml/kg/hour x 12 hours</td>
</tr>
<tr>
<td>Failure</td>
<td>↑ creatinine by 2 times Or GFR ↓ 75%</td>
<td>Urine output &lt; 3ml/kg/hour x 24 hours Or Anuria x 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent ARF = complete loss of kidney function &gt; 4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESKD</td>
<td>End stage kidney disease &gt; 3 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.1 RIFLE Criteria for progression and severity of ARI

- **Investigations**
  - Urinary indices in ARI (see table 7.2)
    - Hyaline cast (Pre renal)
    - Granular cast – ischaemia or nephritic injury
    - WBC cast – interstitial nephritis
    - Fractional sodium excretion - less than 1% indicates pre-renal ARI, more than 1% indicates intrinsic or post renal ARI
  - Blood investigation
    - Full blood count
    - Blood urea and serum electrolytes
    - Serum creatinine
    - Calcium/Phosphates (inorganic)
    - Liver function test
    - Lactate dehydrogenase (LDH)
    - Collagen screening
    - Total creatine phosphokinase
Table 7.2 Urine findings in pre-renal, renal and post-renal ARI.

- Imaging in ARI
  - Ultrasound - able to exclude obstruction reliably. A normal size and normal echogenicity will indicate non chronicity. Small shrunken kidneys on ultrasound indicate chronicity.
  - Unenhanced CT scan (CTU) is valuable in suspected nephrolithiasis
  - Magnetic Resonance Angiography (MRA) - used to assess the patency of renal vasculature in suspected vascular obstruction.
- Renal biopsy - reserved for intrinsic renal failure when the cause of renal vascular failure is not clear

- Complications of ARI
  - Expansion of extracellular fluid volume leading to life threatening pulmonary oedema
  - Hyperkalaemia
  - Hyperphosphatemia
  - Uraemia leading to anorexia, nausea, vomiting,
  - Anaemia
  - Pericarditis
  - Infections

- Treatment of ARI
  1. **Pre-renal ARI**
     - This must be ruled out quickly as in the initiation phase, the condition is completely reversible. If the renal hypoperfusion is left uncorrected it will lead to established acute tubular necrosis.
     - Replacement of fluid composition should be tailored according to the fluid loss. There may be cases where one is not sure if there is a volume deficit. In these cases, a fluid challenge test may be conducted. Central venous pressure (CVP) measurements are useful to follow trends in a patient’s response to fluid therapy. For fluid challenge test:
       - Note the CVP reading. Normal CVP from mid-axillary line is about 5 to 10 cm of water.
Infuse normal saline at 3 ml/kg body weight or up to maximum of 250 ml in 15 minutes.

- Note the CVP at the end of the 15 minutes and at 30 minutes.
- See table 7.3 for interpretation.

- Hypovolaemia from haemorrhage should be corrected with whole blood.
- Hypotonic solutions (0.45%) are used for gastrointestinal losses.
- Fluid should be administered slowly and if necessary central venous pressure should be monitored. Strict monitoring of the input and output of fluids is required as there is a risk of fluid overload.
- In the oliguric patient in whom pre-renal causes have been corrected, a loop diuretic (e.g frusemide) is given to enhance urine output and convert a oliguric to a non-oliguric ARI.
- Low dose dopamine (<5 ug/kg/minute) may increase renal blood flow and allow a response to diuretics.
- The patient should be weighed daily and up to a daily weight loss of 1 kg may occur. As the diuretic phase comes, large volumes of fluids may be needed to maintain balance.

<table>
<thead>
<tr>
<th>CVP measurement</th>
<th>Interpretation</th>
<th>Comments / Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing (minute)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Low</td>
<td>No need fluid challenge</td>
<td>No need fluid challenge</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Increase by 5 cm</td>
<td>Decrease to normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Increase by 5 cm</td>
<td>Remain high</td>
</tr>
<tr>
<td>High</td>
<td>No need fluid challenge</td>
<td>Fluid overload or heart failure</td>
</tr>
</tbody>
</table>

Table 7.3 Table showing interpretation of CVP reading during fluid challenge.
II. *Intrinsic ARI*
   → Glomerular nephritis may respond to immunosuppression (glucocorticoids, cyclophosphamide, plasma exchange)
   → Glucocorticoids hasten remission in acute interstitial nephritis

III. *Post-renal ARI*
   → In completely anuric patients, post-renal obstruction must be excluded first as the other causes of renal failure usually does not cause anuria. Urgent ultrasound and other imaging investigation may be needed.
   → Relief of obstruction will reverse acute renal insufficiency

*Indications for dialysis* - the overall clinical status of the patient should be considered:
→ High blood urea >30 mmol/L (with uraemic symptoms)
→ Fluid overload – such as pulmonary oedema
→ Persistent oliguria / anuria
→ Hyperkalaemia (level > 6.5 mmol/L) or presence of ECG changes
→ Hyponatremia - life threatening
→ Acidosis pH < 7.1
→ Symptomatic patient, whatever the blood urea or serum creatinine level.
→ Pericarditis

- Management of complications
  - Volume overload
    → Restrict fluid intake to an average of 500 ml/day in an anuric individual.
    → Diuretics may help convert oliguric to a non oliguric ARI
    → Renal replacement therapy (dialysis will be needed for pulmonary oedema in an anuric individual)
  - Hyperkalaemia
    → Hyperkalaemia is carefully looked for via serum potassium and monitoring. Hyperkalaemia associated with ECG changes must be treated urgently.
    → Treatment includes:
      - Calcium gluconate 10 ml (15-30 mg/kg) given intravenously- this directly antagonizes the effect of potassium on the myocardium. The effect lasts only about 1 – 2 hours.
      - Sodium bicarbonate 50-100 mEq given intravenously (50 ml of 8.4% sodium bicarbonate). The onset of effect is in 15 minutes and lasts 1 - 2 hours only. There is danger of Na+ overload.
      - 50% dextrose in 50 ml with 10 units regular insulin given via slow intravenous push. Response in 30 minutes and lasts about 4 to 6 hours.
      - Administer beta-2 adrenergic agonist by inhalation of aerosol.
      - Cation exchange resins – this will bind K+ and actually remove K+ via the gastrointestinal tract. Commonly available formulation is calcium polystyrene sulfonate (Kalimate), given orally at a dose of 15 – 30 gm daily in 2 or 3 divided doses.
Dialysis is the definitive therapy for hyperkalaemia.

- Hypophosphataemia – dietary restriction, phosphate binders, dialysis
- Metabolic acidosis- treat with sodium bicarbonate and dialysis
- Anaemia - use erythropoietin or consider blood transfusion.
- Nutrition - adequate protein and caloric intake to avoid negative nitrogen balance. A high CHO diet is given to provide calories, with 0.8 gm/kg/day of protein. No fruit or fruit juices are allowed as they contain significant amounts of potassium. Referral to a dietician for advice and patient counseling should be done.
- Adjust dosage of drugs administered, based on the degree of renal impairment.

2. Specific Syndromes

2.1 Rhabdomyolysis

- This refers to a rapid destruction of skeletal muscle resulting in leakage of muscle protein (myoglobin) into the urine.
- Acute renal insufficiency (ARI) is a potential complication of rhabdomyolysis.
- Causes:
  - crush syndrome,
  - alcohol withdrawal,
  - disorders of lipid metabolism, glycogenolysis and glycolysis
  - Infections (leptospirosis, clostridium)
  - Heat stroke
  - Drugs - fibrates, statins, heroin
  - Autoimmune disease such as systemic lupus erythematosus (SLE)
  - Dermatomyositis
  - Polymyositis
  - Idiopathic (sometimes recurrent)
- Clinical features:
  - may be asymptomatic or present with muscle aches, pain, stiffness and muscle weakness
- Investigation
  - Urine examination – presence of pigment granular cast, reddish brown urine (due to excretion of myoglobin)
  - A markedly raised serum creatine phosphokinase level
  - A low ratio of blood urea to serum creatinine level
  - Electrolyte abnormalities such as hyperkalemia, hyperuricemia, hyperphosphatemia, metabolic acidosis, hypermagnesemia
- Management
  - Check volume status
  - Initiate volume replacement with normal saline, preferably with CVP monitoring. Target urine output to 3 ml/kg body weight/hour
  - Check urine pH, if < 6.5 alternate 1 litre of normal saline with 1 litre of 5% dextrose or 0.45% saline, plus 100 ml of bicarbonate. (AVOID POTTASIUM OR LACTATE CONTAINING SOLUTIONS)
  - Correct hypocalcaemia if symptomatic (with tetany or seizures)
  - Consider treatment with mannitol (up to 200 g/day)
- Maintain volume replacement until myoglobin is cleared, as evidenced by clear urine or urine dipstick is negative for blood.
- Consider dialysis if resistant hyperkalemia, oliguria, volume overload or resistant metabolic acidosis

### 2.2 Abdominal Compartment Syndrome

- Seen in the following clinical settings:
  - Trauma patient following massive volume resuscitation
  - Post liver transplant
  - Mechanical limitation to the abdominal wall
  - Bowel obstruction
  - Pancreatitis
- Clinical features:
  - Respiratory compromise
  - Decreased cardiac output
  - Intestinal ischaemia
  - Hepatic dysfunction
  - Oliguric acute renal insufficiency
- Diagnosis
  - Suspect in patients with tensely distended abdomen and oliguria
  - Intraabdominal pressure can be found by measurement of urinary bladder pressure (studies show good correlation but not routinely done)
- Treatment
  - Abdominal decompression
  - Management of acute renal insufficiency

### 2.3 Renal failure in patients with cirrhosis

Types
- 2.3.1 Hepatorenal syndrome
- 2.3.2 Hypovolemic induced renal failure
- 2.3.3 Parenchymal renal disease (presence of proteinuria of > 500 mg/day and hematuria > 50 RBC/hpf)
- 2.3.4 Drug induced renal failure

#### 2.3.1 Hepatorenal syndrome - can be classified into 2 types:

i. Type 1 - there is doubling of serum creatinine by more than 221 µmol/L in less than 2 weeks or reduction in creatinine clearance by 50%
ii. Type 2 - moderate stable decrease in renal function, less rapidly progressive than type 1

- Diagnostic criteria
  - Major criteria-
    - low GFR - serum creatinine >132 µmol/L or creatinine clearance of < 40 ml/minute
    - absence of shock, sepsis, nephrotoxic agents and fluid loss
    - no improvement in renal function with volume expansion using 1.5L of isotonic saline
→ proteinuria of < 0.5 gm/dL
→ No ultrasound evidence of renal obstruction

Additional criteria
→ urine volume of less than 500 ml/day
→ urine Na of < 10 mmol/L
→ urine osmolality more than plasma osmolality
→ serum Na less than 100 mmol/L
→ urine sediments less than 50 RBC’s per high power fields.

• Management
  ➢ Treat complications such as bleeding and infections. For infections, use of third generation cephalosporins as the initial antibiotic of choice.
  ➢ Use of hydrocortisone in sepsis may be beneficial in association with relative adrenal insufficiency.
  ➢ Avoid excessive intravenous fluid administration.
  ➢ Avoid potassium sparing diuretics.
  ➢ Gross ascites is managed with abdominal paracentesis
  ➢ Intravenous administration of albumin.
  ➢ Specific therapies for hepatorenal syndrome patients:
    → Vasoconstrictor drugs - telipressin 0.5-1 mg every 4 to 6 hours, given intravenously for 5-15 days.
    → Norepinephrine 0.5 – 3 mg/hour, continuous intravenous infusion
    → Midodrine 7.5 mg given orally 3 times a day in association with octreotide 100 µg subcutaneously 3 times daily.
    → Albumin infusion - 1 g of albumin /kg body weight on day 1 followed by 20 to 40 g per day
    → Other therapies - TIPPS (transjugular intrahepatic porto-systemic shunts), renal replacement therapy should be considered in patients who have not responded to vasoconstrictor drugs

2.4 Radio-contrast Nephropathy

• It is the most frequent aetiology of nephrotoxic acute tubular necrosis (ATN).
• Risk factors:
  ➢ Chronic renal insufficiency
  ➢ Volume depletion
  ➢ Diabetes mellitus
  ➢ High volume of radiocontrast agent
• Typically characterized by acute elevation of serum creatinine 48 hours after contrast administration peaking at day 4 to 5. Oliguria develops about 72 hours post contrast exposure
• Prevention
  ➢ Hydration (Isotonic 0.9% or 0.45% saline) at the rate of 1 ml per/kg per hour starting 12 hours before the procedure and to be continued 24 hours after procedure
  ➢ Use of N-acetylcysteine at a dose of 600 mg twice a day for three days prior to administration of contrast agent
Chapter 8
Gastro-intestinal emergencies and hepatic encephalopathy

Table of contents
1. **Acute upper gastrointestinal bleeding (UGIB)**
2. **Treatment of Hepatic Encephalopathy**

1. **Acute upper gastrointestinal bleeding (UGIB)**
   - Peptic ulcer is the commonest cause of acute upper gastrointestinal bleeding (UGIB).
   - Consider variceal bleeding in patients with
     - history of alcohol ingestion
     - hepatitis B or C infection
     - previous variceal bleed
     - presence of stigmata of chronic liver disease (e.g. palmar erythema, spider naevi, etc), or portal hypertension (e.g. ascites, splenomegaly, caput medusae).
   - Clinical presentation
     - presents with either haematemesis or melaena or both.
   - Investigations
     - Urgent full blood count
     - Blood grouping and cross matching
     - Coagulation screen
     - Blood urea and electrolyte
     - Liver function tests.
   - Management
     - Clinical assessment - this should include:
       - Frequent measurement of blood pressure, pulse rate and oxygen saturation. Postural hypotension of 10 mmHg or more usually indicates at least 20% reduction in blood volume.
       - Level of consciousness - look for alcoholic intoxication or withdrawal.
       - Severity (amount) of bleeding
       - Urine output
     - Altered consciousness, with agitation, pallor, cold peripheries, hypotension and tachycardia may indicate shock requiring immediate volume replacement. Resuscitation must be commenced immediately.
       - Insert at least two large bore intravenous cannulae, which should be inserted into large peripheral veins.
       - Supplemental oxygen may help a confused, agitated elderly patient.
       - Central venous pressure (CVP) monitoring is advisable in patients with profound shock or organ failure and in elderly patients with significant co-morbidity.
       - Fluid resuscitation can be commenced with isotonic crystalloid solutions (normal saline or lactated Ringer’s solution) or colloids while waiting for blood products. Transfuse blood to maintain a haemoglobin level of at least 10 g/dl. Fresh frozen plasma may be given if the prothrombin time is at least 1.5 times higher than the control value.
Initial hemoglobin or haematocrit level obtained in a patient with acute bleeding may not be reflective the degree of blood loss. This is due to haemoconcentration.

→ Consider intubation for airway protection in severe uncontrollable bleeding, encephalopathy and inability to maintain oxygen saturation adequately and to prevent aspiration.

→ Continuous haematemesis or persistent hypovolaemia despite aggressive resuscitation suggest bleeding is still active. Passage of "fresh" malaena, which is maroon coloured or passage of bright red visible clots suggest active bleeding.

➢ Specific treatment

→ Early upper gastrointestinal endoscopy after resuscitation (within 12 to 24 hours) is the cornerstone of management of upper gastrointestinal bleed (UGIB). Early endoscopy has 3 major roles, which is for diagnosis, treatment and risk stratification.

→ High dose intravenous proton pump inhibitors (e.g i.v Omeprazole or Pantoprazole 80 mg stat followed by an infusion of 8 mg hourly for 72 hours) should be commenced.

→ Interventional radiology (embolization therapy) or surgery should be considered when bleeding is unresponsive to endoscopic haemostasis or failure of endoscopic visualization of the bleeder due to profuse hemorrhage or inaccessibility.

→ In patients with variceal bleeding,
  - Terlipressin is administered as IV injection of 2 mg bolus and 1 mg every four to six hours for 48 hours. Alternatively, Octreotide is administered as a bolus injection of 50 mcg followed by an infusion at a rate of 50 mcg per hour.
  - Antibiotic prophylaxis (such as quinolones or third generation cephalosporins) should be given for 7 days.
  - If endoscopy is unavailable, consider balloon tamponade with a Sengstaken – Blakemore tube and referral to the nearest tertiary center.
  - When there is failure to control bleeding, consider repeating endoscopy, surgical intervention or transjugular intrahepatic portasystemic shunts (TIPS).

2. Treatment of Hepatic Encephalopathy

- Definition - Hepatic encephalopathy is a complex neuropsychiatric syndrome, characterized by disturbance in consciousness and behaviour, personality changes, fluctuating neurological signs, asterixis or “flapping tremors” and distinctive electroencephalographic changes.

- Aetiology - look for precipitating factor such as
  ➢ infection, including spontaneous bacterial peritonitis,
  ➢ electrolyte disturbance,
  ➢ inappropriate medication,
  ➢ constipation,
  ➢ gastrointestinal bleeding,
  ➢ portal vein thrombosis,
- hepatocellular carcinoma.
- The West Haven criteria of altered mental state in hepatic encephalopathy
  - Stage 0 – lack of detectable changes in personality or behaviour. Asterixis absent.
  - Stage 1 – trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia or inversion of sleep pattern. Euphoria or depression. Asterixis can be detected.
  - Stage 4 – coma.
- Management
  - Treat the underlying cause or the precipitating factors.
  - Lactulose should be given to ensure the patient has at least 2 bowel actions daily; omit if the patient has diarrhoea. Consider inserting a nasogastric tube to deliver lactulose if unable to take orally.
  - For short term measure (but not normally longer than 5 to 7 days), oral Neomycin 1 to 2 mg daily or metronidazole 400 mg t.d.s can be used.
  - Low protein diets are rarely indicated. Efforts should be directed at correcting or treating the underlying precipitating factors and to maintain or improve the nutritional status.

Chapter 9
Sepsis

Table of contents
1. Definition
2. Clinical aspects
3. Initial Resuscitation of Sepsis
4. Other Supportive Therapies

1. Definition
- Definition - sepsis is considered present if infection is highly suspected or proven and two or more of the following systemic inflammatory response syndrome (SIRS) criteria are met:
  - Heart rate > 90 beats per minute (tachycardia)
  - Body temperature < 36 °C (96.8 °F) or > 38 °C (100.4 °F) (hypothermia or fever)
  - Respiratory rate > 20 breaths per minute or, on blood gas, a $P_aCO_2$ less than 32 mm Hg (4.3 kPa) (tachypnea or hypocapnia due to hyperventilation)
  - White blood cell count < 4000 cells/mm³ or > 12000 cells/mm³ (< 4 x 10⁹ or > 12 x 10⁹ cells/L)
Sepsis occurs in different stages. Some patients may progress to all the different stages of sepsis despite receiving appropriate treatment.

- Uncomplicated sepsis
- Severe sepsis
- Septic shock
- Multiple organ dysfunction syndrome (MODS), which often results in death.

2. Clinical aspects

- Aetiology
  - Bacterial infections are the most common cause of sepsis.
  - Sepsis can also be caused by fungal, parasitic, or viral infections.
  - The source of the infection can be any of a number of places throughout the body.
  - Common sites and types of infection that can lead to sepsis include:
    - The abdomen and pelvis - An inflammation of the appendix (appendicitis), bowel problems, infection of the abdominal cavity (peritonitis), gallbladder, liver or pelvic organs
    - The central nervous system - Inflammation or infections of the brain or the spinal cord
    - The lungs - Infections such as pneumonia
    - The skin - Bacteria can enter skin through wounds or skin inflammations, or through the openings made with intravenous (IV) catheters (tubes inserted into the body to administer or drain fluids). Conditions such as cellulitis (inflammation of the skin's connective tissue) can cause sepsis.
    - The urinary tract (kidneys or bladder) - Urinary tract infections are especially likely if the patient has a urinary catheter to drain urine.

- Clinical presentation
  - General
    - Fever, chills (especially in the early phase)
    - Hypothermia (especially if they are young or old)
    - Hyperventilation
    - Warm skin, sometimes associated with a skin rash
    - Tachycardia and hypotension
    - General weakness
  - Specifics
    - Other symptoms and signs of sepsis also depend on the source and site of the infection such as neurological, cardiovascular, renal, pulmonary, hepatic, haematologic, endocrine, reproductive and cutaneous.

- Investigations
  - Full blood count
  - Blood cultures (before antibiotics are given)
  - Tissues / fluid / pus culture (before antibiotics are given)
  - Urine profile and culture
  - Renal profile
  - Liver function test
Blood film for malaria parasite
- Lumbar puncture
- Disseminated intravascular coagulation (DIC) screen
- Imaging: CXR, abdominal X-ray, ultrasound, CT scan

3. Initial Resuscitation of Sepsis
(Adapted from Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock Intensive Care Med 2008 34:17-60)

- Fluid Therapy: fluid resuscitation with colloids or crystalloids. Target a CVP of >8 mmHg (>12 mmHg if mechanically ventilated)
- Vasopressor – Maintain mean arterial pressure (MAP) ≥ 65 mmHg or systolic pressure of more than 90 mmHg. Dopamine or norepinephrine is the initial vasopressor of choice. Doses of dopamine often required are 0.5–25 μg/kg per minute. If the respond is inadequate, norepinephrine at dose of 0.01–0.5 μg/kg per minute should be started. Insert an arterial catheter as soon as possible if patient requires vasopressors. Once the blood pressure and perfusion have been stabilized, always use the lowest dosage that maintains blood pressure in order to minimize the complications of vasoconstriction.
- Steroid: consider low dose corticosteroids for adult septic shock when hypotension remains poorly responsive to adequate fluid resuscitation. Hydrocortisone dose should be ≤ 300 mg/day. Do not use corticosteroids to treat sepsis in the absence of shock unless patient’s endocrine or corticosteroid history warrants it.
- Diagnosis of sepsis: Obtain appropriate cultures (e.g. 2 or more sets of blood cultures, tissues, pus or other sites as clinically indicated) before starting antibiotics provided this does not significantly delay antibiotic administration.
- Antibiotic therapy: Begin antibiotic as early as possible (within one hour of recognizing sepsis). Antimicrobial therapy is often an empiric choice and generally broad spectrum antibiotics (one or more agents) are used.
- Source identification and control: A specific anatomic site of infection should be established as rapidly as possible. Implement source control measures (e.g. abscess drainage, debridement, removal of intravascular access device if potentially infected) as soon as possible following successful initial resuscitation.

4. Other Supportive Therapies
- Respiratory support - maintain oxygen saturations above 90 %. Intubation and mechanical ventilation is often needed in almost all patients with ARDS.
- Renal replacement therapy - acute renal failure can occur in patients with severe sepsis due to hypoperfusion and hypotension. Renal dysfunction is reflected by decreasing urine output, increasing blood urea and increasing creatinine. The aim is to maintain urine output of greater than 30 ml per hour. Insert urinary catheter to monitor urine output. However, avoid prolonged catheterization if possible.
- Glucose control - hyperglycaemia is common in sepsis. Blood glucose must be monitored. Continuous insulin infusion may be necessary to maintain target blood glucose levels.
- Sedation and analgesia – Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients.
- **Deep vein thrombosis (DVT) prophylaxis** – use either low dose unfractionated heparin or low molecular weight heparin (LMWH), unless contra-indicated.
- Stress ulcer prophylaxis with any of the proton pump inhibitors (PPI) agent such as omeprazole, lansoprazole, esomeprazole, rabeprazole or pantoprazole.
- Blood products – Give red blood cells when hemoglobin is < 7.0 g/dL, to target hemoglobin of 7.0-9.0 g/dL in adults.
- Replace deficient haemostatic factors in decompensated *disseminated intravascular coagulation (DIC)* using cryoprecipitate, fresh frozen plasma or platelets. A referral to a haematologist may be necessary as both anticoagulants and factors replacement therapy is potentially dangerous and should be used with caution.
Chapter 10
Poisoning

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C. General Approach to Management
D. Specific poisoning
   1. Salicylate
   2. Paracetamol
   3. Narcotics Analgesic
   4. Recreational Drugs – Amphetamines, MDMA (3,4-methylenedioxymethamphetamine), Methamphetamines, Hallucinogens (LSD, Ketamine)
   5. Pesticide
      a. Organophosphorus Compounds
      b. Paraquat
   6. Methanol
   7. Warfarin
   8. Petroleum Distillate / Hydrocarbons
   9. Carbon Monoxide
   10. Sedative Hypnotics
   11. Caustics

A. Concept

- A high index of suspicion for intoxication and poisoning is warranted in the practice of medicine. The inconsistent manifestations of poisoning are a challenge, particularly if patients present with altered sensorium or when there is no history of intoxications. Recognition of specific toxic syndrome (or toxidrome) is essential, but often the symptoms are often nonspecific or masked by other condition.

- Poisons are substances that can cause damage, illness, or death to organisms, usually by chemical reaction or other activity on the molecular scale, when a sufficient quantity is absorbed by an organism. The term poisoning suggests an acute event demanding immediate care and attention. Poisoning may, however, be chronic resulting from environment sources such as food, water supplies etc. The cause for poisoning can be classified as accidental or deliberate.
Accidental poisoning is due to an exposure to a poison resulting in symptoms which arises by accidental action and it is common in young children. Deliberate poisoning is part of the spectrum of disorders now classified as deliberate self harm. It is also in the past referred to as parasuicide.

Toxicity and poisoning
- the toxicity of a substance and the features of poisoning generally can be predicted from:
  - Its physicochemical properties
  - Its pharmacological properties
  - The route of exposure
  - Exposed dose to an individual
- Features of poisoning can be categorized into either Local or Systemic
  - Local toxicity is confined to the site of contact of the substance with body surfaces.
  - Systemic toxicity depends on the fraction of the dose of the poison that is absorbed into the circulation. Systemic toxicity is usually dose related and may be organ specific or may have multi organ involvement.

B. General Approach to Management

I. **Resuscitation – Airway, Breathing and Circulation**
II. **Prevention of Absorption**
III. **Enhancement of Elimination**
IV. **Antidotes**
V. **Toxidromes**

- Assessment of an acutely poisoned patient involves
  - the taking of an accurate history.
  - physical examination and proper assessment of conscious level, ventilation (airway) and circulation system.
  - requesting appropriate emergency toxicological and non toxicological investigations.
- Diagnosis of poisoning is based on the history, physical signs, circumstantial evidence or third party information, a cluster of common features (toxidrome) and occasionally, on the result of biochemical or toxicological analyses.
- Always try to obtain a sample of the poison either from relatives or patient which includes gastric lavage, blood and/or urine sample for toxicology.

I. **Resuscitation – Airway, Breathing and Circulation**

Good early supportive care is the key to the management of poisoning.

**Airway and Breathing**
- Airway patency must be ensured in ALL cases. Presence of cough and gag reflexes together with adequate spontaneous ventilation DO NOT warrant endotracheal intubation. However, when there is concern regarding airway protection and clinical deterioration, it is recommended to secure the airway.
- Intubation is indicated in;
  - Acute respiratory failure or impending respiratory failure
- Requirement for high level of supplemental oxygen in carbon monoxide poisoning
- Protection of airway for gastric emptying.
- Deterioration of conscious level.

Circulation

- Patient may present with hypotension or hypertension, bradycardia, or tachycardias depending on the poison or level of toxicity.
- Hypotension may be due to hypovolaemia, myocardial suppression, cardiac arrhythmias, and systemic vasodilatation. Treatment should be tailored to the most probable cause, however the initial bolus of 1 litre (in adult) of normal saline is recommended. Inotropic support may be required for refractory hypotension.
- Hypertension may occur in the setting of sympathomimetic drugs such as amphetamines, ecstasy, methamphetamine (ice, crystals), cocaine, anticholinergic, withdrawal from alcohol, nicotine and sedatives. Treatment of hypertension depends on its chronicity and severity. Hypertensive emergencies (evidence of end organ damage) require prompt treatment. Intravenous glyceryl trinitrate (GTN) can be initiated together with close monitoring of the patient blood pressure.
- Coma “cocktail” should be administered to patient with depressed conscious level. This cocktail is both therapeutic and diagnostic. The coma “cocktail” consists of:
  - Thiamine 100 mg iv,
  - Dextrose 50% 50 g and
  - Naloxone 0.2 to 0.4 mg iv, titrated up to 2 mg.
- Flumazenil should be considered in cases of suspected benzodiazepines overdose. However, one should beware of the risk of seizures with flumazenil administration.

II. Prevention of Absorption

The route of entry for poisons can be dermal, ocular, gastrointestinal, or parenteral. Medical personnel handling the patient MUST at all times adhere to practices using personal protective equipments (PPE) or standard universal protection.

- If poisoning is by dermal/percutaneous absorption, dermal decontamination is required which involve the following steps;
  - Remove clothes with caution and placed in plastic bags or containers that are impervious to toxins,
  - Wash the skin (‘dilution is the solution to the pollution’) with non abrasive soap and water.
- If poisoning is by ocular route, ocular decontamination should be carried out. It involves prolong period of irrigation with normal saline solution and subsequent referral to the ophthalmologist.
- In the case of poisoning by the oral or gastrointestinal route, various methods listed below may be used:

  a. Gastric Lavage
     - Gastric lavage should not be routinely performed in all cases of poisoning by the oral or gastrointestinal route. Caution should be exercised in
patients with medical conditions such as bleeding diasthesis and combative patients.

- Empty the stomach by lavage in cases of selected poisons that was taken less than 1 hour. Efficacy which lavage removes gastric contents decreases with time.
- Gastric lavage should be performed using specially design disposable orogastric lavage tubes which sizes between 28F to 40F. Insertion of orogastric lavage tube requires special care as known potential complications such as tracheal intubation, esophageal tear, stomach rupture trauma, arrhythmias and aspiration may occur.
- After insertion, proper positioning need to be confirmed by aspirating acidic stomach fluid contents and auscultation the left upper abdominal quadrant during insufflations of air.
- Non intubated patients must be alert and have adequate pharyngeal and laryngeal protective reflexes.
- In patients with depressed conscious level, orogastric lavage should ONLY be performed after protection of the airway through cuff endotracheal intubations.
- Oropharyngeal lavage is performed by instilling up to 300 ml warm water or normal saline until there is clearing of aspirated fluid. Stomach content should be retained for analysis.
- Contraindications to gastric lavage are:
  - Petroleum distillates because of risk of bronchial aspiration and lipoid pneumonia.
  - Corrosives (acids or alkalis) – this will cause additional damage to upper gastrointestinal tract.
  - Known esophageal strictures or gastric bypass surgery.

b. Whole bowel irrigation
- Whole bowel irrigation is done to empty the distal bowel and to induce intestinal hurry. Use Polyethylene Glycol 1 – 2 Liter/hour orally until diarrhea occurs and clearing of rectal effluent.
- Whole bowel irrigation may be considered following potentially toxic ingestion of sustained release or enteric coated drugs and in body packers. Whole bowel irrigation is contraindicated in bowel ileus, gastrointestinal bleeding and bowel perforation.

c. Absorbents – Activated charcoal, Bentonite, Fuller’s Earth, Cholestyramine or Colestipol
- Activated charcoal adsorbs wide variety of drugs and poisons; exceptions are strong acids and alkalis, lithium and irons.
- Activated charcoal can be administered after orogastric lavage or as sole GI decontaminating agents. The dose is 1g/kg body weight and best administered within one hour of ingestion of the poisons.
- Administration of charcoal is contraindicated in patient who demonstrates compromised airway protective reflexes.

d. Cathartics
- The use of cathartics with activated charcoal may reduce transit time of drugs and toxins in GI tract and decrease the constipating effect of
charcoal. Sorbitol is cathartics of choice. The usual dose is 1 to 2 ml/kg of 70% solution of sorbitol titrated to several loose stools over the first day of treatment.

- The administration of a cathartic alone has no role in the treatment of a poisoned patient and is not recommended as a method of gut decontamination

e. Induce emesis

- Ipecac-induce emesis can occur within 30 minutes of its administration. Although syrup ipecacuanha is an effective emetic, there is little evidence that its use prevents significant absorption of poisons and therefore rarely use nowadays.

III. Enhancement of Elimination

a. Multiple-dose Activated Charcoal (MDAC)

- Multiple-dose Activated Charcoal involve repeated administration of oral activated charcoal to increase elimination of a drug that has already been absorbed into the body. Activated charcoal adsorbs material in the gut, adsorbed drugs are secreted in the bile and binds any drug that diffuses from the circulation into the gut. Multiple-dose Activated Charcoal should be considered in patients who ingested life threatening amount of carbamazepines, dapsone, phenobarbitones, quinine and theophylline.

- Activated charcoal should administered in an initial dose of 50 to 100g and then followed by 0.5 g/kg every 4 hours, preferably via nasogastric tube.

- Multiple-dose Activated Charcoal is contraindicated in patients with evidence of bowel obstruction.

b. Force Diuresis and Urinary pH Manipulation

- The goal for this technique is to enhance elimination of renally excreted toxins through inhibition of tubular reabsorption.

- Forced Alkaline diuresis is use for;
  - Salicylates
  - Carbamates
  - Barbiturates
  - Chlorpropamide

- However, except salicylates urine alkalinization should NOT be used as first line therapy for poisoning of phenobarbitones as MDAC is far superior. For carbamates poisoning, supportive therapy together with atropine is adequate.

**Technique of Forced Alkaline Diuresis (urine pH > 7)**

- Correct the plasma volume depletion, electrolytes abnormalities and metabolic abnormalities first before commencing.
- Catheterize, if necessary
- One cycle includes infusion of:
  - 500 ml D5% with 50 ml of 8.4% NaHCO₃
  - 500 ml D5% with 1 gm KCl
° 500 ml N/S with 40 mg Frusemide
Give at a rate of 500 ml per hour
One cycle over 3 hours, repeated for 24 - 48 hours
Targeted urine pH is between 7.5 to 8.5.

OR

50 ml of 8.4% NaHCO₃ in D5% infused at 250 ml/hour at a
dose 1 to 2mEq/kg every 3 to 4 hour.
→ Monitor blood urea and electrolytes twice daily. Correct / replace
the Potassium and ensure adequate urine output.

➢ Complications
→ Fluid overload, pulmonary oedema, therefore encourage central
venous pressure monitoring.
→ Electrolyte imbalance (hypokalaemia, hypernatremia).
➢ Contraindications
→ Congestive cardiac failure
→ Shock
→ Renal Failure

c. Haemodialysis/Peritoneal Dialysis.
➢ This therapy significantly increases elimination of the following toxins;
→ Methanol / Ethylene Glycol
→ Ethanol
→ Amphetamines
→ Boric Acid
→ Lithium
→ Salicylates
➢ This therapy is the treatment of choice in severe poisoning involving the
above agents.

d. Charcoal Haemoperfusion
➢ This therapy can be use to increase the elimination of;
→ Barbiturates / Phenobarbitones
→ Carbamazepines
→ Phenytoin
→ Paraquat
→ Theophylline
➢ However, MDAC is as effective and simpler to use.

IV. Antidotes

• An antidote is a substance that increases the mean lethal dose of a toxin, or that
can favorably affect the toxic effect of a poison. Some antidotes are toxic
themselves and therefore should be used only when indicated.
The following tables list out some of the common antidotes for specific drugs / poisons.

<table>
<thead>
<tr>
<th>Poison/Drug</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Anticoagulants, e.g. warfarin</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Opiods</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>Methanol</td>
<td>Ethanol or fomepizole</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium nitrite &amp; sodium thiosulfate</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Atropine and pralidoxime</td>
</tr>
<tr>
<td>Carbamates</td>
<td>Atropine</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Calcium Gluconate and/or Glucagon</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>Oxygen</td>
</tr>
</tbody>
</table>

**Table 10.1: Common Poisons and Antidotes**

V. Toxidromes

- The term toxidrome refers to constellation of physical signs that can provide clues to narrow the differential diagnosis. However, polydrug or polypharmacy may result in overlapping and confusing mixed syndromes.
- The most common toxidromes are the anticholinergic syndrome, sympathomimetic syndrome, opioid/sedative/ethanol syndrome and cholinergic syndrome.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Common Sign</th>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Delirium, tachycardia, dry flushed skin, dilated pupils, urinary retention,</td>
<td>Antihistamines, atropine, antipsychotic, antidepressants,</td>
</tr>
<tr>
<td></td>
<td>slightly elevated temperature, decrease bowel sounds</td>
<td></td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Delusions, paranoia, tachycardia, hypertension, hyperpyrexia, diaphoresis,</td>
<td>Cocaine, amphetamines, methamphetamine, theophylline</td>
</tr>
<tr>
<td></td>
<td>piloerection, hyperreflexia</td>
<td></td>
</tr>
<tr>
<td>Opiods/sedative/hypnotic</td>
<td>Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia,</td>
<td>Narcotics, barbiturates, benzodiazepines, ethanol</td>
</tr>
<tr>
<td></td>
<td>pulmonary oedema, hyporeflexia, needle marks,</td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Confusions, CNS depression, weakness, salivation, lacrimation, urinary/faecal</td>
<td>Organophosphates, carbamates, insecticides</td>
</tr>
<tr>
<td></td>
<td>incontinence, emesis, diaphoresis, pulmonary oedema, miosis, bradycardia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tachycardia</td>
<td></td>
</tr>
</tbody>
</table>

**Table 10.2: Toxidromes**

- A diagnosis of acute poisoning should never be made on the basis of one clinical sign, but there are typical clusters of signs that make a diagnosis of poisoning. The common cluster of clinical signs useful in identifying the poisons are as follows;
<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>Possible Poisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pin point pupils,</td>
<td>Opiates</td>
</tr>
<tr>
<td>• Respiratory depression,</td>
<td></td>
</tr>
<tr>
<td>• Needle marks /scars.</td>
<td></td>
</tr>
<tr>
<td>• Pin point pupils,</td>
<td>Organophosphate / Carbamates / nerve agents</td>
</tr>
<tr>
<td>• Sweating, salivation, bronchorhea,</td>
<td></td>
</tr>
<tr>
<td>• Abdominal colic,</td>
<td></td>
</tr>
<tr>
<td>• Muscular twitching</td>
<td></td>
</tr>
<tr>
<td>• Widely dilated pupils,</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>• Absent bowel sounds,</td>
<td></td>
</tr>
<tr>
<td>• Cardiac arrhythmias,</td>
<td></td>
</tr>
<tr>
<td>• Distended bladder,</td>
<td></td>
</tr>
<tr>
<td>• Coma, hypertonia,</td>
<td></td>
</tr>
<tr>
<td>• hyperreflexia, extensor plantar responses, myoclonus</td>
<td></td>
</tr>
<tr>
<td>• Dull white burns on buccal mucosa</td>
<td>Corrosives</td>
</tr>
<tr>
<td>• Coma, hypotonia, hyporeflexia, flexor plantar response</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>• Blisters on skin in comatosed patient</td>
<td></td>
</tr>
<tr>
<td>• Flushed, sweating, Tinnitus, deafness, Hyperventilation</td>
<td>Salicylates</td>
</tr>
<tr>
<td>• Restlessness, agitation, Dilated pupils (mydriasis), Anxiety, tremor</td>
<td>Sympathomimetics,</td>
</tr>
<tr>
<td>• Tachycardia, convulsions, arrhythmias</td>
<td></td>
</tr>
<tr>
<td>• Dilated pupils (mydriasis) Hypertension Profuse sweating Hyperthermia CNS</td>
<td>Amphetamines, MDMA (3,4-Methylenedioxy-</td>
</tr>
<tr>
<td>• excitation (delirium, agitation)</td>
<td>methamphetamine-Ecstasy), methamphetamines</td>
</tr>
</tbody>
</table>

**Table 10.3: Common cluster of Clinical Signs Suggestive of Certain Poisons**
C. Specific poisoning

1. Salicylate

Mechanism of Toxicity
- Rapidly absorbed from the gastrointestinal tract reaching toxic level within 30 minutes of ingestion. Peak levels may occur in 2 to 4 hours.
- Route of exposure via the oral and cutaneous route. 1 ml 25% liniment methyl salicylate (LMS) equivalent to 300 mg salicylate.
- Salicylate is available over the counter in the form of aspirin, sports liniments, Oil of wintergreen, traditional Chinese medicine, ‘minyak gosok’ and ‘minyak kuda’

Clinical Features
- Patients with severe salicylate toxicity may appear well initially.
- Clinical feature is manifested by the level of toxicity. Simple side-room test for salicylate is feric chloride test which is performed with adding a few drops of FeCl₃ solution to 5 ml of boiled acidified urine. This will turn violet colour if positive.

  ➢ _Mild to moderate intoxication:_
    ➢ Deafness, nausea, tinnitus, vomiting, hyperventilation, sweating, vasodilatation, tachycardia.
    ➢ Always look out for these early signs of salicylates toxicity.

  ➢ _Severe intoxication:_
    ➢ All above symptoms and signs, plus confusion, coma, delirium, hypotension, convulsions and cardiac arrest.

- Ingestion of more than 10 – 30 grams (150 mg/kg) salicylates is potentially fatal.
- Other complications: Pulmonary oedema, cerebral oedema, renal failure, hyperpyrexia, encephalopathy, tetany, hypoglycaemia
- Pulmonary oedema is more cardiogenic and is also caused by increased pulmonary capillary permeability.
- Biochemical and metabolic abnormalities:
  ➢ The salicylates have a direct stimulant effect on the respiratory centre. Hyperventilation causes respiratory alkalosis. Salicylates induces uncoupling of oxidative phosphorylation and interferes with metabolism and causes accumulation of organic acids. This causes metabolic acidosis.
  ➢ Acidosis reduces the inoisation of salicylates and hence increases intracellular distribution. This is associated with CNS toxicity and a poor prognosis.
  ➢ Hypokalaemia and hypo/hypernatraemia may occur
  ➢ When serum salicylates levels cannot be estimated, Arterial blood gas provide a clue to the severity of the condition.
    ➢ Mild - respiratory alkalosis
    ➢ Severe - metabolic acidosis
**Specific Management**

- Serum levels are useful if available. One value is inadequate for management. Serial values done 6-hourly is necessary.
- The most important guide is however NOT any blood value but the patients’ clinical condition. Energetic measures are taken if the patient is ill or deteriorating, whatever the blood level. Monitor prothrombin time (PT), platelet count, blood urea and serum electrolytes.
  - Gastric lavage is recommended up even beyond 1 hour after ingestion because salicylates cause pylorospasm that leads to delay gastric emptying
  - Give activated charcoal 50 gm (1 gm/kg in children).
  - Correct dehydration with guided estimation for replacement. Maintain urine output at 2 to 3 ml/kg/hour.
  - Correct electrolytes imbalance, especially potassium depletion.
  - Correct acidosis.
  - **Forced alkaline diuresis** in patients with serum salicylates >50 mg/dl and in symptomatic patients (most useful method) as being describe above.
  - Haemodialysis / haemoperfusion / peritoneal dialysis is used in severe cases i.e. rapidly rising blood level or blood levels >100 mg/dl; severe acid-base imbalance (e.g. pH less than 6.8), progressive clinical deterioration; pulmonary edema; severe CNS symptoms/comatose patient; patients with impaired renal function, severe cardiac toxicity, acute respiratory distress syndrome (ARDS).

![Figure 10.1 showing the serum Salicylate levels after ingestion](image-url)
NB: Poisoning with liniment methyl salicylate is commoner than with aspirin in Malaysia. The ingestion of 10 – 30 gm of aspirin or more than 30 ml of 25% liniment methyl salicylate (LMS) is potentially fatal. Toxic symptoms correlate poorly with serum levels and initiation of treatment must be based on clinical findings.

Approximate serum salicylates level.

\[
\text{Amount ingested (mg) } \times \frac{100}{60\% \text{ Body weight (gm)}}
\]

Forced alkaline diuresis is started if;

i. Poor clinical condition

ii. Salicylates level > 30 mg/dL in children or > 50 mg/dL in adults

iii. Ingestion of > 50 tablets

Patient with suspected salicylates poisoning must be admitted for at least 24 hours for further evaluation and management.

2. Paracetamol

**Mechanism of Toxicity**

- Paracetamol is converted in the liver to a toxic intermediate metabolite (NAPQI – N acetyl – p – benzoquinoneimine) causing acute centrilobular hepatic necrosis and occasionally acute tubular necrosis. The toxic intermediate is usually rapidly inactivated by conjugation with reduced glutathione. Liver damage is maximal 3 – 4 days after ingestion hence liver failure may not be seen until 2 to 3 days later.

- Toxic dose for paracetamol depend on the body weight and underlying premorbid status of each individual.

  - Adult - Toxicity occurs when ingestion of more than 7.5 grams in average size adult or more than 150mg/kg body weight in 24 hour. Toxicity may occur at lower doses i.e ingestion of more than 4 grams within 24 hour in patient with liver dysfunction or with hepatic enzyme induction (malnourish, chronic alcohol consumption)

  - Children - Toxicity occur when ingestion of more than 150mg/kg within 24 hour period or more than 75mg/kg within 24 hour for children who are malnourished, having acute febrile illness or on medications such as isoniazid and anti convulsants

**Clinical Features**

- Patients with paracetamol overdose often look well in the initial stages except for nausea and vomiting.

- Clinical features of paracetamol toxicity based on the progression paracetamol induced liver injury.
Stage 1: Pre-injury period within first 24 hours. Non-specific symptoms such as nausea, vomiting, lethargy, malaise and diaphoresis. Patient may also be asymptomatic.

Stage 2: Onset of liver injury usually after 24 hours or possibly 12 to 36 hours. Nausea, vomiting, right upper quadrant pain and discomfort.

Stage 3: Maximum liver injury occurs usually at day 3 or day 4 post ingestion. Symptoms of liver injury such as liver tenderness, jaundice, altered sensorium, easy bruising and even coma. Some may develop fulminant liver failure.

Stage 4: Recovery period is usually after one week or even longer. It is vital to avoid further injury to liver cells.

Threshold dose for hepatotoxicity is blood level of > 250 mcg/ml at 2 hours after ingestion or > 100 mcg/ml at 8 hours after ingestion.

**Specific Management**

- Resuscitate and stabilize the patients, ensure patent airway and perform definitive airway measure if patient is obtunded or the gag reflex is absent.
- Establish intravenous line and monitor the vital sign which include blood pressure, pulse rate, respiratory rate, temperature and pulse oximetry regularly.
- Perform orogastric lavage if present within 1 hour after ingestion of potentially toxic amount of paracetamol and collect first effluent for toxicological investigations.
• Administer activated charcoal via gastric lavage tube at 1g/kg or 50 g for adult.
• Administer N-acetylcysteine if;
  ➢ The history is suggestive and convincing of a significant overdose. DO NOT wait for serum paracetamol level to return
  ➢ The 4 hour serum paracetamol level lies in the toxic range on the Rumack Matthew normogram
  ➢ The initial serum paracetamol already in toxic range
  ➢ The liver function test shows evidence of hepatotoxicity.
• N-acetylcysteine - specific antidote, presumably acts as a glutathione substitute or precursor. Give as Intravenous infusion.
  ➢ Initially 150 mg/kg in 200 ml D5% over 15 minutes
  ➢ Followed by 50 mg/kg in 500 ml D5% over 4 hours
  ➢ Then 100 mg/kg in 1,000 ml D5% over 16 hours.
  ➢ Total dosage; 300 mg/kg in 20 hours
• Adverse effects of N-acetylcysteine includes nausea, flushing, urticaria and pruritus. If these are present, the infusion should be stopped for 15 minutes and restart at slower rate.
• Paracetamol by itself does not cause coma, hence if comatose, the patient is either in liver failure or has taken another drug.
• If in doubt, treat with N-acetylcysteine (give the patient the benefit of doubt).

3. Narcotic analgesics

Clinical features
• Cardio-respiratory - respiratory depression, pulmonary oedema, hypotension, cardiac arrhythmias
• Central nervous system – hypothermia, constricted pupils, convulsions, coma
• Renal failure

Specific Management
• IV Naloxone acts almost immediately. The dosage is IV 0.4 – 0.8 mg, with peak effect in 1 – 2 minutes. May be repeated if necessary at 5 minutes and 10 minutes. If there is NO response, think of NON-OPIATE poisoning e.g. barbiturates. Close observation is needed because of the very short half life of Naloxone (1 - 2 hours). Watch for return of respiratory depression as the effect of the drug wears off before the opiate effect is over. Naloxone may be given by infusion of 2 mg in 500 ml Normal Saline at a rate adjusted to response. There may be an overreaction with hyperventilation, muscle tremors, tachycardia and hypertension. The cardinal sign of successful opiate antagonism is an increased respiratory rate and pupil dilatation. The patient may remain drowsy as there is little effect on level of consciousness.
• Give oxygen and ensure continuous monitoring of the clinical status.
• Intermittent positive pressure ventilation may be required
• Chronic narcotic abusers may develop acute withdrawal symptoms. Careful titration of the naloxone dose may prevent this.
4. Recreational drugs

These are drugs that being used in the street namely, they are also call as designer drugs.

- Amphetamines (syabu, pep pills, speed, cat)
- Cocaine (coke, crack, snow, white lady)
- Methyleneoxyamphetamine (MDMA) (Ecstacy, XTC, Adam)
- Methamphetamine (crank, crystal, ice)

Mechanism of Toxicity

- These agents cause central nervous system (CNS) stimulation.
- In general they cause release of catecholamines and block their reuptake, resulting both in alpha and beta adrenergic receptors stimulations. Therefore, these groups of drugs are call sympathomimetics.

Clinical Features

- The primary clinical effect is the excitation of the sympathetic nervous system which includes hypertension, tachycardia, mydriasis, diaphoresis, hyperthermia and central nervous system excitation (agitation, combative, hallucination, twitching).
- Methamphetamine use is particularly associated with delusions of parasitosis (sensation of bugs or ants crawling under the skin) known as formication.

Specific Management

- This includes the management of the complications that may arise from the intoxicated patients.
- The focus is on identification and treatment of rapidly fatal complications specifically hyperthermia, hypertensive emergencies and cardiac arrhythmias.
- Agitation and seizures should be managed aggressively. If uncontrolled, it may lead to rhabdomyolysis and life threatening hyperthermia.
- The utmost priority ensuring adequate oxygenation.
- Ensuring adequate haemodynamic circulation with intravenous fluids
- Treat hyperthermia (temperature more than 40 degree Celcius) with rapid cooling using ice packs, fans, wet sheet. Ensure continuous monitoring of core temperature (rectal or tympanic)

- Hypertensive Emergencies
  - The goal is to reverse promptly the vasoconstriction of noradrenaline at peripheral alpha receptors.
  - Administer benzodiazepines to reduce the psychomotor agitations
  - Start infusion of Nitroglycerin (GTN) to reduce the blood pressure to normal level. Beta blockers is contraindicated in patient with cocaine abuse because of the paradoxical hypertension, when the primary cause of cocaine induced vasoconstriction is untreated and unopposed.
Infusion of Nitroprusside also can be used as alternative to GTN, however it require very close monitoring (intra arterial) of the blood pressure and best done in intensive care settings.

**Arrhythmias**
- Atrial arrhythmias often responded to benzodiazepines.
- Administer intravenous bolus of sodium bicarbonate 1 to 2 mmol/kg, with close cardiac monitoring to empirically treat sodium channel blockade and potential cardiotoxicity from hyperkalaemia. This is when the etiology of wide complex tachycardia from cocaine is unknown.
- Lignocaine may increase seizure risk and mortality and is reserved for patient who have failed bicarbonate therapy.
- Lignocaine also is best use for ventricular arrhythmias in the setting of cocaine associated myocardial infarction.

**Rhabdomyolysis**
- Treated with intravenous fluids crystalloids and ensure urine output at least 2ml/kg per hour
- This complication can be minimize with adequate fluid administration at the initial phase of the intoxication and together with the control of the psychomotor agitation.

**Cocaine related chest pain**
- The etiology of the chest pain is diverse which includes cardiac and non cardiac causes.
- Cardiac causes are endocarditis, pericarditis, ishaemia and infarction. Treatment for myocardial ischaemia or infarction induce by cocaine is similar to those not induce by cocaine. Management include crush aspirin 300 mg, heparin, nitrates either given sublingual or intravenous, sedation with benzodiazepines, and morphine for analgesic properties.
- Non-cardiac causes includes pneumothorax, pneumomediastinum, pneumopericardium, aortic dissection, pulmonary infarction and infections and all these should be look out for.

**Other Adjunct Management**
- Send blood for creatine kinase
- Chest X ray and ECG is mandatory
- CT scan of brain should be considered if there is persistent altered mental status, neurological deficit or seizures.

**Body packers**
- These are individual who attempt to smuggle drugs across national borders by ingesting multiple small packets (condom, foil or cellophane) that are swallowed for later retrieval from vomit, faeces, or are inserted into the vagina or rectum. They often swallowed large numbers of packages with each containing a potentially fatal dose of drug.
- These drugs are identifiable with plain X rays. Therefore, all suspected body packers should undergo abdominal X-ray
- These drugs can breaks and they can be presented with evidence of intoxication and may be fatal.
- The management of Body Packers includes;
  - Send urine for drugs
  - Packets retain in the stomach can be retrieve by
a. Endoscopy and induce emesis, but these are potentially dangerous
b. Use Sorbitol or Lactulose to increase bowel transit time. DO NOT USE liquid paraffin as it may soften the rubber and causing breaks of the packages.

→ Packets that lead to intestinal obstruction should be referred to the Surgeon for further management.
→ Ensure security and safety of personnel and patients
→ Anticipate the possible toxicity that may arise from the drugs/agents. Common agents that are smuggled through this method are: cocaine, methamphetamines and heroin.

5. Pesticides

5a. Organophosphorous compounds
   I. Organophosphate
   II. Carbamates
5b. Paraquat

5a. Organophosphorous compounds

I. Organophosphate - It is locally available as Malathion, Tamaron, Cythion and also called Kopi ‘O’. The routes of exposure includes dermal, inhalation, ingestion and ocular

**Mechanism of Toxicity**
Organophosphate bind to and phosphorylate carboxylic esterase enzymes, inhibit cholinesterase activity therefore excessive acetylcholine accumulates at nicotinic and muscarinic receptor sites.

**Clinical Features**
Present with classical cholinergic syndromes, manifested by hyperactivity of cholinergic responses at receptors sites causing SLUDGE Syndrome

<table>
<thead>
<tr>
<th>Salivation</th>
<th>Lacrimation</th>
<th>Urinary Incontinence</th>
<th>Defecation</th>
<th>Gastrointestinal cramps</th>
<th>Emesis</th>
</tr>
</thead>
</table>

Hallmark features are miosis, bradycardia, excessive salivation and muscle twitching and fasciculation may appear within few minutes to 12 hours after exposure.

**Diagnosis**
- History of ingestion
- Classical symptoms and signs
- Plasma/Red blood cells cholinesterase activity measurement helpful in making diagnosis.

**Specific Management**
Decontamination
- Prevent further exposure by removing all contaminated clothing (shoes, cloths, socks and jewelries), keep the clothing in plastic bag.
- Wash with soap and water thoroughly.
- If involves the eyes, wash with water copiously until no solid bits of chemical on the lashes or eyebrows or in the skin folds.
- Ensure that the water affluent is being managed accordingly.

Patient should be managed in an intensive care settings.

Resuscitation and supportive measures which includes ensuring patent airways, adequate ventilation and circulation. Rehydrate the patients to avoid circulatory compromised.

Perform gastric lavage if ingestion occurs within one hour.

Administer activated charcoal at a dose of 1 gm/kg/body weight

Atropinazation
- Atropine – counteracts against the muscarinic features which are nausea, vomiting, abdominal cramps, diarrhoea, bradycardia, bronchorrhea, bronchospasm and miosis.
- Give Atropine 1 to 2 mg intravenously slowly and with doubling of each subsequent dose every 5 minutes until full atropinisation achieved.
- Start on Atropine infusion via the infusion pump. The doses must be titrated to achieve adequate atropinisation. Dosage varies greatly from 5 mg/hour to 100 mg/hour to maintain adequate secretion control.

Adequate atropinisation indicated by complete clearing of rales and drying of pulmonary secretions. The patient should be kept well atropinised for at least 5 – 7 days. Do not over-atropinise the patient (present with very dry mouth and skin, PR >160/min)

\[\text{‘hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter’}.\]

Pralidoxime
- Most effective especially if given within 24 hours of ingestion of poison.
- Too rapid administration may lead to hypertension, vomiting and a transient reversible neuromuscular blockage.
- It reactivates phosphorylated cholinesterase and form an inert complex with the organophosphate.
- Give bolus 1 to 2 gm IV over 30 minutes; then infusion 500 mg/hour OR can be administered as intermittent bolus over 30 minutes every 4 to 8 hours. Continue for 24 – 48 hours depend upon clinical response and serum cholinesterase levels.
- Effects are mainly at the skeletal – neuromuscular junctions and muscle weakness and fasciculation should improve within minutes
Little effect occurs in the autonomic receptor sites and almost none in the central nervous system.

- IV Diazepam 10 – 15 mg helps to prevent seizures and reduces twitching of muscles. Phenytoin may be also be used for frequent seizures.
- Do not use phenothiazines, morphine, pethidine, aminophylline as it may potentiate organophosphorus effect.

II. Carbamates

Mechanism of Toxicity
- Inhibition of acetylcholinesterase at the esteric sites on the enzymes molecules. The chemical bond is much more labile (minutes to hours) than that characterizing the phosphorylation by organophosphate insecticides.
- Carbamates-cholinesterase binding is reversible therefore carbamates poisoning less prolonged than poisoning by organophosphates, but they are acutely severe.
- Available as Furadan 3G, Abate 500E and route of exposure can be dermal, inhalational or ingestion.

Clinical features
- Similar to organophosphate poisoning

Management
- Similar to organophosphates poisoning EXCEPT pralidoxime is NOT recommended.

5b. Paraquat

Mechanism of Toxicity
- Paraquat is reduced in biologic tissues to free radicals, which react with oxygen to form superoxide and hydrogen peroxide which is thought to induce tissue damage.
- Paraquat selectively concentrates in the lungs causing direct injury to alveolar-capillary membrane followed by surfactant loss.
- Multi-system failure can develop within a few hours if a massive dose is taken. Death often results from pulmonary oedema. This is a very toxic agent and it is essential that its absorption should be prevented. Treatment must be started at the earliest opportunity.
- Routes of exposure includes dermal, inhalation, ingestion and ocular
- Available as Gramoxone or locally known as Kopi ‘O’ and used as herbicide

Clinical features
- Extremely corrosive and causing severe chemical burns of the oropharynx soon after ingestion.
- Nausea, vomiting, diarrhea, coma, metabolic acidosis, pulmonary oedema,
- Myocardial depression.
- After 3 - 4 days of poisoning, patient will develop severe painful mouth ulcers, hepatocellular necrosis and acute renal failure occurs. During the 2nd week, pulmonary fibrosis and oedema occurs due to selective accumulation of paraquat in lung tissues.

**Specific Management**

- Decontamination
  - Prevent further exposure by removing all contaminated clothing (shoes, cloths, socks and jewelries), kept the clothing in plastic bag.
  - Wash with soap and water thoroughly.
  - If involves the eyes, wash with water copiously until no solid bits of chemical on the lashes or eyebrows or in the skin folds

- Patient should be managed in an intensive care settings.
- Resuscitation and supportive measures, rehydrate the patients. No oxygen as this tends to increase the toxic effects on the lungs. Give oxygen only if PaO\textsubscript{2} falls to < 60 mmHg
- Aggressive gastric lavage as soon as possible and send stomach contents for testing for paraquat
- Administer activated charcoal and/or
- Give Fuller's earth 1,000 ml stat, 200 mls every hourly till frank diarrhea with Fuller's earth seen. It may be necessary to give the Fuller's earth via a large bore Ryle's tube.
- Purgatives: Give mannitol 200 ml (20%) via Ryle's tube stat and followed by 20 ml of magnesium sulphate (MgSO\textsubscript{4}) given hourly.
- Charcoal haemoperfusion to lower plasma paraquat may be recommended.
- Give supportive / relieving treatment
- If facilities available, send for plasma paraquat level
  - Urine for paraquat daily for 3 days
  - Blood Urea and Serum Electrolytes daily
  - Liver Function Test and serum alanine transaminase (ALT) (Days 1, 5)
  - Chest X-Ray (Days 1, 7, 10)
  - Arterial blood gases
- Early endoscopy and surgical intervention may be necessary if there is evidence of esophageal perforation and mediastinitis.

6. Methanol

**Mechanism of Toxicity**

- Toxicity is seen in consumption of adulterated alcohol and denatured ethanol. Methanol is a common solvent. Ingestion of >10 ml can cause blindness and >30 ml is potentially fatal. Methanol is oxidized by alcohol dehydrogenase first to formaldehyde and then to formic acid.
- These metabolites cause the toxic manifestations and metabolic acidosis. Alcohol dehydrogenase has a much higher affinity for ethanol
and hence ethanol is used to competitively inhibit the metabolism of methanol.

Clinical Features
- Confusion, ataxia, nausea, epigastric pain, visual disturbance, pupils dilated and unresponsive to light, papillitis, severe metabolic acidosis, Kussmaul’s breathing.
- Blood levels of 500 mg/l indicate severe poisoning.

Specific Management
- Gastric lavage if less than one hours of ingestion.
- Correct acidosis with sodium bicarbonate (NaHCO₃). Large amounts may be necessary. Return of acidosis is frequent after initial dose and additional alkali may be required.
- Inhibit metabolism with ethanol:
  - Minor intoxication – oral loading dose: 1gm/kg of 20% ethanol, then 80 – 130 mg/kg/hr
  - Severe intoxication – IV ethanol loading dose of 1gm/kg BW in D5% over 30 minutes then 7 to 10 gm/hour.
  - Monitor blood ethanol concentration frequently and maintain between 1,000 – 2,000 mg/l.
  - 4-Methylpyrazole: new antidote with lesser side effects but more expensive than ethanol. Loading dose 15 mg/kg; also add pyridoxine & thiamine
- Removal of methanol and its metabolites by dialysis.
  - Peritoneal dialysis is less effective. Add 1 – 2 gm of ethanol to each liter of peritoneal dialysate
  - Haemodialysis is more effective. Indicated if plasma methanol level is > 500 mg/l, severe acidosis, visual disturbance, or when > 30 ml of methanol was ingested.

7. Warfarin

Mechanism of Toxicity
- Warfarin depress the hepatic Vitamin K dependent synthesis of substances essential to blood clotting such as prothrombin (Factor II), Factor VII, IX and X. The duration of anticoagulant effect is up to 7 days.
- Locally available as warfarin, dicussat and used as rodenticides

Clinical Features
- Patient can be presented with evidence of an anticoagulated state with nose bleed, bleeding gums, haematuria, malaena, ecchymoses or haematemesis.
- Investigation reveal increase prothrombin time (PT).

Specific Management
- Decontamination
Prevent further exposure by removing all contaminated clothing (shoes, cloths, socks and jewellaries), kept the clothing in plastic bag.

Wash with soap and water thoroughly.

If involves the eyes, wash with water copiously up to 15 to 20 minutes until no solid bits of chemical on the lashes or eyebrows or in the skin folds.

- Resuscitation and supportive measures which include ensuring patent airways, adequate ventilation and circulation. Provide fluid for volume replacement to avoid circulatory compromised.
- Perform gastric lavage if ingestion occurs within one hour.
- Administer activated charcoal with dose of 1g/kg or 50 g on average adult size of 70 kg.
- Administer Vitamin K to protect against anticoagulant effect of warfarin.
- Monitor coagulation profile (INR) and look for signs of bleeding. If bleeding, give FFP.
- Patient should be admitted until the coagulation profile has normalized.

8. Petroleum distillate poisoning /Hydrocarbons

Common poisons
- Diesel
- Kerosene
- Thinner

Mechanism of Toxicity
- These are central nervous system depressants. Pulmonary damage is manifested as pulmonary oedema or pneumonitis.
- Poisoning is via inhalation or ingestion or aspiration.
- Inhalation may lead to profound drowsiness or coma. Death is from respiratory depression.
- Oral ingestion causes irritation of mucous membranes. When large amounts are ingested, coma with respiratory depression may occur.

Clinical Features
- Patient may initially have mild symptoms and then develop difficulty in breathing, bronchospasm, wheezing, rales and fever within 6 hours. Alteration in mental state is a sign of hypoxia or hypercapnia.
- Vomiting or lavage may lead to aspiration. The low surface tension of petroleum distillate allows minute amounts to spread widely throughout the lungs, producing pulmonary oedema or pneumonitis. Pulmonary damage may also arise from absorption of ingested petroleum distillates.
- Kerosene is 1,000 times more toxic if aspirated.

Specific Management
- Be extremely careful to prevent aspiration. Coughing is a bad sign indicating aspiration.
- Give Oxygen and ensure patent airway.
• Early definitive airway (intubation) in patient with severe aspiration
• No role for steroids.
• Prophylactic antibiotics are not indicated.
• Supportive treatment if comatose or having respiratory depression.
• Common complications of aggressive decontamination after ingestion of benign hydrocarbon is aspiration, which convert non toxic ingestion into toxic aspiration.

9. Carbon monoxide

Mechanism of Toxicity
• Carbon monoxide is a clear colourless and odorless gas. The mechanisms of carbon monoxide (CO) toxicities are not fully understood. The binding affinity of CO to haemoglobin is 220 times than that of oxygen, therefore impairing the delivery of oxygen to the tissue. This will cause profound tissue hypoxia. CO also binds to myoglobin, resulting in worsening of the hypoxia in cardiac muscle, and to the mitochondrial cytochrome oxydase, causing impairment of ATP production.
• CO poisoning causes platelet and neutrophil activation, free radical formation, and lipid peroxidation in brain, heart and other tissue.

Clinical Features
• Acute exposure leads to multisystem signs and symptoms.
• CNS: headache, peripheral neuropathy, altered mental status, coma, seizure, cerebral oedema, personality changes, ataxia and memory impairment. Sign of neurological injury may persist from time of poisoning till after 2 to 21 days.
• Respiratory: Dyspnoea dan hyperpnoea, bronchopneumonia and non cardiogenic pulmonaty oedema
• Cardiovascular: Ventricular arrhythmias, ST elevation myocardial infarction (STEMI), heart block, ST segment changes, cardiac arrest.
• Renal: signs of acute renal failure such as oligouria, proteinuria, myoglobinuria and haematuria
• Haematological: carboxyhaemoglobinuria, polycythaemia, haemolytic anaemia, disseminated intravascular coagulation (DIC)
• Musculoskeletal: rhabdomyolysis, myonecrosis and compartment syndrome
• Dermatological: cyanosis or cherry red discoloration

Specific Management
• Evaluate and support the airway and perform definitive airway measure by endotracheal intubation if ventilation is compromised
• Administer 100% oxygen via tight fitting high flow non re-breathing face mask. Oxygen therapy speed the elimination of CO from the body. Without therapy, the elimination half life of CO is 4 to 5 hours. Administration of 100% Oxygen decreases the half life to approximately 1 hour.
• Monitor vital signs includes blood pressure, pulse rate, respiratory rate, pulse oxymetry, temperature every 10 to 15 minutes
• Perform electrocardiography (ECG) and do continuous monitoring
• Consider sodium bicarbonate infusion if evidence of significant metabolic acidosis (arterial pH less than 7.1)
• The elimination half-life of CO further decreases to 20 minutes in a hyperbaric oxygen (HBO₂) chamber at 2.5 atmosphere absolute pressure.
• Refer patient for Hyperbaric therapy as soon as possible or within 24 hours for the following patients (please refer to local protocols);
  ➢ All patient with syncope, neurological abnormalities, and cardiac abnormalities with elevated COHb (Carboxyhaemoglobin)
  ➢ All patient with COHb more than 25%
  ➢ Pregnant patients with COHb more than 10%
  ➢ Evidence of myocardial ischaemia
  ➢ Worsening symptoms despite Oxygen therapy
  ➢ Symptoms persist after 4 hours of therapy
  ➢ Neonate
• Asymptomatic patients are unlikely to develop complications and can be discharged from Emergency Department. However, patient should seek treatment if there is respiratory, cardiovascular or neurological symptoms. Patient should be asked to refrain from smoking for at least 72 hours. If in doubt, admit patient for observation.

10. Sedative hypnotics
A broad range of drugs fall under this group. Common ones are benzodiazepines and barbiturates. In general, the toxic effect is depression of the central nervous system.

Clinical manifestations
• Nystamus, ataxia, dysarthria, somnolence, respiratory depression, hypotension, hypothermia and coma.
• Absence of brain stem reflexes indicate severe poisoning.

General measures
• Ensure patent airway and perform definitive airway measures with ventilator support if adequate oxygen saturation cannot be maintained with 100% oxygen.
• Gastric lavage if ingestion occur within one hour; followed by activated charcoal if ingestion occurs within 4 hours. Cathartics may be considered.
• Coma nursing
• Arterial blood gases monitoring to assess adequacy of respiration.
• Treat hypotension with crystalloids infusion and inotropes such as dopamine at dose of 0.5–25 μg/kg/minute.
• Prevent hypothermia
• If Benzodiazepines poisoning is suspected, administer IV flumazenil in a dose of 0.2 mg over 15-30 seconds and repeated after one minute
interval until a total of 2 mg is administered. Flumazenil have short half life therefore repeated doses may be required. However, flumazenil is contraindicated if:

- There is concomitant ingestion of tricyclic antidepressant overdose, because reversal of benzodiazepine effects may precipitate seizures.
- Flumazenil may precipitate an acute withdrawal reaction,
- Manifested by seizures, autonomic instability and arrhythmias in patients who may addicted to benzodiazepines.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal half life (h)</th>
<th>Clinical presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloral Hydrate</td>
<td>4 – 8</td>
<td>CNS depression, Gastritis, Arrhythmias</td>
<td>Supportive care for cardiorespiratory function</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.5 – 3</td>
<td>Respiratory depression and severe poisoning is uncommon unless taken with other drugs</td>
<td>Supportive care and Flumazenil as antidote.</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>7 – 28</td>
<td></td>
<td>Caution for withdrawal symptoms for abrupt cessation of benzodiazepines</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>18 – 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>6 – 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>20 – 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>60 - 100</td>
<td>Mild toxicity cause drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability and impaired cognition. Severe intoxication leads to coma and respiratory arrest.</td>
<td>Supportive care especially to cardiovascular and respiratory. Multidoses of activated charcoal will hasten elimination, given as 50gm in water. Repeat if necessary. Consider haemodialysis in severe poisoning when involve renal or cardiac failure, acid base or electrolytes abnormalities</td>
</tr>
</tbody>
</table>

Table 10.4 showing the different types of sedative hypnotics poisoning and the appropriate management.
11. Caustics

- Caustic agents are diverse group of substance that have the potential to cause tissue burns on contact with gastrointestinal tract, upper and lower airways, eye, and skin.
- List of agents capable causing chemical injury include alkalis such as Sodium Hydroxide (NaOH), Potassium Hydroxide (KOH), Ammonia (NH₃), acids such as Hydrogen Chloride (HCL), Hydrogen Sulphate (H₂SO₄) and other chemical such as phenol, formaldehyde, iodine, and hydrogen peroxide. These agents frequently used as part of the formulation for household cleaning product such as toilet bowl cleaner, floor detergents, rust remover, drain cleaner, oven cleaner, dishwashing detergents and many more.

Mechanism of Toxicity

- The effect of the caustic can be minimal to invariably fatal, based on the agent, the amount ingested, the concentrations of the agents, the duration of exposure and the route of exposure, and whether there is presence or absence of food in the stomach. When strong acid in contact with the epithelium, a coagulum or eschar is created, limiting further spread of the acid.
- Alkaline contact causes liquefaction necrosis, fat saponification and protein disruption, allowing further penetrance of alkali into the tissue. Caustic injury is categorized as follows, based on appearance at endoscopy:
  - First Degree - oedema and hyperaemia and do not progress into stricture
  - Second Degree - superficial ulcers, whitish membranes, exudates, friable tissue and haemorrhage. Up to 75% will develop stricture especially if involve circumferential burn at the oesophagus.
  - Third Degree - full thickness burns and 90% result in stricture.

Clinical Features

- Clinical features are due to direct contact to the victims mucosal area. Small ingestions of potent ot highly concentrated caustic agents can be as serious as larger ingestions. In severe cases it involves symptoms of upper and lower airway compromise such as coughing, wheezing, throat pain, stridor and dysphonia. This is due to an airway irritations and oedema.
- Also look for evidence for direct burns to the face, lips and oral cavity. Victims also may complain of abdominal pain and this may be due to hollow viscus perforation or extension of the burn injury to the adjoining visceral areas.
- Signs of systemic toxicity includes evidence of haemodynamic instability such as hypotension, tachycardia, tachypnoea, fever and acidosis.

Specific Management
• The goal of treatment is to identify the extend and severity of the burn injury.
• Asymptomatic patient can be observe in the Emergency Department for up to 24 hours and referral to surgical or gastroenterology team for possible endoscopy.
• Symptomatic patient should be admitted to high dependency or intensive care unit for close monitoring and further management.
• The utmost priority is to ensure adequate oxygenation and ventilation by ensuring a patent airway by either high flow mask with 100% oxygen or definitive airways by endotracheal intubations. Intubation should be carried out EARLY if significant exposure is suspected.
• Insert large bore intravenous cannula with fluids resuscitation to ensure adequate circulation.
• Keep patient nil by mouth except in alert patients who is not vomiting, milk and small volume of water can be given few minutes after ingestion however later dilution is not indicated as burn injury occurs immediately after ingestion
• Activated charcoal and gastric lavage is NOT indicated and has no role in this type of poisoning.
• Emergent investigations should be carried out;
  ➢ Arterial blood gasous
  ➢ Full Blood Count
  ➢ Chest X ray
  ➢ Abdominal X ray

• Referral to surgical team is indicated for further investigations in view of endoscopy for symptomatic patient and also for patient who have evidence of peritonitis.
• Role of corticosteroids is controversial and generally not recommended.
• Role of prophylactic antibiotic also is controversial as it may mask evidence of impending perforation.
• IF exposure occur to the eyes, immediate and aggressive lavage with at least 2 liters of Normal Saline per eye is indicated except in frank perforation, then followed by urgent referral to ophthalmologic team.

References
Chapter 11
Poisonous snake bites

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2. Specific snake bites
   A. Elapidae (Cobra, Kraits and Coral Snakes)
   B. Hydrophidae (Sea Snakes)
   C. Viperidae (Pit Viper)
3. Specific treatment of venomous snake bites

1. Introduction - Venomous snake bite

- Snake bites remains an important cause of mortality and morbidity in developing countries. It is estimated that up to 125,000 people annually die of snake bite worldwide.
- The average reported incidence rate for snake bite in Peninsular Malaysia was 50 over 100,000 population.
- There are 141 species of land and sea snakes in Peninsular Malaysia. Of these, 18 species of land and all 22 species of sea snakes are venomous. There are 3 main types of venomous snakes in Malaysia
  A. Elapidae (Cobras)
  B. Hydrophidae (Sea Snakes)
  C. Viperidae (Vipers)

2. Specific snake bites

A. Elapidae (Cobra, Kraits and Coral Snakes)
   - Elapids are snakes with short, fixed front fangs 3-5mm long in adults. Cobra, kraits, coral and sea snakes are the main species in this family.
   - The cobra is the commonest species that bites man. Cobra bites are painful and accompanied by slow local swelling, necrosis and later wet gangrene. There is no or minimal pain with other elapids.
   - Constitutional symptoms are more prominent than local. The venom is predominantly neurotoxic.
   - Systemic symptoms involve the neuromuscular system affecting mainly the muscles of the eyes (ptosis), tongue, difficulties in swallowing (dysphagia), throat and chest leading to respiratory failure. Cardiovascular depression is seen in severe poisoning.
   - Observe and look for ptosis, paralysis of upward gaze, total external ophthamoplegia, movements of pharynx, tongue, speech and respiratory muscles. Onset may be delayed for up to 10 hours. In severe poisoning, the patient is unable to speak, cough, swallow, protrude his tongue or move the jaw.
   - Suspect severe poisoning if neurotoxic signs are present within 1 hour.

B. Hydrophidae (Sea Snakes)
   - All sea snakes in Malaysia are poisonous. Sea snakes are recognizable by having flat tail like a blade.
There is little pain and no oedema at the site of bite. The effect is exclusively systemic. The venom is both myotoxic and neurotoxic. Systemic effects include injury to skeletal muscle is predominant and is characterized by generalized muscle pain, weakness and myoglobinuria. Tendon reflexes may be depressed. Neurotoxic effect also include ptosis, trismus and blurring of vision. Respiratory failure may occur within a few hours to 60 hours after the bite. Patients die from acute renal failure or hyperkalaemic cardiac arrest. Suspect severe poisoning if myoglobinuria is seen within 2 hours.

C. Viperidae (Pit Viper)
- The pit viper has a triangular shaped head and long retractable fangs. The commonest species found in Malaysia is Malayan pit viper.
- The effect of the venom are mainly cytotoxic and haematotoxic. Predominantly vasculotoxic with rapid swelling of the bitten part followed by dry gangrene. Early shock is common and is the main cause of death.
- Haemorrhage into vital organs is another cause of death. Bleeding may be delayed for up to several days. The bleeding is related to the coagulation defect and also to direct endothelial damage by ‘hemorrhaging’. The blood clots poorly because of absent or very little fibrinogen.
- Minimal venom is sufficient to cause complete consumption of fibrinogen, hence poor clotting provides a sensitive marker of systemic poisoning.
- Observe for abnormal bleeding from bites, injection sites, sputum, gums, vomit, stools, bruising, or a positive Hess test. Monitor bleeding time, coagulation time, prothrombin time and platelet count at least 4 hourly.
- Suspect severe poisoning if swelling is above the knee or elbow, hypotension is present or if haemorrhagic signs develop within 1 to 2 hours.

Investigation
- Full blood count - Hb, platelets count
- Urine for haemoglobinuria or myoglobinuria
- Coagulation screen – BT, CT, PT, PTT
- Serum electrolytes, particularly the potassium levels
- ECG

Snake Venom
- Snake venom varies greatly, from species to species and among the different varieties of the same species and also even from time to time from the same snake. Proteins contribute more than 90 percent of the dry weight includes enzymes, peptides, glycoproteins and other substances.
- Not all snake bites by venomous snake result in envenoming.
- Early sign and symptoms of snake bite may be unpredictable and its depend on species of venomous snake and the amount of venom injected into the victim.
- The following table (Table 11.1) describe the accepted grading of envenomation and can be used as a guide of the dosaging of antivenom.

3. Specific treatment of venomous snake bites
Pre-hospital

- All snake bites should be considered as an emergency
- Reassure the victims, then a firm local dressing is applied over the bitten area and the rest of the limb especially for elapids bite. The limb is then immobilized with a splint. Minimize movement of the limb. DO NOT INCISE the wound.
- Snake venom is absorbed mainly via lymphatics and the use of a tourniquet is controversial and may cause further harm. Keep the limb below the level of the heart.
- Transfer the victims to the nearest appropriate hospitals or health care facilities. Please do not attempt to kill the snake, as this may be very dangerous.

Hospital

- Monitor the patient cardiac status.
- Provide analgesics and intravenous fluids.
- GXM blood and blood components such as fresh frozen plasma.
- Observation – done either every 30 minutes or hourly, depending on severity. Use the snake bite chart (Table 11.2) for monitoring.
- Monitor the coagulation profile regularly, at least every 4 hours.
- Monitor urine output and serum electrolytes.
- ECG monitoring might be necessary in those with more severe grade of envenomation.
- For Viperidae bites, regularly monitor circumference of the affected limb above and below the bite to look for signs of increasing swelling and neurovascular compromise. Fasciotomy may be required if there are signs of compartment syndrome. Local necrosis and gangrene may require orthopedic or vascular surgical consultation for debridement.
### Table 11.1 showing the grade of envenomation caused by snake bites.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1: Minimal</strong></td>
<td>Not indicated</td>
</tr>
<tr>
<td>There is minimal envenomation, and snakebite is suspected. A fang wound is usually present. Pain is moderate or throbbing and localized to the fang wound, surrounded by 1 to 5 inches of edema and erythema</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 2: Moderate</strong></td>
<td>2 - 4 vials</td>
</tr>
<tr>
<td>More severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, giddiness, and a mild elevation in temperature</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3: Severe</strong></td>
<td>5 -10 vials</td>
</tr>
<tr>
<td>Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia, hypotension, and a subnormal temperature. Laboratory abnormalities include elevated white cells count (leucocytosis), coagulopathy (abnormal aPTT, PT, fibrinogen degradation products, thrombocytopenia, increased bleeding time), deranged renal and liver function.</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4: Very severe</strong></td>
<td>10 - 15 vials or more</td>
</tr>
<tr>
<td>Sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 minutes of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face, muscle fasciculations, painful cramps, pallor, cold clammy skin.</td>
<td></td>
</tr>
<tr>
<td>Time (Hourly)</td>
<td>Elapidae (cobras)</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ptosis</td>
<td>+ : Present</td>
</tr>
<tr>
<td></td>
<td>- : Absent</td>
</tr>
<tr>
<td>Speech</td>
<td>N : Normal</td>
</tr>
<tr>
<td></td>
<td>S : Slurred</td>
</tr>
<tr>
<td>Tongue</td>
<td>N : Normal</td>
</tr>
<tr>
<td>Protrusion</td>
<td>W : Weak</td>
</tr>
<tr>
<td>Breathing</td>
<td>N : Normal</td>
</tr>
<tr>
<td></td>
<td>S : Shallow</td>
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<td></td>
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</tr>
</tbody>
</table>

Table 11.2 Snake Bite Observation Chart

Chemotherapy
- Tetanus prophylaxis is recommended.
- The value of antibiotics is unclear. Liberal use of antibiotics for prophylaxis in snake bite is not required. However bites by certain species especially Malayan pit viper are likely to be complicated by bacterial infections as the venom or fangs are often contaminated with microorganism. In this case prophylaxis antibiotic may be indicated.

Antivenom
- Antivenom is the cornerstone of treatment of venomous snake bites. Snake bites are usually defensive acts, hence the dose of venom injected is usually small.
Anti-venom is usually prepared from plasma of immunized horses. As such, there is a risk of anaphylaxis. Patients with atopy are especially vulnerable. The intravenous route is the most effective.

Antivenom is effective against systemic envenomation and to lesser degree, local envenoming. Antivenom therapy is indicated if the victim develops one or more of the following systemic symptoms and also based on the grade of envenomation *(see Table 11.1)*.

- Hypotension, shock, abnormal ECG or other sign of cardiovascular toxicity
- Ptosis, ophthalmoplegia, respiratory paralysis or other signs of neurotoxicity
- Hemostatic abnormalities such as spontaneous bleeding, coagulopathy or thrombocytopenia
- Generalized rhabdomyolysis
- Evidence of severe intravascular haemolysis
- Evidence of acute renal failure for example oligouria, uraemia or impaired renal function test.
- Supporting laboratory evidence of systemic envenoming: elevated serum CPK and aminotransferase, peripheral leukocytosis, haemoglobinuria, myoglobinuria, hypoxia and acidosis.

Local envenoming that also warrants the uses of anti venom are;

- Swelling involving more than half of the bitten limb
- Swelling after bites on digit or other tight fascial compartment (compartment syndrome).
- Rapid progression of swelling.

Antivenom therapy must be given as soon as the criteria of severe envenomation are fulfilled. To be specific, antivenom must be specific to the species of the snake responsible for the bite, therefore monovalent antivenom is ideal if the the biting species is known, however polyvalent is more popular as in majority of cases the snakes cannot be identified.

**Dosage and Routes of Administration Antivenom**

- Both polyvalent and specific (monovalent) anti-venom are available, though the specific anti-venom is preferable. The doses of anti-venom depend on the make and type. The effective dose also depends on the potency of the anti-venom.
- Anti-venom must be given in adequate doses. Inadequate anti-venom can result in envenomation persisting.
- The dose of antivenom has to be repeated if signs/symptoms recur or persist.
- Successful or adequate anti-venom treatment will be indicated by stabilization of vital signs and cessation or reversal of systemic envenomation.
- If clinical improvement is not distinct within an hour, the dose is repeated. The dose for children is the same as adult. There is NO maximum dose of antivenom.
- *Table 11.3* provides some guide on the initial dose recommended to be administered based on types of the antivenom;
<table>
<thead>
<tr>
<th>Species (Latin)</th>
<th>English</th>
<th>Type</th>
<th>Approximate Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. rhodostoma</td>
<td>Malayan Pit Viper</td>
<td>Monovalent</td>
<td>100 ml</td>
</tr>
<tr>
<td>N. naja</td>
<td>Common Cobra</td>
<td>Polyvalent</td>
<td>50 ml (local) 100 ml (systemic)</td>
</tr>
<tr>
<td>O. hannah</td>
<td>King Cobra</td>
<td>Monovalent</td>
<td>50 ml (local) 100 ml (systemic)</td>
</tr>
<tr>
<td>T. albolabris</td>
<td>Green Pit Viper</td>
<td>Monovalent</td>
<td>100 ml (local)</td>
</tr>
<tr>
<td>E. schistosa</td>
<td>Common Sea Snake</td>
<td>Polyvalent</td>
<td>1000 unit</td>
</tr>
</tbody>
</table>

Table 11.3 showing the type of antivenom and approximate initial dose

- Local administration of the antivenom at the site of the bite is not recommended as it is extremely painful and may increase intra compartmental pressure.
- The antivenom is diluted with normal saline or sterile water. Reconstitute antivenom can be given either slow intravenous push or diluted in isotonic fluid and administered over 1 hour. Reconstituted antivenom should be used immediately.
- Patient must be carefully observed for allergic or anaphylactic reactions. If there are no reactions, the antivenom is infused over 30 minutes to 1 hour. The infusion should be administered under close monitoring of cardiac function and vital signs.
- Skin tests for sensitivity are NOT recommended. Adrenaline, hydrocortisone and antihistamine solutions must be at hand for treatment of anaphylaxis.
- Anti venom must be readily available when required once diagnosis a poisonous snake bite being made. Antivenom is produced either liquid form or freeze dried. Liquid antivenom is very unstable at room temperature and must be stored in a dark, cool place with temperature 2-8 degree Celcius. Anti-venoms have a limited shelf life and its potency may decrease with time.

**Adverse Reactions to Antivenom Therapy**

- Early anaphylactic reaction - this may develop within 10 to 180 minutes of starting intravenous antivenom. Symptoms include itching, urticaria, cough, nausea, vomiting, fever and palpitations. A small percentage may develop severe anaphylactic shock which characterized by hypotension, bronchospasm and angioedema.
• Pyrogenic reaction - this may occur within 1 to 2 hours of treatment result from contamination of antivenom with endotoxin like compounds. Symptoms include fever, rigor and vasodilatation with febrile convulsion can occur in children.

• Late serum sickness reactions - this may occur 5 to 10 days after treatment. Clinical features includes urticaria, fever, athralgia, periarticular swellings occur, lymphadenopathy and proteinuria. Patient can be started on a 5 days course of antihistamine and in severe cases or those fail to respond in 24 to 48 hours, oral prednisolone for 5 to 7 days is indicated.

• In a patient suspected to be sensitive to horse serum or sheep serum:
  → Give IV antihistamine (10 mg IV Chlorpheniramine)
  → Give S.C adrenaline 0.5 mg (0.5 ml of 1:1000)
  → Give the antivenom very slowly and observe the patient carefully. Should any features of allergy appear, stop the infusion and institute further treatment with adrenaline.

• If the severity of the snake bite makes anti-venom mandatory, given further cover with steroids, adrenaline and antihistamine. Give the antivenom in small and divided doses under careful observation.

Adjunct to Antivenom Therapy

• Respiratory support
  → Maintaining a patent airway with definitive measure using rapid sequence induction, with endotracheal tube is the priority in patient with bulbar and respiratory paralysis. Mechanical ventilation should be initiated followed by intensive care support. All the effect of neurotoxins is eventually reversible.
  → Acetylcholinesterase inhibitors such as Neostigmine may have a beneficial effect on neurotoxic symptoms. A ‘tensilon’ test using 10 mg edrophonium chloride after atropine 0.6 mg is recommended in all severe neurotoxic envenoming. Victim with unequivocal response should be maintained on Neostigmine 50-100 µg/kg, and Atropine 4 hourly, or by continuous infusion.

• Fluid therapy and blood products
  → Severe envenomation may result in hypovolaemic shock. Adequate amount of volume replacement which includes crystalloids, colloids and blood may be required to correct the volume deficit.

• Wound care
  → The wound should be cleansed and the effected limb immobilized. Do not disturb the blisters, it will heal completely if no underlying necrosis.
  → If necrosis develops, referral to orthopaedic surgeon should be made for possible surgical debridement and skin grafting. Local swelling usually will resolve after adequate dose of antivenom.

• Compartment Syndrome
  → This is one the complication that may occur due to bite by the Malayan pit viper. Increased intra compartmental pressure within the tight fascial compartment due to tissue oedema leading to
ischaemia and subsequently necrosis. The main signs include severe pain, swelling, muscle weakness and hypoeasthesia.

→ Orthopaedic referral should be made for the potential surgical intervention (fasciotomy). Fasciotomy should be done after correction of blood coagulation. This complication can be avoided if antivenom is given early.

Reference
### Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EYE OPENING</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 = Eyes open, not necessarily aware</td>
</tr>
<tr>
<td>To pain</td>
<td>2 = Pain from sternal/limb/craniotomy pressure</td>
</tr>
<tr>
<td>To speech</td>
<td>3 = Non-specific response, not necessarily to command</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4 = Eyes open, not necessarily aware</td>
</tr>
<tr>
<td><strong>MOTOR RESPONSE</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 = To any pain; limbs remain flaccid</td>
</tr>
<tr>
<td>Extension</td>
<td>2 = Shoulder adducted and shoulder and forearm externally rotated</td>
</tr>
<tr>
<td>Flexor response</td>
<td>3 = Withdrawal response or assumption of flaccid posture</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>4 = Arm withdraws to pain, shoulder abducts</td>
</tr>
<tr>
<td>Localizes pain</td>
<td>5 = Arm attempts to remove supra-orbital/chest pressure</td>
</tr>
<tr>
<td>Obey's commands</td>
<td>6 = Follows simple commands</td>
</tr>
<tr>
<td><strong>VERBAL RESPONSE</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 = No verbalization of any type</td>
</tr>
<tr>
<td>Incomprehensible</td>
<td>2 = Mourns/groans, no speech</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>3 = Intelligible, no sustained sentences</td>
</tr>
<tr>
<td>Confused</td>
<td>4 = Converses but confused, disoriented</td>
</tr>
<tr>
<td>Oriented</td>
<td>5 = Converses and oriented</td>
</tr>
</tbody>
</table>

*The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person).*

**TOTAL (3–15): _____**

### Scoring for Glasgow Coma Scale

### Reference

**Chapter 7 Renal emergencies**

Chapter 10 Poisoning


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