Clinical Pathways in Emergency Medicine

Volume I

Suresh S. David
Editor

Springer

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ISBN 978-81-322-2708-3 ISBN 978-81-322-2710-6 (eBook)
DOI 10.1007/978-81-322-2710-6

Library of Congress Control Number: 2016931333

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer (India) Pvt. Ltd

Preface

In the history of humankind, Medicine has never been more exciting and challenging than in the twenty-first century. One of the great challenges of being a contemporary academic clinician is to find ways to correlate pertinent Basic Sciences to clinical application, at the bedside. When I set out to prepare *Clinical Pathways in Emergency Medicine*, it evoked a thought for contemplation. 'Do we need one more book in the specialty of Emergency Medicine?' That helped to harness an unprecedented approach: from the perspective of a nascent, yet inquisitive emergency physician who is keen to understand the rationale of occurrence, manifestation, and management of acute clinical conditions. And this book differs significantly by providing an algorithm at the end of each chapter, which, at a glance, provides a roadmap for the journey ahead.

Clinical Pathways in Emergency Medicine is an international congregation of contributors, who have offered their expertise which has immensely flavored the global approach to Emergency Medicine. The authors include a remarkable blend of colleagues, friends, former students, and new stars on the horizon of Emergency Medicine. A multi-author manuscript of this nature cannot be delivered without the dedication exhibited by them. In addition to being luminaries from around the globe, they are among the most progressive clinicians in various sub-specialties of Emergency Medicine. And I could not have wished for a better bunch of Section Editors, who superbly orchestrated the creation and revision of manuscripts. Each one of them is an enviable embodiment of clinical excellence.

Sound clinical experience, coupled with knowledge, based on authoritative books and peer-reviewed publications, remains the foundation, on which clinical management needs to be built. In my three decades of clinical practice, I have been humbled multiple times, by the way in which anecdotal experience and written literature is flouted by the human body.

Today's dogma becomes tomorrow's heresy. *Clinical Pathways in Emergency Medicine* is a compendium of contemporary evidence-based knowledge. However, no book remains perfect and a shrewd clinician knows very well that the practice of medicine, based out of a book, has its own limitations. Nevertheless, I am optimistic that this edition of the book would facilitate satiation to the hunger for knowledge among increasing numbers of aspirants in the field of Emergency Medicine.

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Prof. Suresh S. David

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Part I
Resuscitation

Chapter 1
Airway Management in ED

Venugopalan Poovathumparambil

Key Points

- Hypoxia secondary to poorly managed airway leads to increased morbidity and mortality.
- Assess the patient to determine the type of airway intervention needed based on the set of circumstances and presentation.
- It is important to be conversant in the use of various anaesthetic agents.
- Avoid hypoxaemia or hypercarbia while preparing or while intubating the patient.
- Always have a backup plan in case of a failed airway. It is important to be conversant with the airway algorithms and also have the correct equipment available.

Introduction

- Airway management is considered a core responsibility of emergency physicians as airway assessment and management is the first step in the management of any acutely unwell patient.
- Patients in extremis requiring resuscitation often have a compromised airway, usually due to decreased consciousness.
- Prompt airway management followed by adequate ventilation mitigates secondary hypoxic damage to the brain and other vital organs.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_1

- Rapid sequence intubation is a key skill for any physician working in an emergency department.
- Mismanagement of the airway can lead to catastrophic and often devastating consequences for both the patient and the providers caring for them [1].

Signs and Symptoms of a Potential Airway Problem

A conscious patient who is able to speak is deemed to have a patent airway.

Threatened Airway

- Loud noisy breathing
- Accessory muscles supported respiration
- Abdominal muscle using expiration

Airway Management

Basic Airway Management

- Clear airway of any secretions and look for foreign bodies.
- Head tilt and chin lift (not in trauma).
- Jaw thrust (in trauma cases).

To continue patency of airway that is amenable to basic airway manoeuvres, one of the two basic airway adjuncts can be used.

- Oropharyngeal airway (OPA)
  - The size an OPA by measuring the length from the angle of the mouth to the tragus of the ear. Stand at the head end of the patient. Open the mouth and insert gently behind the tongue. In adults, insert the OPA with the concave side facing the palate. Once the tip reaches the posterior end of the hard palate, turn the OPA to have the concave surface in line with the tongue. Gently push it in until it sits comfortably on the tongue. Never force the OPA. It is not indicated if the patient is gagging on the airway. Alternatively, use tongue depressor or laryngoscope blade for OPA insertion. Tolerance of an OPA indicates loss of gag reflex and becomes an indication for definitive airway management
- Nasopharyngeal airway (NPA)
  - NPA is useful in patients who are not tolerating OPA. Size an NPA by measuring the distance between the tip of the nose to the tragus. Approximate the diameter of the NPA to the patient's nostrils. Lubricate the NPA adequately

and insert by facing the bevel to the septum in order to avoid turbinate injury. Assess patency of the nose and any signs of fracture to the base of the skull (like CSF leak, Battle sign, Raccoon eye). Basal skull or midfacial fractures are only relative contraindications, and an NPA can still be used albeit with caution.

Endotracheal Intubation

It is extremely important to assess the airway prior to intubation. LEMON is a useful mnemonic to perform this assessment which can predict a difficult airway:

(i) L – Look externally
(ii) E – Examine 3-3-2
(iii) M – Mallampati score
(iv) O – Obstructions
(v) N – Neck mobility

In an emergency, where a patient has not been prepared for anaesthetic, airway can be secured with some safety by performing a rapid sequence induction (RSI) for intubation.

Seven Ps of Intubation

1. Preparation
2. Preoxygenation
3. Premedication
4. Paralysis with sedation
5. Protection and positioning
6. Placement of tube and confirmation
7. Post-intubation care

There are three axes, oral axis, pharyngeal axis and laryngeal axis, to consider for positioning of the patient during intubation Fig. 1.1.

Ideally, these three axes should be aligned. In neutral supine position, these axes are in different directions. Recently, one of the most popular methods to improve the chances of successful airway management is called the 'ramp' position. This position is to align the auditory canal with the sternum in a straight line. This 'ramp' position has been studied and validated as one of the most important steps in enhancing the chances of successful airway management [2]. The most common mistake made during intubation is 'cranking back' on the laryngoscope handle to lever the top of the blade to provide better visibility. This manoeuvre may improve glottic visualisation; however, it restricts the operator's ability to

Fig. 1.1 Patient head position for intubation

manipulate the tube by limiting the size of the oral opening and also jeopardises the teeth.

Paralysing agents facilitate intubation and are beneficial in:

1. Tight heads (head injury, ↑ ICP)
2. Tight hearts (CAD, vascular heart disease)
3. Tight lung (bronchial asthma, hyperreactive airway, COPD)
4. Tight vessels (HTN, coarctation of the aorta)

Check the following equipment for their availability and functioning before intubation:

- Suction, oxygen, BVM device and transportable ventilator
- Airway adjuncts – appropriately sized OPA and NPA

- Appropriately sized supraglottic airway devices (SGD) like laryngeal mask airway (LMA0 or iGel)
- Laryngoscope with appropriate blade available and light source checked
- Spare laryngoscope handle
- Appropriately sized ETT: cuff checked plus a size above and below
- Stylet/bougie
- Monitors including $EtCO_2$ monitor
- Drugs
  - Sedatives/anaesthetics – etomidate, midazolam, fentanyl, propofol, thiopentone and ketamine
  - Paralytics – suxamethonium, pancuronium, vecuronium, atracurium and rocuronium
- Others – atropine, lignocaine, preservative free spray 4 % or 10 %, Lubricant

It is important to wear proper personal protection equipment like gloves, plastic apron and visors. Ideally, three assistants are required in performing an RSI: one person for managing the airway, second person for applying cricoid pressure and third person for drug administration. For crash intubation, even one assistant is acceptable.

Preoxygenation

This can be achieved by using BVM device with 100 % O_2 for 3–5 min or by 100 % O_2 through eight vital capacity breaths.

Premedication

This is best remembered by the mnemonic LOAD:

- L: Lignocaine 1–1.5 mg/kg
- O: Opioid – Fentanyl 3 mcg/kg
- A: Atropine 0.02 mg/kg
- D: Defasciculating agents [1/8th of intubating dose of non-depolarising muscle relaxants prior to suxamethonium will reduce the fasciculations]

Induction and paralytic agents Agents used to sedate and obtund reflexes prior to paralysis and intubation are called 'induction' agents – midazolam, fentanyl, propofol, etomidate, ketamine, thiopentone, etc. are agents currently available (Tables 1.1, 1.2 and 1.3).

Suxamethonium is one of the best paralytic agents for emergency intubation. Rocuronium is another paralytic agent that gives equal intubating condition but within just 60 s and without any adverse effects of suxamethonium.

Table 1.1 Sedative induction agents

Agent	Dose	Induction	Duration	Benefits	Caveats
Thiopental	3–5 mg/kg IV	30–60 s	10–30 min	↓ ICP	↓ BP
Methohexital	1 mg/kg IV	<1 min	5–7 min	↓ ICP short duration	BP seizure, laryngospasm
Ketamine	1–2 mg/kg IV	1 min	5 min	Bronchodilator, 'dissociative' amnesia	↑ Secretions, ↑ ICP emergence phenomenon
Etomidate	0.3 mg/kg IV	<1 min	10–20 min	↓ ICP	Myoclonic excitation, vomiting, no analgesia
				↓ IOP, neutral BP	
Propofol	0.5–1.5 mg/kg IV	20–40 s	8–15 min	Antiemetic, anticonvulsant	Apnea, ↓ BP, no analgesia
				↓ ICP	
Fentanyl	3–8 μg/kg IV	1–2 min	20–30 min	Reversible analgesia, neutral BP	Highly variable dose ICP: variable effects, chest wall rigidity

Table 1.2 Succinylcholine

Adult dose	1.0–1.5 mg/kg
Onset	45–60 s
Duration	5–9 min
Benefits	Rapid onset, short duration
Complications	Bradyarrhythmias
	Masseter spasm
	Increased intragastric, intraocular and possibly intracranial pressure
	Malignant hyperthermia
	Hyperkalaemia
	Prolonged apnea with pseudocholinesterase deficiency
	Fasciculation-induced musculoskeletal trauma
	Histamine release
	Cardiac arrest

Table 1.3 Non-depolarising muscle relaxants

Agent	Adult intubating IV dose	Onset	Duration	Complications
Vecuronium (intermediate/long)	0.08–0.15 mg/kg	2–4 min	25–40 min	Prolonged recovery time in obese or elderly or if there is hepatorenal dysfunction
	0.15–0.28 mg/kg (high-dose protocol)		60–120 min	
Rocuronium (intermediate/long)	0.6 mg/kg	1–3 min	30–45 min	Tachycardia
Atracurium (intermediate)	0.4–0.5 mg/kg	2–3 min	25–45 min	Hypotension
				Histamine release
				Bronchospasm

Intubation

Proper laryngoscope technique is essential for successful placement of endotracheal tube (ETT). Failure to intubate is usually due to wrong or poor technique. One of the more common mistakes made during laryngoscopy is of not having adequate control of the tongue. Human tendency is to tilt the laryngoscope blade forward. It results in not only damaging the incisors but also decreasing the chances of having an unobstructed view of the larynx.

- *Straight blades*: The tip should extend underneath the epiglottis and lift it.
- *Curved blades*: The tip should extend into the vallecula with the action of upward movement on the hyoepiglottic ligament exposing the glottic opening.

Optimal External Laryngeal Manipulation (OELM)

This manoeuvre is also known as backward, upward, rightward pressure (BURP) and was first described in 1993 by R. L. Knill [3]. The primary aim is to bring the larynx into view where the glottic opening is located too anteriorly or to the left both of which can impede the view (Fig. 1.2).

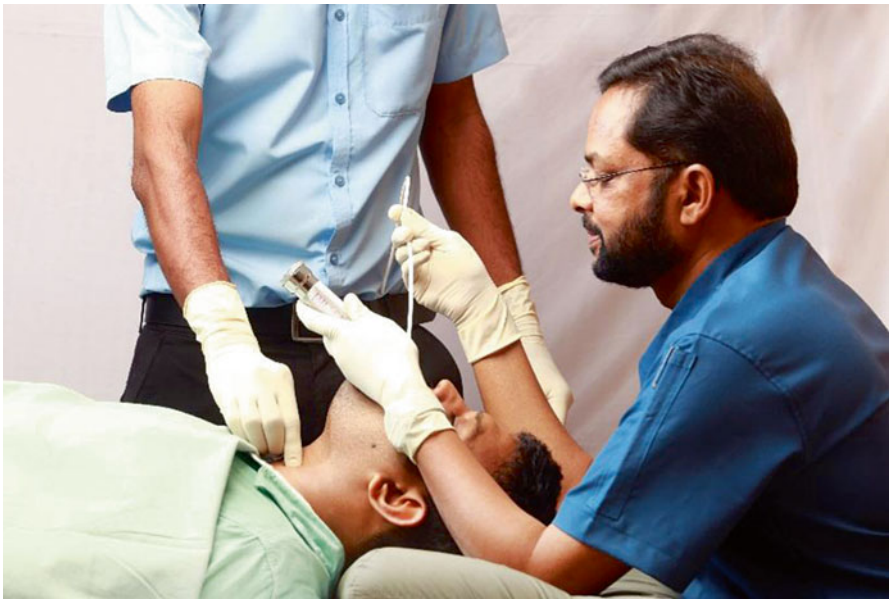


Fig. 1.2 Optimal external laryngeal manipulation (OELM)

Two methods have been described:

1. The assistant should know the principle and place pressure on the thyroid cartilage (upwards and to the right).
2. The person performing the laryngoscopy should guide the assistant into the optimal direction and with a degree of pressure that yields the best glottic view.

It is important to note that BURP manoeuvre is not the same as cricoid pressure. Cricoid pressure is applied usually during RSI, where the patient has not been fasted prior to intubation. The usefulness of cricoid pressure during intubation is questionable [4].

Cricoid Pressure

Cricoid pressure is a direct posterior pressure applied over the cricoid ring, by which the oesophagus will be occluded between the cricoid cartilage and vertebral column to prevent regurgitation and aspiration of gastric contents.

Confirmation of Tube Position

Confirmation of a properly placed tube is as important as intubation. A wrongly placed tube in the oesophagus will kill the patient within minutes. An endobronchial intubation will cause hypoxia and contralateral lung collapse.

Primary Confirmation of Tube

1. Intubation under direct vision
2. Chest movement
3. Five-point auscultation
4. Bag compliance
5. Fogging in the tube

All primary confirmation methods are not absolute and sometimes misleading.

Secondary Confirmations

1. $ETCO_2$ – All intubations should be confirmed by $ETCO_2$. This is now considered as a gold standard.

2. X-ray chest – Though this cannot rule out oesophageal intubation, it helps confirm endobronchial intubation.
3. SPO_2 – This is useful to detect misplaced tube in the late phase only.
4. Oesophageal tube detection device [EDD] – This helps to rule out oesophageal tube placement.
5. Ultrasound – This modality can also be used to help confirm correct tube placement.
6. Fibre-optic laryngoscopy and bronchoscopy – These are absolute ways to confirm tube position.

Post-intubation Care

Once the correct tube placement is confirmed, secure the tube to prevent tube migration or accidental extubation. The most common method is with adhesive tape; however, in individuals who have excessive secretions or have full beards, a circumferential tape around the neck has been recommended. Various products available commercially that combine the features of adhesive and nonadhesive methods are available. If the patient is in a hard C-collar, tie ETT over the collar. Manually ventilate patient to achieve $EtCO_2$ of 35–40 mmHg. Give post-intubation sedation for tube tolerance as required. Continue comprehensive monitoring including $ETCO_2$.

Standard timeline for rapid sequence intubation	
T – 10 min	Prepare
T – 5 min	Preoxygenate
T – 3 min	Pretreat
T = 0	Paralysis with induction
T + 30 s	Protection
T + 45 s	Placement
T + 90 s	Post-intubation management

Plan B

If plan A fails, rapidly move to alternate plans. Plan B must be a difficult airway plan.

Difficult Airway

Difficult airway is not just synonymous with difficulty with laryngoscopy and endotracheal intubation but rather is a continuum of degrees of difficulty with:

- Bag mask ventilation (BMV)
- Conventional direct laryngoscopy/intubation (DL)
- Video laryngoscopy Intubation
- Supraglottic airway placement
- Surgical (invasive) airway access.

The difficulty may be provider dependent, situation dependent, patient dependent, equipment and/or device dependent or a combination of these factors.

The '*can't ventilate and can't intubate*' situation is the most difficult and disastrous in airway management.

Can't Ventilate Situation: Plan B

- Change BMV unit.
- Use OPA and NPA.
- Use two-hand ventilation.
- Use two-person ventilation technique.
- Use gauze around the mouth – useful in oedematous patient.
- Use two pillows or remove pillow.
- Use ramp position.

Can't Intubate: Plan B

- Use BURP.
- Release cricoids.
- Release C-collar and change to manual in-line stabilisation.
- Use two pillows, no pillow or pillow under the shoulder.
- Use ramp position and align external auditory canal and sternal angle in the same line.
- Change laryngoscope blade to the next size.
- Change Macintosh to Miller blade or use McCoy laryngoscope blade.
- Use SGD, Combitube or King's airway.
- Use stylet- or bougie-assisted intubation.
- Use video laryngoscope.

Always do call for expert help.
Switch to plan C.

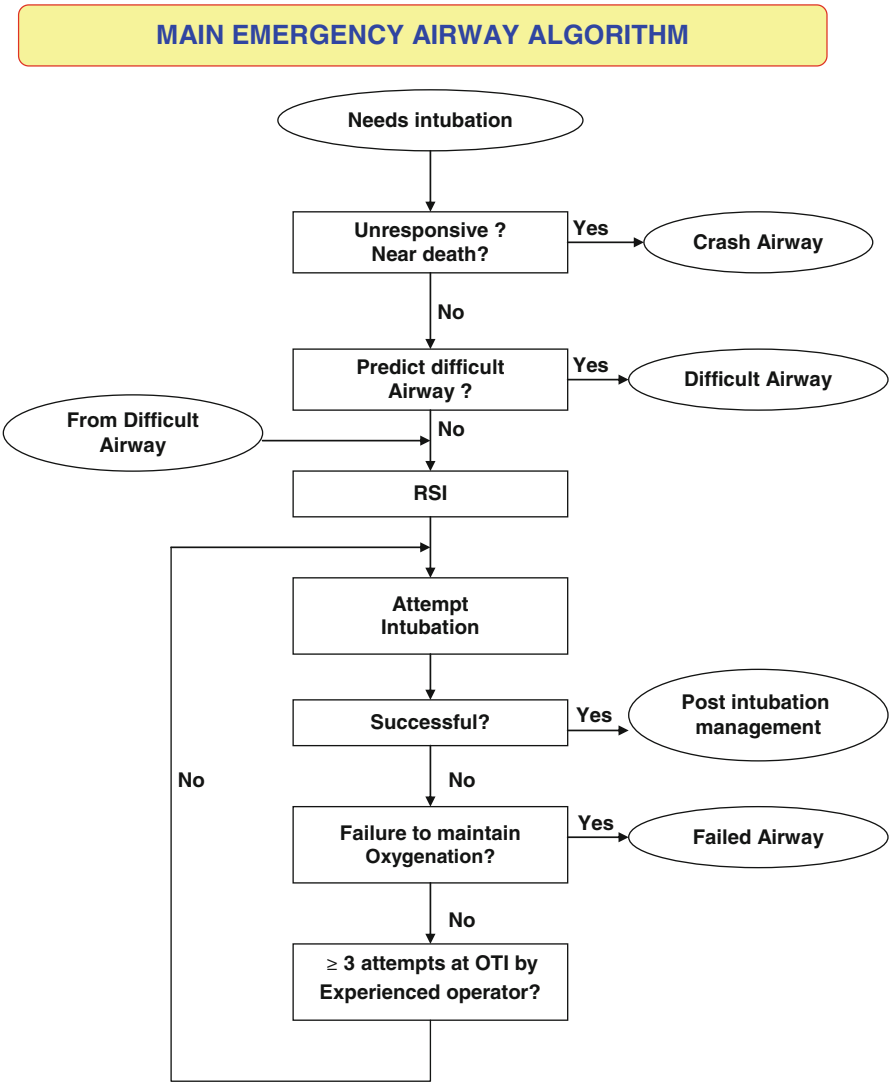
Plan C

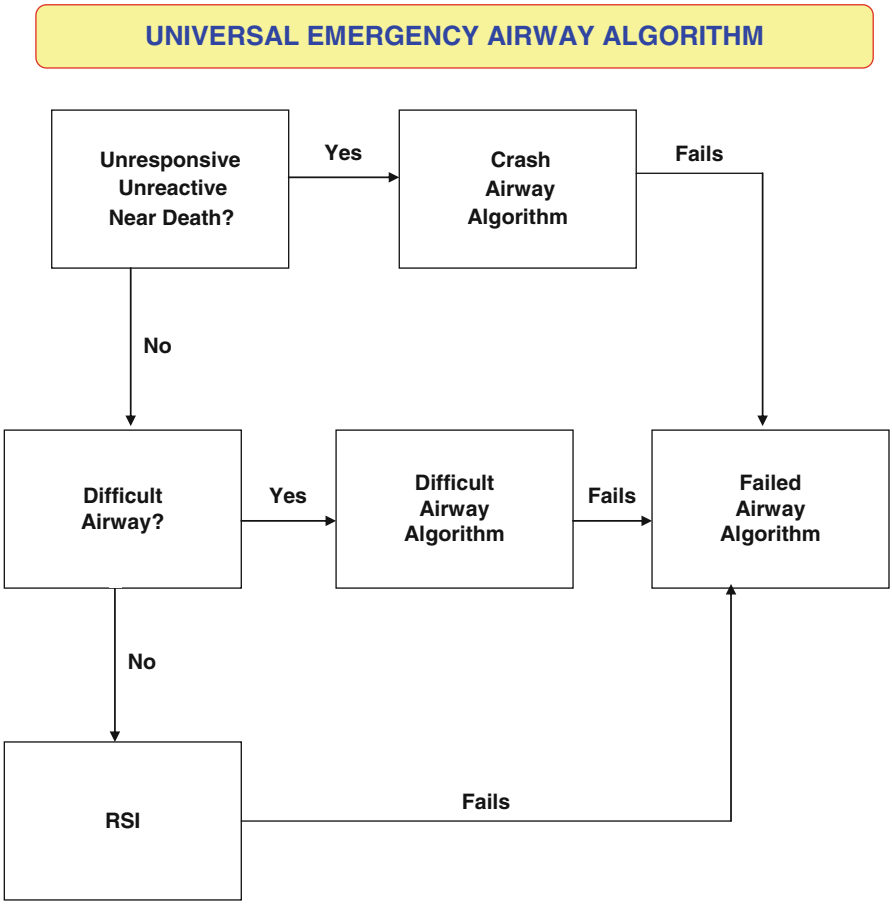
Urgent surgical airway:

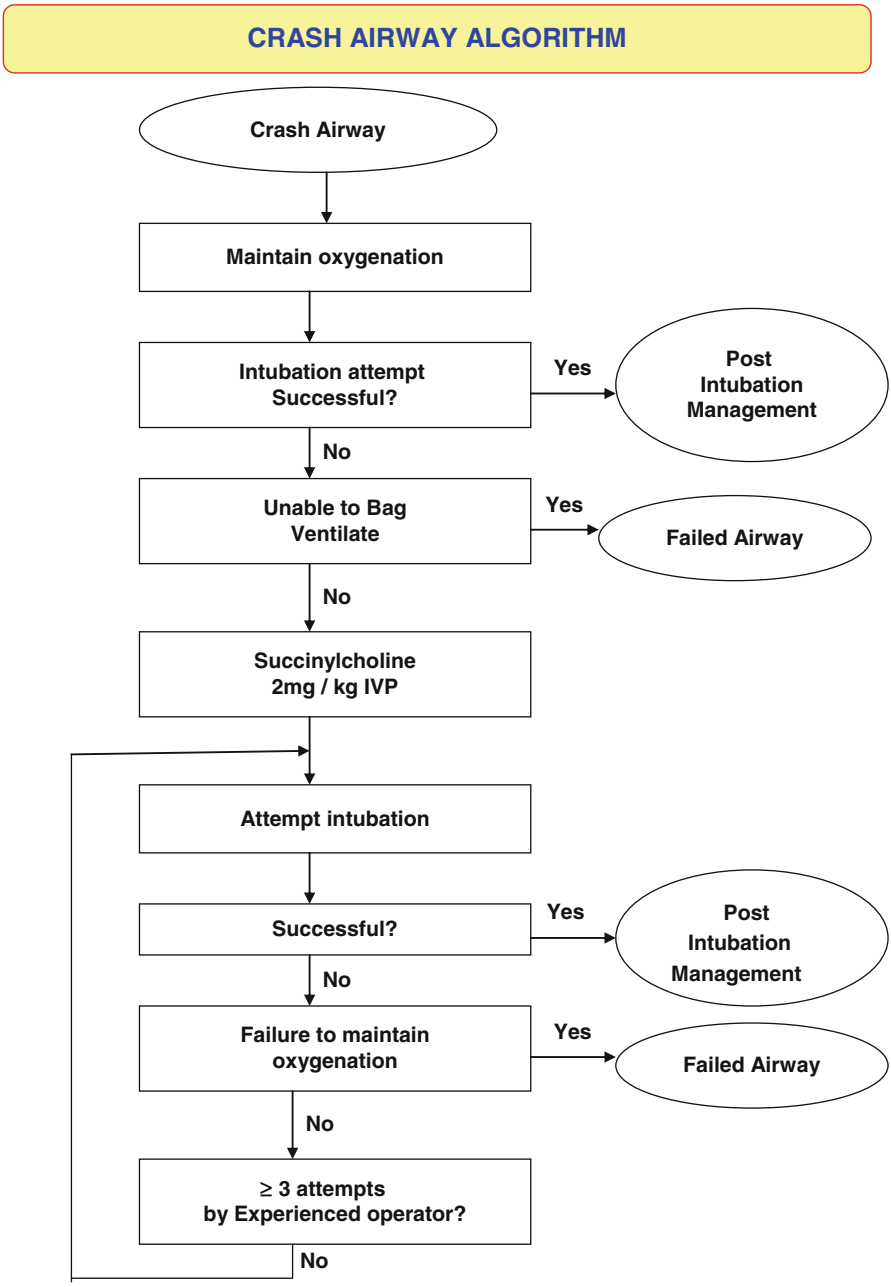
- Needle cricothyrotomy
- Surgical cricothyrotomy

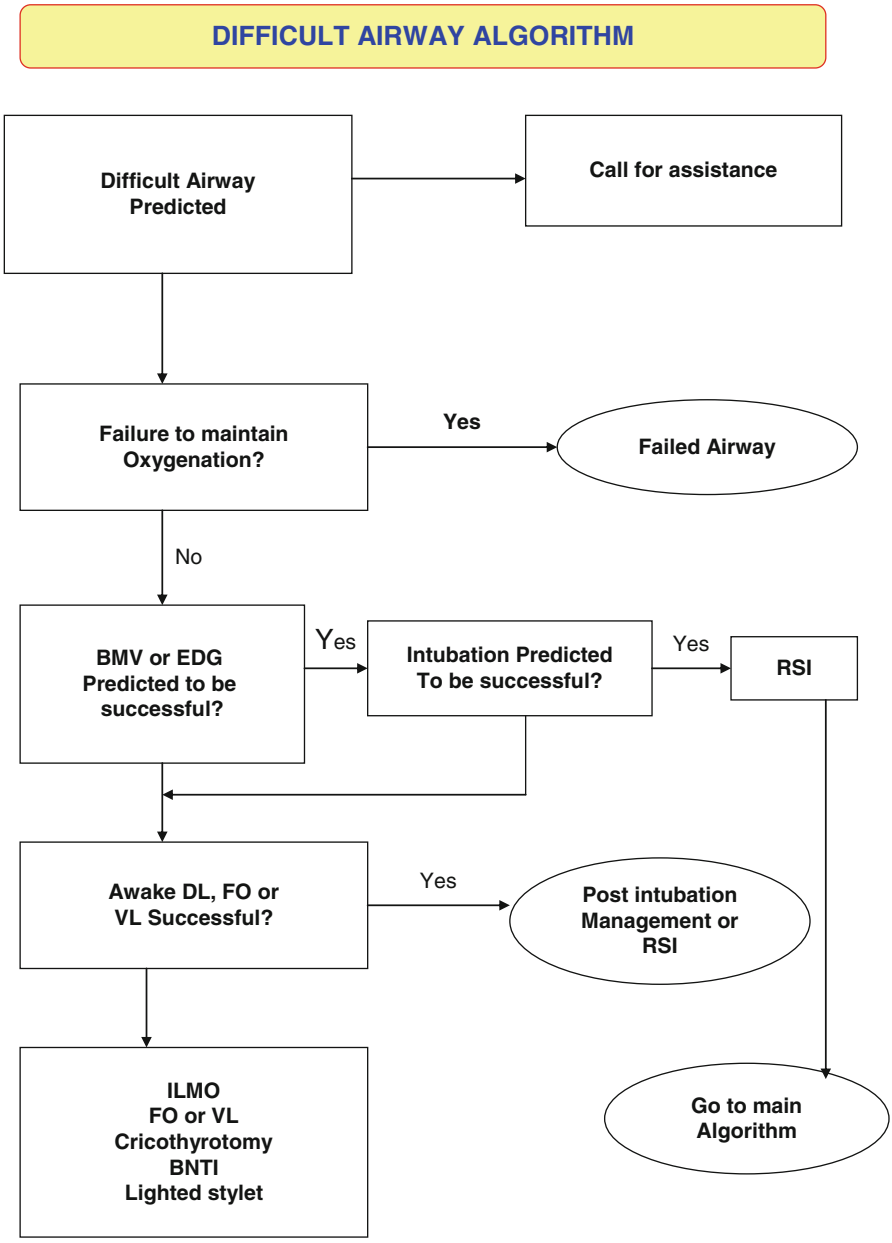
Anticipated Difficulty

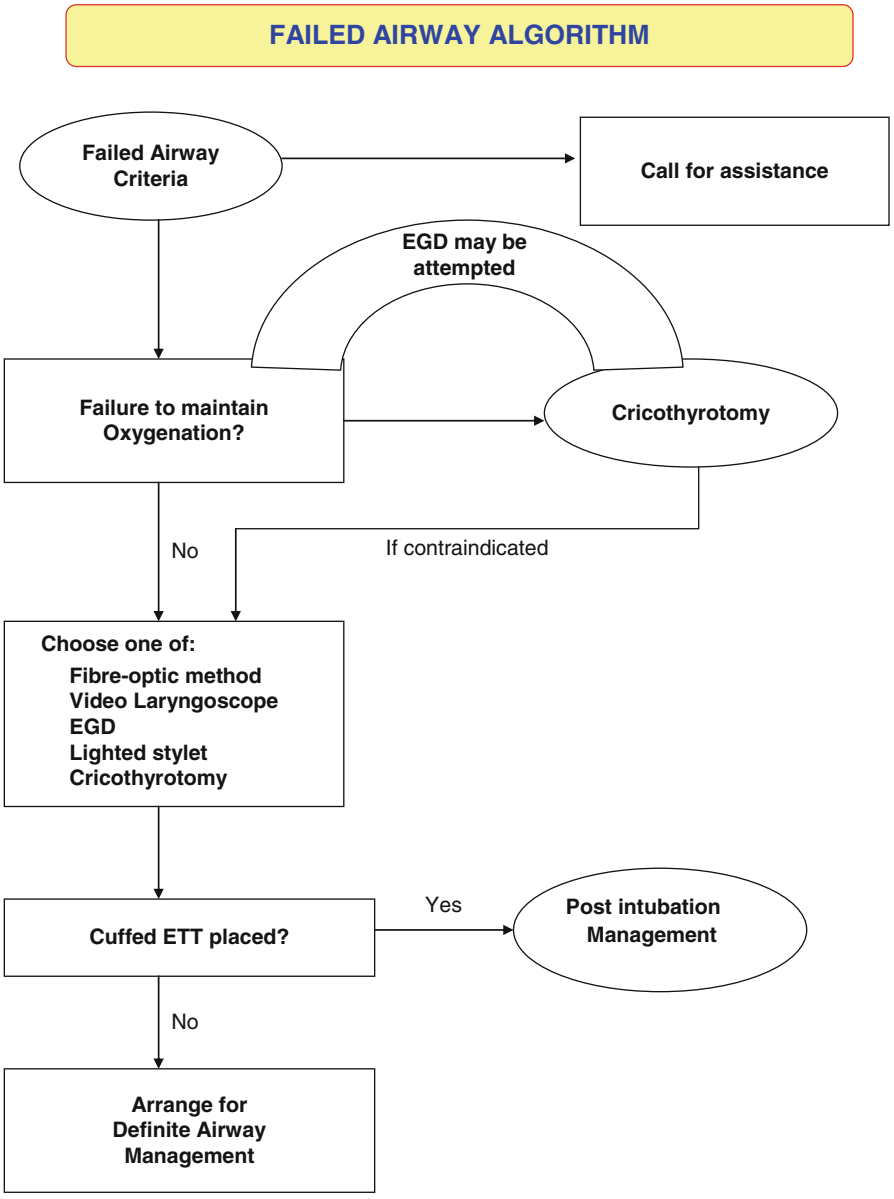
- Call expert help.
- Awake intubation under local anaesthesia.
- Blind nasal intubation.
- Retrograde intubation.
- Fibre-optic laryngoscopy.
- Surgical airway – tracheostomy.




UNIVERSAL EMERGENCY AIRWAY ALGORITHM
Unresponsive
Unreactive
Near Death?
Yes
Crash
Airway
Algorithm
Fails
No
Difficult
Airway?
Yes
Difficult
Airway
Algorithm
Fails
Failed
Airway
Algorithm
No
RSI
Fails


CRASH AIRWAY ALGORITHM
Crash Airway
Maintain oxygenation
Intubation attempt Successful?
Yes
Post Intubation Management
No
Unable to Bag Ventilate
Yes
Failed Airway
No
Succinylcholine 2mg / kg IVP
Attempt intubation
Successful?
Yes
Post Intubation Management
No
Failure to maintain oxygenation
Yes
Failed Airway
No
≥ 3 attempts by Experienced operator?
No


DIFFICULT AIRWAY ALGORITHM
Difficult Airway Predicted
Call for assistance
Failure to maintain Oxygenation?
Yes
Failed Airway
No
BMV or EDG Predicted to be successful?
Yes
Intubation Predicted To be successful?
Yes
RSI
Awake DL, FO or VL Successful?
Yes
Post intubation Management or RSI
ILMO
FO or VL
Cricothyrotomy
BNTI
Lighted stylet
Go to main Algorithm


FAILED AIRWAY ALGORITHM
Failed Airway Criteria
Call for assistance
EGD may be attempted
Failure to maintain Oxygenation?
Cricothyrotomy
No
If contraindicated
Choose one of:
Fibre-optic method
Video Laryngoscope
EGD
Lighted stylet
Cricothyrotomy
Cuffed ETT placed?
Yes
Post intubation Management
No
Arrange for Definite Airway Management

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Chapter 2
Anaphylaxis

Rosie Furse

Key Points

1. Anaphylaxis is a generalised reaction. However, its effect on skin and mucosal changes, hypotension and respiratory compromise are noteworthy.
2. The mainstay of treatment is intramuscular epinephrine plus intravenous fluids if hypotensive. All other drug interventions are secondary measures.
3. Detailed history is the key for diagnosis.
4. Serial mast cell tryptase levels will be helpful to the allergy specialist at follow-up.

Introduction

- Anaphylaxis is a severe, potentially life-threatening, generalised, hypersensitivity reaction that is characterised by a rapid onset of airway and/or breathing and/or circulatory problems usually associated with skin or mucosal changes [1]. These occur in response to exposure to a precipitant (e.g. food, insect venom, drugs or exercise) and can be either allergic (IgE mediated) or non-allergic.
- Irrespective of this underlying pathophysiology, the clinical features, investigations and acute treatment are the same, and all of these patients should be given a diagnosis of 'anaphylaxis' or 'suspected anaphylaxis'. Terms such as 'anaphylactoid' or 'severe allergic reaction' are confusing and should be avoided.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_2

- The incidence of anaphylaxis is as yet not fully defined. This is due to the inconsistency in definition, diagnosis and record-keeping. In 2012, anaphylaxis was retrospectively found to account for 0.1 % and 0.3 %, respectively, of paediatric and adult ICU admissions in the UK [2]. These patients were equally admitted from the ED, from theatres and from other areas of the hospital [3]. The World Allergy Organization (WAO) analysis of international data suggests that the prevalence is increasing worldwide (estimated lifetime prevalence of 0.1–2 %) although it still appears to be more common in the Western world [4, 5]. Fatalities from anaphylaxis remain uncommon [5].
- The diagnosis of anaphylaxis remains a clinical one during the initial presentation, and it is important to consider the main differential diagnoses. It is now recommended that all anaphylaxis patients are referred for outpatient allergy specialist care [2].
- The mainstay of treatment remains the early administration of intramuscular epinephrine. Secondary-level treatments remain non-evidence based, with dosing strategies being extrapolated from other allergy-based diseases.

Pathophysiology

- There are multiple triggers for anaphylaxis, and on occasion it can necessitate two triggers occurring simultaneously (e.g. food and exercise) for the reaction to occur [2, 6].
- Irrespective of the trigger, the body undergoes a widespread release of inflammatory mediators, primarily from mast cells, including histamine, leukotrienes and platelet-activating factor. Mast cells occur in highest concentration in the skin followed by the respiratory tract and then the gastrointestinal system, thus accounting for the distribution of clinical features [7]. They also occur around the coronary vessels and between the myocardial muscle fibres [5].
- The inflammatory mediators cause bronchoconstriction, vasodilatation, increased vascular permeability and weakening of myocardial contractility. They can also cause coronary artery spasm which can mimic an acute coronary syndrome [5].
- Effects occur most rapidly after intravenous administration of a drug, whereas there will be some delay after venom exposure and the potential for an even slower onset after an ingested food allergen [5].
- In children, the majority of reactions are in response to exposure to a food allergen. Most of the children will have a background of atopic disease, and they will present with predominantly respiratory symptoms. Insect venom-related reactions are also more common than in adults [2, 5].
- In adults, reactions to food and drugs are fairly similar in frequency for the first episode and are more common than exposure to insect venom. Atopy is not usually present, and the cardiovascular symptoms and signs become more prominent. In the more elderly population, almost all initial reactions are drug induced [2, 5].

- Amplifying cofactors can either increase the likelihood of a reaction to a trigger (e.g. exercise) or cause the subsequent reaction to be more severe [2]. Alcohol and NSAIDs cause increased gastrointestinal permeability which allows more of the ingested allergen to be absorbed [5, 6]. Intercurrent infections and emotional or physical stress can also amplify the reaction.

IgE Mediated

1. Food triggers
    - In the West, these are most commonly peanuts or other nuts, fish or shellfish, eggs and cow's milk. In the Middle East, sesame seeds are a common allergen, and in Asia chickpeas and rice are prominent [5].
    - There is a significant degree of cross-reactivity, and patients may react to more than one plant-related food. This association also extends to pollens; patients with allergy to grasses or pollens may be at risk of anaphylaxis to plant-based foods [6].
    - Asthma and other atopic diseases are a risk factor for food-based anaphylaxis [6].
2. Drug triggers
    - Antibiotics – This particularly occurs with penicillin-related antibiotics and sulphonamides. These contain haptens which bind to serum proteins and produce IgE antibodies [5]. Unlike the food allergens, past history of atopy does not increase the risk of drug-related anaphylaxis [2]. Reactions are twice as likely to occur after intravenous or intramuscular administration when compared to the oral route [5].
    - Other antimicrobials – antivirals, antihelminthics and TB medications.
    - Muscle relaxants.
    - Antineoplastics/cytotoxics/immunomodulators.
3. Insect venom triggers
    - This includes bees, wasps, yellow jackets, hornets and fire ants. The venom contains enzymes and proteins that provoke an IgE response [6]. Elderly patients or those with very rapid onset of symptoms and/or have minimal or absent skin changes are at increased risk of death [2]. Venom-allergic patients respond well to immunotherapy [2, 5, 6].
4. Other triggers
    - Latex – Note that this is derived from rubber tree sap and has a potential cross-reactivity with stone containing fruits, bananas, kiwis and chestnuts [2, 6].
    - Seminal proteins/human PSA [2].
    - Horse-derived antitoxins (e.g. snake antivenoms) [2]
    - Helminths [2].

Non-IgE Mediated

1. Immune complex – complement mediated
   - This includes reactions to blood products, immunoglobulins and dextrans and occurs due to immune complexes activating complement which leads to mast cell degranulation [6].
2. Non-immunological mast cell activators
   - Radiocontrast media comes into this group (e.g. iodine and other medical dyes) as do narcotics, cold, heat, sunlight and alcohol [5, 6].
3. Modulators of arachidonic acid metabolism
   - This includes aspirin and NSAIDs and is thought to relate to the acetyl group [6].
4. Idiopathic
   - Idiopathic anaphylaxis is a diagnosis of exclusion after careful history taking, skin prick and blood testing plus allergen challenges in certain cases [5]. Tryptase levels help to differentiate these patients from a diagnosis of mastocytosis [5].
5. Exercise
   - This can occur as a single trigger or more commonly as cofactor amplification in conjunction with exposure to a food or pollen trigger [5, 6]. Careful history taking regarding episodes will aid in identification.

Clinical Features

- The World Allergy Organization provides a definition of anaphylaxis based on any one of the three criteria being fulfilled within a timescale of a few minutes to a few hours [5]:
  (a) Acute onset of involvement of the skin/mucosal tissue with respiratory compromise and/or reduced blood pressure (BP).
  (b) Two or more of (i) skin/mucosal changes, (ii) respiratory compromise, (iii) reduced BP and (iv) persistent gastrointestinal symptoms, after exposure to a likely allergen.
  (c) Reduced BP after exposure to a known allergen for that individual patient.
- This definition helps to remind physicians that the presentation of anaphylaxis can vary between patients. This variation may occur between different patients responding to the same or similar allergen or even an individual responding differently each time they have an anaphylactic reaction [5].

- Children are more likely to present with predominantly respiratory symptoms which can mimic an acute asthma exacerbation.
- Adults (and in particular, the elderly) can present primarily with cardiovascular collapse and can mimic other cardiac diseases [2, 3, 5, 6]. Less than 20 % of anaphylaxis episodes will present with mild or no skin or mucosal changes. In these cases, it is usually due to a venom-related allergen and presents primarily with cardiovascular collapse [7].
- Most patients will present with symptoms within the first 5–30 min after exposure to the allergen, but this can be delayed particularly if the allergen has been ingested orally.
- Patients will often report as sense of impending doom or uneasiness prior to symptoms starting [2, 6].
- The speed of onset is quicker with intravenous drug administration, more likely to involve cardiovascular collapse and more likely to result in cardiac arrest and death. In most extreme cases, this can occur over the course of minutes [5] (Table 2.1).

It is important to remember:

- Skin or mucosal changes alone do not constitute anaphylaxis but that anaphylaxis does not have to have skin changes.
- Patients with significant cardiac or respiratory co-morbidity may show a deterioration in this condition during an anaphylactic episode giving a poorer outcome [2, 5, 6].
- Symptom patterns may be altered by prior antihistamine or steroid use.

Table 2.1 Symptoms and signs of anaphylaxis

Skin	Erythema/flushing
	Urticaria/pruritus (itching of palms, soles and perineum is a good indicator of more severe anaphylaxis [8])
	Angioedema – periorbital, lips, tongue
A – Airway	Obstruction secondary to upper airway angioedema
	Stridor/hoarse voice
B – Breathing	Bronchospasm/wheeze
	Hypoxia/cyanosis
	Chest tightness/cough/tachypnoea
C – Circulation	Hypotension/distributive shock
	Arrhythmias/palpitations
	Chest pain/abnormal ECG
D – Disability (neurology)	Irritability/confusion
	Headache
	Dizzy/tunnel vision
E – Enteral, ENT, eyes	Abdominal pain/cramps/diarrhoea
	Dysphagia/nausea and vomiting
	Rhinitis/sneezing
	Conjunctival erythema/tearing
	Metallic taste in the mouth

- Anaphylaxis severity may be worse in patients on concurrent antihypertensives or diuretics [2, 5, 6].
- Infants, pregnant women and the elderly are more vulnerable to the effects of anaphylaxis [2, 5, 6].

History taking and documentation are vitally important. A detailed exploration of the minutes to hours prior to the onset of symptoms may reveal the likely trigger. Even if there are multiple possibilities, this will aid further testing and follow-up and/or correlation with future episodes. It is also important to record the symptoms shown and the speed of onset as well as the response to treatment.

Biphasic Reaction

- Up to 25 % of adult patients (10 % children) will have a biphasic reaction as part of their anaphylaxis episode [5]. This is when further symptoms or signs occur after a symptom-free period [6].
- There are no reliable means of identifying these patients unless they have a prior history of this.
- Severe reactions, predominant hypotension, oral triggers and a background of asthma have all been associated with an increased risk of a biphasic reaction [6].
- The delayed reaction may be milder, similar or, rarely, more severe than the initial symptoms. It will usually occur within the first 4–10 h after the onset of symptoms but has been reported anything up to 72 h from onset [5, 3]. The clinical findings are likely to be attenuated by the earlier administration of epinephrine, antihistamines and glucocorticoids [6].

Differential Diagnosis

Although early treatment of anaphylaxis with intramuscular adrenaline is key, it is also important to consider the possible differential diagnoses. This should be possible with a rapid focussed history and examination considering those most likely for the different age groups (Table 2.2).

The symptoms and signs of surgical emphysema secondary to pneumothorax can mimic the angioedema and breathlessness of anaphylaxis. Hereditary angioedema is usually of a slower onset than anaphylaxis with an average of 3.7 h of angioedema before breathlessness occurs [2].

Mastocytosis is an uncommon condition, which can have two forms: cutaneous or systemic. The systemic version can increase the risk and severity of anaphylaxis episodes particularly from insect venom triggers and to a lesser extent, drugs [2]. In these patients, their baseline tryptase levels will be high which differentiates them from simple anaphylaxis where the levels return to normal.

Table 2.2 Differential diagnoses

Massive surgical emphysema secondary to pneumothorax
Hereditary angioedema (C1 esterase inhibitor deficiency)
Cold urticaria
Cholinergic urticaria
Acute asthma
Pulmonary embolism or amniotic embolism
Choking secondary to foreign body
Acute coronary syndrome
Anxiety attack
Phaeochromocytoma or carcinoid
Scombroid
Red man syndrome secondary to vancomycin
Mastocytosis

- Massive surgical emphysema secondary to pneumothorax
- Hereditary angioedema (C1 esterase inhibitor deficiency)
- Cold urticaria
- Cholinergic urticaria
- Acute asthma
- Pulmonary embolism or amniotic embolism
- Choking secondary to foreign body
- Acute coronary syndrome
- Anxiety attack
- Phaeochromocytoma or carcinoid
- Scombroid
- Red man syndrome secondary to vancomycin
- Mastocytosis

Investigations

- There are currently no biomarkers or laboratory tests than can resolutely confirm or refute the diagnosis and no biomarker that increases in concentration irrespective of trigger [2].
- Tryptase levels
  - These are now recommended for patients presenting with anaphylaxis, but this only needs to be done for one episode [3].
  - When present, the degree of rise in tryptase does correlate with severity of the symptoms, but a rise may not be found in all patients [2].
  - Food-based triggers and patients presenting without hypotension seem to have the lowest incidence of tryptase rise, and as such normal levels do not exclude the diagnosis [5, 7, 3].

  - The levels rise rapidly after the onset of symptoms and remain elevated for 4–6 h. Serial blood tests are recommended as soon as possible after the onset of symptoms, at 1–2 h after (but within 4 h of onset) and then again at baseline (at least 24 h after the episode) [3]. The baseline level should be normal.
  - Tryptase levels are not recommended in children under 16 unless the trigger is likely to be insect venom, drug administration or idiopathic [3].
- Skin prick tests and allergen-specific serum IgE levels can be performed by the allergy specialist after 3–4 weeks to avoid false-positive results.
- Challenge or provocation tests can be performed but should be done with caution in a facility that has the resources to manage any subsequent anaphylaxis [2].

Treatment

- There is no high-quality evidence to support any of the treatments currently used for acute anaphylaxis.
- However, extrapolation from other allergic and atopic disease management plus observational-level evidence in anaphylaxis had led to fairly standardised treatment recommendations [5, 9].
- General measures
  - Ensure removal of the trigger. This includes stopping any drug or contrast or removing an insect sting.
  - If hypotension is a significant symptom, then the patient should be laid flat (or in the left tilt if pregnant). If respiratory symptoms predominate, then the patient may be more comfortable sitting up.
  - Manage in a high-care facility with full cardiac and respiratory monitoring including prompt intravenous access.
  - If airway compromise is present or threatened, early involvement of an anaesthetist is recommended as the airway can deteriorate rapidly and can become difficult to intubate.
  - If the patient progresses to cardiorespiratory arrest, the resuscitation efforts should be carried out in accordance with international advanced life support recommendations [9].
- Specific measures
  - Epinephrine:

    This forms the mainstay treatment of anaphylaxis and has the strongest evidence base of all the interventions [5].

    The earlier it is given, the better and quicker the response appears to be [2, 9]. This is likely due to inhibition of inflammatory mediator release, thus attenuating the severity of the episode [2, 9].

Current recommended doses are shown in the algorithm in Appendix 2.1, but if the only epinephrine available is the patient's own auto-injector pen, then this should be used.
Doses can be repeated every 5–15 min as needed and should be administered in the anterolateral aspect of the middle third of the thigh [9].
Epinephrine works on alpha and beta adrenoceptors to reverse the vasodilatation, bronchospasm and urticaria as well as provide inotropic and chronotropic benefits [5].
Side effects include pallor, tremor, anxiety, palpitations and headaches.
Adverse events can include hypertensive crisis, cerebrovascular events or cardiac failure.
In refractory cases, epinephrine can be given intravenously, but this should be done only by those experienced in its use.
Alternative vasopressors can also be considered for those with refractory hypotension.

– Antihistamines:

Their primary role is to reduce the symptoms from skin and mucosal changes. Both H_1 and H_2 receptor blockers have been used [2, 5, 7].

– Glucocorticoids:

These work by switching off the production of pro-inflammatory proteins.
Their role is to attenuate any protracted symptoms and may help prevent a biphasic response in susceptible individuals [2, 5].

– Intravenous fluids:

Current recommendations suggest crystalloids given as 20 ml/kg boluses for children and 500–1,000 ml boluses for adults [9].
The evidence for this is extrapolated from studies of other conditions. So management should be tailored to the individual patient's needs [5].

– Others:

Salbutamol nebulisers can be used in those with significant or refractory respiratory symptoms.
Glucagon can be used in patients on B-blockers to allow the epinephrine to be able to work on the B-receptors especially in those with significant hypotension [9].

Observation Period

- Patients should be monitored for a minimum of 6 h after resolution of symptoms. This observation period may need to be longer depending on the presence of any of the following high-risk features [9]:

- Extremes of age
- Significant co-morbidity
- Severe reaction with slow onset
- Severe asthma
- Likely continued absorption
- History of significant biphasic reaction
- Evening or night presentation
- Difficulty accessing emergency care

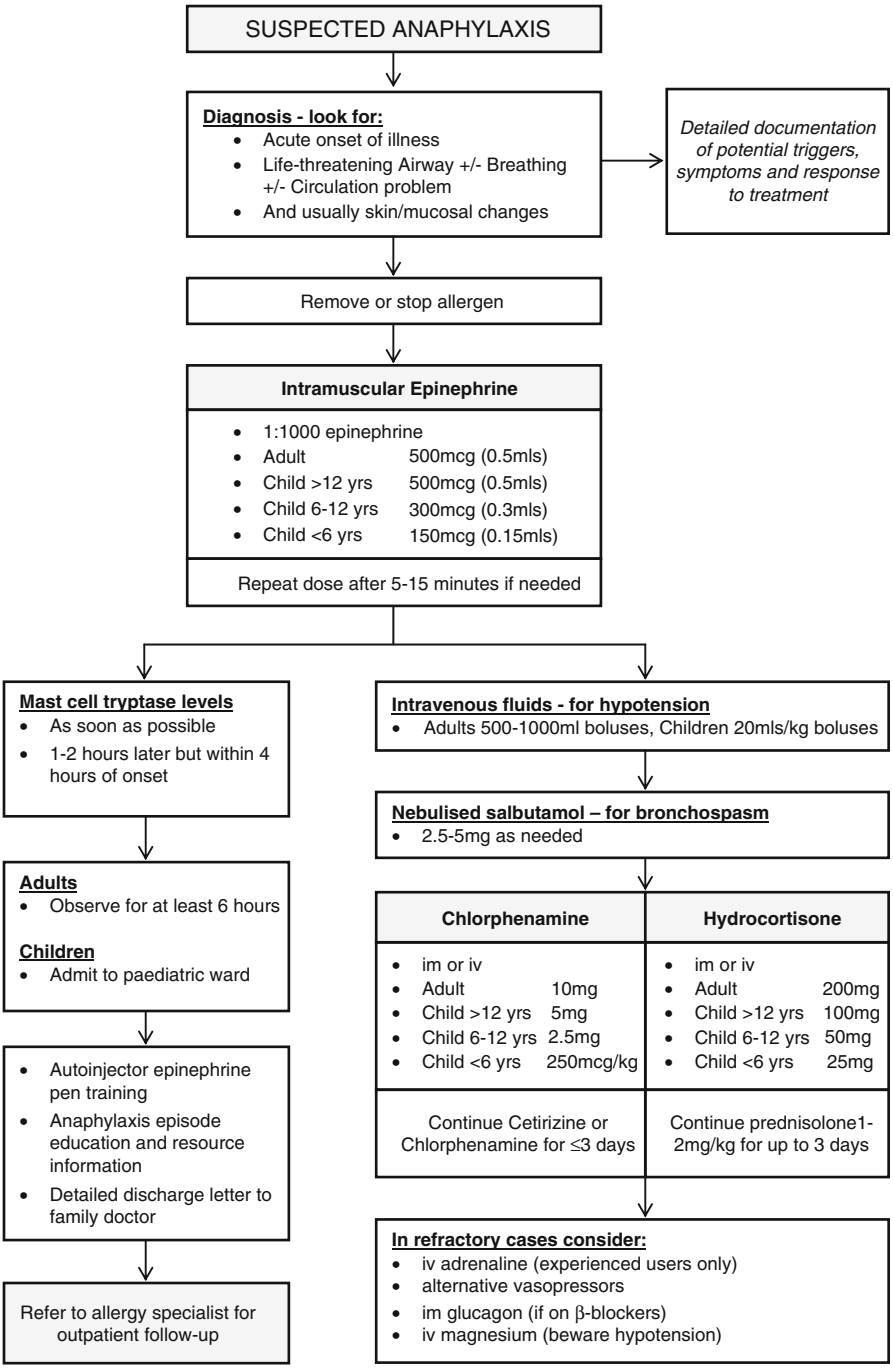
Prognosis and Prevention

The following points should be considered relevant to the patient's prognosis:

1. There is some evidence that children with anaphylaxis at an early age can develop tolerance to the trigger as they get older. This may take years however and primarily relates to food-based triggers [2].
2. Teenagers have the highest morbidity associated with anaphylaxis due to increased exposure to potential triggers and greater risk-taking behaviour [5].
3. Information, both verbal and written, given at the time of the episode and then repeated at health-care follow-up visits is vital in terms of trigger avoidance and anaphylaxis episode management. There are now multiple support organisations and internet-based resources available [2].
4. Epinephrine auto-injector devices should be given to all patients with anaphylaxis unless the trigger is easily avoided (e.g. medication or contrast). If these devices are unavailable, then a simple ampoule and careful instructions regarding its preparation and administration can be used [2].
5. Ongoing education and training surrounding auto-injector device use is vital. Unfamiliarity with the device and anxiety over its use are commonly reported reasons for non-administration of epinephrine [3].
6. Patients should be encouraged to wear medic-alert bracelets or carry alert wallet cards [6, 9].
7. Referral to an allergy specialist can aid specific trigger identification and consideration of further immunological treatments [3, 9]:

    - Subcutaneous venom immunotherapy – This can protect up to 90 % of adults and 98 % of children from further anaphylaxis due to insect venom [2, 5, 6].
    - Desensitisation – This can be via the oral or the sublingual route and is used primarily for food-based triggers and occasionally for drug-induced anaphylaxis if the specific drug cannot be avoided in an individual. The initial treatment takes months, and the effect is only maintained by regular exposure to the trigger, and permanent tolerance has not yet been proven [6]

Appendix 2.1: Suspected Anaphylaxis Algorithm



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Chapter 3
Cardiopulmonary Resuscitation

Raja Sekhar Maroju

Key Points
- Early recognition and initiation of basic or advanced life support is associated with better outcomes.
- Key component of basic and advanced life support is to provide early and uninterrupted chest compressions.
- During cardiopulmonary resuscitation, any potential reversible causes should be identified and treated.

Introduction

- Cardiopulmonary resuscitation (CPR) is an emergency procedure performed in the event of a cardiac arrest.
- Cardiac arrest essentially means the sudden stopping of heartbeat. CPR involves providing chest compressions and ventilation to ensure some circulatory flow and oxygenation is maintained.
- Another important aspect of resuscitation is cardiac defibrillation where indicated.
- The most common cause of cardiac arrest is ischaemic heart disease (IHD) [1, 2]. This usually results in ventricular fibrillation (VF) or pulseless ventricular tachycardia (pulseless VT). These arrhythmias are associated with no cardiac output.
- The other rhythms that are associated with cardiac arrest are asystole and pulseless electrical activity (PEA).

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_3

- Some of the patients in a cardiac arrest may or may not have a diagnosed cardiac disease.
- In addition to certain treatments and medications causing arrhythmias, it can also be caused by drowning, electrocution, trauma, electrolyte imbalances and respiratory failure.
- Irrespective of the cause, early initiation of CPR is vital as even a delay of 4–6 min leads to irreversible brain damage and death [4].

Chain of Survival

- The sequence of actions that would be essential to ensure a good outcome following a cardiac arrest can be represented as the chain of survival [3].

  Key links in this chain are:

  1. *Early recognition and call for help*
  2. *Early initiation of CPR*
  3. *Rapid defibrillation*
  4. *Post-resuscitation care*

Outcomes are poor when any of the above links are not in place or are not done effectively (Fig 3.1).

Indications for CPR

- CPR should be commenced immediately on any person who has suddenly become unconscious and has no palpable pulse.
- Absence of spontaneous circulation (no cardiac contractility) is due to one of the following non-perfusing arrhythmias:

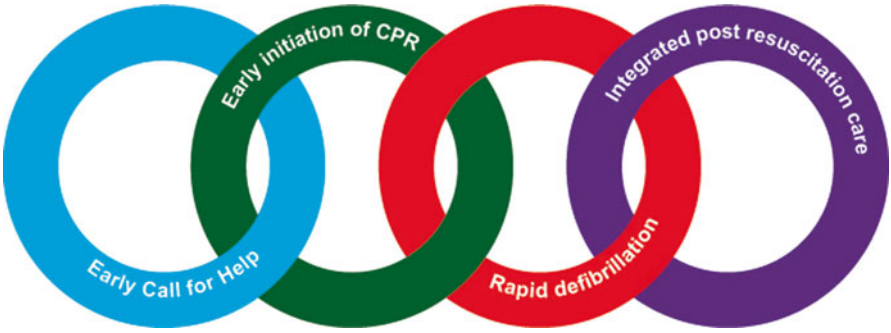

Fig. 3.1 Chain of survival

- Ventricular fibrillation (VF)
- Pulseless ventricular tachycardia (pulseless VT)
- Pulseless electrical activity (PEA)
- Asystole

Contraindications for CPR

- Except when there is 'do not attempt resuscitation' (DNAR) order in place, CPR is indicated in all other situations of cardiorespiratory arrest [5].
- It becomes a relative contraindication in situations where the medical team looking after the patient feels that it would be futile or not in the best interests of the patient (as in terminal illnesses or very poor general condition).

CPR

- Use universal precautions (like gloves, mask and apron).
- Though it is advisable to use universal precautions, it is not always possible, particularly in the prehospital setting. Fortunately, to date, no cases of disease transmission have been reported in persons providing CPR.
- Standard CPR consists of the following (C-A-B):
  - Chest compressions
  - Airway management
  - Breathing support

  However, in case of lay rescuers, compression-only CPR (CoCPR) is advised.

Please note that the order of resuscitation has been changed from A-B-C to C-A-B for adults, children and infants (excluding the newly born).

Chest Compression (Fig. 3.2)

- Place one hand on the middle of the patient's sternum and the other hand on top of the first with fingers interlocked.
- Keep the elbows extended.
- Compress the chest to a depth of at least 2 in. (5 cm).
- After compression, allow the chest to recoil completely.
- Ensure that the rate of compression is at least 100/min.

Fig. 3.2 Chest compression – Hand position

- In patients without and advanced airway, ensure a compression-to-ventilation ratio of 30:2.
- In patients with an advanced airway, chest compressions can be continuous at a rate of 100/min. Ventilation can then be provided at one breath every 6–8 s (eight to ten breaths/min).

For Effective Chest Compressions

- Place the patient on a relatively hard surface instead of a soft mattress or any other soft surface for effective compressions of the sternum.
- Position yourself high enough to use your body weight for compressions.
- Note that the depth of compression is 'at least' 2 in. and not 'up to'. Also note that the previously used '1.5–2 in.' is not correct anymore.
- Remember to 'push hard and fast'.
- Ensure that a new provider swaps in for compressions every 2–3 min to avoid fatigue and poor quality CPR.
- Untrained bystanders should perform CoCPR.

Airway

- Clear airway of any secretions or foreign bodies under direct vision.
- Use 'head tilt-chin lift' manoeuvre to open the airway if no trauma is suspected. Where trauma is suspected, use a 'jaw thrust' (Figs. 3.3 and 3.4).
- Use appropriately sized oropharyngeal or nasopharyngeal airways to ensure airway patency.

Fig. 3.3 Head tilt chin lift manoeuvre

Fig. 3.4 Jaw thrust manoeuvre

- Where available, supraglottic airway devices (SGD) like laryngeal mask airway can be used.
- Endotracheal tube (ETT) is the definitive airway of choice in a cardiac arrest scenario. Though desirable, one should try not to interrupt chest compressions to facilitate intubation.

Ventilation

If a patient is in cardiorespiratory arrest, two ventilations by mouth to mouth are given by the provider. One can also use a pocket mask if available. This procedure is performed as follows (Fig. 3.5):

- Pinch the patient's nostrils closed to get an airtight seal.
- Provider puts his mouth completely over the patient's mouth.
- Provider gives a breath for approximately 1 s with a steady force watching for the chest to rise.

Ventilations can also be achieved with a bag-valve mask (BVM), ideally by two people.

Single-person technique for BVM ventilation (Fig. 3.6):

- Ensure a tight seal between the mask and the patient's face with one hand.
- Squeeze the bag with the other hand for approximately 1 s, aiming to deliver approximately 500 ml of air into the patient's lungs. Look for the chest to rise.

Two-person technique for BVM ventilation (Fig. 3.7):

- One person holds the mask with both his hands to the patient's face throughout the CPR without removing it and ensuring a tight seal.
- The person performing chest compressions squeezes the bag after every cycle of 30 compressions.

Fig. 3.5 Mouth to mouth ventilation with a pocket mask

Ventilation

- 'Look, listen and feel for breathing' is now not part of the algorithm. The lay rescuer should now be taught to commence CPR if the patient is not breathing or only gasping.
- Avoid excessive ventilation
- Use of cricoid pressure during ventilations is generally not recommended.
- The person performing chest compressions squeezes the bag after every cycle of 30 compressions.

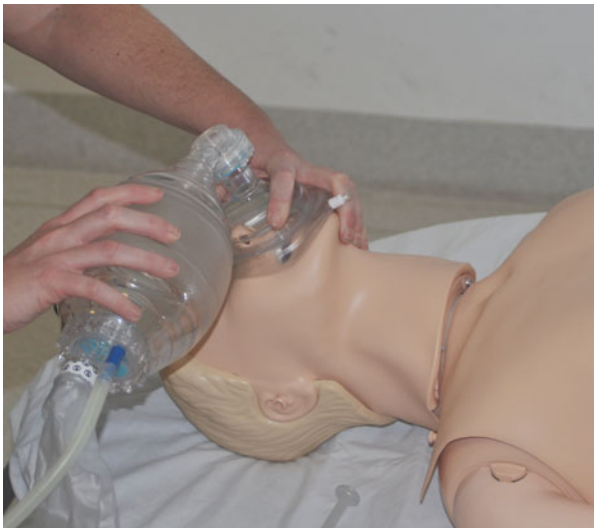

Fig. 3.6 Bag valve mask ventilation – One person method

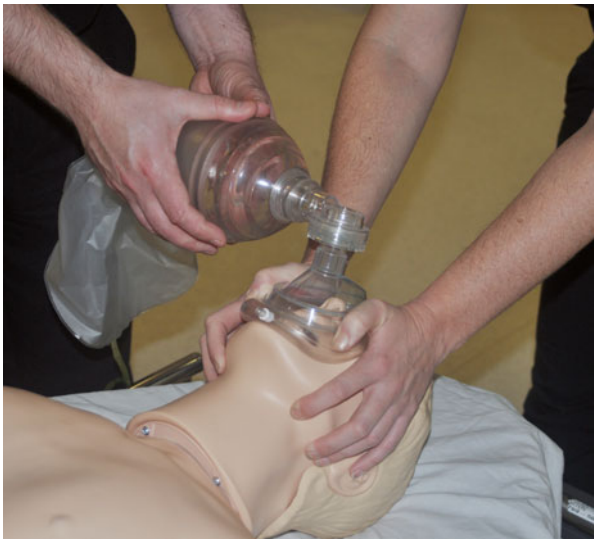

Fig. 3.7 Bag valve mask ventilation – Two person method

Advanced Life Support/Advanced Cardiac Life Support (Fig. 3.8)

- Though the algorithms are called differently as either advanced cardiac life support (ACLS) or advanced life support (ALS) in different countries, they are essentially based on the same principles which have been developed and standardised from extensive review of literature on resuscitation.
- This international ALS algorithm was published in the Consensus on Science and Treatment Recommendations (CoSTR) documents produced after the last International Consensus Conference in Dallas in 2010 conducted by American Heart Association (AHA) in collaboration with International Liaison Committee on Resuscitation (ILCOR) [1] (Fig. 3.8).
- This should be seen more as a guideline than a rule and gives a simplistic approach to CPR.
- One should avoid following it rigidly, particularly when specialist help is available as some of the recommendations are not supported by a high level of scientific evidence.
- As part of the ALS algorithm, it is important to continue chest compressions.
- Apply defibrillator pads at the earliest opportunity to recognise and treat the cardiac arrest rhythm appropriately.
- The chances of defibrillation resulting in a sustained, perfusing spontaneous circulation are greatest when initiated within 90 s after cardiac arrest and declines rapidly thereafter.

Precordial Thump

- It should not be used for unwitnessed out-of-hospital cardiac arrest.
- It should be considered for a witnessed unstable VT or pulseless VT if a defibrillator is not immediately available. This should not delay defibrillation or even starting CPR.

Attaching Defibrillator/Monitor

- Do not interrupt chest compressions while applying the self-adhesive defibrillation pads.
- The position of the pads is usually antero-apical. In most cases, the manufacturer provides instructions for ideal placement of the pads. Usually, one pad is applied just below the right clavicle and the second one over the cardiac apex (V6 position over the midaxillary line).
- In case of automated external defibrillator (AED), follow the instructions after switching on the machine as it gives verbal prompts for the next action after automatically analysing the rhythm.

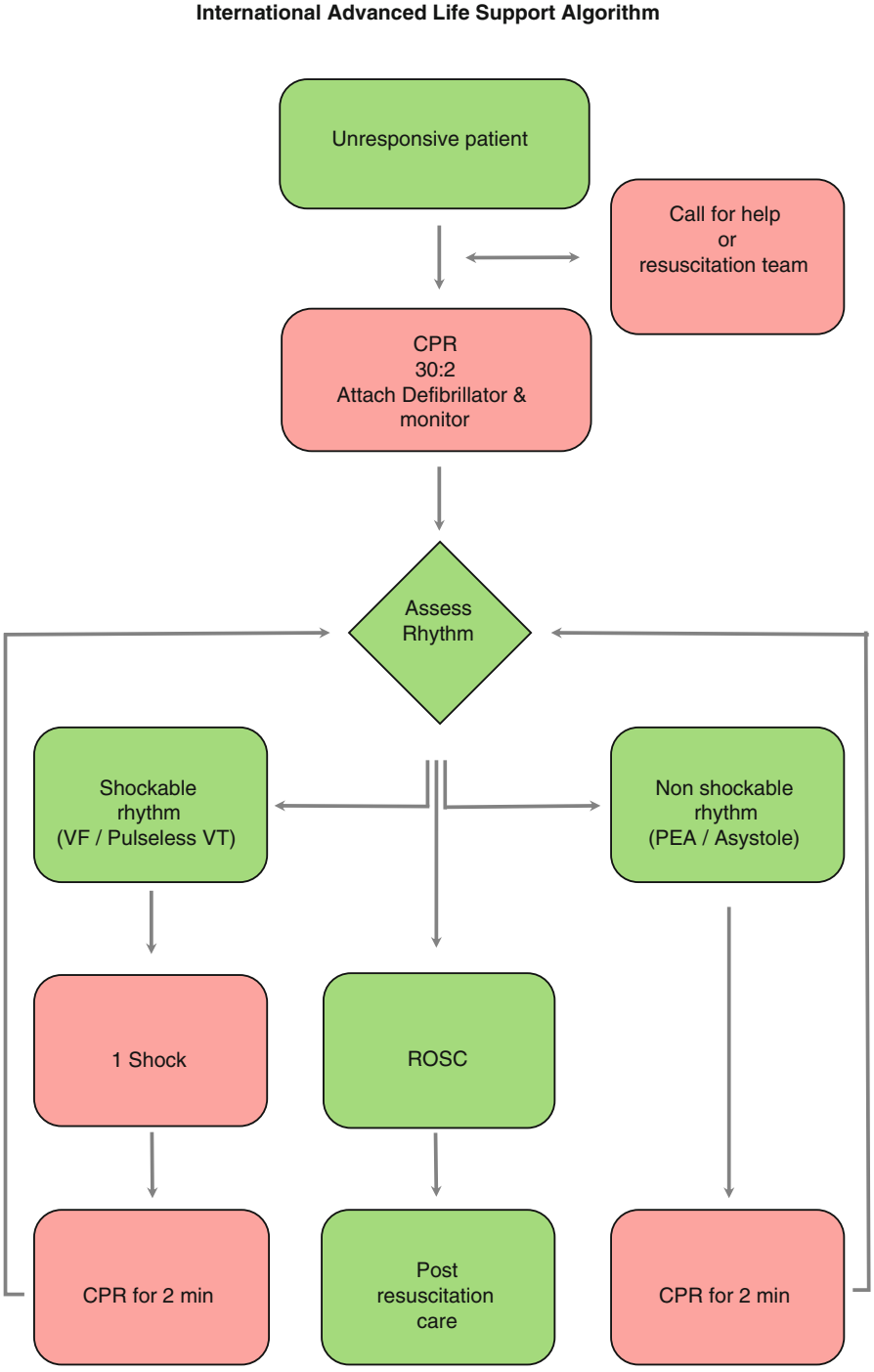

Fig. 3.8 International advanced life support algorithm

- For manual defibrillator:
  - After attaching the pads, pause briefly to analyse the rhythm. If the rhythm is VF or pulseless VT, restart chest compressions while charging the defibrillator. Safety issues should be planned beforehand to minimise interruptions to chest compression while delivering the shock.
  - Once the defibrillator is charged, and everyone other than the person delivering compressions is clear, pause chest compressions briefly ensuring everyone including any open source of oxygen is clear, and deliver the shock.
  - Recommence chest compressions immediately after delivering the shock for another 2 min before stopping to analyse the rhythm. Avoid the temptation to assess the rhythm or check for pulse immediately after delivering the shock.

Other interventions

- Procedures like intravenous cannulation and drug administration can be carried out once adequate help is available.
- It is useful to have a dedicated person for 'timekeeping' and also chart the different cycles and interventions being carried out.
- Scheme for the sequence of chest compressions; pause for analysis of rhythms; drug administration is represented in the international ALS algorithm.

It is important to:
- Minimise the delay between stopping chest compressions and delivering the shock. Studies have shown that every 5 s increase in this time delay halves the chance of a successful defibrillation.
- Address safety issues prior to stopping chest compressions to avoid doing the 'top-to-toe' safety checks traditionally done.
- Ensure safety of the patient and staff nevertheless.

Shockable Rhythms (VF/Pulseless VT)

In about a quarter of the case of cardiac arrest, the first rhythm that is seen on the monitor is a VF or VT. Even if it is not seen initially, it might occur during the resuscitation at some stage.

Treatment

1. Immediately commence uninterrupted chest compressions while defibrillation pads are being applied.
2. Pause briefly for analysis of the rhythm. Once VF/VT is confirmed, recommence chest compressions.
3. The designated person should then charge the defibrillator to the appropriate energy. Check for the manufacturer's recommendation as this figure varies.

This is usually 15–200 J (biphasic) for the first shock and 150–360 J (biphasic) for subsequent shocks
4. The person operating the defibrillator should ensure safety of the team at all times. Before delivering the shock, this person should give a loud and clear instruction to all of the team to stand away. Also ensure that any open source of oxygen is kept clear.
5. Once charged, the chest compressions are paused briefly before the shock is delivered safely. Ensure that this pause is not longer than 5 s.
6. Resume chest compressions immediately and continue CPR (30:2) without reassessing the rhythm or pulse.
7. The team leader should then start preparing the team for subsequent actions and also for the next pause in 2 min.
8. At 2 min, pause briefly again. If the patient is in VF/VT, then repeat the steps from 3 to 6 and deliver second shock.
9. Repeat steps 3–6 again if VF/VT persists. Also give 1 mg of adrenaline IV (10 ml of 1:10,000) and 300 mg of amiodarone IV after the third shock. Lidocaine (1 mg/Kg) can also be used as an alternative if amiodarone is not available.
10. Continue the 2 min cycles until VF/VT persists ensuring adrenaline is given every other cycle (3–5 min).
11. During treatment, ensure good-quality compressions and also constantly look for and treat the reversible causes (Table 3.1).

If during rhythm check an organised electrical activity is seen that is compatible with an output, then check for pulse.

- If there is a ROSC, then start post-resuscitation care.
- If there are no signs of ROSC, then continue CPR and switch to the non-shockable side of the algorithm for treatment of PEA.

If however, during rhythm check there is asystole, then continue CPR and switch to the non-shockable algorithm for treatment of asystole.

Non-shockable Rhythms (PEA and Asystole)

1. After confirming cardiac arrest and attaching the defibrillation pads, if the rhythm is PEA/asystole, then continue CPR at 30:2.
2. Give 1 mg of adrenaline IV as soon as an access is available.

Table 3.1 Reversible causes of cardiac arrest (4 Hs and Ts)

H	T
Hypoxia	Thrombosis (pulmonary or coronary)
Hypovolaemia	Tamponade (cardiac)
Hypo/hyperkalaemia or metabolic	Toxins
Hypo/hyperthermia	Tension pneumothorax

3. Check rhythm after 2 min.
   - If VF/VT at rhythm, then check. Then switch to shockable side of algorithm.
   - If asystole or agonal rhythm, continue CPR at 30:2, giving 1 mg adrenaline IV every other cycles (3–5 min).
   - If there is organised rhythm compatible with an output, then check for ROSC.
     i. If ROSC present, then start post-resuscitation care.
     ii. If no ROSC, continue CPR at 30:2, giving 1 mg adrenaline IV every other cycle (3–5 min).
4. During treatment, ensure good-quality compressions and also constantly look for and treat the reversible causes (Table 3.1).

Airway and Ventilation

- In the absence of staff trained in intubation skills, it is preferable to continue using a BVM or SGD.
- When there are trained personnel, an endotracheal intubation should be performed with minimal disruption to the ongoing CPR, particularly chest compressions.
- Once an ETT or SGD is sited, then attempt to perform continuous chest compressions at a rate of at least 100/min without stopping for ventilations. Ventilation should be given at eight to ten breaths per minute being mindful not to hyperventilate.
- Where available use end-tidal CO_2 (ET CO_2) monitoring. In addition to confirming correct position of ETT, it also is a useful monitor for determining the progress of CPR. There would be a sharp rise in ET CO_2 when there is a ROSC. However, a persistently low ET CO_2 could mean ineffective CPR either due to inadequate ventilation or due to poor cardiac output because of poor compressions. It could also be due to potentially reversible causes like hypovolaemia, pulmonary embolus (PE) or pericardial tamponade [1].

Vascular Access

- Securing an intravenous cannula (IV cannula) into a large vein in the upper limb is ideal. Alternatively, this can be sited into the external jugular vein.
- Due to poor venous return from below the level of diaphragm, lower limb veins should be avoided.
- All intravenous drug administrations should be followed by a big flush.
- If an IV cannula cannot be secured after one attempt, it is advisable to insert an intra-osseous needle (IO).
- If already in place prior to cardiac arrest, one can use a central venous cannula (CVC). However, it is not advisable to insert one during CPR as it is time consuming and also needs skill and practice to introduce without causing interruptions.

Arterial/Venous Blood Gases (ABG/VBG)

- ABGs are of limited value during cardiac arrest as they do not represent the severity of tissue hypoxaemia, hypercarbia or acidosis. However, VBG may represent the acid-base balance a bit more accurately.
- Once a ROSC is obtained, an ABG should be done to get a baseline status from which the progress of post-resuscitation care can be monitored.

Post-resuscitation Care

- It is very important to have a system of comprehensive, multidisciplinary team input that is very structured and integrated to ensure good outcomes in patients with ROSC.
- Soon after a ROSC, the team leader should ensure that any airway intervention is carried out if not already done.
- Also, blood samples should be taken for ABG analysis and workup for inflammatory markers as well as organ function (cardiac, renal and liver).
- Where suspected, samples for toxicology screen should also be sent for analysis.
- A 12-lead ECG should also be done to see any ischaemic changes or arrhythmias which are very common in the peri-arrest period.
- A portable chest x-ray should also be ordered.

One of the key objectives of post-resuscitation care is to ensure perfusion to vital organs by optimising cardiopulmonary function. It is important to look for any evidence of organ dysfunction and treat it early.

New Technology

- Several mechanical CPR devices aimed at improving the perfusion during resuscitation from cardiac arrest and to improve survival have been developed.
- Though several clinical trials have been done, none of these addresses if routine use of these devices irrespective of patient demographics, place it is used and the level of experience of the user has any better outcomes. Further studies are required to assess this.
- These devices at least initially need more personnel and training, and commencing treatment with them has the danger of either delaying treatment or interrupting ongoing CPR. However, with appropriate training, these hurdles can be overcome.

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Chapter 4
End of Life Care in the Emergency Department

Arti Baskaran

Key Points
- End of life (EoL) care is aimed at patients with chronic or terminal illnesses and can be initiated in the emergency department.
- Religious and cultural beliefs often influence the type of EoL care the patient wishes for.
- Communicating bad news is a useful skill for all physicians and should be done with empathy.

Introduction

Emergency department visits are increasing each year, and studies have shown that 51 % of patients aged 65 years or older visited the emergency department in the last month of life and about 75 % in the last 6 months of their life [1]. This study also showed that 77 % of 51 % of patients were admitted to the hospital and 68 % of those admitted died there. In many of these cases, patients would actually prefer to die at home with their family around them [2].

Emergency medicine physicians have a unique opportunity to discuss end of life (EoL) care and help the patient understand their illness and articulate their needs, thus setting the path for the high-quality care that they deserve. The emergency physician can refer patients to palliative care or hospice directly, and this has shown to reduce ED visits and hospital admissions and also improved patient satisfaction [3, 4].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_4

Definition

End of life (EoL) care aims to relieve suffering and provides appropriate medical, physical, psychological, legal and cultural/spiritual help to patients with terminal illnesses and enables them to live their final days with dignity. Emphasis is placed on patient autonomy and shared decision-making.

EoL involves a multidisciplinary team approach, consisting of doctors, nurses, palliative or hospice team, pharmacist, nutritionist, social worker, home health nurse, spiritual counsellor and the family.

Consider the Following During EoL Conversations

- Initiate discussion by assessing patient's understanding of the disease.
- Discuss the disease course, treatment options and prognosis.
- How effective is the current treatment and does it meet the patient's expectation?
- Check who is coordinating their medical care and refer them to palliative care or hospice care as needed.
- Discuss patient's wishes regarding resuscitation measures (chest compression, intubation, medications to prolong life and defibrillation) and about withdrawing care.
- Ask about advance directives, living will and a surrogate medical decision maker.
- Do involve family and spiritual advisor/priest in discussions.

Levels of Care (Fig. 4.1)

In some countries, there are set pathways and models in place for EoL care, while in others EoL care is still an emerging specialty with limited resources. In countries with limited resources, the family physician often provides pain control, the home health nurse provides help to families and their temple priest provides the spiritual support.

In Eastern countries, the patient's family plays a vital role in the EoL decision-making and the patient is not the primary decision maker. This often determines or changes the level of care that the patient needs. Often, hospice care and palliative care are used synonymously and are not based on life expectancy.

Palliative Care

- Palliative care improves the quality of life for patients with chronic debilitating or terminal illness and for their families.

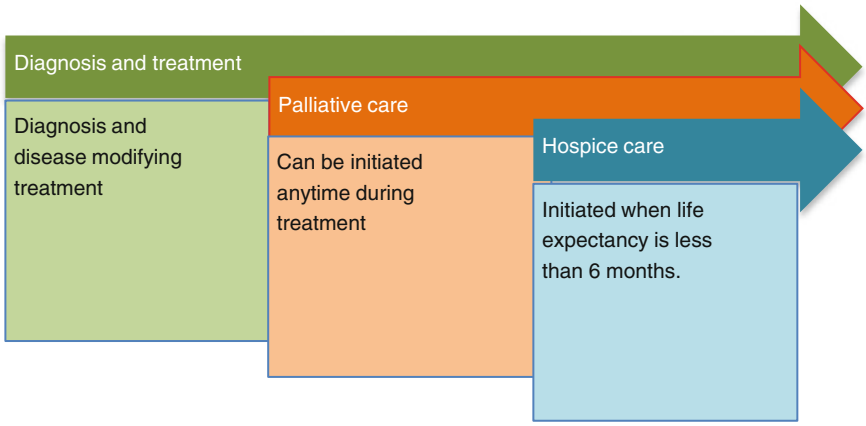

Fig. 4.1 EoL: levels of care

- A patient can be referred for palliative care at any stage of the illness regardless of their age and the outcome of their illness.
- Patients that may benefit are those with chronic CHF, severe COPD, HIV/AIDS, end-stage renal disease (ESRD), end-stage liver disease (ESLD), Alzheimer's, Parkinson's, strokes, advanced cancer, etc.
- They coordinate care between the various specialties involved and are a point of contact for the families.
- They provide pain relief, medical decision-making, home care, childcare, physical and occupational therapies and also help with transport to and from clinic appointments.

Hospice Care

- The hospice team provides comprehensive care to terminally ill patients whose expected life expectancy is less than 6 months.
- This can be provided either at the hospital, nursing home, hospice centres or even in the patient's home.
- They help with:
  - Symptom control and pain management
  - Providing medical equipment like home ventilator, oxygen, wheelchair, etc.
  - Performing required procedures like paracentesis, thoracentesis and dialysis
  - Counselling and psychological support
  - Legal EoL planning – advanced directives or living will
  - Any ancillary help that family members require – like childcare, respite care and even transport to and from appointments
  - Funeral arrangements and bereavement support

Common Symptoms and Their Management

Pain

- This is the most frequent presenting symptom to the ED.
- Treatments include NSAIDs, muscle relaxers, opioids, bisphosphonate (bone pain), steroids and regional blocks.

Respiratory System

- Dyspnoea is secondary to increased secretions, recurrent pleural effusion, cancer spread and spontaneous pneumothorax.
- Mainstay of treatment is to treat the underlying cause.
- Control secretions with glycopyrrolate or a scopolamine patch.
- Adjuvant treatments include home oxygen, non-invasive ventilation, home ventilators and opioids.

Gastrointestinal System

- Nausea and vomiting are usually treated with ondansetron (5-HT3 blockers).
- With loss of appetite or inability to swallow, treat with parenteral nutrition, PEG-tube placement, intravenous fluids or protein shakes.
- Constipation commonly causes abdominal pain and is due to medications and dehydration. Correct underlying cause and treat with either stool softeners, laxatives, polyethylene glycol or osmotic agents.

Renal and Genitourinary System

- Symptoms include bladder/bowel incontinence and urinary retention. Treatment options include diapers, intermittent or long-term bladder catheterisation.
- Some patients may require dialysis.

Central and Peripheral Nervous Systems

- Involve neurosurgery and neurology teams early in the treatment.
- Increased intracranial pressure and cerebral oedema – consider corticosteroids.
- Neuropathy and paraesthesias – tricyclic antidepressants and gabapentin.

- Paraneoplastic syndromes – treatments includes steroids, high-dose intravenous immunoglobulin, irradiation or plasmapheresis.

General

- Infections – treat with antibiotics.
- Anaemia and blood loss require blood transfusions.
- Anxiety – treat with anxiolytics and psychotherapy.

Opioids

Pain and dyspnoea frequently bring patients to the hospital. Opioids are used to treat these symptoms and also for comfort care closer to the end of life. In low- to moderate-income countries, there are regulatory barriers that limit narcotics prescriptions, and this interferes with appropriate patient care [5].

- Opioids act on μ-receptors in the brain and inhibit the respiratory drive by decreasing responsiveness to hypoxia and hypercapnoea. This along with its anxiolytic properties decreases dyspnoea. Nebulised opioids can also be used with similar benefits [6–9].
- In the community setting, a low-dose, sustained release morphine can be used safely. Start at a lower dose and titrate up until the patient's symptoms are controlled, especially in opiate naïve patients.
- When prescribing opioids, take into consideration the patient's age, prior opioid use and other coexisting illnesses (renal, hepatic, cardiac or pulmonary) and modify dose as needed.
- Calculate the total oral opioid dose requirement by calculating the total intravenous opioid used in the last 24 h and converting that to an equivalent total daily dose for the desired oral opiate. Then divide that number by the number of doses/day. Morphine equivalents are given in Table 4.1.
- For example, if the total dose of IV morphine used in 24 h is 30 mg, then an equivalent oral morphine dose for 24 h is 90 mg. So the patient may be prescribed 30 mg of oral morphine three times/day.

Social, Psychological and Cultural Needs of the Patient

- Many patients experience anxiety, depression, anger and sense of hopelessness as they approach the end of their illness. Recognise these symptoms and involve the psychiatrists, psychologists and social workers in the patient's care.
- Patients have not usually made plans for when they die; they will need guidance with regard to their finances, funeral arrangements, writing their wills and appointing a medical surrogate decision maker.
- Be empathetic and respectful of the patient's cultural and religious beliefs.

Table 4.1 Opiate equivalent doses

Opioid agonist	IV/IM/SQ dose	Equivalent oral dose	Frequency
Morphine	10 mg	30 mg	Q4 h
Hydromorphone	1.5 mg	7.5 mg	Q3–4 h
Oxymorphone	1 mg	10 mg	Q3–6 h
Oxycodone	N/a	15–20 mg	Q4–5 h
Hydrocodone	N/a	30 mg	Q4 h
Codeine	100–120 mg	180–200 mg	Q4 h
Fentanyl	100 mcg (0.1 mg)		Q2 h
Methadone	5 mg	10 mg	Q6–8 h
Meperidine	75 mg	300 mg	Q4 h
Buprenorphine	0.3 mg slow iv	N/a	Q6 h

- Encourage patients to talk openly about their wishes with their family and spiritual advisor.
- Be cognisant of some of the following cultural practices:
  - Mentioning death is taboo, as it brings bad luck and hastens death.
  - Patients are often not informed of their diagnosis in case the patient becomes depressed and gives up hope.
  - Asking for pain medicines is considered a sign of weakness.
  - Physicians are held in high regard and patients believe that asking questions about their care is disrespectful.
  - Families often make EoL decisions on the patient's behalf.
  - Some believe that it is the will of God and may decline medical care in favour of faith healing.
  - Jehovah's witnesses will refuse blood transfusions.

Legal and Ethical Details

Emergency medicine physicians skilfully manage the critically ill patients and yet find asking patients about their resuscitation wishes challenging. This discussion becomes easier if there are legal documents stating the patient's EoL wishes.

Advance Directives (Fig. 4.2)

- This states the patient's EoL wishes that are to be followed in the event that the patient loses his or her decision-making capacity. The advance directive can be made at any point in the patient's life and includes a living will, name of the patient's medical power of attorney and do not resuscitate (DNR) wishes.

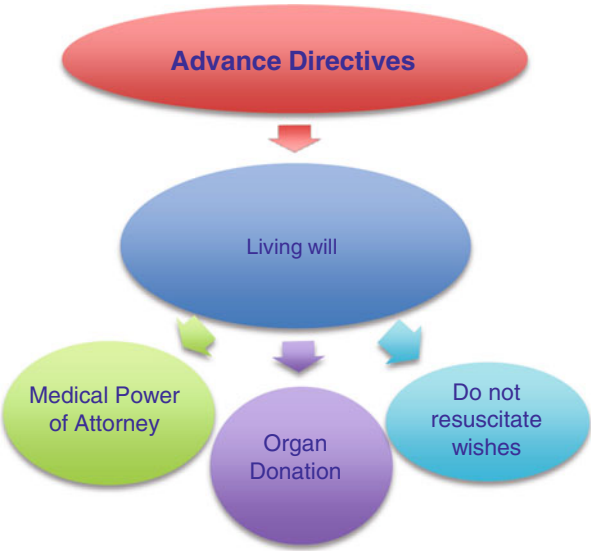

Fig. 4.2 Advance directives

Living Will

- The living will addresses the medical treatment the patient would like to receive as part of their EoL care. This also addresses life-sustaining treatment vs. withdrawing care and organ donation. The medical power of attorney or the court of law executes this living will when the patient is critically ill.

Medical Power of Attorney (MPA)

- The patient can elect a person, either temporarily or permanently, as their 'medical surrogate' or 'health-care agent' to make decisions on his/her behalf when he/she is too ill to communicate their wishes. The physician should deem a patient incapable to make his/her own medical decisions for this document to go into effect. The MPA can also make decisions regarding life-sustaining or withdrawing treatments.

Organ Donation

With each passing year, there is a widening gap between the number of patients on the transplant list and the number of organs being donated. In recent years, the emergency department has been under focus to identify potential organ donors.

Studies have shown an increase in the number of organ donors when patients are referred from the ED, as compared to when they are referred from the ICU – 19.3 % vs. 5.2 % [10].

- Ethically, the emergency medicine physician, who is treating the patient, should not discuss organ donation with the family.
- Once a potential donor is identified, the physician should call the organ donation team, and only that team should speak to the family or the patient's medical surrogate decision makers. This applies to all patients treated in the ED, be it trauma patients, out of hospital cardiac arrests, terminally ill or children alike [11–13].

Communicating Bad News

Communicating bad news is a daily occurrence in the emergency department. How the physician communicates bad news plays a critical role in how the patient perceives the physician and the care they are receiving. There are several effective protocols available for breaking bad news like the SPIKES [14, 15] and the GRIEV_ING [16] protocols. Below is a simple PIEE protocol (Fig. 4.3).

Preparation

- Switch off all pagers and cell phones.
- Take a nurse and the spiritual counsellor with you for the interview.
- Invite the patient, their significant other and family to quiet interview room.
- Have a phone available for them to use in the room.

Interview

- Sit down, make good eye contact, introduce yourself, state your role and also introduce everyone else with you in the room.
- Enquire if they would like anyone else to be present during the discussion and offer to call them.
- Determine how much the patient understands about their condition.
- Explain the condition, treatment options and prognosis.
- Assess how much the patient understood of what was discussed.
- Give enough time for the patient to ask questions.
- Be empathetic and avoid using medical jargon during the discussion.

Fig. 4.3 Communicating bad news – PIEE

EoL Care

- Ask if they would like to pursue the treatment or focus on symptoms control.
- Discuss cultural and religious beliefs.
- Give them information about advance directives and living will.
- Give patient time to come to their decision.
- Tell them that they are allowed to change their mind at any point.

Exit

- Check first if patient has any further questions.
- Confirm and summarise the agreed treatment plan.
- Provide your name and contact details and state that you are available for any further questions.

Barriers to End of Life Care in the ED

- Time constraints in the ED
- Physician and nurse perception of palliative care [17]
- Unaware of the availability of EoL care and how to access it
- Not informing patient of the disease progression and outcome
- Talking to the family instead of the patient
- Difference between patient's and family's wishes
- Not treating pain or undertreating pain
- Financial barriers
- Religious and cultural barriers
- Lack of availability of legal documents that support the patient's wishes

Conclusions

Emergency physicians frequently treat critically ill patients. It is important that they help their patients make a shared decision with regard to how they would like to be managed in their final days. The subject of dying is a very sensitive issue and many people avoid discussing it. It is necessary for the physicians to start these conversions and provide treatment options without using medical jargon. As religious and cultural views often dictate how the patient perceives end of life care and death, the emergency medicine physician must remain empathetic and respectful to these views. There is a need to educate physicians and public health policymakers to make EoL care a public health concern. As emergency medicine physicians, we can make a difference in improving EoL care.

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Chapter 5
Fluid Resuscitation

Jonathan Leung and Derek Hicks

Key Points
- The physiology of fluid compartments and fluid deficit in health and disease states are different.
- Crystalloids are the initial fluid of choice for resuscitation in most situations.
- Fluid resuscitation requires rational treatment end points during, i.e. fluid responsiveness, in order to prevent negative effects.
- The effect of over-resuscitation with fluid can be detrimental and lethal.

History of Intravenous Fluid Administration

The modern use of intravenous fluid began with William Harvey's demonstration of the human's circulation in 1616 [1]. Throughout the seventeenth century, various attempts were made to restore blood using animal to human blood transfusion and injection of various impure compounds into human veins, which resulted in poor outcomes. In 1832, Thomas Latta recognised that dehydration is the primary cause of morbidity in cholera and transfused 25 patients with 330 ml of normal saline solution over 12 h and noted 'a third of my patients have been restored to life' [2, 3].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_5

In 1880, Ringer's solution was discovered as the 'balanced and physiological' solution, which can retain better organ function than 'normal saline'. The solution was then refined in 1930 to make what is now known as lactated Ringer's solution.

In the early twentieth century, discovery of blood groups and the general acceptance of blood transfusion for the treatment of shock in World Wars I and II encouraged the modern development of intravenous fluid therapy.

Pathophysiology of Fluid Management

During illness or injury, fluid balance and distribution are impaired in different ways:

Intracellular and Extracellular Fluid Disturbance

- Cellular destruction, due to tissue hypoxia, can lead to release of intracellular contents including potassium and cytokines, which lead to imbalance in the equilibrium between intracellular and extracellular fluids [4]. This effect is more pronounced when renal function is compromised, e.g. acute kidney injury (AKI).
- In response to physiological stress such as illness or injury, the body increases metabolic rate and protein breakdown in order to deal with the physiological demands and promote healing. A degree of oliguria is a non-specific pathophysiological response to severe illness. This does not necessarily mean that the patient is fluid depleted. For these reasons, a critically unwell patient in the catabolic phase may become overloaded as a consequence of poorly controlled fluid therapy.
- During the recovery/rehabilitation phase after the inflammatory response has subsided, loss of the excess sodium and water accumulated during the catabolic phase results in negative fluid balance.
- During disease states, leaky capillary membranes allow intravenous fluid to leak into the interstitial space as extravascular volume until equilibrium is reached across the capillary membrane. Recent studies have shown that the resuscitative volumes of crystalloid and colloid are often similar in clinical practice [6–8]. Theoretically, this could be explained by the physiological leakage of colloid particles into the extravascular space, resulting in an increase of tissue oncotic pressure; this exacerbates fluid losses into the interstitial compartment and thereby worsens the associated problems (tissue and pulmonary oedema). This leads to a worsening of fluid distribution abnormality (Fig. 5.1).

Treatment Administration Strategy

- A tailored approach to fluid management is required for each patient, taking into account the phase of illness in which they present and the severity of their fluid/

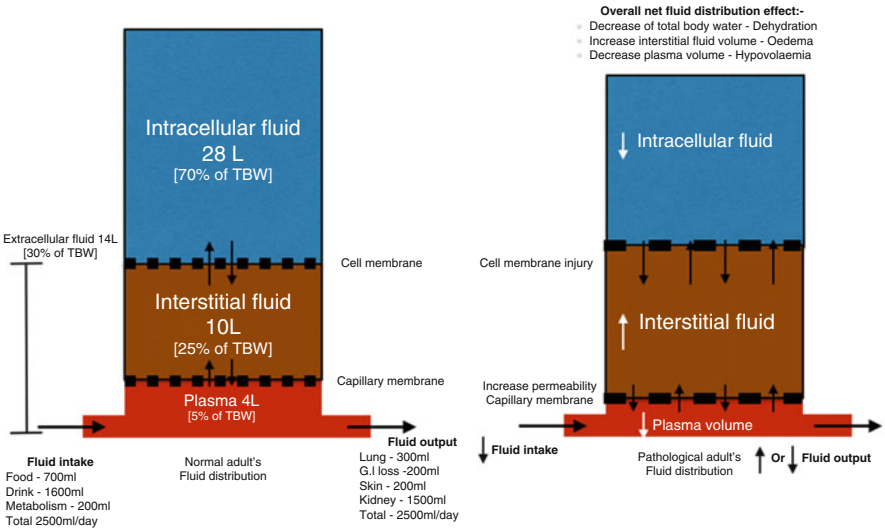

Fig. 5.1 Diagram of physiology and pathophysiology of fluid distribution

electrolyte disturbance. In order to make this assessment, a detailed medical history and examination are required. Important components of the 'fluid history' are:

- Any previous restriction of fluid intake
- Any ongoing fluid losses and its quantity and composition
- Co-morbidity, i.e. renal, liver and cardiac failure and gross oedema

Examination should include:

- Signs of shock: [quoted from NICE guideline [5] criteria for IV fluid resuscitation]
  - Systolic blood pressure <100 mmHg.
  - Heart rate >90 bpm.
  - Capillary refill time >2 s/cold peripheries.
  - Respiratory rate >20 breaths per minute.
  - National Early Warning Score (NEWS) ≥5.
  - Positive passive leg raise test, i.e. compared to a baseline measurement of stroke volume index (SVI). The patient is placed supine and the legs raised to approximately 30°. This produces a transient increase in preload of approximately 50 ml. An increase in SVI of ≥10 % indicates that a patient is not fluid responsive, while an increase of ≤10 %indicates fluid responsiveness and suggests further fluid therapy is required.
- *Signs of intravascular depletion*

  - Dry mucous membranes
  - Decrease skin turgor
  - Orthostatic hypotension and orthostatic increase in pulse rate
  - Cold peripheries
  - Low jugular venous pressure [JVP]
  - Fast and weak pulse

- *Signs of volume overload*
  - Pulmonary oedema
  - Increase in weight
  - Moist mucous membranes
  - Peripheral oedema
  - Elevated JVP

It is important to note that oral rehydration is often the preferred route of rehydration, if tolerated, in the maintenance and replacement phase of fluid administration.

Fluid administration should be divided into three stages:

1. *Resuscitation phase*
   - When intravascular volume is deplete resulting in inadequate tissue oxygenation, high flow oxygen should be administered. A bolus of 500 ml of IV fluid should be given within 30 min.
   - Effect should be reassessed immediately in order to assess the need for further fluid boluses.
   - Minimal clinical response to a total of 30 ml/kg of fluid administration [e.g. 2,100 ml in a 70 kg man]; a vasopressor would need to be commenced and alternative causes of shock would need to be considered.
2. *Replacement phase*
   - Characterised by a fluid deficit composed of fluid losses (i.e. haemorrhage, third space losses, diarrhoea, etc.) and an overall negative fluid balance (i.e. fluid losses exceed those given), but the patient is not in shock.
   - Detailed assessment is needed to determine the source of fluid loss as it determines the choice of replacement fluid.
   - Fluid therapy should include the routine maintenance requirement plus additional fluid and electrolyte supplements to replace the 'measured' abnormal 'ongoing' losses, i.e. a close titration of fluid and electrolyte losses to the choice of replacement fluid. Enteral supplement is often preferred if tolerated (see Table 5.1).
3. *Maintenance phase* – is characterised by a state with no identified ongoing fluid losses, no signs of shock and a balanced fluid input–output. Maintenance treatment should meet the normal daily fluid and electrolyte requirements, which are as follows:
   i. 25–30 ml/kg/day water – approximately 2 L in a 70 kg man

Table 5.1 Composition of fluid loss

Type of fluid loss	Na+[mmol/l]	K+[mmol/l]	Cl-[mmol/l]	H+ [mmol/l]	HCO3-[mmol/l]	Effect and ideal replacement
Gastric fluid [vomiting/NG tube loss]	20–60	14	140	60–80	Minimal	Excessive gastric fluid loss leads to hypochloraemic and hypokalaemic metabolic alkalosis
						Replace – K+ and Cl-
						Tx- 0.9 % NaCl +/– KCl
Biliary drainage	145	5	105	Minimal	30	High salt loss
						Tx- Hartman's/Plasmalyte
Diarrhoea/colostomy fluid	30–140	30–60	–	–	20–80	Dehydration with high salt loss especially potassium loss
						Tx- 0.9 % NaCl +/– KCl
High-volume ileal loss via new or high stoma/fistula fluid	100–140	4–5	75–125	–	0–30	Dehydration with hypochloraemic metabolic alkalosis if high volume
						Tx- Hartmann's solution
Lower volume ileal loss via established stoma/low fistula	50–100	4–5	25–75		0–30	Dehydration mainly
						Tx- Hartmann's solution/ Plasmalyte
Pancreatic fluid	125–138	8	56	–	85	Tx- Hartmann's solution/ Plasmalyte
Jejunal loss via stoma/fistula	140	5	135	–	8	Excessive fluid loss will lead to hypochloraemic acidosis
						Tx- 0.9 % NaCl +/– KCl
Urinary loss	Variable	Variable	Variable	Variable	Variable	Monitor electrolyte and treat accordingly
Insensible loss [i.e. fever/ hyperventilation, etc.]	Minimal	Minimal	Minimal	–	–	Tends to be 'pure water' loss with minimal electrolyte loss

ii. 1 mmol/kg/day sodium, potassium and chloride
iii. 50–100 g/day glucose [e.g. 5 % glucose = 5 g/100 ml]

The most common fluid of choice for maintenance fluid is 0.18 % NaCl with 4 % glucose and 30 mmol/KCl in each litre. Two litres of such solution would meet the daily requirement.

Choice of Fluid

Fluid choices can be categorised into three main groups; (1) crystalloid, (2) colloid and (3) blood-related products. This section will focus mainly on the differences between crystalloids and colloids. Blood products are beyond the scope of this chapter.

Crystalloid

A crystalloid is defined as an aqueous fluid containing substances with properties of a crystal, i.e. glucose or salts. Crystalloids can be classified into:

1. *Isotonic crystalloid,* i.e. 0.9 % sodium chloride, lactated Ringer's solution and other types of balanced crystalloid. Infusion of isotonic solution into plasma does not cause any loss or gain of water by osmosis. Isotonic crystalloids are most useful during the fluid resuscitation phase.
2. *Hypotonic crystalloid,* e.g. dextrose saline, which is available in various percentages (including 0.18 %, 0.45 %, 4 %). Infusion of hypotonic solution is equivalent to a bolus of water which is distributed to all fluid compartments including the intracellular fluid by osmosis until osmotic equilibrium is achieved. The main use of hypotonic solution is as a maintenance fluid.
3. *Hypertonic crystalloid,* i.e. 1.8–7.5 % sodium chloride. Infusion of hypertonic solution can draw water from intracellular and interstitial compartments into the intravascular compartment in order to increase intravascular volume. 7.5 % saline has been quoted to have a volume expansion of four to ten times of the infused volume. The main use of hypertonic solution is to provide a temporary treatment in osmotic intracranial pressure rescue and severe hyponatraemia (Table 5.2).

Colloid

Colloid is defined as a suspension of particles, with a diameter between 1 and 1,000 nm, which is homogenously mixed within the solvent and does not settle with gravity, i.e. milk is an example of emulsified colloid solution. The solvent often

Table 5.2 Composition of crystalloid therapy

Fluid	Plasma	0.9 % sodium chloride [normal saline]	Ringer's lactate [Hartmann's solution]	Sodium 0.18 % + 4 % dextrose	5 % dextrose	50 % dextrose	5 % sodium chloride
Na+ mEql/L	144	154	130	31	–	–	855
K+ mEql/L	5	–	4	–	–	–	–
Cl- mEql/L	107	154	110	31	–	–	855
Ca mEql/L	2.3	–	2	–	–	–	–
Mg mEql/L	1.8	–	–	–	–	–	–
Glucose mEql/L	5	–	–	222	278	2,778	–
Buffer mEql/L	Lactate-<1	–	Lactate – 28	–	–	–	–
Kcal/l	–	–	–	136	170	1,700	–
Calculated osmolality	290	308	275	262	278	2,778	1,711
Advantage		Cheap	Cheap	Glucose provision during fasting			Increase intravascular volume
		More sustainable volume effect than Hartmann's	Physiological composition with less chloride content can reduce the chance of hyperchloraemic acidosis	Treatment of hypoglycaemia			Small volumes can resuscitate effectively
		Common solvent for administration of drugs		Allows I.V. water to be supplied without haemolysis			Improved microcirculation with splanchnic vasodilatation

(continued)

Table 5.2 (continued)

Fluid	Plasma	0.9 % sodium chloride [normal saline]	Ringer's lactate [Hartmann's solution]	Sodium 0.18 % + 4 % dextrose	5 % dextrose	50 % dextrose	5 % sodium chloride
Disadvantages		Saline is an acidotic solution	Outcome benefit has not yet demonstrated	Hyponatraemia			Hypernatraemia and hyperchloraemic acidosis
		Hyperchloraemic acidosis	Dilutional procoagulant effect	Thrombophlebitis			Risk of central pontine myelinolysis
		Associated with renal failure		Poor intravascular volume expander			Rebound intracranial hypertension and coagulopathy
		Abdominal discomfort					No evidence of improved outcome in head injury patient
		Subtle cognitive deficit					
		Dilutional procoagulant effect					
Ideal choice		Fluid replacement	Fluid resuscitation during hypovolaemic shock of any cause	Fluid maintenance –25 ml/kg/day if added K+ to solution [30 mmol/L]	Intravenous glucose provision		Intracranial hypertension
		Dehydration secondary to G.I losses					Prehospital/low-volume resuscitation
Tonicity of solution		Isotonic crystalloid		Hypotonic crystalloids			Hypertonic crystalloids

contains water and electrolytes, either isotonic (i.e. Hartmann's solution) or hypertonic (i.e. 5–7.5 % hypertonic solution) properties.

The colloid component contains large molecules which theoretically should not cross the capillary membranes and instead remain in the intravascular compartment. These can exert an oncotic pressure and encourage fluid to be retained intravascularly. The breakdown of these colloid particles occurs over several hours; hence, it has a theoretical advantage compared with crystalloid as the effects are prolonged. In general, colloid solutions can be classified into two main categories:

1. Natural colloids, i.e. albumin
2. Synthetic colloids, i.e. starches, dextran and gelatins

Natural Colloids

Human Albumin Solution [HAS]

Albumin has been in use since the 1950s. It has a molecular weight of 66,000 Da and contributes up to 80 % of the plasma colloidal oncotic pressure. It has been quoted that it can expand to five times of its own volume over 30 min. Albumin preparations usually come in two different concentrations: 4–5 % or 20–25 %. It is usually diluted with either 5 % dextrose or 0.9 % normal saline. Albumin solution (4–5 %) is an isotonic solution, which has been used particularly for hypovolaemic resuscitation in some parts of the world, like Australia. Twenty to 25 % albumin is a hypotonic but hyperoncotic solution. It is often referred to as salt-poor albumin solution, as it can minimise the requirement for infusion of additional salts and fluid with high oncotic pressure.

The use of albumin remains controversial. Over the past two decades, there have been two meta-analyses produced by the Cochrane Review group comparing the use of albumin to crystalloid in managing critically ill patients. The current recommendation is not to use albumin as a resuscitation fluid [8, 9] as it is not deemed to be cost-effective.

Synthetic Colloids

Gelatins

Gelatins are derived from bovine collagen – gelatin. They have an average molecular weight of 35,000 Da with half-life of 2 h. They are rapidly excreted by the kidney, and only 20 % remains in the intravascular compartment by 90 min. Gelatins have fewer incidences of coagulopathy, pruritus or renal impairment on comparison with synthetic colloids. However, the major disadvantage is that they have relatively high rate of anaphylaxis [1 in 290] as the source of collagen is from cattle bone.

There is also a theoretical risk of new-variant Creutzfeldt–Jakob disease (CJD) transmission (see Table 5.3 for its properties). Gelatins are most suitable for short-term plasma expansion during anaesthesia; however, it is not the ideal solution for resuscitation, and there is a lack of evidence supporting its use.

Dextrans

Dextrans are polysaccharide molecules with a tendency to precipitate coagulopathy and acute renal failure. There is an intermediate risk of anaphylaxis. Due to these side effects, dextrans are rarely used in current clinical practice.

Starches

Starch solutions are derived from hydrolysed maize, and the newer generation molecule is commonly referred to as hydroethyl starch [HES]. This has a variable molecular weight from 130 to 200 kDa and a half-life of 24 h, which results in prolonged elimination of the drug relative to other fluids. The permissible daily maximum dose is 20 ml/kg/day. The advantage of HES is that it can have a sustained volume expansion effect and that there is a relatively low incidence of anaphylaxis. However, the disadvantages of HES are:

- Poor clearance of the drug.
- Reduction of factor VIII and von Willebrand activity and prolongation of the APTT, resulting in coagulopathy.
- Pruritus [approximately 10 %].
- Renal impairment – HES has been demonstrated to cause an increase in the incidence of acute renal failure and even nephrotoxicity. There is also the risk of raised serum amylase levels and anaphylactoid reaction [10, 11].
- Currently, the use of HES is not recommended (Table 5.3).

Ideal Choice of Fluid

Neither crystalloids nor colloids can improve oxygen-carrying capacity, and theoretically, both have the effect of diluting the oxygen-carrying capacity. The ideal resuscitative fluid should be a blood product, especially in acute haemorrhage. Blood products are precise, but expensive, and carry a risk of fatal transfusion reactions and may necessitate a delay for ‘crossmatching’. Consequently, these products should be restricted to bleeding patients or septic patients with critical anaemia. Recommended fluid strategies for various conditions are given in Fig. 5.2.

Table 5.3 Composition of colloid therapy

Fluid	Albumin 4.5 %	Albumin 20 %	Gelofusine	Haemaccel®	Dextran 40	Dextran 70	HES
Natural/synthetic	Natural colloidal solution		Synthetic – gelatins		Synthetic – glucose polymers		Synthetic –starches
Colloid	Albumin	Albumin	Succinylated gelatine	Urea-linked gelatin	Dextran 40	Dextran 70	Hydroxyethyl starch [tetrastarch]
MWw (kDa)		154	110	98	31	–	–
Plasma half-life[hr]	16	16	2	2	4	6	3
Acidity of solution	Neutral [7.4]				Acidotic		
Oncotic effect	++	++++	+	+	++++	+++	++
Calculated osmolarity	300	300	279	300	310	309	309
Overall initial intravascular volume effect [infusion volume: intravascular volume effect ratio]	1:1	1:2.5	1:1	1:1	1:2	1:1.4	1:1
Coagulopathy	+		++		+++++		+++
Skin itch	–		–		–		+++
Renal impairment	–		–		+++		+++
Anaphylactic reaction risk	++		+++		+++		+
Infection risk	+		+ [new-variant CJD risk]		–		–

(continued)

Table 5.3 (continued)

Fluid	Albumin 4.5 %	Albumin 20 %	Gelofusine	Haemaccel®	Dextran 40	Dextran 70	HES
Special note	Safe for septic patient		Collagen source from cattle bone		Poor side effect profile		Poor body clearance
	Safest colloid for use		High risk of anaphylaxis [1 in 290]		Out of favour due to its side effect		HES can accumulate in the skin, kidney and various organs
	No overall mortality benefit noted		Potential risk of new-variant CJD transmission				Coagulopathy, renal impairment and skin itch for up to 13 %
			Better side effect profile compare with starches and dextrans in coagulopathy and renal impairment				FDA has recently withdraw HES from its market due to its side effect profile
			No evidence to support its role in resuscitation				

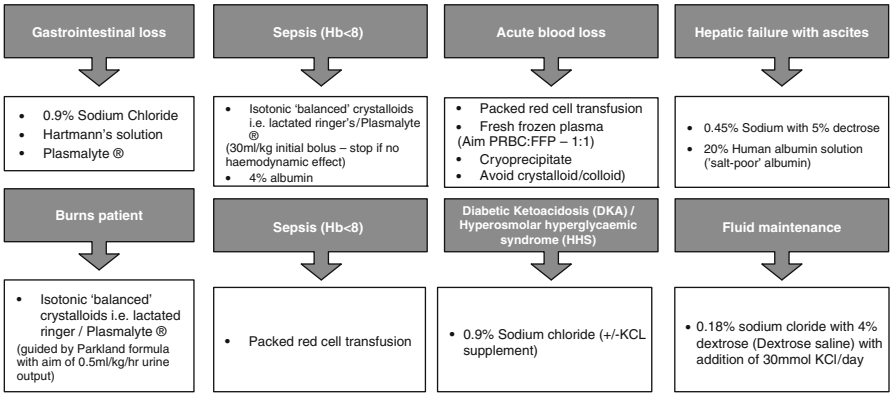

Fig. 5.2 Recommended choice of fluid in various situations

Treatment End Points

There is an increasing body of evidence suggesting the detrimental effect of fluid over-resuscitation. A cumulative positive fluid balance has been associated with longer period of 'ventilator-dependent days' and impaired renal function. If patients require renal replacement therapy to remove fluid as a result of a persistent positive fluid balance, it is associated with higher mortality [12]. Hence, fluid resuscitation should be rational and titrated to its treatment end points.

The risk–benefit ratio of fluid resuscitation can be demonstrated by the Frank–Starling curves. Intravenous fluid is beneficial when improving the preload results in improved cardiac output. However, when increasing the preload no longer results in improved cardiac output, it will lead to harm. It is termed 'fluid responsiveness'.

There are various different techniques to predict fluid responsiveness. Central venous pressure [CVP] has been commonly used to guide fluid management in critically ill patients; however, the correlation of CVP measurement and fluid responsiveness is very poor [13].

In spontaneously ventilating patients, the passive leg raise test and 'mini-challenge' test should be used to predict fluid responsiveness (Fig. 5.3a, b).

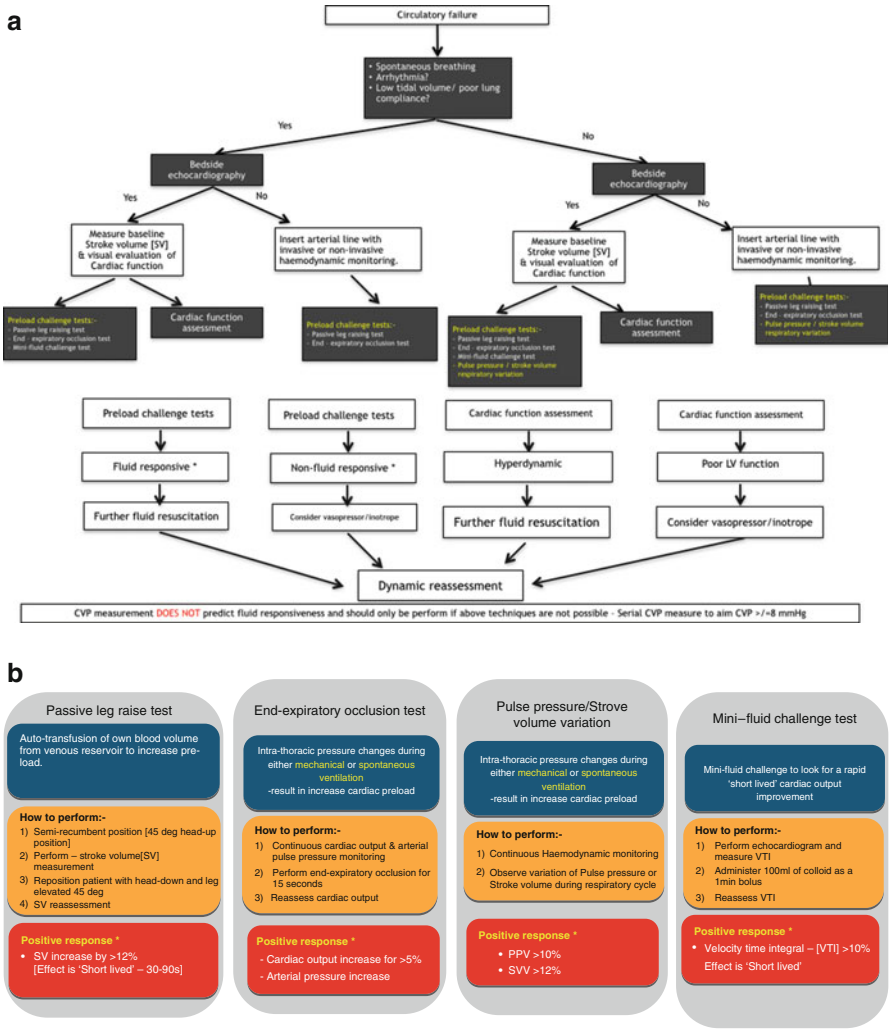

Fig. 5.3 (**a**) Fluid responsiveness decision making flowchart. (**b**) Fluid responsiveness test summary and its positive response

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Chapter 6
Post-cardiac Arrest Care

Neal Durge and Chris Solomonides

Key Points
- The post-cardiac arrest patient is time critical.
- Immediate goals are to optimise physiology and identify the precipitating cause.
- Consider coronary reperfusion techniques in all patients.

Introduction

The management of patients who have achieved a return of spontaneous circulation (ROSC) following cardiac arrest is one of the most exciting areas of research and development in emergency medicine over the past decade. The emergency physician has a primary role in instituting care in the minutes and hours immediately after ROSC which can have a dramatic effect on eventual outcome.

A multidisciplinary team approach needs to be maintained in the post-cardiac arrest period, although the actual team members may change to those with expertise specific to the individual patient needs. The majority of deaths occur in the first 24 h

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_6

after ROSC [1]. The aims of immediate post-cardiac arrest care can be broadly categorised into three main areas:

- Physiological stabilisation to optimise organ perfusion
- Identification and treatment of the underlying cause of the arrest
- Prognostication – generally not accurate within the first 24 h

However, the underpinning principle of management of any critically unwell patient is concurrent activity and a linear approach to investigation and management is time consuming and detrimental. Several important actions and interventions are outlined below, but the most important of these is the treatment of the underlying precipitant cause of the cardiac arrest.

The Post-cardiac Arrest Syndrome

During cardiac arrest, there is a prolonged period during which delivery of oxygen and metabolic substrates to the tissues is interrupted. This whole-body ischaemia causes global tissue and organ injury. During and immediately after cardiac arrest, there is microcirculatory failure, with increased capillary permeability and endothelial cell activation, which leads to a systemic inflammatory response [2, 6]. Reperfusion, following global ischaemia, leads to significant tissue damage which can result in brain injury, myocardial dysfunction and a systemic response with activation of immunological and coagulation pathways, which is highly predictive of subsequent multi-organ failure. The superimposition of this ischaemia-reperfusion response with the persistent precipitating pathology constitutes the *post-cardiac arrest syndrome*. It has many pathophysiological features in common with sepsis, and indeed, there is an increased risk of infection [5]. Sixty per cent of initially unconscious patients following ROSC will develop pneumonia. The most common causes of death in patients with post-cardiac arrest syndrome are brain injury and myocardial dysfunction; therefore, management of patients with ROSC, following cardiac arrest, requires a complex and targeted phase of resuscitation.

Principles of Management

Airway and Breathing

- Following ROSC, unconscious patients and those with absent or inadequate spontaneous ventilatory effort will require endotracheal intubation and mechanical ventilation.
- Awake patients, who have recovered from a brief cardiac arrest and are able to maintain their airway and breathe adequately, may not require endotracheal intubation.

- Patients, who have been managed initially with a supraglottic airway, or other airway adjuncts, should have them replaced with an endotracheal tube.
- Intubated patients, in the post resuscitation phase, should be maintained on adequate sedation. This is best achieved with combinations of short-acting agents, with or without a neuromuscular blocking agent, to allow a timely neurological assessment to take place on their cessation [5, 6].
- Death rates in patients with ARDS are improved by reducing tidal volumes. Several studies recommend ventilating patients to maintain a VT of 6–8 ml/kg and maintaining peak pressures <30 cm H2O to reduce the incidence of lung injury [5, 6].
- Ventilation with continuous pulse oximetry and end-tidal capnography aid confirmation of correct placement of the tracheal tube and are essential monitoring devices.
- Essential investigations include a chest radiograph, both to confirm correct placement of the endotracheal tube and to identify any pathology that requires intervention including pneumothorax and pneumonia. An arterial blood gas is vital to assess the adequacy and response to ventilation and to understand the extent of the metabolic debt accrued during the cardiac arrest phase.
- Hyperoxaemia induces oxidative stress and damages postischaemic neurones by generating oxygen-derived free radicals. Ventilation with 100 % oxygen worsens outcome compared with ventilation titrated to a pulse oximeter reading of between 94 % and 98 % [3–5]. Currently, therefore, to avoid potential oxygen toxicity in the reperfusion phase, the inspired oxygen concentration should be titrated to oxygen saturations of 94–98 %.
- Patients should not be hyperventilated. This is to avoid both hyperoxaemia and the reduction in cardiac output precipitated by hyperinflation. Hyperventilation aggravates gas trapping, especially in patients with pre-existing lung pathology, which compromises cardiac output by increasing intrathoracic pressure and decreasing venous return to the heart [5].
- Hyperventilation also lowers the paCO2 which causes intracerebral vasoconstriction and may exacerbate cerebral ischaemic injury. One study has demonstrated that hypoventilation, with hypercapnia (which induces cerebral vasodilatation), increased survival. Thus, the current recommendation is to maintain a normal paCO2 of 35–45 mmHg [2, 5, 6, 7].

Circulation

- The principle of management is to balance the need for adequate organ perfusion, in particular the brain, without putting undue strain on the postarrest myocardium.
- Even though the cerebral response to paCO2 is preserved after cardiac arrest, there is loss of the autoregulation of cerebrovascular pressure; hence, brain perfusion is dependent on the cerebral perfusion pressure (CPP). As CPP = mean

arterial pressure (MAP) – intracranial pressure (ICP) and, unless the cause of the cardiac arrest in intracranial, the ICP is invariably not raised, then brain perfusion is directly dependent upon MAP.

- The optimal MAP is dependent on a number of variables and targets should be set for each individual with these in mind. In light of the available evidence, MAP of 65–100 mmHg is recommended. Other measure includes blood transfusion, if haemorrhage is believed to be major precipitating cause of the arrest [6].
- Lactate clearance provides a reasonable surrogate marker of haemodynamic optimisation, but it will almost always be elevated in the postarrest patient. However, it must also be remembered that several confounders affect lactate clearance including hepatic impairment, seizures and, notably, hypothermia.
- Essential monitoring post-cardiac arrest includes continuous ECG, non-invasive blood pressure and urine output. Invasive blood pressure monitoring is mandated in cases where inotropic or vasopressor support is required. Urine output is increased in hypothermia, and as the core temperature of the patient will always fall during arrest and in the immediate postarrest period, then it is not unreasonable to aim for a relatively high urine output goal, particularly when being treated with mild therapeutic hypothermia.
- Blood pressure can be regulated using crystalloid, colloid, blood and vasopressors. Currently, no evidenced-based transfusion threshold exists to guide blood transfusion. However, if hypovolaemia is deemed to be a significant contributory factor to the cardiac arrest, then aggressive transfusion strategies are warranted. If preload has been attended to with intravenous fluids but haemodynamic optimisation not yet achieved, then inotropes and vasopressors should be considered.
- Essential cardiovascular investigations in the immediate postarrest period include a 12-lead ECG and echocardiogram. The most common cause of cardiac arrest is coronary artery disease [8]. Evidence of ST elevation or new left bundle branch block (LBBB) on ECG should activate pathways to initiate immediate access to coronary reperfusion, ideally percutaneous coronary angiography and angioplasty more commonly referred to as percutaneous coronary intervention (PCI). Importantly, absence of ST elevation or new LBBB does not exclude coronary artery disease as the cause of the arrest and the same treatments and interventions should be considered. An echocardiogram can provide valuable information not only on the presence or severity of any myocardial dysfunction but also on potential causes of arrest. Cardiac tamponade is readily visible on bedside echo and right heart dilatation must lead the physician to strongly consider massive pulmonary embolus as a persisting precipitating cause and to consider immediate corrective therapy in the form of thrombolytic agents or surgical embolectomy. Regional wall abnormalities, in this context, need to be assumed to be the result of myocardial infarction and coronary reperfusion once again considered.

Therapeutic Hypothermia

- International guidelines for survivors of cardiac arrest recommend mild therapeutic hypothermia as a strategy for improving functional outcome in the post resuscitation phase [6, 9]. Randomised controlled clinical trials and a meta-analysis have concluded that in the comatose survivor, cooling to between 32 and 34 °C, initiated within minutes to hours of ROSC and maintained for up to 24 h after ROSC, confers a neurological function outcome benefit [10, 11].
- A large international randomised controlled trial found no benefit in cooling to 33 °C over 36 °C [12]. It must also be emphasised that this study reinforces the importance of therapeutic hypothermia in the emergency physician's approach to the post resuscitation phase of care but questions whether resources devoted to attaining and maintaining a lower core temperature are warranted.
- An elevated temperature in the postarrest phase is a common complication and increases the risk of a poor functional outcome for every degree above 37 °C [13]. All therapeutic strategies for the care of the post-cardiac arrest patient must include the avoidance of hyperpyrexia as a minimum.
- Mild therapeutic hypothermia remains one of the only interventions instituted in the postarrest phase that has been shown to confer an outcome benefit. Both during and immediately after cardiac arrest, the patient's core temperature will fall; a reasonable strategy is to attain a core temperature of 36 °C which is likely to involve temperature preservation in the absence of any active cooling or rewarming.
- Induction, maintenance and rewarming are the three phases of therapeutic hypothermia. Induction and maintenance are the remit of the emergency physician. Infusion of ice-cold crystalloid is an easily available and inexpensive technique, but standard regimes of 30 ml/kg run the risk of volume overload and resultant pulmonary oedema and hence, this method should be avoided unless volume expansion is required for other indications. Frequently replenished ice packs placed around the neck and in the axillae and groin are equally inexpensive and effective. More expensive cooling blankets which circulate cold fluid or air are probably more effective in maintaining mild hypothermia but confer no other benefit and can be replicated by the placement of wet blankets over the torso.
- Accurate temperature monitoring is essential. This is best achieved with an oesophageal temperature probe. Tympanic probes are unreliable, particularly with temperature manipulation, and rectal and bladder probes often indicate the temperature of the cavity contents rather than true core temperature. A pulmonary artery catheter represents the gold standard in temperature monitoring and can be used if there are other indications for placement.
- Inducing hypothermia is not without complications. Shivering is prevented by neuromuscular blocking agents, but coagulopathy, hyperglycaemia and an increased propensity for cardiac arrhythmias, and in particular pneumonia, are also unintended consequences which need to be actively sought and managed.

- In summary, a targeted temperature of 36 °C should be attained as quickly as possible in the immediate postarrest period, by the judicious use of frequently replenished ice packs. Core temperature should be monitored with an oesophageal temperature probe and vigilance maintained for potential complications.

Seizure Control

- Unrecognised and prolonged seizures are detrimental and in the sedated and paralysed patient can be difficult to diagnose clinically. Few patients receive continuous electroencephalograph monitoring, but empiric treatment with neuroprotective agents has not been shown to improve morbidity or mortality.
- Treatment of seizures in the post-cardiac arrest patient should follow the same treatment regime as seizures in any other patient.

Glycaemic Control

- Both hypoglycaemia and hyperglycaemia have a detrimental effect on functional outcome, but tight glycaemic control appears to confer no benefit and increases the risk of hypoglycaemia [5, 6, 14].
- Blood glucose concentrations should be maintained between 6.1 and 8 mmol/L. Frequent monitoring is essential particularly during temperature manipulation and if insulin is initiated.

Traumatic Cardiac Arrest

Survivors from cardiac arrest of traumatic aetiology have increased in recent years. Reasons for this substantial improvement are multifactorial but highly dependent on the increased focus and attention paid to this cohort of patients, particularly during times when westernised countries are involved in conflict.

As with non-traumatic cardiac arrest, the essential component of management of the cardiac arrest is the rapid identification and treatment of potentially reversible causes. Naturally, these causes are very different in the victim of traumatic cardiac arrest (TCA) and efforts need to be directed at reversing hypovolaemia, poor oxygenation, tension pneumothorax and cardiac tamponade [15].

In the case of cardiac tamponade caused by penetrating torso trauma, the resuscitative or emergency thoracotomy is now well established as a surgical intervention that can reverse traumatic cardiac arrest and result in a good functional outcome. This procedure should be considered an essential skill for the emergency physician.

TCA caused by haemorrhage has universally poor outcomes with very few survivors reported in the published literature. Postarrest care of these patients must concentrate on identifying the site of the haemorrhage and providing a definitive surgical repair. External haemorrhage is generally obvious and can be controlled with direct pressure and the use of arterial tourniquets. Internal, noncompressible haemorrhage presents more of a challenge, as the site of bleeding may be located in the thoracic or abdominal cavities, the pelvis or long bones, particularly the femurs. Immediate chest and pelvic radiographs are essential and further imaging by focussed assessment with sonography for trauma (FAST) scans should also be readily available. A FAST scan can accurately identify bleeding within the peritoneal cavity and can be used as an aid to direct the trauma surgeon to the causative site. Computed tomography (CT) provides much more detailed and accurate information but should be reserved for haemodynamically stable patients.

ROSC is unlikely to be achieved in the patient with TCA secondary to hypovolaemia without volume expansion. Blood and blood products are the ideal resuscitative fluids, with crystalloid and colloid potentially causing harm [16].

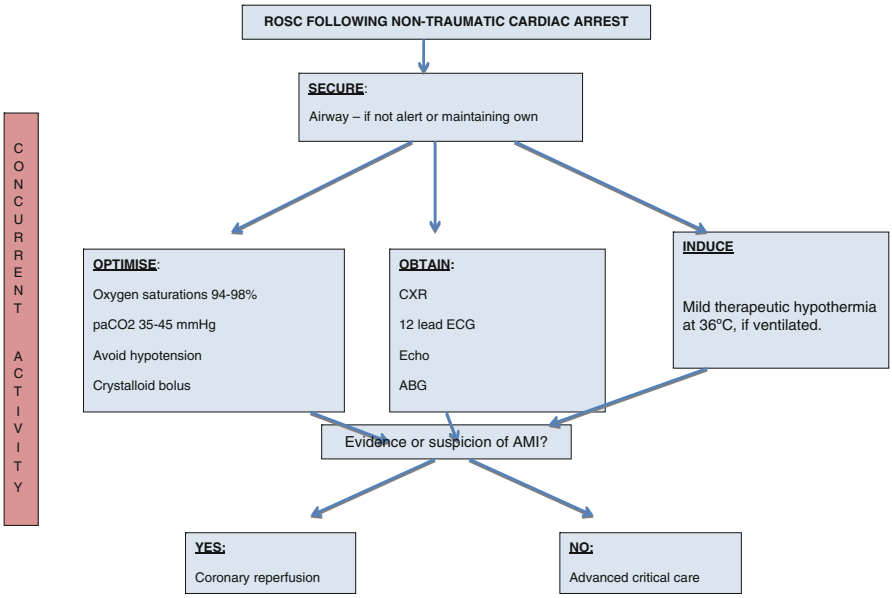
TCA secondary to poor oxygenation is readily reversed by basic or advanced airway manoeuvres. There are numerous potential causative factors, but brain injury causing loss of consciousness and airway reflexes is probably the most common. Once the airway has been secured and ventilation commenced, a CT head scan is mandatory. In patients with a primary brain injury, simple measures can be taken to minimise secondary brain injury. These include a ventilation strategy to control the paCO2 in the normal range, placing the patient in a 30° head up position, ensuring there are no constrictions around the face or neck (including cervical spine collars and endotracheal tube ties) and maintaining normothermia.

In contrast to non-traumatic cardiac arrest, therapeutic hypothermia has no proven role in the post resuscitation phase. Indeed, as coagulation is impaired in lower core body temperatures, normothermia should be the goal.

Obstructive causes of shock and TCA also need to be ruled out. A tension pneumothorax should be diagnosed clinically and is definitively treated by chest decompression. Needle decompression is quick and easy, but unlikely to be of much value in TCA, not least because the thoracic cavity will not be breached in a significant proportion of adult male patients, by using a standard 14-gauge cannula [17]. Of much greater value is a thoracostomy. In patients receiving intermittent positive pressure ventilation (IPPV), a simple finger thoracostomy will suffice in the initial stages. In spontaneously ventilating patients, a tube thoracostomy is necessary.

In summary, the post-traumatic cardiac arrest patient presents significant challenges for the emergency physician. A well-organised multidisciplinary approach is required to rapidly and accurately detect the cause of the arrest and provide definitive intervention.

Appendix: Algorithm for the Management of Non-traumatic Cardiac Arrest



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Chapter 7
Vascular Access

Mir Saaduddin Ahmad

Key Points
- For rapid fluid infusion, wide bore cannulae of short length will facilitate resuscitation.
- Rate of flow can be affected by external factors like gravity, infusor devices and fluid viscosity.
- Difficult cannulation can be aided by the use of high-frequency (8–5 MHz) ultrasound.
- If direct cannulation fails, techniques like intra-osseous access, endotracheal access and venous cutdown can be used for drug administration.

Introduction

The commonest form of access obtained in emergency department resuscitation is peripheral intravenous access by an intravenous cannula (Latin for *little reed*). The indications for this include the following:

1. Obtaining blood samples
2. Administering intravenous fluids
3. Administering intravenous drugs
4. Provision of blood and blood products
5. Providing nutritional support
6. Administering radio-opaque dyes for contrast imaging

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_7

Also quite common is the utilisation of central venous catheters, which can be used for, in addition to the above, the following reasons:

1. Replenishing loss of circulating volume
2. Difficult peripheral access
3. Measurement of central venous pressure
4. Administering irritant drugs

Both of the above, as well as arterial access below, can be facilitated by the use of ultrasound [1]. In the circumstances where such procedures fail, one can proceed to a venous cutdown or (although strictly not directly accessing a vessel) intra-osseous (Fig. 7.1) and endotracheal access.

Vascular access also includes arterial access, the indications for which include:

1. Sampling of arterial blood gases
2. Monitoring of invasive blood pressure

Pathophysiology

When obtaining venous access, it is important to remember some basic principles. Veins are elastic, capacious, valvular vessels that return blood from the peripheries to the heart. To optimise the chance for a successful cannulation, compression can be applied proximally, or the site should be kept dependant; both allow for the pooling of blood in the vein. Valves should be avoided as they may obstruct the progression of the cannula in to the lumen.

When choosing a cannula, size matters. To obtain the best flow rates for patients with a severe loss in circulating volume, a cannula with the largest internal diameter is required. The flow rate (see Table 7.1) is governed by Poiseuille's law [2]:

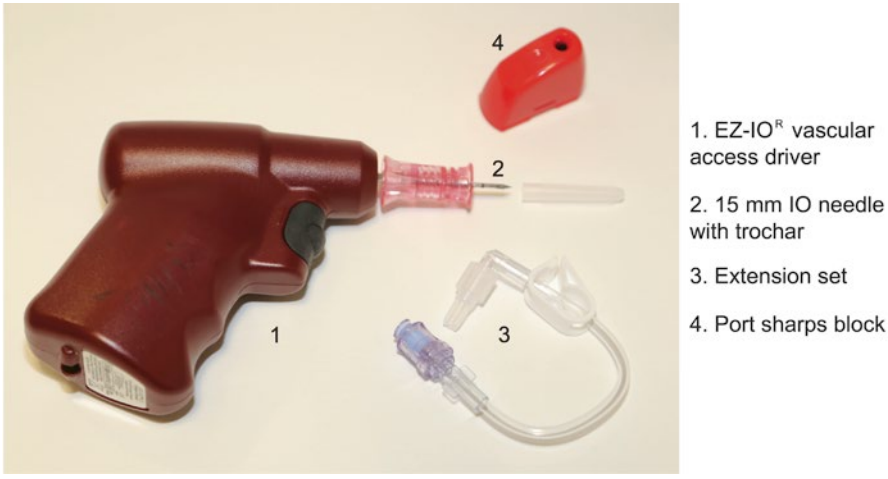

Fig. 7.1 A mechanical intra-osseous device and parts

Table 7.1 Sizes and flow rates of intravenous cannulae

Size	Colour	Length (mm)	Flow rate (ml/min)
14 G	Orange	45	240
16 G	Grey	45	180
18 G	Green	45	80
20 G	Pink	32	54
22 G	Blue	25	31
24 G	Yellow	19	13

$$\text{Rate of flow} = \frac{\pi \times (\text{cannula internal radius})^4 \times \text{pressure difference}}{8 \times \text{fluid viscosity} \times \text{length of cannula}}$$

From the equation above, it is seen that simply doubling the internal diameter increases the flow rate 16 times. Other factors that affect the rate of flow are pressure gradient (pressure bags, infusor devices or gravity), viscosity of the fluid administered and length of the cannula (the shorter the cannula, the greater the flow).

Box 7.1
Cannulae are sized in accordance to the old needle gauge system, where the gauge specified is the external diameter as a division of an inch (e.g. a 16-G cannula is 1/16 of an inch). This is contrary to French gauge, which is a straightforward estimate of the external diameter. Therefore, the larger the gauge annotation of a cannula, the smaller the cannula is, and the larger the French gauge annotation of a catheter, the larger the catheter is.

Box 7.2
A blood set has a drop factor of 10, a regular set is 15 and that of a microburette is 60. The drop factor is the number of drops that make up 1 ml. A drop is abbreviated as gtt (plural gtts) from the Latin gutta. When administering fluids to a patient, the flow rate can be calculated by the formula below:

$$\text{Flow Rate}(\text{gtts}/\text{min}) = \frac{\text{Volume}(\text{ml}) \times \text{Drop Factor}(\text{gtts}/\text{ml})}{\text{Time}(\text{min})}$$

So, if a litre of fluid is to be administered by a regular set over 2 h, then the flow rate can be found by

$$\text{Flow Rate}(\text{gtts}/\text{min}) = \frac{1000(\text{ml}) \times 15(\text{gtts}/\text{ml})}{2 \times 60(\text{min})} = 125 \text{drops}/\text{min}$$

Venous Access Sites

Peripheral Veins of the Upper Limb

Common sites of access include the dorsal venous plexus and the ante-cubital fossa. Veins on the ventral surface of the forearm and wrist can also be accessed. Ultrasound can be used to visualise the cephalic and basilic veins in the arm, which are deeper but tend to remain patent.

Peripheral Veins of the Lower Limb

Veins of the dorsal venous plexus can be accessed but tend to be difficult. The great saphenous is the vein of choice for venous cutdown, and this is performed at about 2 cm above and in front of the medial malleolus.

Peripheral Veins of the Neck and Scalp [3] (See Fig. 7.2)

The external jugular vein can be accessed as it crosses over the sternocleidomastoid. In neonates, placing an elastic band as a tourniquet across the crown and cannulating in a proximal direction can access veins of the scalp. In extreme cases, the superior sagittal sinus can be accessed in the midline, at the posterior border of the anterior fontanelle.

Central Venous Access

Femoral

The femoral vein lies in the femoral triangle, bounded by the inguinal ligament above, the medial border of the adductor longus medially and the medial border of the sartorius laterally. It is the medial most structure, having the femoral artery and femoral nerve laterally, respectively. Landmarks for access are immediately medial to the pulsation of the femoral artery and about 2 cm below the inguinal ligament. The vein tends to lie posterior to the artery further distally making access difficult. It is the easiest central access to use during cardiac arrest as it does not interfere with chest compressions or control of the airway [4].

Subclavian (See Fig. 7.3)

The subclavian vein lies behind the middle third of the clavicle, with the subclavian artery lying posterior to it. Two approaches have been described, one above and one

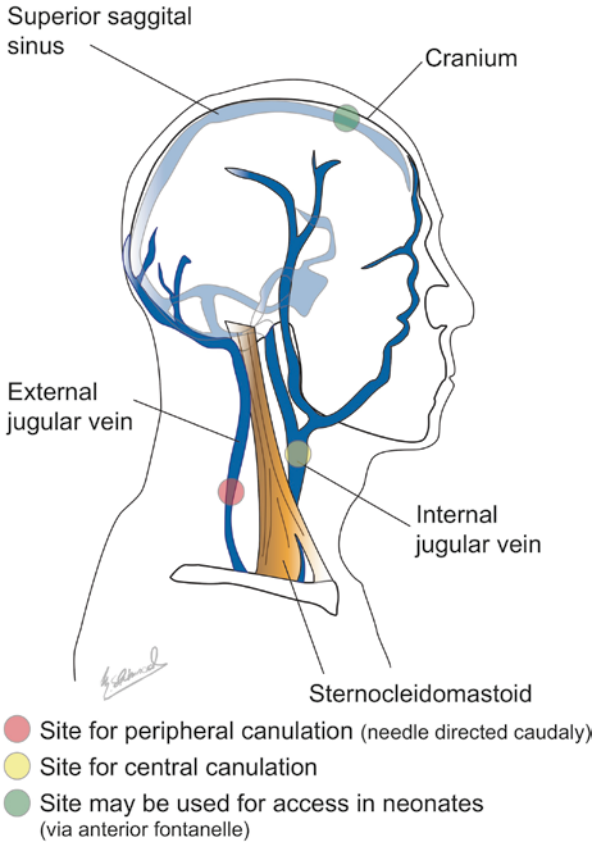

Fig. 7.2 Veins of the head and neck

below the clavicle. Landmarks for the supraclavicular approach are 1 cm lateral to the clavicular head of the sternocleidomastoid and 1 cm behind the clavicle. The needle should be held parallel to the coronal plane of the chest wall and aimed at 45° between the clavicle and sternocleidomastoid. Landmarks for the infraclavicular approach are at the junction of the medial third and lateral two thirds of the clavicle and 1 cm below it, aiming the needle towards the sternal notch.

Internal Jugular (See Fig. 7.4)

The internal jugular vein lies deep to the sternocleidomastoid running down the neck from the jugular foramen to the brachiocephalic vein, just posterior to the sterno-clavicular joint. Given the position of the superior vena cava, it is shorter and straighter on the right-hand side, where there is no concern of damaging the thoracic duct [5]. The central, posterior and anterior approaches have been traditionally described for catheterisation. Landmarks for the central approach lie in a triangle

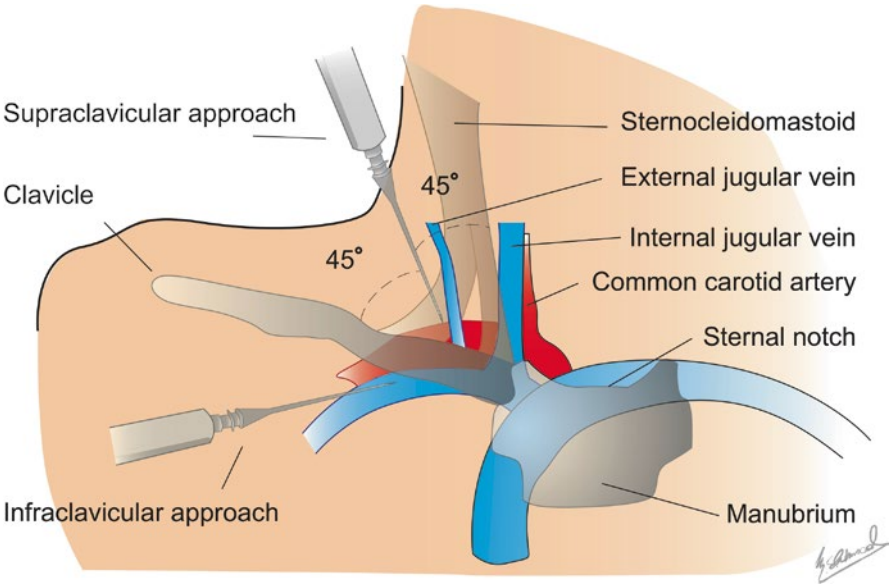

Fig. 7.3 Accessing the right subclavian vein

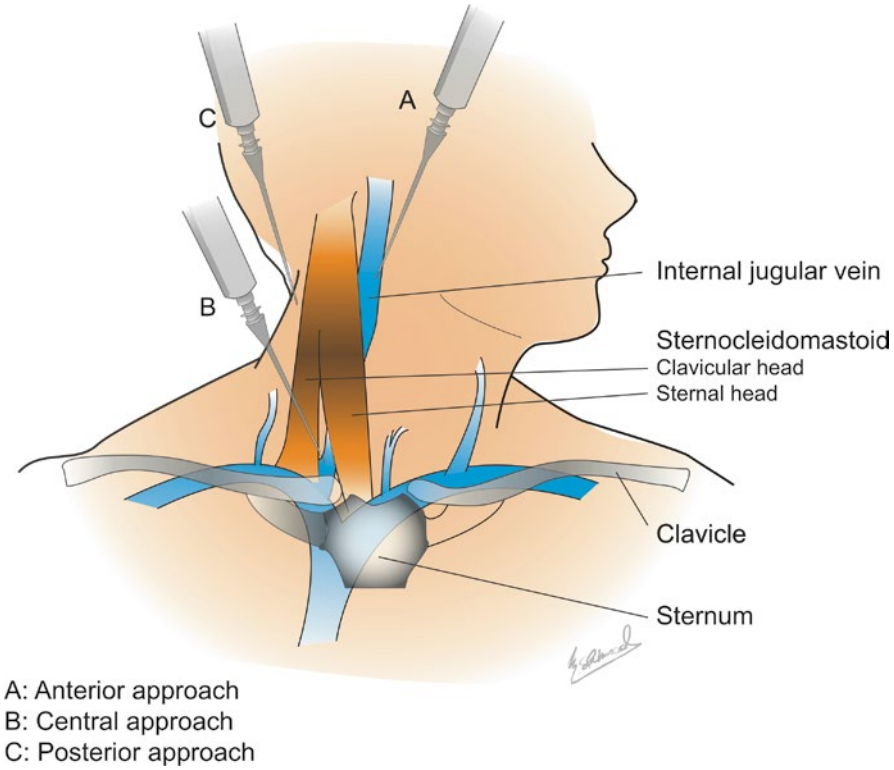

Fig. 7.4 Accessing the right internal jugular vein

created by the two heads of the sternocleidomastoid above, and the clavicle below, with the needle aimed towards the ipsilateral nipple. Due to the proximity of this approach to the thoracic cavity, iatrogenic pneumothorax is a potential complication. The two other approaches are higher up, roughly midway the length of the sternocleidomastoid. With the posterior approach, the lateral border of the sternocleidomastoid is sought, aiming towards the sternal notch, while with the anterior approach, the landmark is just lateral to the pulsation of the carotid artery, again aiming towards the ipsilateral nipple.

In trauma scenarios where haemorrhage is suspected in the abdomen, pelvis or long bones of the lower limbs, it is good practice to obtain access (peripheral, central or IO) in veins that drain into the superior vena cava as it is quicker to fill the heart, and there may be concerns to the integrity of the vasculature more distally. Subclavian catheterisation is ideal due to its easy access and proximity to the heart while allowing ample space at the head end of the patient for securing the airway and cervical spine.

Intra-osseous Access (See Fig. 7.5)

Although not directly entering a vessel, access is achieved into the medullary cavity of a bone, wherein lies a vascular plexus that communicates directly with the peripheral venous system via the Haversian system and Volkmann canals that are present in the bony cortex.

A number of access sites (see Table 7.2) have been described based on manual and mechanical devices; these include the ilium, clavicle, sternum and more commonly the extremities.

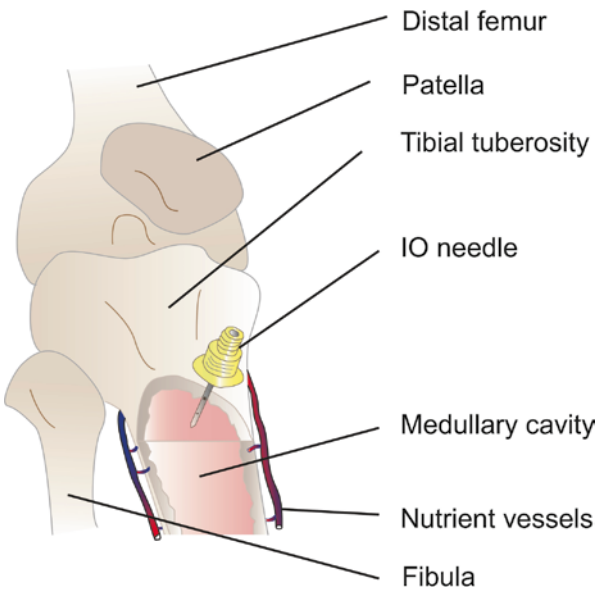

Fig. 7.5 Accessing the right tibial tuberosity

Table 7.2 Various intra-osseous devices and their approved sites

Device	Sites advised
Cook intra-osseous needle	Proximal tibia, distal tibia
EZ-IO®	Head of humerus, tibia, distal femur
FAST1®	Sternum
Bone injection gun (B.I.G.)	Proximal tibia, distal tibia, humerus, radius

Table 7.3 Reasons for using ultrasound for peripheral access

1. Obese patients
2. Dehydrated patients
3. Overlying oedema
4. Burn injury
5. Increased pigmentation
6. Thrombosed veins due to repeated prior cannulations

Umbilical Access

In neonates of up to 2 weeks of age, the umbilical vein can be accessed in situations requiring resuscitation. The larger and more capacious umbilical vein resides with two smaller umbilical arteries in the umbilical stump.

Arterial Access

The arteries commonly accessed are the radial, ulnar, brachial and femoral located by palpation on the radial and ulnar aspect of the wrists, the ante-cubital fossae and just distal to the mid-inguinal points, respectively.

Using Ultrasound

Peripheral

There are many reasons why peripheral cannulation may prove to be difficult (see Table 7.3). These may be overcome by using ultrasound to locate peripheral veins that lie deeper in the tissue and using longer cannulae like angio-catheters. In the upper limb, the basilic, cephalic and brachial veins (see Fig. 7.6) may be located with a high-frequency (8–5 MHz) linear array probe in the arm and ante-cubital

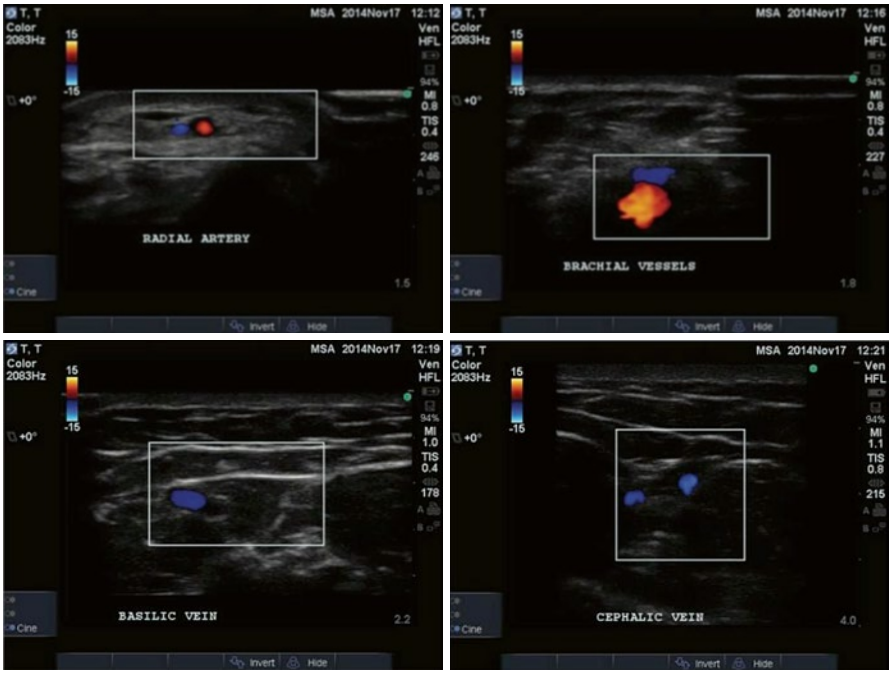

Fig. 7.6 Ultrasound of vessels of the right upper limb. Veins are in *blue* and arteries are in *red*

fossa. The great saphenous vein may similarly be accessed anterior to the medial malleolus in the ankle.

Central

The central vessels described above can all be visualised using ultrasound by placing a linear vascular probe within the landmarks mentioned. By convention, the marker situated on the top left of the screen is always placed on the patient's right when held transversely or in cephalic orientation when held longitudinally.

Arteries (See Fig. 7.6)

When palpation proves difficult, the vascular probe can yet again be used over the conventional landmarks to locate the relevant arteries, adjusting for depth. Colour Doppler can be used to highlight the pulsation of the artery and distinguish it from the non-pulsatile vein.

Techniques

Facilitating Venous Access

Before going on to discuss the details of various vascular access techniques, it will probably be useful to list a few methods of improving the chance of identifying vessels prior to cannulation [6]:

(i) Positioning: Keeping the site of access to dependant prior to cannulation allows for the pooling of blood in venous reservoirs by the aid of gravity.
(ii) Warming: This encourages vasodilatation and hence improves local blood flow. It can be achieved by wrapping a part of the limb in hot moist towels, immersing it in warm water or exposing it to a radiant heat source.
(iii) Transillumination: Various devices are available to help identify superficial veins by means of infrared light or cold light fibre optics.
(iv) Topical nitroglycerine: Various studies have shown that dermal GTN can increase the vascular diameter thus improving chances of cannulation.

Tables 7.4, 7.5 and 7.6 provide a standard procedural overview of obtaining peripheral, central and intra-osseous access.

Table 7.4 Obtaining peripheral access

Action	Plan
Gather equipment	Personal protective equipment (e.g. gloves, apron, eye shield)
	Tourniquet
	Cleansing agent (e.g. alcohol wipes, iodine)
	Cannula (appropriately sized)
	Sterile drape
	Sterile gauze
	Sterile clear dressing (e.g. Tegaderm™)
	Tape
	Saline flush
	Clean tray for assembly
	Disposal bin (for sharps)
Locate vein	Inspect both upper limbs for best vein
	Palpate and tap the vein
	Utilise methods to facilitate venous access
	Veins that run straight for a length are ideal
	The junction at which two veins unite is also easy to access
Clean area	Allow for the fluid to dry before cannulation
Apply tourniquet	Tying this around the arm allows for compression of a greater number of vessels

Table 7.4 (Continued)

Action	Plan
Insert cannula set	Use a shallow angle for accessing superficial veins
	Angle up to 60° for deeper veins
	Holding the cannula in the dominant hand, use the non-dominant fingers to hold down the skin on either side to steady the vein
Wait for flashback	This signifies entry into the lumen
Proceed further	Very gently, introduce the cannula further into the lumen
	Be wary of double puncturing the vein
	Slide the rest of the catheter over the needle so that it sits inside the lumen
Remove tourniquet	Blood samples can be taken prior to this
Attach adjuncts	An obturator or an extension set may be now connected
Confirm	Clear the lumen of the cannula and check its effectiveness by flushing with saline
Secure	With sterile dressing and tape

Table 7.5 Obtaining central access

Action	Plan
Gather equipment	Personal protective equipment (e.g. sterile gloves, gown, eye shield, face mask, hair cover)
	Sterile drape
	Cleansing agent (e.g. chlorhexidine, iodine)
	Local anaesthetic
	Sterile saline flush
	Central venous catheter Seldinger set
	Single-/multi-lumen catheter
	Introducing needle
	Syringe
	Guide wire
	Scalpel
	Dilator
	Obturators
	Sterile gauze
	Sterile dressing
	Silk suture with straight needle
	Ultrasound machine with sterile probe sheath
Don sterile PPE	Maintain full asepsis
Prep and drape the patient	Position the patient to ensure ease of access
	Ensure a sterile field so that all relevant landmarks can be palpated
Locate vein	Use landmarks as described
	Ultrasound can determine whether there is any variation from normal anatomy

(continued)

Table 7.5 (continued)

Action	Plan
Prepare the catheter set	Open the set on a sterile work surface
	Inspect the contents
	Flush catheter to check all lumens
Apply anaesthetic	Calculate maximum safe dose of anaesthetic
	Raise a subcutaneous bleb at potential site of insertion
	Remember to infiltrate areas where stitches will be applied
	Reorient after application
Insert introducer	If using ultrasound, hold probe in non-dominant hand
	Align introducer, attached to syringe, with vein using dominant hand
	On penetrating the skin, apply negative pressure to the syringe and introduce further
Wait for flashback	This signifies entry into the lumen
	Ensure steady and constant aspiration
Stabilise introducer	Place ultrasound probe down and stabilise with non-dominant hand
	Maintain stream of aspiration
Introduce guide wire	Remove syringe from introducer and occlude with thumb to prevent air embolism
	Gently introduce the guide wire, remembering not to let it go
	If resistance is met, stop and reposition
	Do not use force
	Onset of any dysrhythmias on insertion may signify that the guide wire has entered the heart – if so, pull back
Remove introducer	Keeping a firm grasp on the guide wire, pull the introducer back over the wire
Facilitate entry of central line	Still maintaining a hold on the wire, use the scalpel to split the skin at the entry site
	Following this, use the dilator to create a path for the catheter by gently pushing down and rotating it both in a clockwise and anticlockwise fashion
	Use sterile gauze to soak up any blood that issues from the widened opening
Introduce central line	Ensure that a sufficient length of guide wire is exposed to allow for the full length of the catheter
	Stabilise guide wire at entry site with non-dominant hand
	Feed the catheter over the guide wire with dominant hand until it reaches the entry site
	Allow for the guide wire to come out of the distal end of the catheter, making sure any locks have been opened
	Once guide wire is exposed distally, secure it with non-dominant hand
	Feed the catheter over the wire keeping a note of the depth inserted
Remove guide wire	Do this by providing constant gentle traction
	Do not forcefully remove

Table 7.5 (continued)

Action	Plan
Aspirate and flush	Ensure that blood can be aspirated from all channels
	If resistance is met, try rotating the catheter or withdrawing slightly
	Take blood samples now if required
	Flush all ports to prevent blockage and cap off all channels
Secure	Attach suture anchor over the exposed catheter
	Suture loosely to skin
	Apply sterile transparent dressing
Confirm position	Depending on the location, either x-ray or ultrasound can be used

Table 7.6 Obtaining intra-osseous access

Action	Plan
Gather equipment	Personal protective equipment (e.g. gloves, apron, eye shield)
	Cleansing agent (e.g. alcohol wipes, iodine)
	Intra-osseous device (appropriately sized)
	Sterile drape
	Sterile gauze
	Sterile dressing
	Syringe
	Saline flush
	Local anaesthetic
	Clean tray for assembly
	Disposal bin (for sharps)
Locate landmark	Ensure site is clear of overlying injury or infection
	Avoid sites that are distal to any bony injury
Prepare patient	Clean area with suitable cleansing agent
	If patient is conscious, infiltrate local anaesthetic to skin and periosteum
	Position and stabilise the limb with non-dominant hand
Insert IO needle	Position needle at 90° to the bone
	Depending upon the device, the technique will vary slightly
	For manual application, apply constant pressure and twist clockwise and anticlockwise until there is a sudden give that signifies the medullary cavity has been reached
	Ensure that the base of the needle is not flush with the surface of the skin
Remove stylet	In most cases this will need to be unscrewed
Confirm position	This can be done by aspirating bone marrow by means of a syringe
	Bone marrow can be sent to the lab for analysis, but do remember that marrow aspirate cannot be used for blood gas analysis
Flush	Administer a bolus of normal saline by means of a syringe
	It will require a minimum amount of pressure to infuse the fluid
	Alternately a saline drip can be set up by means of a pressure bag
	Check for signs of extravasation
Secure	For manual needles a dressing can be fashioned out of rolls of sterile gauze and bandage
	Other devices have specialised dressing sets

Complications

Tables 7.7, 7.8 and 7.9 list the complications of peripheral, central and intra-osseous access.

Table 7.7 Complications of peripheral access

	Actions to take
Early complications	
Pain	Ensure best possible vein selected
	Practise clean, seamless penetration of cannula
Haematoma formation	Remove tourniquet before removing needle
	Apply pressure following removal
Extravasation of fluid	Elevate the site
	Provide hot or cold compress
Neurovascular injury	Be aware of relevant anatomy
Late complication	
Cellulitis	Ensure aseptic technique used
	Work in a sterile field
	Treat with appropriate antibiotics
Phlebitis	Identified by discomfort along venous path, may also be palpable
	Treat with anti-inflammatories
Deep vein thrombosis	Be vigilant to subsequent tenderness, oedema and swelling
Bacteraemia	Ensure cannula does not remain in situ for more than 3–4 days
Tissue necrosis	Sequelae of extravasation due to increased pressure or irritant fluids

Table 7.8 Complications of central access

Complications	Information
Infection/sepsis	Maintain a sterile field and use an aseptic technique
Pneumothorax	Risk minimised with use of ultrasound
	Ultrasound can also detect small pneumothoraces immediately post-procedure
Air embolism	Ensure system is flushed prior to use
	Utilisation of valve-tipped catheters reduces the risk
Thrombosis	Use frequent flushes with added thrombolytic agents if needed
Arterial puncture	Apply pressure to avoid haematoma formation
Catheter malposition	Anchor in place with sutures and cuff
Chylothorax	Caused by injury to the thoracic duct on the left side
	If suspected, confirm on x-ray and insert a chest drain
Catheter rupture	Can be caused by forceful flush insertion
Cardiac injury	If catheter inserted too far
	May result in haemothorax, tamponade or dysrhythmias
Hydrothorax/hydromediastinum	Caused by infusing fluids into the pleural space

Table 7.9 Complications of intra-osseous access

Complications	Information
Infections	Cellulitis, osteomyelitis
Compartment syndrome	If needle exits cortex on the other side
Iatrogenic fracture/growth plate injury	Mainly due to incorrect placement and technique
Fat embolism	Of little clinical significance, rare

Other Modes of Access

Venous cutdown and endotracheal access have been described as methods utilised in austere and emergency conditions. Boxes 7.3 and 7.4 provide some insight into both of the methods.

Box 7.3: Venous Cutdown
This is a surgical procedure used to access the great saphenous vein just above and in front of the medial malleolus, when more conventional methods have failed.

The principal involves making a full thickness transverse incision of about 2.5 cm and then bluntly dissecting down to the vein. Once exposed, a cannula is inserted and then secured. This can then be used as a standard peripheral access.

Box 7.4: Endotracheal Access
Endotracheal access is described in life-threatening circumstances, when all other modes have failed and immediate drug administration is required. The pharmacokinetics and dynamics of the following drugs have been studied via this route: adrenaline, atropine, lignocaine, naloxone and vasopressin.

Recommendation in adults is for the drug to be drawn up in a 10 ml solution with 2–2.5 times the equivalent dose of the intravenous route. In children, a total of 5 ml is to be drawn up, with up to ten times the equivalent dose of the i.v. route.

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Part II
Cardiology

Chapter 8
Acute Cardiac Arrhythmias

Rachel Gnanaprakasam and Suresh S. David

Key Points
- ECG is the key diagnostic modality in case of arrhythmias. Careful interpretation of the ECG before and after intervention is mandatory.
- When in doubt, treat any wide complex tachycardia as VT.

Introduction

Arrhythmias or dysrhythmias are defined as abnormal heart rhythms which is anything other than the normal sinus rhythm or normal sinus rate of 60–100 beats/min. The incidence of arrhythmias increases with ageing. Some of the arrhythmias are life-threatening, but others do not compromise the cardiorespiratory function and are better tolerated. The chances of surviving acute dysrhythmias like ventricular tachycardia(VT) or ventricular fibrillation(VF) also depend on factors like time duration before treatment commences, the site of occurrence and the immediate level of care provided. One of the studies conducted in an urban, South Indian hospital reveals an odds ratio of 18.5 for VT/VF, for in-hospital cardiac arrest with

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_8

regard to discharge from hospital [1]. A general overview of the various arrhythmias in the acute setting will be discussed in this chapter.

Pathophysiology

Understanding the pathogenesis of the various arrhythmias requires knowledge of the anatomy, physiology of the electrical wiring of the heart and its baseline mechanism of action.

Anatomy

Cardiac rhythm is generated at the sino-atrial (SA) node which is a collection of specialised pacemaker tissue and produces an impulse at the rate of 60–100 beats/min. The generated impulse spreads through atrial musculature and specialised atrial conduction tracts to reach the atrioventricular (AV) node. The AV node tissues utilise slow channel ion depolarisation and thus slow the rate of impulse conduction. From the AV node, impulses propagate through the bundle of His which has three fascicles, namely, right bundle branch (RBB), left anterior-superior branch (LASB) and left posterior-inferior branch (LPIB). Finally impulses are passed on to the Purkinje fibres before reaching the ventricular myocardium (Fig. 8.1). Conducting system of the heart consists of three types of specialised tissue which are pacemaker cells, Purkinje cells and contractile cells. Purkinje cells conduct electrical waves faster than the cardiac cells but do not have pacemaker property. The end point of this conducting system is the cardiac contractile cells which contract when electrically depolarised.

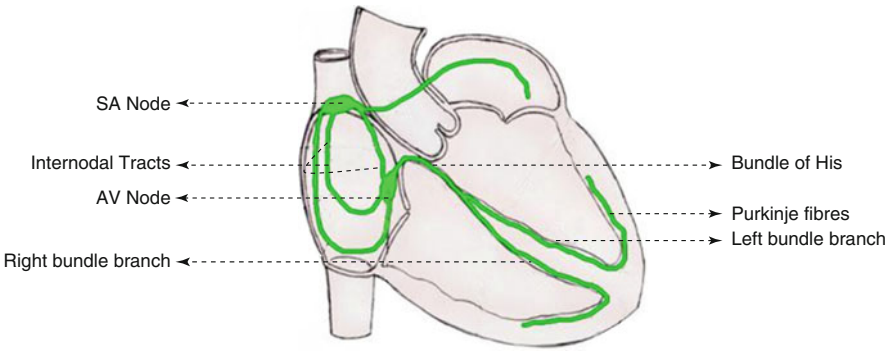

Fig. 8.1 Skeleton of the heart showing the conducting system

Physiology

'Pacemaker potential' is unique to pacemaker tissues which involve calcium, sodium and potassium channels in three distinct phases. These cells maintain a hyperpolarised state and the 'If' or 'funny current' causes spontaneous depolarisation (phase 4) once the membrane reaches −60 mV, due to inward movement of sodium ions (Fig. 8.2). This automatic depolarisation further activates inward calcium current creating 'phase 0' and causes depolarisation. Repolarisation or 'phase 3' follows depolarisation which is caused by outward movement of potassium ions and closure of the calcium channels.

The normal resting membrane potential (RMP) of the non-pacemaker cells is −90 Mv. Rapid depolarisation occurs when the RMP becomes less negative through the electric stimulus and opening of fast Na channels. Repolarisation begins with the closure of Na channels or 'phase 1' and continues slowly through 'phase 2' by the opening of Ca channels unique to myocardial contractile cells. The effective refractory period is the period before the membrane potential reaches −60 mV, and the relative refractory period begins thereafter. An impulse from an ectopic focus during the 'relative' refractory period can result in a premature depolarisation.

Mechanism of Dysrhythmia

(a) *Enhanced automaticity* is spontaneous depolarisation of non-pacemaker cells or reduction in the threshold for depolarisation of normal pacemaker cells, e.g. ischaemia, electrolyte imbalance and drug toxicity. (b) *Triggered activity* is due to early (e.g. torsades de pointes) or delayed (calcium overload in digi-toxicity) after-depolarisations. Oscillations of membrane potential during or after repolarisation

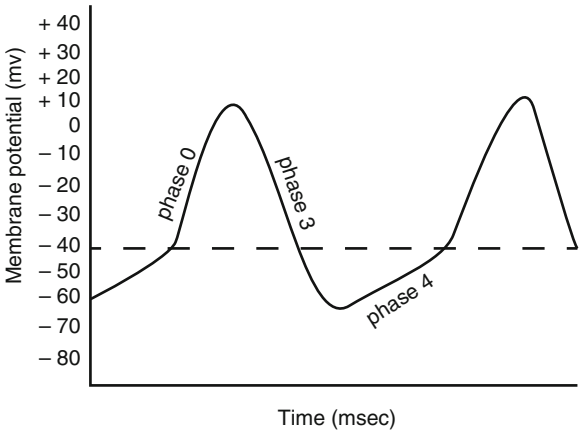

Fig. 8.2 Pacemaker potential

Table 8.1 Symptoms in tachyarrhythmias and bradyarrhythmias

Tachyarrhythmias	Bradyarrhythmias
Palpitations	Syncope
Dizziness/light-headedness	Dizziness/light-headedness
Syncope	Loss of consciousness
Chest pain	Confusion
Loss of consciousness	Fatigue
Dyspnoea	
Nausea	
Confusion	
Fatigue	

(after potential) can reach threshold potential therewith triggering a complete depolarisation which is named as after-depolarisation. (c) *Re-entry* happens when there is an additional pathway of conduction between the atria and ventricles apart from the AV node, and one of the two has a longer refractory period causing an unidirectional block, e.g. ventricular or supraventricular tachycardia. Re-entry can also happen via the myocardial syncytium causing the generation of a chaotic rhythm as seen in atrial fibrillation (AF). (d) *Failure of impulse generation or conduction* can result in bradycardia, e.g. SA node dysfunction and AV conduction block.

Clinical Features

Symptoms can be vague in case of arrhythmias, but rapid identification of patients with unstable vital signs is essential. Arrhythmias arising from an ectopic focus have 'gradual onset' and offset compared to the 'abrupt' beginning and termination of triggered or re-entrant arrhythmias. The tables (Table 8.1 and Table 8.2) contains several of the clinical signs, and the patient might present with any combination of them.

Differential diagnoses include vasovagal syncope, myocardial ischaemia, congestive cardiac failure, pulmonary embolism, seizures, vertigo, acute anxiety and panic attack.

Investigations

- The most important investigation in case of arrhythmias is the ECG. A 12-lead ECG should be obtained and interpreted as soon as possible. Also the patient should have continuous monitoring of cardiac rhythm.
- Investigations seeking for underlying medical conditions are serum electrolytes, thyroid profile, serum troponin, BNP, chest x-ray, CBC, etc.

Table 8.2 Clinical signs of dysrhythmias

Clinical signs
Abnormal peripheral pulsations – changes in rate, rhythm and character
Abnormal blood pressure – hypotension/cardiogenic shock
Cardiac failure – S3, tachypnoea, lung crepitations, JVP elevation, pedal oedema
Thromboembolic episodes – cerebral ischaemia, limb ischaemia, mesenteric ischaemia, etc.
Underlying structural heart disease – murmurs and abnormal point of maximum impulse (PMI)
Mental status changes (due to hypoperfusion) – agitation, lethargy or coma
Recurrent fainting spells – physical injuries

- Transthoracic echocardiogram can be ordered to assess cardiac function, in the investigation of cardiac ischaemia and other causes of arrhythmia, and also to rule out blood clots in case of atrial fibrillation.

Tachyarrhythmia

Rise in heart rate above 100 beats/min is called tachyarrhythmia. Though the mechanism underlying each abnormal rhythm may be different, they are grouped together to simplify identification and management. These are further classified based on the site of origin, mechanism and clinical manifestations as follows:

Supraventricular

1. Sinus tachycardia
2. Atrial tachycardia
3. Atrial fibrillation
4. Atrial flutter
5. AV nodal re-entrant tachycardia
6. AV re-entrant tachycardia
7. Junctional tachycardia

Ventricular

1. Ventricular tachycardia
2. Ventricular fibrillation

They can also be classified based on the width of the QRS complexes as wide (QRS >0.12 s) or narrow complex (QRS <0.12 s) tachyarrhythmia. In general, rhythms with narrow QRS complexes originate at or above the AV node, whereas those with wider complexes have their origin below the AV node. However, conditions with aberrant conduction such as bundle branch blocks can produce rhythms

with wide complexes even though they are of supraventricular origin. Mechanisms surrounding tachyarrhythmias are increased automaticity, re-entry or after-depolarisations. A brief description of some of the common, clinically significant tachyarrhythmias will be mentioned in the following paragraphs.

Sinus Tachycardia

- Heart rate >100 beats/min is described as sinus tachycardia and rarely goes beyond 180 beats/min in healthy adults.
- ECG shows a normal 'p' wave before each QRS complex (lead II), short and regular R-R intervals with a rate >100 beats/min.
- Onset and offset are gradual and never abrupt.
- Usually acts as a compensatory mechanism in case of hypovolaemia, anaemia, exercise, etc. and also due to sympathetic activity.
- Addressing the primary problem is more important than bringing the heart rate into the 'normal range'. However, compromise of the cardiac output can be caused by the decreased filling time in cases of decompensated heart failure or aortic stenosis, and even then rapid treatment of the primary cause is recommended.

Atrial Tachycardia

- Atrial rhythm with a rate >100 beats/min which is produced from any atrial site apart from the SA node.
- ECG reveals morphologically abnormal 'p' waves with an AV conduction ratio of 1:1, 2:1 or higher (Fig. 8.3).
- Commonly seen in young patients with structural heart disease. Also occurs in patients with hypoxaemia, metabolic disturbances and drug toxicities. Atrial tachycardia with AV block is characteristically seen in digi-toxicity.
- Multifocal atrial tachycardia is one with three or more morphologies of 'p' waves with changing PR and P-P intervals. Most commonly seen in patients with COPD.

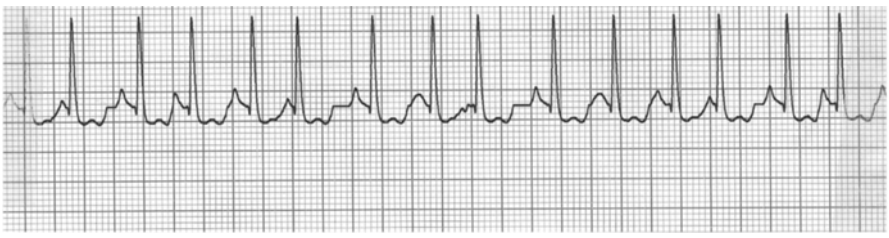

Fig. 8.3 Atrial tachycardia

- Treatment of the underlying cause leads to resolution but recurrence rates are high. Vagal manoeuvres, adenosine and cardioversion have limited efficacy on atrial tachycardia. If rate control is desired in stable patients, drugs that slow AV conduction can be used.

Atrial Fibrillation (AF)

- Most common, clinically significant arrhythmia encountered in the emergency department.
- Multiple micro-re-entry circuits or focal atrial activity due to increased automaticity or re-entry gives rise to an atrial rate of 300–600 beats/min with the ventricular rate limited to 110–170 beats/min due to the longer refractory period of AV node. If the ventricular rate is >200 beats/min, then think of an accessory conduction pathway (mimics polymorphic VT) or a bundle branch block if there is a wide QRS complex.
- This leads to reduced cardiac output caused by chaotic, inefficient atrial contraction and a rapid ventricular rate. Healthy adults can tolerate higher ventricular rates without much symptoms, whereas those with compromised cardiac function can become symptomatic with even minor increase in heart rate.
- Classified based on the duration of occurrence as paroxysmal (<7 days), persistent (>7 days) and permanent (>1 year).
- ECG is characterised by absent 'p' waves, irregularly irregular rhythm, absent isoelectric baseline, variable ventricular rate and fibrillatory waves (fine <0.5 mm or coarse >0.5 mm).
- Causes include valvular heart disease, systemic hypertension, ischaemic heart disease, cardiomyopathy, cardiac failure, thyrotoxicosis, pericarditis, sick sinus syndrome, acute ethanol intoxication (holiday heart syndrome), myocardial trauma, pulmonary embolus, electrolyte imbalance, drug toxicity, etc. Rheumatic heart disease is a very common cause of atrial fibrillation in the Indian population [2].
- *Rhythm control* is preferred in patients with new onset AF in the ED, either by electrical or chemical cardioversion (depending on resources available). Converting the rhythm should not be attempted if there is high risk of stroke (mechanical heart valve, rheumatic heart disease, recent stroke/TIA) or high risk of ventricular tachycardia/fibrillation (digoxin toxicity, hypokalaemia) [3].
- *Rate control* is advised for patients with AF after 48 h of onset or unknown time of onset, without anticoagulation in chronic AF or acute worsening of chronic AF. Heart rate less than 110–100 beats/min is a reasonable target. Beta blockers and calcium channel blockers are commonly used in the ED for rate control but should not be used when an accessory pathway is present or suspected. Digoxin is added when rate control is inadequate with beta blockers or calcium channel blockers alone [4, 5].
- Risk assessment for stroke is mandatory for all patients with AF and should be started on anticoagulants/antiplatelets if required. The American Heart Association

recommends using CHA2DS2-VASc score for calculating the stroke risk [5]. While initiating anticoagulants, risk of bleeding should be taken into account. HAS-BLED is an acronym for a bleeding risk calculation tool which is widely used and denotes factors like hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age, drugs and alcohol [6]. ED studies have shown that actual anticoagulant medication in high-risk patients is prescribed far less than needed [7] which ultimately impacts the long-term stroke risk.

- Electrical cardioversion should be synchronised and start with 150 J along with adequate sedation and pain relief. Anteroposterior pad placement is preferred.
- Chemical cardioversion usually involves drugs like procainamide, amiodarone, ibutilide, flecainide and propafenone with a response rate of 40–65 % in the ED. Drugs from class IC are contraindicated in case of structural or ischaemic heart disease.

Atrial Flutter (AFl)

- Atrial rate of approximately 300 beats/min with an AV conduction ratio of 2:1 and hence a ventricular rate of ≈150 beats/min or rarely 1:1 (only if there is any accessory pathway of conduction) with a higher ventricular rate. AFl with 1:1 AV conduction ratio has a high risk of progression to ventricular fibrillation.
- Usually caused by micro-re-entry in the right atrium and commonly associated with valvular heart disease and cardiomyopathy.
- ECG reveals a regular, narrow complex tachycardia with the characteristic 'saw-tooth' flutter waves best seen in leads II, III and aVF (Fig. 8.4).
- Vagal manoeuvres and adenosine have little effect in converting the flutter rhythm. In comparison with AF, atrial flutter has a higher resolution rate with DC cardioversion (synchronised). Otherwise, the management of Afl is essentially the same as that of AF, which is described above.

Atrioventricular Nodal Re-entrant Tachycardia (AVNRT)

- Narrow complex tachycardia caused by re-entry circuit within the AV node leading to conduction down the His bundle and then back up into the atria. Characterised by sudden onset and offset, usually related to physical or emotional stress. Also called as paroxysmal supraventricular tachycardia (PSVT).

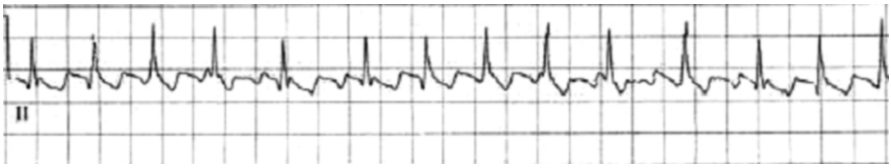

Fig. 8.4 Atrial flutter with variable AV block

- ECG shows regular, narrow complex tachycardia with a heart rate of 140–280 beats/min with 'p' waves hidden in the QRS complex, before or after the complex.
- Treatment starts with vagal manoeuvres (if no contraindications) followed by adenosine and, if still no response, should be supplemented with synchronised cardioversion (100–200 J).

Junctional Tachycardia (JT)

- Junctional rhythm with a heart rate >100 beats/min describes JT. It is usually due to increased automaticity of AV node along with decreased automaticity of SA node. When a junctional rhythm shows a heart rate of 60–100 beats/min, it is accelerated junctional rhythm, and if <60 beats/min, it's called junctional escape rhythm.
- Causes include digi-toxicity, myocardial ischaemia, cardiac surgery, myocarditis, electrolyte imbalance and beta agonists.
- ECG features include narrow complex rhythm with an inverted 'p' wave before, on or after the QRS complex, best seen in inferior leads (II, III and AvF) (Fig. 8.5).
- Treatment centres around managing the underlying medical condition.

Pre-excitation

- Depolarisation of ventricular myocardium with impulses generated from the atria passing through an accessory pathway (other than AV node) is defined as pre-excitation. Special bypass tracts are necessary which conduct the impulses from atria to ventricles much quicker than the normal pathway of AV node would

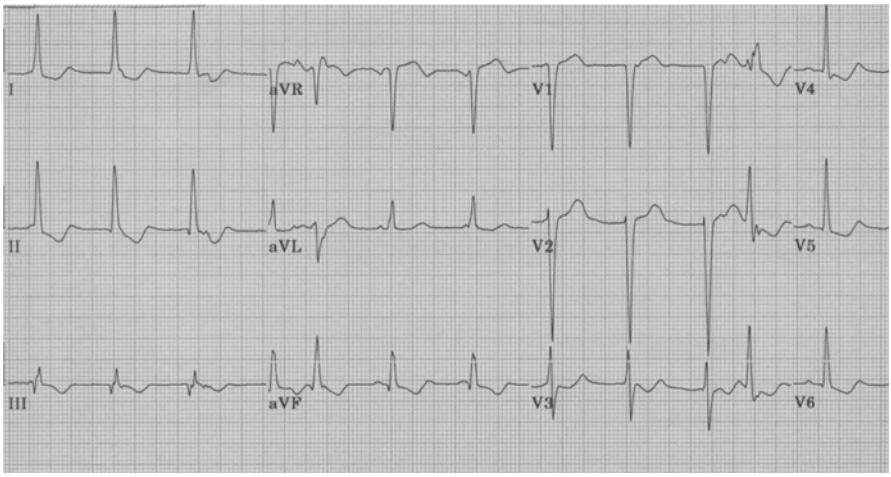

Fig. 8.5 Junctional rhythm

take. This generates a tachyarrhythmia called atrioventricular re-entrant tachycardia (AVRT). Pre-excitation includes Wolff-Parkinson-White (WPW) and Lown-Ganong-Levine (LGL) syndromes.

- AVRT is classified as orthodromic and antidromic based on the direction of current flow. Orthodromic AVRT is seen when atrial impulses pass down the AV node and come back into the atria through the accessory pathway. Antidromic AVRT happens when the atrial impulses are transmitted down the accessory pathway and then up the AV node. AV nodal blocking agents are contraindicated in antidromic AVRT as unstable ventricular rhythm can result.
- Wolff-Parkinson-White syndrome is characterised by paroxysmal supraventricular tachycardia along with short PR interval (<0.12 s), narrow QRS (>0.10 s) or delta wave (slurred upstroke of 'R'wave) as seen in Fig. 8.6. Bundle of Kent has been identified in WPW syndrome to be the bypass tract, and it may conduct impulses from atria to ventricles, other way around or in both directions.
- Lown-Ganong-Levine syndrome is characterised by an accessory pathway called James fibres and a short PR interval but normal QRS morphology on the ECG.

Ventricular Tachycardia (VT)

- Wide complex tachycardia arising anywhere below the His bundle gives rise to VT. It is classified as either sustained or non-sustained VT based on duration of the abnormal impulses. It is also described as monomorphic or polymorphic VT based on similar or dissimilar morphologies of the QRS complexes, respectively. Haemodynamic instability reflected as cardiogenic shock, chest pain, cardiac failure or reduced mental status is called as unstable VT, and VTs not accompanied by the above features are labelled as stable VT (Fig. 8.7).

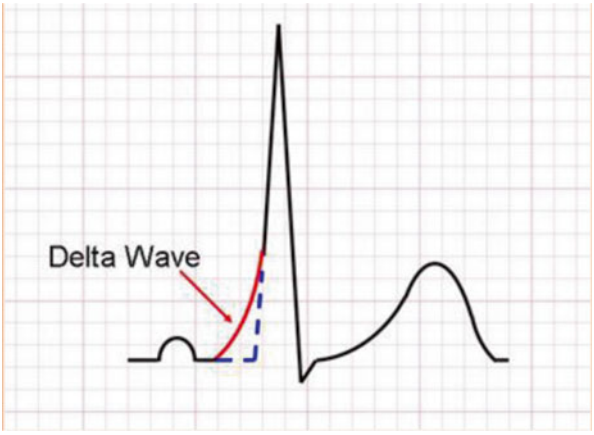

Fig. 8.6 Delta wave, seen in WPW syndrome

- The incidence of ventricular fibrillation (VF) and ventricular tachycardia (VT) is declining which can be explained by the improved treatment of ischaemic heart disease and also greater utilisation of implantable cardiac defibrillators (ICD) [8].
- Re-entry and increased automaticity are the two main mechanisms which precipitate VT.
- Causes of VT include ischaemic heart disease, cardiomyopathy, Chagas' disease, etc.
- ECG features include broad QRS complexes and heart rate >100 beats/min.
- Torsades de pointes is a polymorphic VT with long QT interval causing paroxysmal VT. It can either be congenital or acquired. Empiric intravenous magnesium, overdrive pacing or beta agonists are used for treatment of stable patients with torsades. Unstable patients with torsades get the same treatment as unstable VT.
- Brugada's criteria for diagnosis of VT includes one of the following: (a) RS duration >100 ms, (b) AV dissociation (best seen in leads II, III, AvF and V1), (c) the absence of RS complexes in the chest leads and (d) specific VT morphologic criteria. If the answer is 'no' to all the criteria described above, then it indicates SVT with aberrant conduction.
- When in doubt, treat any wide complex tachycardia as VT.
- Unstable patients should immediately be cardioverted with delivery of synchronised DC current.

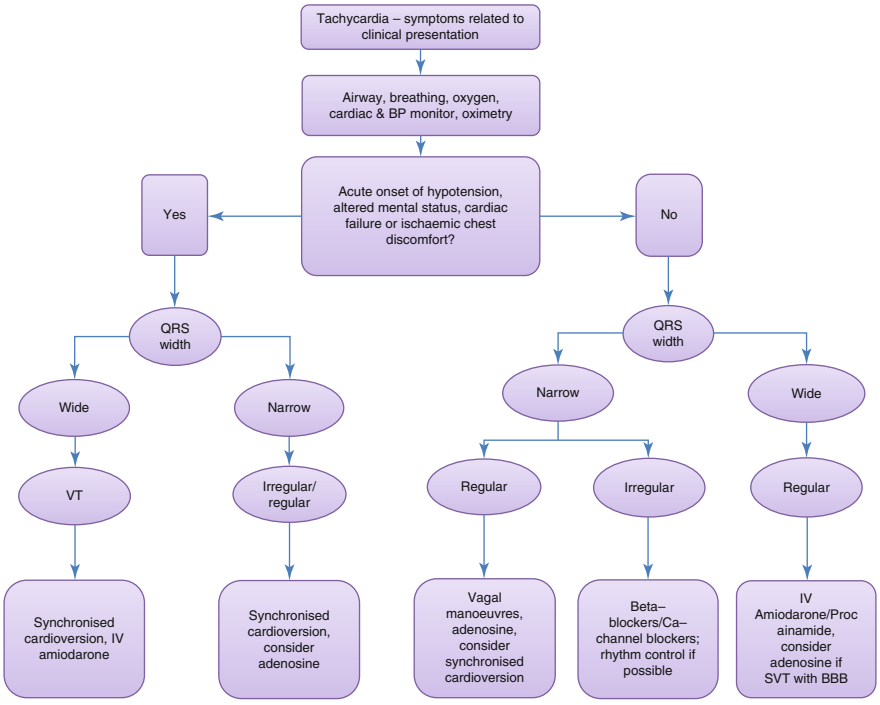

Fig. 8.7 Management of tachyarrhythmia with peripheral pulse

- Stable patients with VT should be treated with drugs like amiodarone or procainamide. Adenosine can be used if SVT with bundle branch block is suspected (Fig. 8.7).

Ventricular Fibrillation (VF)

- Rapid, irregular electrical activity results in chaotic contraction of the ventricles at a high speed and is termed as VF. There is no cardiac output due to the ineffective ventricular contractions.
- Continued progression of coarse VF reduces the amplitude and becomes fine VF or ultimately asystole.
- ECG shows irregular deflections of varying amplitude at a rate of 150–500 beats/min. There is no specific 'p' wave, QRS complexes or T waves.
- Treatment is immediate commencement of CPR and defibrillation as soon as possible (Fig. 8.8).

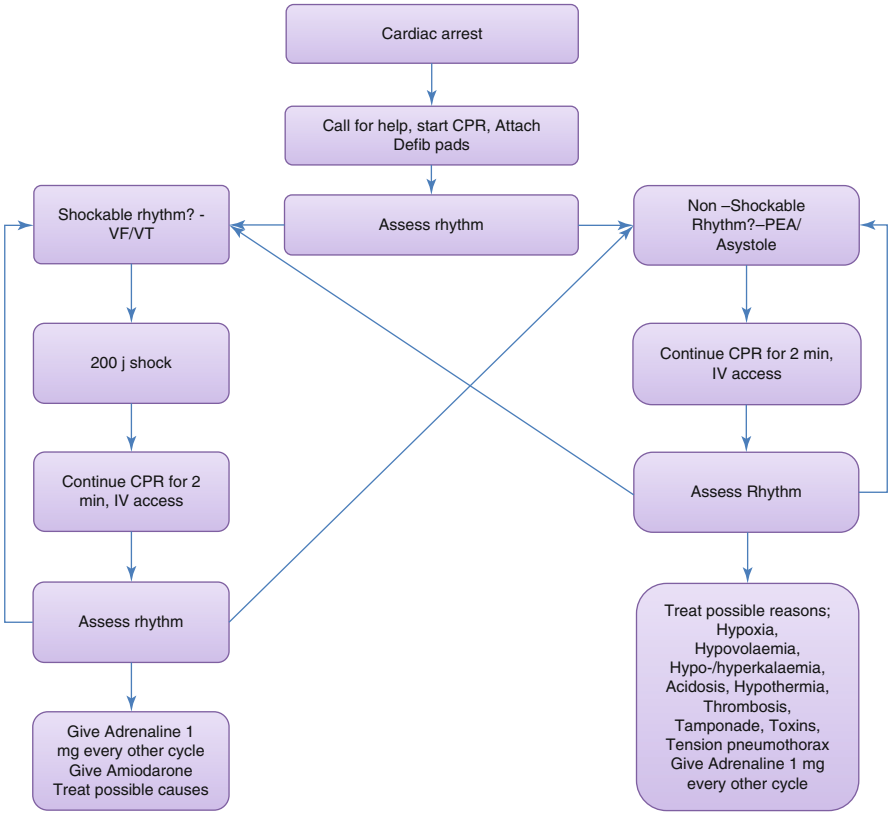

Fig. 8.8 Management of arrhythmias during cardiac arrest

Bradyarrhythmias

Heart rate <60 beats/min denotes bradycardia which is either due to failure of impulse generation or conduction of it. SA node dysfunction and AV conduction block are the most common causes of primary bradyarrhythmia.

Sino-atrial Node Disease

- SA nodal disease can be either intrinsic or extrinsic (Table 8.3). The most common presentation of SA node degeneration is sick sinus syndrome (SSS). Onset of SSS can be earlier in patients with structural and vascular heart disease.
- Presentation can be asymptomatic, with sinus arrest or tachycardia-bradycardia syndrome. Mortality is not affected with SA node dysfunction alone but mostly due to associated conditions.
- ECG may show pauses without visible p waves, intermittent or complete absence of P waves or SVT in tachycardia-bradycardia syndrome. Chronotropic incompetence is the absence of appropriate rise in heart rate with regard to physical or chemical stress.
- Management includes temporary transcutaneous pacing in symptomatic patients followed by a permanent pacemaker insertion.

Atrioventricular Conduction Disease

- AV conduction block can be due to structural or functional alterations in the AV node. Causes include coronary artery disease, drugs, electrolyte imbalance, idiopathic progressive fibrosis, inflammatory or infectious causes, local trauma or congenital heart defect. Anterior wall myocardial infarction usually causes distal AV node or His bundle/branches, but inferior wall MI causes AV nodal block.
- First-degree AV block is benign and is diagnosed by a prolonged PR interval (>0.2 s). Second-degree AV conduction block has Mobitz types I and II. Type

Table 8.3 Common causes of sino-atrial nodal disease

Intrinsic causes	Extrinsic causes
Sick sinus syndrome (SSS)	Vasovagal stimulation
Coronary artery disease	Carotid sinus hypersensitivity
Congenital heart disease	Hypothyroidism
Amyloidosis	Hypoxia
Myocarditis	Drugs
Myocardial trauma	Raised intracranial pressure
Iatrogenic	Sleep apnoea

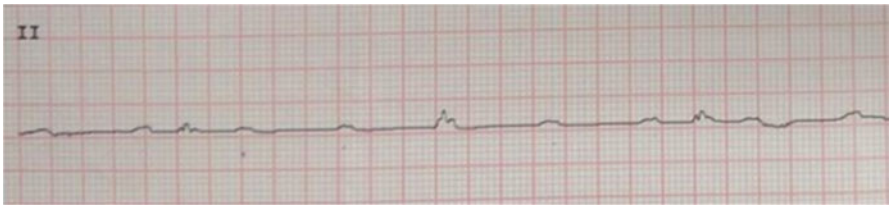

Fig. 8.9 ECG lead II showing complete heart block (Courtesy: Dr. Suja Sadhasivam)

I shows gradual lengthening of the PR interval followed by a dropped atrial impulse denoting AV conduction block. Type II reveals dropped atrial impulses (p waves not followed by a QRS complex) without the gradual lengthening seen in the previous type. Third-degree or complete heart block shows complete AV dissociation (Fig. 8.9). Both complete heart block and type II second-degree AV block are pathologic and need further investigation and treatment.

Management

- Emergency treatment is indicated for those patients with a heart rate <50 beats/min and evidence of hypoperfusion.
- Transient pacing is required for haemodynamically unstable patients. Start at the lowest voltage that allows electrical capture and provide adequate analgesia and sedation. If by increasing the voltage, capture does not happen, prepare for transvenous pacing.
- Atropine is recommended for symptomatic bradycardia. Give 0.5 mg intravenously every 5 min up to a maximum of 3 mg. Atropine should be used as a temporising measure, while transcutaneous pacing is being prepared. Most of the SA and AV node problems respond to atropine alone, but patients with infranodal block (types IIb and III) need immediate transvenous pacing.
- Epinephrine or dopamine infusion can be considered when both pacing and atropine prove unsuccessful at bringing up the heart rate.

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Chapter 9
Acute Coronary Syndromes

George Koshy and Raja Sekhar Maroju

Introduction

- Most cardiac arrests in the adult population are caused by coronary artery disease and are attributed to one of the acute coronary syndromes (ACS).
- Management of cardiac disease has evolved by the findings of large randomised clinical trials. Research and development of new cardiac biomarkers, antiplatelet agents and anticoagulants and many improvements in percutaneous revascularisation therapies have refined the care of ACS patients.
- Guidelines for care of ACS patient have been laid down by the American College of Cardiology (ACC) [1, 2], American Heart Association (AHA) and European Society of Cardiology (ESC) [3].

Time is not only cardiac muscle but also life.

Every 30-min delay from symptom onset to initiation of treatment increases 1-year mortality by 7.5 % in acute myocardial infarction (AMI).

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_9

Table 9.1 The spectrum of ACS

ACS	Pathophysiology	Initial treatment
UA	Nonocclusive thrombus in an epicardial coronary vessel with associated ischaemia but no evidence of infarction	Aspirin
		LMWH
		Direct thrombin inhibitors (bivalirudin)
		β-blockade
NSTEMI	Nonocclusive thrombus in an epicardial coronary vessel with associated infarction	Aspirin
		Heparin
		LMWH
		β-blockade
		Consider GP IIB/IIIA inhibitor
STEMI	Occlusive thrombus in an epicardial coronary vessel with transmural ischaemia	Urgent reperfusion via thrombolysis or primary PCI

Classification

- Acute coronary syndromes (ACS) are parts of the same spectrum of disease comprising the following:
  1. Unstable angina
  2. Non-ST elevation (NSTEMI)
  3. ST elevation myocardial infarction (STEMI) (Table 9.1)
- The basic pathophysiology is in most cases initiated by rupture of an atherosclerotic plaque in a coronary artery, thus exposing subintimal collagen. This triggers platelet adhesion and activation causing subtotal occlusion of coronary artery (NSTE-ACS) or total occlusion of coronary lumen (STEMI). Fissuring can also cause hemorrhage or dissection into the plaque leading to localised swelling causing narrowing of the lumen.
- History, clinical examination, ECG analysis and cardiac biomarker results are crucial in guiding the management of ACS.

Signs and Symptoms

- The presenting symptom is classically chest/epigastric discomfort.
  - This can occur at rest or during exertion.
  - Its character is usually described as heaviness, burning, suffocation, squeezing, tightness or crushing in nature.
  - The pain can most often radiate to the jaw, neck, back, left arm or both arms.
  - This can also be usually associated with profuse sweating, nausea and vomiting.
- In elderly and diabetic patients, these symptoms may be mild or absent. They usually present with complaints of breathlessness, fatigue, episode of collapse or even confusion.

Differential Diagnoses

- Differential diagnoses to be considered are:
  - Aortic dissection
  - Acute pericarditis
  - Pulmonary embolism
  - Costochondritis
  - Acute gastritis
  - Acute cholecystitis

Enquire about recent use of phosphodiesterase inhibitors (sildenafil, tadalafil) which should preclude the use of nitrates.

Clinical Examination

- There is very little information that can be gained by clinical examination in diagnosing ACS. However, with a good history and clinical examination, other conditions causing chest pain like pneumonia, pleural effusion, aortic dissection, acute pericarditis and pericardial tamponade (Table 9.2).
- Auscultation of the heart and lungs and rapid neurologic examination (esp. when considering thrombolysis) are very important.
- Also evaluate for signs of possible cardiogenic shock (hypothermia, hypotension and low pulse pressure) [14].

Table 9.2 Physical examination findings and possible diagnosis in patients with chest pain

Examination finding	Alternative diagnosis
Markedly disparate blood pressure between the right and left arm	Aortic dissection
S3, increased jugular venous pressure, oedema	Congestive heart failure. This can also be a consequence of ACS
Irregular heart rhythm	Atrial fibrillation or other rhythms with variable blocks
Murmurs	Valvular heart disease. This could also be a consequence of ACS
Crackles, diminished breath sounds	Pneumonia
Pericardial friction rub	Pericarditis
Wheezing with decreased air movement	Bronchospasm caused by asthma, chronic obstructive pulmonary disease

Table 9.3 Criteria for STEMI

Diagnostic ECG criteria for STEMI	Additional ECG findings (supportive but not diagnostic of myocardial infarction)
New ST-segment elevation at the J point ≥0.2 mV in men {0.15 mV in women} in leads V2 and V3. ≥2 contiguous leads should be involved	Hyperacute T waves often precede ST elevation
New ST-segment elevation at the J point ≥0.1 mV in leads other than V2 or V3. ≥2 contiguous leads should be involved	Reciprocal ST-segment depressions
New left bundle branch block	Development of pathologic Q waves can be seen as the infarction progresses

Diagnosis and Management

- Two essential factors to be considered in the evaluation of a patient with ACS are:
  - Whether a patient's symptoms and signs reflect ACS
  - The likelihood of an adverse clinical outcome from ACS (risk stratification)
- The first clinical decision point is to decide if a suspected ACS patient has a STEMI (Table 9.3). This STEMI patient will need emergency reperfusion, either by primary percutaneous coronary intervention (PCI) or thrombolysis.
- If STEMI is excluded, treatment should proceed via a common pathway for initial treatment of UA and NSTEMI. Immediate contact with a cardiologist is needed to guide appropriate antiplatelet and anticoagulant treatment.
- Treatment should not be delayed to get the results of serum cardiac biomarkers from the lab. Delay in patient presentation and lack of recognition of ACS in patients without chest pain are barriers to deliver prompt treatment [4, 5].

Risk Assessment

- All treatment of ACS, be it drugs or interventional procedures, has inherent risks and benefits which should be considered. Benefits of aggressive treatment override the risks in intermediate-risk and high-risk patients, while low-risk patients may have minimal benefits and substantial risks.
- Various risk stratification/scoring tools like TIMI and GRACE are available. TIMI risk scores correlate well with 14-day, 30-day and 1-year outcomes [8]. GRACE score is also another good scoring system for NSTE-ACS, but it is more cumbersome to use [9].
- The TIMI risk score for NSTE-ACS is validated in multiple patient populations [6, 7]. It is simple and easy to use. The TIMI score for NSTE-ACS assigns one point for each risk actor: (Box 9.1)

- Patients with elevated troponin are a high-risk population and will benefit from aggressive therapies like glycoprotein 2b/3a receptor inhibitors, low-molecular-weight heparin and early invasive strategy [10–12].
- The Killip classification is another risk stratification system used in individuals with an acute myocardial infarction [13]. Patients with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class (Box 9.2).

Box 9.1 TIMI Scoring System

1. Age 65 years or older
2. Aspirin use within last 7 days
3. Known coronary stenosis (≥50 %)
4. Three or more CAD risk factors (family h/o CAD, hypertension, hyperlipidaemia, diabetes and smoking)
5. Severe angina (at least twice within 24 h
6. Increased cardiac biomarker levels (creatine kinase-MB or troponin levels)
7. ST-segment elevation 0.05 mV or more

Box 9.2 Killip's Classification for STEMI Patients

Class	Clinical findings	Mortality rate (30 days)
Class 1	No CHF	6 %
Class 2	Mild CHF, RALES, S3 and congestion on chest x-ray	17 %
Class 3	Pulmonary oedema	38 %
Class 4	Cardiogenic shock	81 %

Investigations

ECG

- This is an indispensable tool for the evaluation and management of ACS.
- A 17-lead ECG should be the norm (standard 12-lead ECG, additional leads, viz. V7, V8, V9 and V3R, V43R) and V7–V9 leads to identify posterior wall MI and V3R and V4R to identify right ventricular MI.
- ECG should be evaluated within 10 min of patient arrival to ED. It can aid in the management of ACS in addition to identifying STEMI (see Table 9.3) by:
  - Suggesting ischaemia in patients whose symptoms are ambiguous
  - Identifying alternate diagnosis which mimic ACS (pericarditis)

  - Risk stratification in suspected ACS (TIMI score for UA/NSTEMI
  - Showing recurrent ischaemia
- ECG findings in the setting of UA/NSTEMI are as follows:
  - Transient ST-segment changes ≥0.05 mV (0.5 mm) during angina.
  - T-wave inversions ≥0.2 mv (2 mm).
  - ST-segment elevation can also be seen in LBBB, pericarditis, LVH, repolarisation abnormality and ventricular aneurysm.
- Suspected ACS patients should be continuously monitored on telemetry since they are at risk for malignant ventricular arrhythmias.

Chest X-Ray

- Useful in the diagnosis and management of ACS by:
  - Identifying noncardiac cause of chest discomfort or dyspnoea (pneumonia, pleural effusion or pneumothorax).
  - Showing pulmonary oedema as a complication of ACS.
  - Suggesting aortic dissection (widened mediastinum). Aortic dissection can involve origin of right coronary artery and so present as inferior wall MI (Figs. 9.1, 9.2 and 9.3).

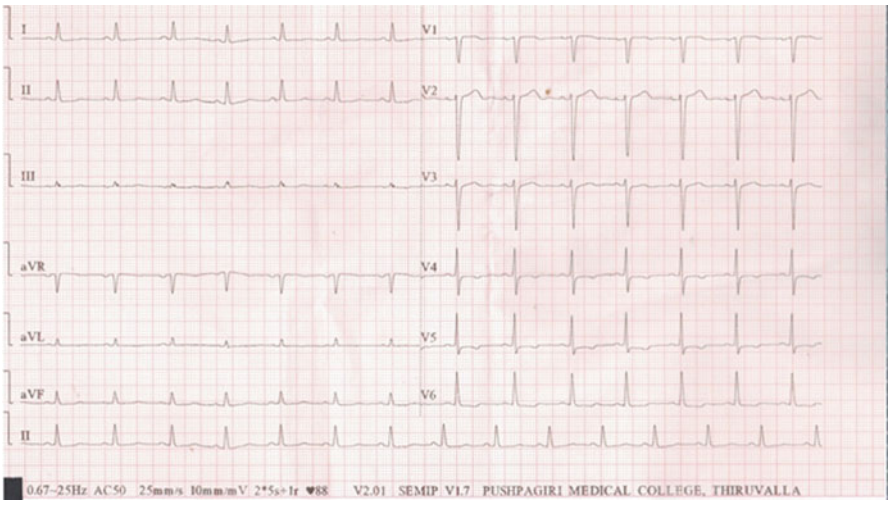


Fig. 9.1 ECG of a patient with unstable angina (Trop –ve NSTE-ACS) who could be managed with initial conservative strategy

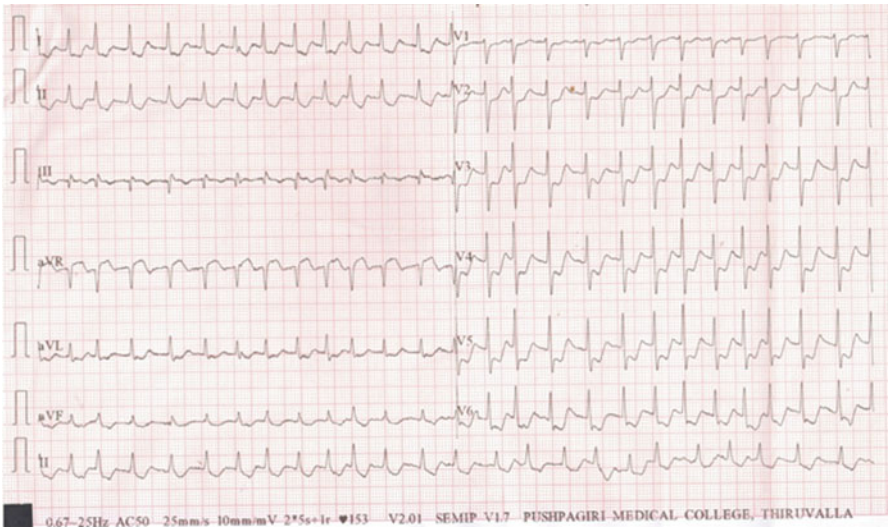


Fig. 9.2 ECG showing features of high-risk NSTE-ACS (Trop +ve) who should receive early invasive strategy

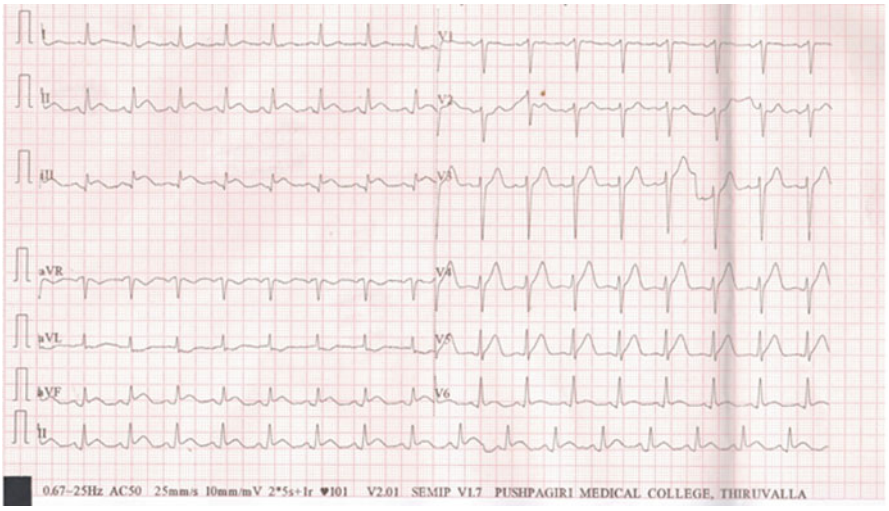


Fig. 9.3 ECG showing evidence of an acute inferior wall STEMI

Cardiac Biomarkers

- High cardiac specificity, rapid release in the setting of myocardial injury and strong correlation to the extent of myocardial damage are hallmarks of an ideal cardiac biomarker.

- Novel cardiac biomarkers like troponin I and troponin T have now largely replaced CK-MB and myoglobin as the tests of choice in ACS [15, 16].
- In the case of STEMI, reperfusion therapy (either thrombolysis or primary PCI) should not be delayed, pending results of troponin.
- Increased troponin level above 99th percentile of normal measurements is defined to represent myocardial necrosis. A single increased troponin level does not discriminate between ischaemic and nonischaemic causes. It may take 6–12 h for troponin level to rise. Hence, serial measurements may be needed to diagnose NSTEMI.
- Positive troponin signifies a high-risk cohort of ACS which benefit from aggressive treatments like low-molecular-weight heparin and early invasive strategy, viz., coronary angiogram and revascularisation.
- CK-MB has shorter half-life and so is useful to diagnose reinfarction and periprocedural MI in a setting of revascularisation.

Echocardiography

- Although not mandatory in the ED, echocardiography is useful to:
  - Confirm the presence of ischaemia (regional wall motion abnormality)
  - Assess LV and RV systolic function
  - Show mechanical complications (mitral regurgitation, VSD) of acute MI
  - See pericardial effusion or presence of cardiac tamponade

Treatment

Immediate Management

- Inhaled oxygen (if spO_2 <90 %).
- Antiplatelet agents: Dispersible aspirin 300 mg tablet stat (to inhibit platelet cyclooxygenase).
- Thienopyridines (platelet P2 Y12 receptor inhibitor): Clopidogrel 300 mg stat (if proceeding for primary PCI, 600 mg to be given) or prasugrel 60 mg stat (avoid if <65 kg weight, >75 years in age or if previous CVA) or ticagrelor 180 mg stat [17].
- IV morphine, 1–10 mg in titrated doses for analgesia and for pulmonary oedema (avoid if there is hypotension, bradycardia or shallow respiration).
- Nitrates: IV nitroglycerine from 2 mcg/min and titrate up to relieve angina and to treat hypertension. Oral isosorbide nitrate 5 mg sublingual can be given if there is no IV access.
- Beta blockers: IV metoprolol 2.5–5 mg is given as a slow IV infusion to reduce ischaemia by decreasing heart rate and BP and thus reducing myocardial O_2 demand (avoid if there is bradycardia, AV blocks, hypotension or pulmonary oedema).

- High-dose statins: Atorvastatin 80 mg or rosuvastatin 40 mg to passivate the ruptured plaque and antiplatelet effect and reversing endothelial dysfunction.

Specific Strategies for STEMI

- Primary goal should be urgent reperfusion [18]. In centers in which primary PCI is unavailable or is delayed for >90 min, prompt thrombolytic treatment is given (if no contraindications) if presenting in <12 h of onset of symptoms (Table 9.4).
- Prehospital thrombolysis: Can be given in ambulance depending on the ability of the accompanying crew in identifying STEMI based on symptoms and ECG. Tenecteplase is best suited for this. In the STREAM study, prehospital lysis vs. primary PCI remained equally effective when done in less than 3 h of symptom onset. But in view of significant increased intracranial bleed (esp. in >75 years age), emphasis should remain on transfer to primary PCI center.
- Door-to-needle time (from presentation to administering lytic drug) should be <30 min. In hospitals with the capability to perform PCI, primary PCI should be the preferred strategy.
- Patients presenting between 12 and 24 h of symptom onset should receive primary PCI if evidence of heart failure, hemodynamic instability (cardiogenic shock), malignant ventricular arrhythmia or persistent ischaemic symptom is present.

Anticoagulants in Treating UA/NSTEMI

- Heparins and direct thrombin inhibitors reduce conversion of fibrinogen to fibrin, thus limiting clot formation.
- Low-molecular-weight heparin (enoxaparin) has more predictable response and less protein binding tendency than unfractionated heparin. Enoxaparin is given in a dose of 1 mg/kg body weight, s/c, bd (od dose if renal impairment).

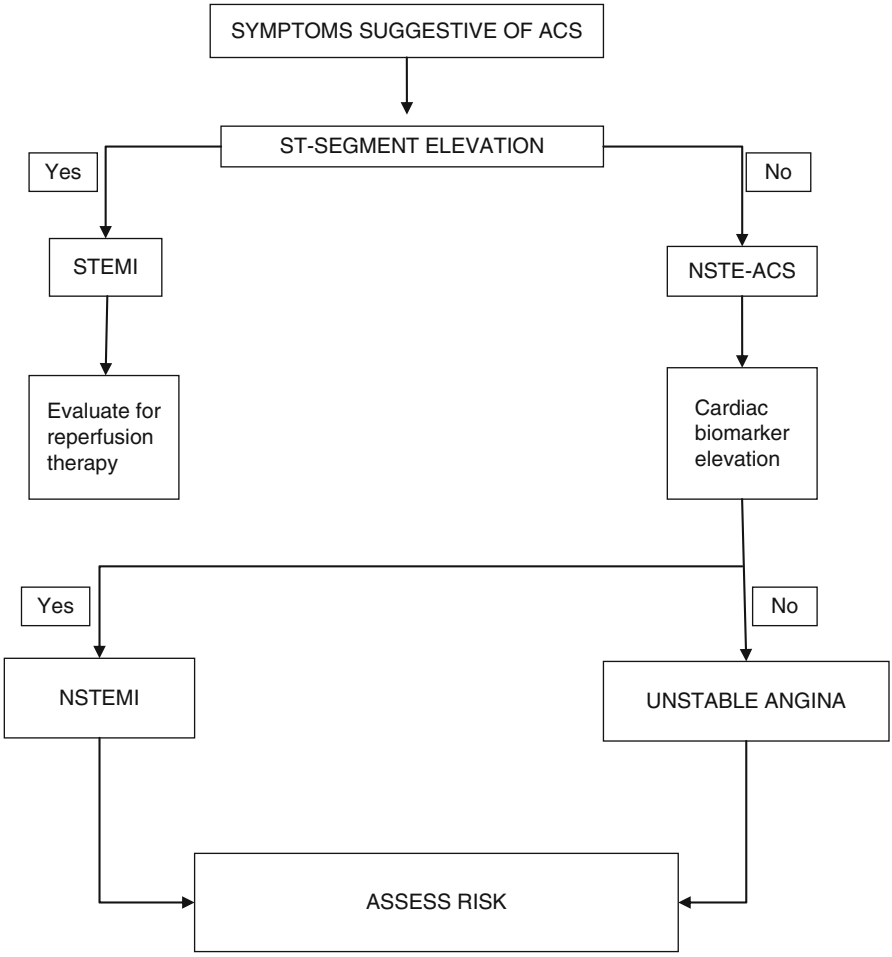
Table 9.4 Thrombolytics used for reperfusion in STEMI

Thrombolytic agent	Special attributes	Dosage
Alteplase	Recombinant tissue-type plasminogen activator. Fibrin specific	15 mg IV × 1, followed by 30 min of 0.75 mg/kg [max dose 50 mg], then 60 min of 0.5 mg/kg [max 35 mg]
Streptokinase	Low cost. Less effective than alteplase, not fibrin specific	15 lakh units over 30 min
Tenecteplase	As effective as alteplase but lower incidents of bleeding	Single IV bolus [weight based]
Reteplase	Less fibrin selective than alteplase, but with longer half-life	10 unit IV bolus followed by another 10 unit bolus IV [after 30 min]

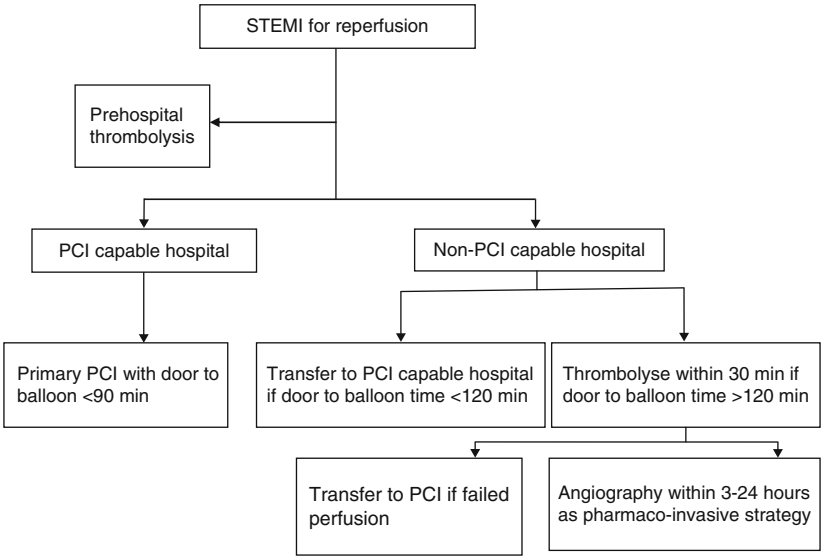
- Fondaparinux is a factor Xa inhibitor given in a dose of 2.5 mg s/c od.
- Glycoprotein 2b/3a inhibitors: Given IV as bolus and then infusion in the cath lab if heavy thrombus burden in heparinised patients.

Disposition

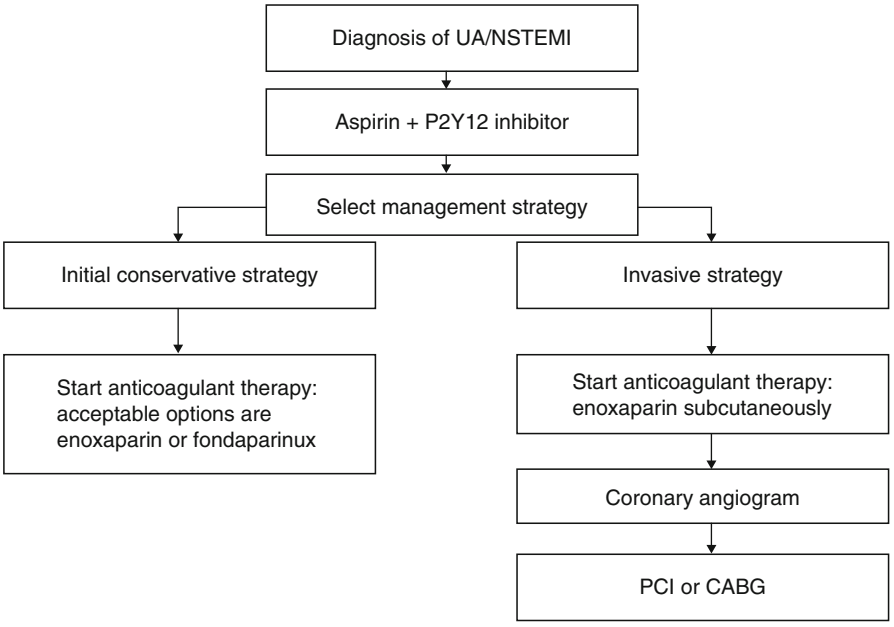
- Patients treated with thrombolytics or who are hemodynamically unstable, show ventricular dysrhythmias or show signs of new-onset heart failure in a setting of ACS should be monitored in the CCU (coronary care unit).
- After stabilisation and initiation of ACS treatment, the ED physician should also address the issue of rehabilitation and discharge (Flowcharts 9.1, 9.2 and 9.3).



Flowchart 9.1 Pathway for the management of ACS



Flowchart 9.2 Management of STEMI



Flowchart 9.3 Management of UA/NSTEMI

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Chapter 10
Heart Failure

Lakshay Chanana

Key Points
- NIV should be considered early in the management of heart failure.
- NTG is an excellent single agent for hypertensive heart failure.
- For normotensive pulmonary oedema, treatment should be focused on diuresis, supplemental oxygen and finding the precipitating cause.
- Vasopressors and inotropes should be started for cardiogenic shock, in the setting of hypotension and signs of poor peripheral perfusion. The options include norepinephrine, dobutamine, dopamine and milrinone.

Introduction

Heart failure is one of the most common reasons for hospitalisation among patients older than 65 years of age [1]. It is the third most common cardiovascular disease in the United States affecting almost five million people [2]. Also, these numbers are increasing with time for various reasons. This makes heart failure a major public health problem associated with a huge financial cost [1].

This chapter is focused on pathophysiology, diagnosis and management of heart failure from an ED perspective.

Emergency physicians play an extremely important role in the management of heart failure, as nearly 80 % of all the heart failure admissions come from the emergency department. Care given in the emergency department certainly affects the final outcome of these critically ill patients.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_10

Based on expert consensus, heart failure is defined as 'traditional signs and symptoms of heart failure requiring urgent or emergent therapy' [3].

Pathophysiology

- In pulmonary oedema, there is leakage of fluid from the pulmonary capillaries and venules into the alveolar space as a result of increased capillary hydrostatic pressure. There can be multiple causes for fluid leakage like LV systolic/diastolic dysfunction, excessive preload or venous return, excessive afterload or peripheral resistance (see Textbox 10.1).
- Initially, the body compensates though the patient may have orthopnoea and paroxysmal nocturnal dyspnoea (PND) as the initial symptoms. Once the system is overwhelmed, it leads to florid LVF.
- This involves a self-perpetuating cycle where acute LV systolic dysfunction leads to decreased myocardial contractility and cardiac output (CO), leading to catecholamine surge that causes increased SVR (afterload) and blood pressure.
- This rise in blood pressure increases the myocardial wall tension and myocardial oxygen demand. This cycle continues and eventually diminishes the myocardial contractility and CO.

Note: Almost half of the patients with acute pulmonary oedema have preserved ejection fraction and have a problem with fluid distribution, not fluid overload [4].

Causes of Heart Failure

The common causes of heart failure that are encountered in the ED are enumerated in Textbox 10.1.

Textbox 10.1 Common Causes of Heart Failure

- Ischaemic heart disease
- Arrhythmias
- Hypertensive heart failure
- Anaemia
- Cardiomyopathies
- Valvular dysfunction
- Cardiac tamponade
- Metabolic: hypothyroidism and hyperthyroidism
- Toxin induced: alcohol, cocaine and doxorubicin
- Iatrogenic: beta blockers and CCB

Diagnosis

History

- Heart failure is primarily a clinical diagnosis.
- Most patients with heart failure present with dyspnoea. Questioning about changes in their peak effort tolerance is important to grade and assess the severity of the disease.
- Orthopnoea and PND suggest acute exacerbation of the disease.
- Symptoms like weight gain, apparent lower extremity or sacral oedema or dyspnoea at rest suggest gradual worsening of the disease.
- It is also important to identify the underlying precipitant of the decompensating factor (see Textbox 10.2).

Textbox 10.2 Precipitants of HF
- Medications non-compliance
- Dietary non-compliance
- Arrythmias
- Infections
- Acute coronary syndrome
- Missed dialysis
- Exacerbation of chronic lung diseases
- Pulmonary embolus

Clinical Examination

- Look at the general appearance, posture, respiratory effort and diaphoresis.
- Assess for pallor, oedema, JVD or hepatojugular reflux, cyanosis, capillary refill time and mental status of the patient to assess cerebral perfusion.
- Check vital signs assessment and classify them as hypertensive, hypotensive or hypertensive heart failure.
- Lung examination often reveals crepitations. Auscultate on the front, back and at the bases of the lungs to diagnose occult disease. A wheeze might also be heard due to smaller airway narrowing and spasm (cardiac wheeze or cardiac asthma). If the air entry is less, then suspect a pleural effusion.
- Auscultation might reveal murmurs that might have precipitated the illness or an S3, which is a specific sign for heart failure.

Imaging and Labs

1. *ECG*
   - A completely normal ECG is extremely unlikely in the setting of heart failure, and it puts the diagnosis into question.
   - ECG may suggest underlying precipitants like pulmonary embolism and chronic hypertension and states leading to acute decompensation of heart failure like myocardial ischaemia and arrhythmias. ST-T changes may also be seen due to LV strain or NSTE-ACS.
   - The ECG image (Fig. 10.1) shows LBBB with LV strain and changes suggestive of LVH.
2. *Chest X-ray*
   - A chest radiograph (CXR) can help in reinforcing the diagnosis of heart failure with characteristic findings like Kerley B lines, prominent pulmonary vasculature in upper lung fields, cardiomegaly and pleural effusions.
   - It may also suggest other differential diagnosis like pneumonia, aortic dissection or a pulmonary embolus.
   - CXR is specific to pick up heart failure but not very sensitive as about 18 % of patients with acute decompensated heart failure have normal CXR [5].
   - A normal CXR cannot rule out heart failure. Always try to compare the current CXR with the former ones.
3. *Lung USG*
   - With the advent of lung ultrasound, it is now possible to do a bedside assessment for these critically ill patients. Lung USG can give valuable information about interstitial oedema (B lines), pleural effusions and consolidation.

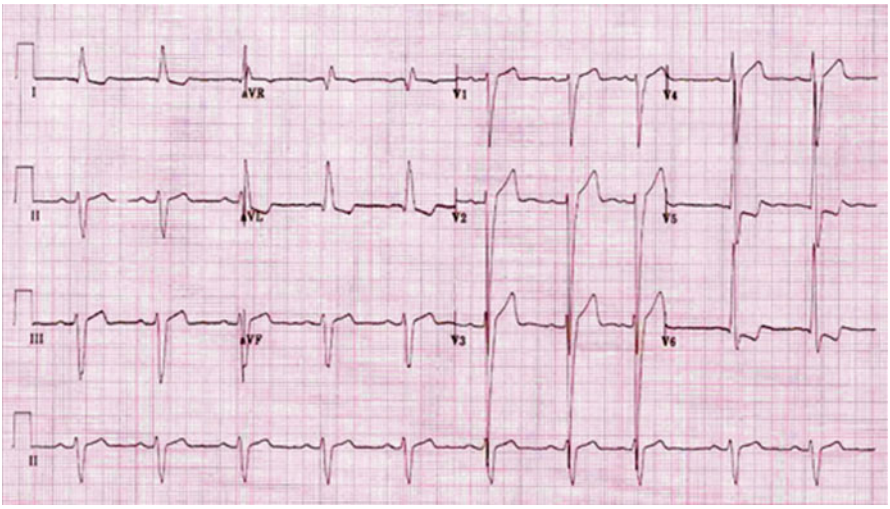


Fig. 10.1 ECG of a 56-year-old male with HF, showing LV strain in the lateral chest leads

4. *Echogram*

   Bedside echogram can assess LV function, presence of pericardial effusion, dilated right heart and valvular heart disease. This helps in diagnosing as well as prognosticating the disease. Emergency department bedside ECHO is often used for undifferentiated hypotension and dyspnoea that aids the diagnosis of heart failure.
5. *Laboratory investigations*

   - Laboratory testing is not required to diagnose heart failure, but to find out the precipitating causes, looking for the complications and prognosticating the disease.
   - The tests which are generally done include a complete blood profile, BNP, troponin and renal function tests (creatinine, urea and electrolytes).
   - Electrolyte abnormalities are commonly found due to the use of diuretics and volume overload. Potassium derangements may precipitate arrhythmias. Hyponatraemia, if present, suggests a poor prognosis and two- to threefold post-discharge mortality.
   - A majority of patients with heart failure suffer from CAD, and also ischaemia might be a potential precipitant of heart failure; therefore, troponin is frequently requested for these patients. But heart failure itself can raise the troponin levels, so often serial troponins are required to diagnose ACS unless straightforward ECG changes are present [6].

BNP

- Natriuretic peptide is synthesised as by the ventricular myocardium in response to raised ventricular pressures.
- Current guidelines recommend BNP assays to aid in the diagnosis or exclusion of acute heart failure [7].
- It is elevated in heart failure and a low level strongly suggests other potential diagnosis. *As always, biomarkers are not stand-alone tests; always use your clinical acumen while interpreting any biomarker and consider additional testing if required.*
- BNP also aids in determining the prognosis, morbidity and mortality. Other illnesses that may affect BNP levels are sepsis or renal dysfunction.

Differential Diagnoses

The differential diagnoses of heart failure include the conditions enumerated in Textbox 10.3.

Textbox 10.3 Differential Diagnoses of Heart Failure

- Exacerbation of chronic lung disease
- Pneumonia
- Pulmonary embolus

- Hepatic failure
- Sepsis
- Acute valvular insufficiency
- ARDS (non-cardiogenic pulmonary oedema)

Emergency Department Management

- From a treatment perspective, acute heart failure can be divided into three subtypes: hypertensive heart failure, normotensive heart failure and hypotensive heart failure (cardiogenic shock).
- Although the majority of patients with acute heart failure syndrome respond well to medical therapy, some patients will require ventilatory assistance.
- Timely interventions and appropriate use of nitrates, diuretics, ACE inhibitors and non-invasive ventilation (NIV) can reduce the need for mechanical ventilation and ICU admissions.

1. *Hypertensive HF*

   - This is the most toxic looking subtype of heart failure patients. Some physicians also refer to this as acute hypertensive decompensated heart failure.
   - The treatment should begin immediately here with non-invasive ventilation (NIV), followed by high-dose NTG drip, diuretics and ACE inhibitors.
   - *Setting up NIV early in the illness is crucial* [8]. Either CPAP or BiPAP may provide non-invasive ventilatory assistance. These devices reduce the need for endotracheal intubation, hospital length of stay and mortality.
   - *NTG is a single excellent first-line agent to relieve symptoms of hypertensive LVF* [8]. Although a large group of experts recommend loop diuretics as the first-line agents for ADHF, NTG is more beneficial in the emergency department set-up. It works almost instantaneously and it has a very short half-life.
   - It lessens both the RV and the LV pressures, decreases the systemic blood pressure and increases the cardiac.
   - Output. In contrast, furosemide, during its initial phases, actually worsens the haemodynamics [8].
   - The oral dose of NTG 0.4 mg is approximately equal to 80 mcg/min infusion. Therefore, starting an infusion at 10 mcg/min after giving an oral dose of 0.4 mg leads to dramatic dose reduction. *Therefore, NTG should be commenced at 80–100 mcg/min at least to start with and then escalated rapidly 10–20 mcg every minute up to 400 mcg/min*, guided by the blood pressure [8].
   - High-dose NTG results in dramatic improvement in symptoms over minutes and averts mechanical ventilation. At such high doses, it acts as both arteriolar and a veno-dilator that decreases both afterload and preload, respectively.
   - Now there is robust literature that proves the efficacy of high-dose NTG in the setting of hypertensive LVF [9–16].
   - *Aggressive diuretic monotherapy is unlikely to prevent the need for endotracheal intubation compared with aggressive nitrate monotherapy* [7].

- Loop diuretics, if given alone, can potentially cause hypotension and worsen the renal function by causing diuretic-induced azotaemia and increasing the mortality [10]. Patients in hypertensive LVF have compromised renal blood flow, so diuretics take up to 1–2 h to show the desired effect. So, add diuretics only after nitroglycerine drip is on flow for at least 30 min.
- When studied it was found that almost half of heart failure are not actually in fluid overload [4]; they just have fluid in the wrong compartment of their body. So, *the treatment should be focused on fluid redistribution with optimisation of haemodynamics using nitroglycerine, not eliminating the fluid and dehydrating them with diuretics.* Therefore, administration of diuretics is recommended only in the smallest possible dose in cases of apparent fluid overload.
- Traditionally, morphine has been recommended to ease anxiety in this subgroup of patients, but the current literature questions the use of morphine. It has been associated with worse outcomes with increased rates of ICU admissions and intubation [17].
- Angiotensin-converting enzyme (ACE) inhibitors may also be used in the initial management of acute heart failure syndromes. Overall, they have been less studied in APE and the evidence is not robust. ACE inhibitors decrease the preload and afterload by shutting off the renin-angiotensin-aldosterone system [8].
- *In summary, the treatment of hypertensive LVF should start with NIV and then high-dose NTG and then followed by diuretics only of there is apparent fluid overload.*

2. *Normotensive heart failure*

- This subtype generally presents with an SBP of 90–140 mmHg.
- They may present with a gradual onset of breathlessness and decreased peak effort tolerance. Treatment for them includes diuresis as the primary modality.
- An initial bolus of furosemide 20–40 mg is recommended [18]. If using high doses of diuretics, beware of their potential to cause renal dysfunction.
- In addition to diuresis, also consider using supplemental oxygen and non-invasive ventilation, guided by the general appearance, respiratory rate/effort and SpO_2.

3. *Normotensive heart failure*

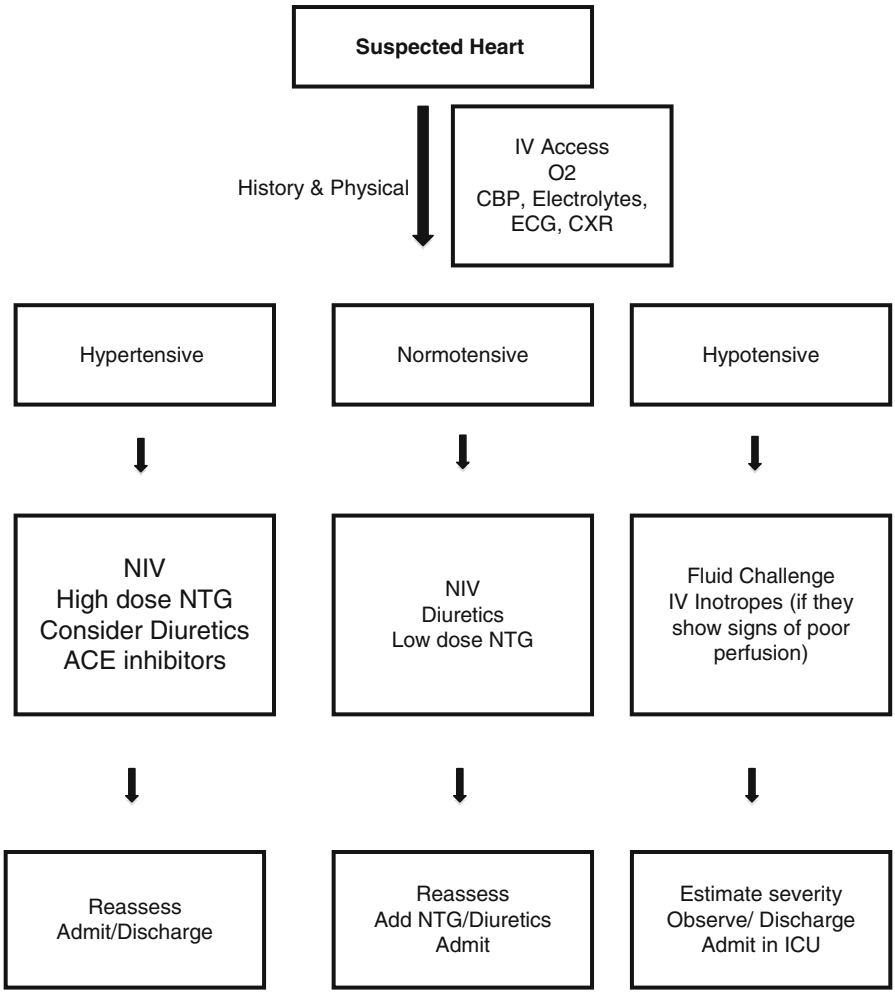
- Only a minority of patients present with hypotension and heart failure; undoubtedly this is the most difficult subtype of patients to manage.
- Look for signs of poor perfusion, do a good history and try to get an estimate about their baseline blood pressure before starting inotropes. If there is an acute decompensation, look for the precipitating event.
- If there are signs of poor perfusion along with hypotension, only then add inotropes temporarily to improve the haemodynamics. Inotropes are necessary evils, associated with an increased mortality, and thus, they are not routinely recommended.
- The choice of inotropes is largely based on the clinician's preference, but in general, dobutamine is the drug of choice for cardiogenic shock [18].
- In cases of florid shock, norepinephrine should be commenced first and supplemented by dobutamine due to initial hypotensive effects of dobutamine via beta 2 receptors. Other potential options are dopamine and milrinone [19].

Other therapies that can be used to buy time or treat heart failure include the use of IABP, LVAD and ECMO. This should be discussed with the patient's cardiologist.

Disposition

Currently, most of the patients who come to the ED with heart failure get admitted. The situation may change in the future with the development of ED-based observation units. There are no well-accepted and validated clinical rules to risk stratify these patients and decide about the disposition. In addition, there is data that suggests high mortality if they are discharged from the ED.

Treatment Algorithm



Patients with the following features are high risk and have a low threshold to admit them.

High-Risk Features
- Poor response
- Inadequate urine output
- Elevated troponin
- Renal dysfunction
- Persistent hypoxia despite using NIV

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Chapter 11
Hypertensive Emergencies

Ashish Nandy and Sanjukta Dutta

Abbreviations

BUN	Blood urea nitrogen
CT	Computerised tomography
CTVS	Cardiothoracic and vascular surgery
CXR	Chest x-ray
DBP	Diastolic blood pressure
ED	Emergency department
EKG	Electrocardiogram
ICP	Intracranial pressure
LMWH	Low molecular weight heparin
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention
PP	Pulse pressure
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
UFH	Unfractionated heparin

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_11

Key Points

- Early detection of target organ failure or imminent target organ failure is important in hypertensive crisis.
- Detailed history and clinical examination can best direct toward the requisite investigations and contribute toward proper diagnosis and management.
- Along with BP control, treatment of the underlying cause and specific organ dysfunction are the keys for the good outcomes in hypertensive emergencies.

Overview of Hypertensive Emergency

Hypertension is a global problem mostly in adults, over one billion people are affected worldwide and the incidence is continuously increasing [1]. Hypertensive emergencies present with sustained elevated blood pressure and acute dysfunction of one or more target organs. A major proportion of all acute medical emergencies in urban emergency department are due to hypertensive emergencies. About 1 % of patients with a background of high blood pressure will have at least one episode of hypertensive emergency in their lifetime. Recent literature provides evidence that 5 out of 1,000 patient-years were admitted to emergency department with hypertensive crisis [2]. Early evaluation and timely intervention can significantly reduce the morbidity and mortality.

(a) *Hypertensive emergency* is a combination of sustained elevated blood pressure (usually *SBP* >180 and *DBP* >120 mmHg) and acute dysfunction of one or more target organs (such as the brain, heart or kidneys). But it is possible to have the symptoms with lower blood pressure in those patients whose previous blood pressure was not high.
(b) *Hypertensive urgency* is a clinical condition where there is sustained elevated blood pressure (usually *SBP* >180 and *DBP* >120 mmHg) without acute target organ dysfunction.
(c) *Hypertensive crisis* includes both hypertensive emergency and hypertensive urgency [3].

Pathophysiology

- Most important pathological mechanism involved in hypertensive emergency is the pressure-dependent flow dysregulation in important vascular beds like the cerebral, renal and cardiac circulations.
- Ischaemia and vasculitis follow and these cause further damage to the blood vessels.

- In normal circumstances, the blood vessels autoregulate the blood flow to the vital organs which is achieved by constriction of the blood vessels beyond a critical mean arterial pressure (MAP).
- When the MAP exceeds the range of normal autoregulatory capacity, blood vessels fail to constrict and there is superperfusion of the tissues, which finally leads to the target organ dysfunction.
- Fibrinoid necrosis, which is seen in the arterioles, is the hallmark pathological finding in hypertensive emergency.
- Further changes in the blood vessels are thrombus formation and fibrin deposition, which manifest as retinal haemorrhage, papilloedema, renal function compromise and heart failure.
- When the MAP is more than 140 mmHg, cerebral autoregulation is also disturbed, leading to disruption of the blood-brain barrier and hypertensive encephalopathy sets in.
- In addition to the elevation of blood pressure, few local mediators like free radicals, prostaglandins, cytokines, proliferation factors, chemoattractant and mitogenic factors contribute to hypertensive emergency. Damage to the endothelium, proliferation of smooth muscles and aggregation of platelets may contribute to the cellular injury.
- Increased levels of renin, angiotensin II, endothelin, catecholamines and vasopressin are some important systemic factors which contribute to the pathological changes. Natriuresis due to increased blood pressure causes hypovolaemia and initiates subsequent release of catecholamine along with rennin.
- All these factors trigger the elevation of blood pressure, potentiate endothelial injury and finally cause tissue ischaemia and tissue damage [4].

Hypertensive Emergency: Common Causes and Presentations

- In chronic hypertensives: sudden rise in BP
- Antihypertensive drug withdrawal: commonly clonidine and β-antagonists
- Drugs: cocaine, amphetamines, phencyclidine hydrochloride (PCP), tricyclic antidepressants (TCA), oral contraceptives, steroids, nonsteroidal anti-inflammatory drugs, nasal decongestants, appetite suppressants, monoamine oxidase inhibitors
- Disease conditions:
  - *Cardiovascular*: acute coronary syndrome, acute pulmonary oedema, aortic dissection
  - *Neurological*: encephalopathy, stroke, head injury
  - *Renal*: renovascular hypertension, chronic renal parenchymal disease, acute glomerulonephritis, renin-secreting tumour, renal crisis in collagen vascular diseases
  - *Obstetrics and gynaecology*: preeclampsia, eclampsia

- *Pheochromocytoma*
- *Vasculitis*
- *Guillain-Barre syndrome or spinal cord syndromes* (*autonomic hyperactivity*)

Approach to Hypertensive Emergency

- History:
  - H/o preexisting hypertension including the degree of BP control
  - H/o previous target organ dysfunction
  - Obstetric history (pregnancy, previous preeclampsia/eclampsia)
  - Antihypertensive medication history and compliance
  - Other medical conditions (thyroid dysfunction, collagen vascular diseases, Cushing disease, etc.)
- *System-specific history*:
  - Chest pain (acute coronary syndrome, aortic dissection)
  - Interscapular pain (aortic dissection)
  - Shortness of breath (acute pulmonary oedema, acute coronary syndrome)
  - Altered mental status: confusion, obtundation and coma (hypertensive encephalopathy)
  - Headache (hypertensive encephalopathy, stroke)
  - Focal weakness and slurring of speech (stroke)
  - Nausea and vomiting (stroke, hypertensive encephalopathy, renal failure)
  - Seizure (hypertensive encephalopathy, eclampsia)
  - Profuse sweating and palpitation (pheochromocytoma, acute coronary syndrome)
  - Blurred vision (papilloedema)
  - Transient cortical blindness (stroke or eclampsia)
- *Physical examination*:
  - Elevated blood pressure
  - Jugular venous distention (pulmonary oedema)
  - Asymmetry of pulse and blood pressure between both the arms (aortic dissection)
  - Significant asymmetry of blood pressure in standing and supine position (acute coronary syndrome, aortic dissection)
  - Basilar lung crackles and third heart sound (pulmonary oedema)
  - New onset murmur (acute coronary syndrome, aortic dissection)
  - Altered sensorium (stroke and encephalopathy)
  - Focal neurological deficit (stroke)
  - Abdominal masses and bruit: systolic and diastolic (renovascular disease)
  - Fundoscopic finding of retinal haemorrhage, cotton wool spots, exudates, papilloedema with blurring of disc margin (retinopathy)

Diagnostic Testing

Complete blood count	EKG
Peripheral blood smear	Urine analysis
BUN and creatinine	CXR
Cardiac markers	Echocardiogram
Serum electrolytes	CT scan: head, chest abdominal and pelvis
	MRI: brain and thorax

Peripheral Smear

- Microangiopathic changes with haemolytic anaemia in ARF, HELLP syndrome

Blood Urea Nitrogen and Creatinine

- Elevated level in renal arterial involvement with dissection

Serum Electrolytes

- For evaluation and treatment of sodium or potassium abnormalities

Urinalysis

- May show protein, microscopic haematuria, erythrocyte casts or hyaline casts

Chest Radiography

- In case of LV dysfunction and pulmonary oedema, CXR may show diffuse opacities.
- Widened mediastinum may be a feature in aortic dissection.

Cardiac Markers

- CK-MB; troponins are usually elevated in case of myocardial infarction.

Electrocardiography

- Diagnostic in case of myocardial ischaemia or infarct.
- Left ventricular hypertrophy, ST-T changes and arrhythmias may be additional findings.

CT Brain

- Diagnostic for the evaluation stroke (ischaemic, haemorrhagic, SAH)

Computed Tomography Angiography

- CT angiography of the chest, abdomen and pelvis is important in case of suspected aortic dissection patients.

Echocardiography

- May show abnormalities of cardiac anatomy, valvular defects and impaired LV function
- May be useful for evaluation of pericardial effusion, tamponade, cardiogenic shock, ACS and dissection

MRI

- May be helpful in evaluation of ischaemic stroke and aortic dissection

Treatment

The aim of initial drug therapy:

- Reduction of the MAP (MAP = DBP +1/3 PP, PP = SBP-DBP) up to 25 % within the first 1 h.
- Further reduction of blood pressure down to 160/100 mmHg in the next 2–6 h in haemodynamically stable patients.
- Gradual lowering of the blood pressure to the normal level is advisable in the next 8–24 h [5, 6].

Continuous monitoring of the blood pressure during the drug therapy is important. The choice of antihypertensive agents, the dose and the rate of reduction of blood pressure need to be individualised according to the underlying disease process.

In case of hypertensive urgency where the target organ damage is not evident, the blood pressure reduction should be done gradually over hours to days. This can be done by oral medications.

Intravenous antihypertensive medications used in hypertensive crisis

Drug	Dosage	Onset/duration	Adverse effects
Enalapril	1.25–5 mg q6 h	30 min/6 h	Hyperkalaemia, renal failure
Esmolol	200–500 μg/kg/min for 4 min and then 150–300 μg/kg/min IV	1–2 min/10–20 min	Hypotension, need to be avoided in asthma and heart failure
Fenoldopam	0.1–0.3 μg/kg per min IV infusion	5 min/10–15 min	Headache, tachycardia, flushing, nausea
Hydralazine	10–20 mg IV	5–15 min/3–8 h	Tachycardia, flushing, marked hypotension
Labetalol	20–80 mg IV bolus every 10 min, 2 mg/min IV infusion	5–10 min/3–6 h	Orthostatic hypotension, heart block
Nicardipine	5–15 mg/h IV	5–10 min/1–4 h	Headache, flushing, nausea, tachycardia
Nitroglycerin	5–100 μg/min as IV infusion	1–5 min/3–5 min	Vomiting, headache, flushing
Nitroprusside	0.25–10 μg/kg/min as IV infusion	Instantaneous/1–2 min	Muscle twitching, nausea and vomiting
Phentolamine	5–15 mg IV	1–2 min/3–10 min	Headache, flushing, tachycardia

System-Specific Management of Hypertensive Emergency

Aortic dissection

ED presentation Patients may present with tearing chest pain, back pain or abdominal pain, depending on the type of dissection.

Treatment option

- Labetalol, esmolol, nicardipine and nitroprusside are the drug of choice for control of blood pressure [7].
  Goal is to attain a SBP of 110–120 mm of Hg. These drugs reduce the blood pressure and heart rate which reduce the shear-force on the vessels.
- Pain management.
- Urgent CTVS referral for interventional or operative management.

Acute hypertensive pulmonary oedema

Comments Aortic dissection carries the highest mortality rate among all the hypertensive emergencies. Incidence of aortic dissection is seen more in patients with connective tissue disorders (e.g. Marfan's syndrome, Ehlers-Danlos syndrome), pregnant ladies and cocaine or methamphetamine users [8, 9].

ED presentation Acute shortness of breath and raised JVP, S3 gallop and bi-basal crepitations.

Treatment option

- One hundred percent oxygen
- Loop diuretics, e.g. furosemide
- Morphine
- Nitroglycerine, enalaprilat, nicardipine and nitroprusside [10] to reduce blood pressure by 20–30 %

Comments Rapid resolution of symptoms and improved outcome can be achieved by more than 30 % reduction of MAP. First-dose hypotension is common with IV enalaprilat.

Acute myocardial infarction

ED presentation Acute chest pain, shortness of breath, sweating, chest heaviness and giddiness

Treatment option

- Antiplatelets (aspirin, clopidogrel).
- Statins.
- Anticoagulants (LMWH, UFH).
- Nitroglycerine, labetalol.
- Thrombolysis or PCI to be considered.
- If SBP is more than 160 mmHg maximum 20–30 % reduction of SBP is desirable [11].

Comments Beware of hypotension.

Acute sympathetic crisis (cocaine, amphetamines)

ED presentation Marked hypertension, tachycardia and occasional chest pain

Treatment option

- Benzodiazepine, nitroglycerine, and IV alpha-antagonist phentolamine [12, 13].
- In less severe cases, oral alpha-antagonist phenoxybenzamine.
- Nitroprusside can be an alternative to alpha-blockers.

Goal of therapy Reduction of excessive sympathetic drive

Acute renal failure

Comments Monitor respiratory rate. Monotherapy with b-blocker is contraindicated, owing to reactive oversecretion of catecholamines.

ED presentation Microscopic haematuria, elevated blood pressure and acute shortness of breath

Treatment option

- Nicardipine, fenoldopam, and labetalol for elevated BP [14]. Blood pressure reduction should be restricted to less than 20 %.
- Consider haemodialysis.

Comments Use of nitroprusside causes cyanide toxicity. In patients having high BP and altered renal function, the use of fenoldopam causes improvement in renal clearance.

Severe preeclampsia, HELLP syndrome, eclampsia

ED presentation Headache, nausea, vomiting, proteinuria, seizure in pregnancy

Treatment option

- Labetalol, hydralazine and nicardipine for blood pressure reduction [15].
- Magnesium sulphate.
- Bed rest.
- Consider early termination of pregnancy.
- MAP reduction to 20 %. Reduction of ICP. Maintenance of placental circulation.

Hypertensive encephalopathy

Comments ACE inhibitors are contraindicated, owing to the potential adverse effects on the fetus.

ED presentation Severe headache, vomiting, altered mental status, seizure, visual disturbance

Treatment option Nicardipine, labetalol [16]
- Reduction of ICP and brain oedema, which will improve brain autoregulation

Comments Workup should include other causes of altered mental status.

Subarachnoid haemorrhage

ED presentation Headache, dizziness, orbital pain, diplopia, seizure

Treatment option
- Labetalol, nicardipine, and esmolol to decrease blood pressure [17] to decrease MAP lower than 130 mm of Hg.
- Nimodipine to reduce cerebral vasospasm and subsequent ischaemia [18].
- Consider neurosurgical intervention.

Intracranial haemorrhage

ED presentation Altered mental status, hemiplegia or hemiparesis, dysarthria, facial droop, ataxia, nystagmus, aphasia, headache, vomiting, seizure

Treatment option
- Labetalol, nicardipine, and esmolol to control blood pressure [17]. Goal is to lower the MAP around 110 mm of Hg or BP around 160/90 mm of Hg and to maintain cerebral perfusion pressure > 60–80 mm of Hg if SBP >180 mm of Hg or MAP > 130 mm of Hg [19].
- Consider neurosurgical intervention.

Comments: Aggressive BP management is indicated when SBP >200 or MAP >150 [20].

Acute ischaemic stroke

ED presentation Altered mental status, hemiplegia or hemiparesis, dysarthria, facial droop, ataxia, nystagmus, aphasia, headache, vomiting, seizure

Treatment option
- Labetalol, nicardipine, and esmolol to reduce the blood pressure
- IV or intra-arterial thrombolytics to be considered
- Oral aspirin (contraindicated within first 24 h of thrombolytic therapy)
- In case thrombolytic therapy is planned, raised BP should be treated and, if it is more than 185/110 mmHg, otherwise not to be treated up to 220/120 mmHg [20].

Disposition

Hypertensive emergency patients warrant admission, ideally in high dependency or intensive care unit. (Please refer to Fig. 11.1 – Algorithm) Patients who present with no symptoms and no evidence of target organ dysfunction can be discharged from

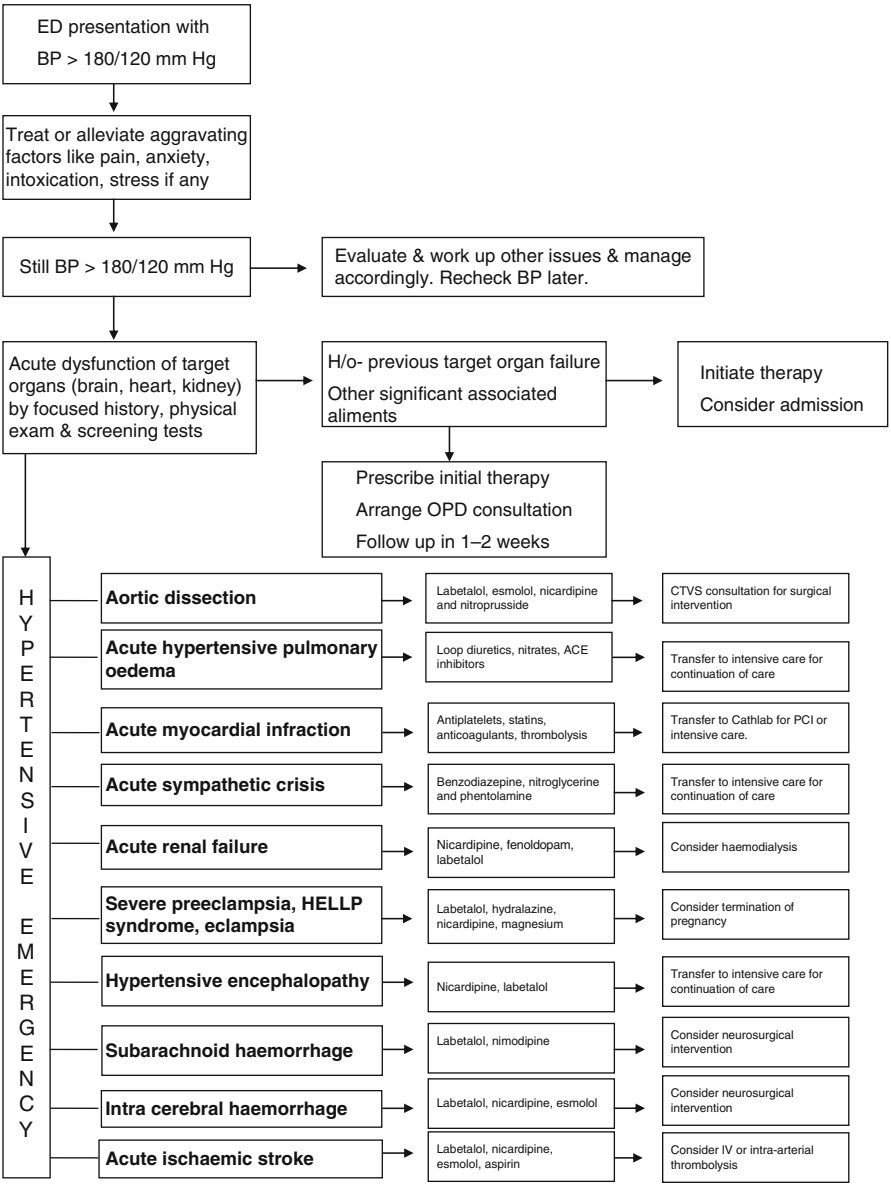

Fig. 11.1 Algorithm

the ED with medications and regular follow-up. It is very important to remember that some individuals may show target organ involvement, with a range of blood pressures less than discussed in this chapter. That is why it is important to keep in mind that we should treat the patient and not the number.

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Part III
Critical Care

Chapter 12
Acid-Base Disorders

Kishore Pichamuthu

Key Points

- Acid-base disorders can either be metabolic (primary change in HCO_3) or respiratory (primary change in $PaCO_2$).
- Every primary acid-base disorder results in a compensatory response. Use rules of thumb to differentiate single from mixed disorders.
- Metabolic acidosis can be partitioned using the Fencl-Stewart equation into strong ion difference, albumin and unmeasured anions.
- A corrected anion gap is useful in determining the cause of metabolic acidosis.
- The underlying cause of the acid-base disorder needs to be identified and treated.

Introduction

> Life is a struggle....sin, not against money power, not against malicious animal magnetism, but against hydrogen... – H.L. Mencken

Disorders of acid-base balance are very common in acutely ill patients, and accurate diagnosis of the acid-base disorder and appropriate management may be life-saving. A systematic approach to the diagnosis and treatment of these disorders is therefore essential. An arterial blood gas (ABG) is required to identify the acid-base disorder and to document its severity. This is best performed by collecting the blood in an anticoagulant-lined syringe designed for this purpose and analysing

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_12

immediately on an analyser placed at point of care. In the absence of a point-of-care device, the sample should be placed in ice and hand carried to the central laboratory as quickly as possible. Transport of ABG samples through pneumatic tube systems is not recommended as such transport can potentially alter blood gas values.

The 'Normal' Arterial Blood Gas [1] (Table 12.1)

The statistical 'normal' is derived from healthy populations. However, clinically relevant abnormal values are those beyond which there is a derangement of function and therapy is mandatory.

The Stepwise Approach to Interpreting Arterial Blood Gas [1]

Step 1: Assess Oxygenation

- First look at the absolute value of PaO_2.
  - Treat hypoxia if <60 mmHg – oxygen therapy.
  - Reduce FiO_2 if >100 mmHg.
- Then assess PaO_2/FiO_2 (P/F) ratio or A-a gradient.
  - For example, FiO_2 21 %, i.e. 0.21, PaO_2 84 mmHg, P/F ratio = 84/0.21 = 400
  - P/F ratio gives an indication of the degree of severity of lung pathology.
  - Normal P/F ratio 400–500. Acceptable >300.

Step 2: Identify the Primary Problem

The $PaCO_2$ and HCO_3 impact the pH and determine the acid-base status of the patient. The $PaCO_2$ is determined by the respiratory system, and the HCO_3 is regulated by the kidney, liver, gut and muscle, collectively referred to as the metabolic system. Therefore, broadly four acid-base disorders are possible (see Table 12.2).

Table 12.1 Normal and clinically acceptable arterial blood gas (ABG) values

	Normal range	Clinically acceptable
pH	7.35 to 7.45	7.30 to 7.50
PCO_2	35 to 45 mmHg	30 to 50 mmHg
PO_2	80 to 100 mmHg	>60 mmHg
HCO_3	24 to 28 mEq/L	24 to 28 mEq/L
Base excess	−2 to +2	−5 to +5

Table 12.2 Primary acid-base disorders

Primary disorder	Primary change
Respiratory acidosis	Increased $PaCO_2$
Respiratory alkalosis	Decreased $PaCO_2$
Metabolic acidosis	Decreased HCO_3
Metabolic alkalosis	Increased HCO_3

Table 12.3 Compensatory acid-base disorders

Primary disorder	Primary change	Compensation	Compensatory change
Respiratory acidosis	Increased $PaCO_2$	Metabolic alkalosis	Increased HCO_3
Respiratory alkalosis	Decreased $PaCO_2$	Metabolic acidosis	Decreased HCO_3
Metabolic acidosis	Decreased HCO_3	Respiratory alkalosis	Decreased $PaCO_2$
Metabolic alkalosis	Increased HCO_3	Respiratory acidosis	Increased $PaCO_2$

Look at pH, $PaCO_2$ and HCO_3 for values outside acceptable range.

If the pH is abnormal, the direction in which it has moved indicates the nature of the primary disorder. For example, if the pH is 7.10, the primary disorder is definitely an acidosis. We can then look at the $PaCO_2$ and the HCO_3 to see if the acidosis is respiratory or metabolic.

If the pH is normal with an abnormal $PaCO_2$, then two possibilities exist. Either it is a mixed state, where there are two primary opposing acid-base disorders, one respiratory and one metabolic, or there is a fully compensated respiratory acid-base disturbance.

Remember, an abnormal $PaCO_2$ or HCO_3 indicates an acid-base disturbance even when the pH is near normal or normal.

Additionally an anion gap >20 usually points to a metabolic acidosis irrespective of the actual values of the $PaCO_2$ or HCO_3.

Step 3: Assess Adequacy of the Compensatory Response – Single (Simple) and Mixed Disorders

The body aims to keep the extracellular pH tightly regulated. Hence, every primary acid-base disorder initiates a compensatory response (see Table 12.3).

It can be observed that the compensatory change moves in the same direction as the primary change. For example, an *increase* in $PaCO_2$ leads to a compensatory *increase* in HCO_3, and a *decrease* in $PaCO_2$ leads to a compensatory *decrease* in HCO_3.

The diagnosis of a single acid-base disorder implies both the initial process and the appropriate compensatory mechanisms. Inappropriateness (excess or inadequate) of the expected compensatory response indicates a mixed disorder. This can be diagnosed for clinical purposes by using a few bedside rules:

1. *Metabolic disorders.*

   In a primary metabolic acidosis, the correct compensatory change is a drop in $PaCO_2$ due to hyperventilation. The numerical value of the reduced $PaCO_2$ should be within + or – 5 mmHg of the number formed by the two digits after the decimal point of the pH value down to 7.10. The $PaCO_2$ usually goes no lower than 10 mmHg even with a profound metabolic acidosis [2]. For example, in a primary metabolic acidosis with a pH of 7.20, the expected normally compensated $PaCO_2$ value will be 20 ±5 (i.e. 15–25 mmHg). If the $PaCO_2$ is within this range (e.g. 20 mmHg), the diagnosis is an appropriately compensated metabolic acidosis. On the other hand, if the $PaCO_2$ is higher than this expected range (e.g. 30 mmHg), then the diagnosis is mixed metabolic and respiratory acidosis, and if it is lower than this expected range (e.g. 10 mmHg), then the diagnosis is mixed metabolic acidosis and respiratory alkalosis. Similarly, in a primary metabolic alkalosis, the appropriate value of the elevated $PaCO_2$ is within ±5 mmHg of the number formed by the two digits after the decimal point of the pH value up to 7.60.

   However, these calculations of appropriate compensation as given above should be applied to spontaneously breathing patients and not to those who are mechanically ventilated because in such patients, ventilator settings determine the $PaCO_2$.

2. *Respiratory disorders.*

   In primary respiratory disorders, the initial change is in the $PaCO_2$ with a compensatory change in HCO_3. The degree of change in HCO_3 depends on both the $PaCO_2$ and also on whether the process is acute or chronic. The differentiation between acute and chronic respiratory disorders is based on the presence of an abnormal pH. If the change in $PaCO_2$ is associated with a pH <7.30 or >7.50, the disorder is *acute*, while in a *chronic* process, the compensatory process brings the pH to the lower limit of the clinically acceptable range (7.30–7.50). Table 12.4 shows the thumb rule of 1, 4; 2, 5 to calculate appropriate HCO_3 response in respiratory disorders.

   The rise in $PaCO_2$ is calculated from a normal value of 40 mmHg.

   As an example, in acute respiratory acidosis, if the CO_2 is 100 mmHg, the rise in CO_2 is (100 minus 40) = 60. Since the expected rise is 1 mEq/L of HCO_3 for every 10 mmHg rise in CO_2, in this situation, the expected HCO_3 rise is 6. The expected HCO_3 is thus 6 mEq/L above the normal range of 24–28. The new expected range for HCO_3 will therefore be 30–34. If the actual HCO_3 is out of

Table 12.4 Appropriate HCO_3 values in respiratory disorders

Condition	Acute	Chronic
Respiratory acidosis (for every 10 mmHg increase in CO_2)	1 mEq/L increase in HCO_3	4 mEq/L increase in HCO_3
Respiratory alkalosis (for every 10 mmHg decrease in CO_2)	2 mEq/L decrease in HCO_3	5 mEq/L decrease in HCO_3

this range, there is a second process affecting it. If the actual HCO_3 is higher than 34, there is an associated metabolic alkalosis and, if less than 30, an associated metabolic acidosis.

3. *Compensatory changes tend to return the pH to near normal.*

   Compensatory mechanisms do not necessarily correct the pH to the middle of the acceptable range as the drive for correction reduces as the acceptable levels are reached. These mechanisms often only bring it to the lower limit of the acceptable range. Compensatory mechanisms *never* overcorrect. Hence, in a chronic respiratory acidosis, for example, the HCO_3 will compensatorily rise and move the pH to between 7.30 and 7.35. It will not move it to 7.40 and will definitely not create an alkalosis by pushing it to 7.50, unless there is a superimposed secondary or mixed acid-base disorder.

Step 4: In a Metabolic Process, Use Story's Modification of the Fencl-Stewart Equation to Identify the Contributing Factors

The previous steps help to diagnose most forms of metabolic acid-base disorders but may miss derangements caused by abnormal chloride or albumin levels. The Fencl-Stewart approach which was suggested to overcome this issue [1, 3] is able to identify other contributors to the metabolic acid-base balance.

The Fencl-Stewart approach to acid-base disorders uses five equations of varying complexity to estimate the base excess effects of the important components: the strong ion difference (sodium and chloride), the total weak acid concentration (albumin) and unmeasured ions. Although this approach is straightforward, most people would need a calculator to use the equations.

D.A. Story simplified these equations into one, making it usable at the bedside [4].

In this approach, the base excess (which represents the metabolic component of the acid-base dysfunction) is partitioned into three domains:

(a) Acidosis/alkalosis caused by the difference between serum Na and chloride (the strong ion difference or SID).
(b) Acidosis/alkalosis caused by the changes in levels of albumin.
(c) Acidosis/alkalosis caused by the unmeasured anions (UMA) such as keto acids, phosphate etc. Lactate used to be considered in this category but is now measured by most ABG machines.

$$\text{BASE EXCESS} = \left[\left(\text{Na} - \text{Cl}\right) - 38\right] + \left[2.5\left(4.2 - \text{serum albumin}\right)\right] + \left[2 - \text{lactate}\right] + \left[\text{minus UMA}\right]$$

The normal SID (Na – Cl) is 38.

Table 12.5 Physiological effects of acidaemia and alkalaemia

Effects of acidaemia	Effects of alkalaemia
Decreased myocardial contractility	Cerebral vasospasm
Arterial vasodilation and venoconstriction	Seizures
Tachyarrhythmias and bradyarrhythmias	Confusion and drowsiness
Reduced renal blood flow and urine output	Tetany and muscle cramps
Confusion and drowsiness	Decreased myocardial contractility
Hyperkalaemia	Supraventricular and ventricular tachyarrhythmias
Hyperglycaemia	Hypokalaemia, hypocalcaemia, hypomagnesaemia

The albumin in this equation is measured as gm/dl.

The UMA represents unmeasured anions. Examples are keto acids and fixed acids in renal failure and sepsis. The algebraic signs must be correctly entered for the above equation to be mathematically correct.

A low Na – Cl difference results in an acidosis and vice versa.

A low albumin level results in a metabolic alkalosis and vice versa.

If the base excess value is not fully explained by its components, there is an unmeasured anion contributing to the process.

This process of teasing out the contributing components of the metabolic acidosis is very useful in the management of critically ill patients who often have many processes affecting the metabolic acid-base balance. For example, a patient with severe metabolic acidosis will often have a bit of SID acidosis, lactic acidosis, hypoalbuminaemic alkalosis and acidosis due to unmeasured anions. Therefore, if the predominant contributor is SID, the best treatment is an infusion of sodium bicarbonate, but if it is UMA, then haemodialysis may probably be the best option.

Causes and Treatment of Acid-Base Disorders

Now that a diagnosis has been made, the cause of the acid-base disorder must be pinpointed and appropriate therapy started as soon as possible since both acidaemia and alkalaemia have adverse physiological effects as listed in Table 12.5.

Respiratory Acidosis

This results from a reduction in minute ventilation.

Causes This could be central (affectations of the respiratory centre) or peripheral (chest wall and muscles or lung parenchyma).

Table 12.6 Peripheral causes of respiratory acidosis

Chest wall and muscles	Lung parenchyma
Phrenic nerve injury	Upper airway obstruction
Myasthenia gravis	Chronic obstructive lung disease
Guillain-Barré syndrome	Severe pulmonary oedema
Organophosphate poisoning	Severe ARDS
Neurotoxic snakebite	Pneumothorax
Flail chest	Large pleural effusions
Severe kyphoscoliosis	

Table 12.7 Causes of respiratory alkalosis

Central	Lung parenchyma
Brainstem stroke	Hypoxia
CNS infection	Asthma
Traumatic brain injury	Acute lung injury
Salicylate poisoning	Pneumonia
Sepsis	Pulmonary embolism
Liver failure	Hyperventilation during mechanical ventilation
Pregnancy	Interstitial lung disease
Pain and anxiety	

Central

- Sedative and narcotic drugs
- CNS injury or infection
- Brainstem infarctions

Peripheral (see Table 12.6)

Treatment Treat the underlying cause. Mechanical ventilation – invasive or non-invasive may be required.

Respiratory Alkalosis

This results from an increase in minute ventilation.

Causes This could be central (affectations of the respiratory centre) or peripheral (lung parenchyma) (Table 12.7).

Treatment Treat the underlying cause.

Metabolic Acidosis

In addition to using the Fencl-Stewart equation, an anion gap is useful in trying to identify the cause of metabolic acidosis.

The anion gap exists because not all electrolytes are measured. The quantity of unmeasured cations is much less than unmeasured anions. The difference between these two is called the anion gap. In practice, it is calculated as:

$$\text{Anion gap} = \left[\text{Na} + \text{K}\right] - \left[\text{HCO}_3 + \text{Cl}\right]$$

The normal value is 16 ± 4 mEq/L. If potassium is not included while calculating anion gap, then the normal value is 12 ± 4 mEq/L. Since the normal value of the anion gap decreases with hypoalbuminaemia, it is useful to correct the anion gap for the albumin level.

The corrected anion gap = calculated anion gap + 2.5 (4.0 – albumin). The albumin in this equation is measured as gm/dl.

Once the anion gap is calculated, it is easy to consider causes of metabolic acidosis as those causing an increased anion gap and those presenting with a normal anion gap.

Causes of High Anion Gap Metabolic Acidosis

High anion gap metabolic acidosis is usually caused by conditions where there is an accumulation of acids with a strong anion, and these can be remembered with the mnemonic 'MUDPILES'.

M methanol; *U* uraemia; *D* diabetic ketoacidosis; *P* propylene glycol; *I* infection, sepsis; *L* lactic acidosis; *E* ethylene glycol, ethanol; *S* salicylates

Lactic Acidosis

Lactic acidosis is very common in acutely ill patients. It can result from an overproduction of lactate or a reduction in excretion. Common reasons for this are:

1. *Impaired oxygen delivery to tissues*: This can happen during shock, when abnormal global haemodynamics cause inadequate perfusion of all tissues, leading to anaerobic metabolism and production of lactic acid. It can also happen when tissue microcirculation is abnormal in the presence of normal global haemodynamics or when there is impaired blood flow to any one region or organ as can be seen in limb or bowel gangrene.
2. *Mitochondrial dysfunction*: This can be seen in sepsis and also as a result of use of drugs such as metformin and nucleoside reverse transcriptase inhibitors.
3. *Pyruvate dehydrogenase deficiency*: This is seen in severe sepsis and thiamine deficiency.

Table 12.8 Causes of normal anion gap acidosis

Mechanism	Dilution	High urinary SID	Loss of high SID enteric fluids	High chloride intake
Causes	Saline infusion Psychogenic polydipsia TURP syndrome	Renal tubular acidosis Amphotericin Lithium Aminoglycosides Valproate ACE inhibitors Spironolactone Adrenal insufficiency	Small intestinal diarrhoea	Total parenteral nutrition Ammonium chloride

Causes of Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidosis results from conditions which reduce the strong ion difference in the extracellular fluid (Table 12.8).

Dilutional acidosis: Large volumes of intravenous fluids produce a metabolic acidosis when the SID of the infused fluids is less than the SID of extracellular fluid. This is typically seen with saline infusions as the SID of saline is 0 (Na 154 mEq/L, Cl 154 mEq/L). This tends to lower the extracellular SID and cause an acidosis.

High urinary SID: In various forms of congenital and drug-induced renal tubular acidosis, urinary SID is high even though extracellular SID is low. This happens because of defects in the proximal or distal renal tubule which impair chloride excretion resulting in hyperchloraemia and a low SID acidosis.

Loss of high SID enteric fluids: Small intestinal, pancreatic and biliary secretions have low chloride content and a high SID. Conditions such as certain diarrheal illnesses result in increased losses of such fluids resulting in a narrowing of extracellular SID.

High chloride intake: Total parenteral nutrition and ammonium chloride administration can sometimes result in this.

Delta Anion Gap/Delta Bicarbonate

The anion gap allows differentiation of high and normal gap acidosis. However, it is possible for a high anion gap acidosis to coexist with a normal anion gap acidosis. The delta/delta concept allows the diagnosis of this situation.

The concept behind delta/delta is based on the assumption that for every increase in anion gap of 1 mmol/L above normal (12 mmol), serum HCO_3- will drop by an equal amount, that is, the change in anion gap should be equal to change in HCO_3. Therefore, in a pure high anion gap acidosis, delta anion gap = delta HCO_3.

When the delta HCO_3 > delta anion gap, it is because a normal anion gap acidosis is present along with the high anion gap acidosis, leading to an additional drop in bicarbonate.

Treatment

In a high anion gap acidosis, there is an accumulation of a strong acid, and treatment is directed first at stopping the production of more acid, e.g. insulin therapy in keto-acidosis, haemodynamic optimisation in shock, and secondly at hastening the removal of the acid, e.g. dialysis. The underlying cause of the acid accumulation needs to be treated.

If the problem is due to a high chloride with a normal sodium (low extracellular SID), the therapy is to use chloride-free IV fluids and to give sodium without the chloride ion, e.g. in the form of sodium acetate or sodium bicarbonate or sodium lactate.

Administration of Buffers

Except for normal anion gap acidosis, the use of $NaHCO_3$ is not recommended for pH > 7.15. In diabetic ketoacidosis, this threshold is lowered to a pH of <7.0.

The aim of administering the $NaHCO_3$ is to increase the SID. Therefore, the active ingredient is Na, not HCO_3. In fact the bicarbonate ion combines with hydrogen ion and is converted to carbon dioxide and water. This potential to increase $PaCO_2$ levels is the reason why it should not be administered as boluses but as a continuous infusion.

$NaHCO_3$ can also adversely result in paradoxical intracellular acidosis, hypernatraemia, hyperosmolarity, hypocalcaemia and decreased oxygen delivery.

Metabolic Alkalosis

Metabolic alkalosis is less common than acidosis.

Causes

Metabolic alkalosis occurs by four main mechanisms (Table 12.9):

Low urinary SID: Loop and thiazide diuretics among other causes result in a tubular loss of chloride resulting in a low urinary SID and therefore a high extracellular SID leading to alkalosis.

Enteric losses of low SID fluid: Gastric secretions have no sodium, only chloride. Loss of this low SID fluid by vomiting or nasogastric aspiration results in a high SID metabolic alkalosis.

Gain of high SID fluid: Administration of large quantities of $NaHCO_3$ or sodium citrate (in transfusions) will also raise the SID and create an alkalosis.

Volume depletion: This has the opposite effect on extracellular SID as dilution. While dilution narrows SID, dehydration widens it.

For another diagnostic approach, see [4].

Table 12.9 Causes of metabolic alkalosis

Mechanism	High urinary SID	Enteric losses of low SID fluid	Gain of high SID fluid	Volume depletion
Causes	Furosemide Thiazides Corticosteroids Mineralocorticoids Cushing's syndrome Post hypercapnia Bartter's syndrome Gitelman's syndrome	Vomiting Nasogastric suction Gastric outlet obstruction Laxative abuse	$NaHCO_3$ administration Massive transfusion Dialysis	Pure water dehydration

Treatment

The underlying cause needs to be treated while also attempting to reduce the extracellular SID. This may include:

1. *Repletion of ECF volume*: Saline or similar low SID fluids need to be administered. Almost all metabolic alkalosis responds to this if enough saline can be given. In hypoalbuminaemic patients, albumin administration accelerates normalisation of the pH as it repletes volume and additionally removes the alkalosis due to low albumin levels (see the Fencl-Stewart equation above).
2. *Replacement of potassium as chloride salt*: While alkalosis produces hypokalaemia that may need replacement therapy, the more important reason to do this is to replace chloride.
3. *Acetazolamide therapy*: Acetazolamide increases proximal tubular chloride reabsorption and increases urinary SID, decreasing extracellular SID.
4. *Administration of chloride-containing solutions*: Ammonium chloride or lysine or arginine hydrochloride has occasionally been used.

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Further Reading

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Chapter 13
Acute Respiratory Failure

John Victor Peter

Key Points

- Respiratory failure may be categorised as hypoxaemic and hypercapnic respiratory failure.
- Simple algorithms help to diagnose and understand the causes of respiratory failure.
- Management goals include treating the underlying problem, improving oxygenation and/or carbon dioxide levels and limiting the deleterious effects of such treatment.
- Respiratory support can be provided by non-invasive devices or by invasive ventilation.

Introduction

Respiratory failure represents the failure of the lung to maintain adequate gas exchange and is characterised by abnormalities of arterial blood gas tensions. Traditionally it is defined using a PaO_2 cut-off of <8 kPa [60 mmHg] with or without hypercarbia [$PaCO_2$ >6 kPa (46 mmHg)]. The onset of respiratory failure is usually acute or subacute. In some patients, such as in chronic obstructive pulmonary disease (COPD), the respiratory failure may be long-standing and chronic. Although sometimes, this demarcation may not be distinct, the management of respiratory failure is often dependent on the extent and duration of symptoms.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_13

Physiology

The respiratory apparatus involves three components – the *pacemaker*, the *pump with tubes* and the *gas exchanger*. Abnormalities of any of these three components can result in respiratory failure. The central nervous system (CNS) functions as the *pacemaker*, setting the pace (respiratory rate) and the amplitude (tidal volume). This net ventilatory drive determines minute ventilation, which is the product of tidal volume and rate. An increased respiratory drive thus results in hyperventilation, while reduced respiratory drive results in hypoventilation. The *pump with the tubes* may be considered akin to bellows, comprising of the lungs and airway, and serves as a device that enables the delivery of adequate alveolar ventilation. Two factors influence the efficiency of the pump – resistance and compliance. Increased resistance of the airway or reduced compliance of the lung or the chest wall reduce the efficiency of the pump and increase the work of breathing (WOB). A sustained increase in the WOB may result in ventilatory fatigue, hypoventilation and respiratory failure. The third component of the respiratory apparatus, the *gas exchanger* comprises of bags of air (alveoli) surrounded by pulmonary capillaries. The pump delivers gas to the alveoli, wherein gas transfer occurs passively across a pressure gradient. Two factors determine the efficiency of this gas transfer – the alveolar-capillary interface and the transit time of blood in the pulmonary capillaries. The transit time of blood in the pulmonary capillaries of about 0.7 s is sufficient for gas exchange unless there are problems with the alveolar-capillary interface. Conditions that increase the thickness of the alveolar-capillary interface (e.g. fluid in the alveoli, interstitial inflammation) impair gas transfer. However, since the diffusion capacity of CO_2 is about 20 times that of O_2, such abnormalities of the gas exchanger generally result in pure hypoxaemia unless the extent of alveolar involvement is marked or if respiratory fatigue ensues due to increased WOB.

Classification

Respiratory failure may be classified based on the blood gas abnormality (*physiologic approach*) or on the pathophysiologic process (*pathophysiologic approach*) that causes respiratory failure. Using a physiologic approach, type I respiratory failure or *hypoxaemic respiratory failure* is defined as hypoxaemia (PaO_2 <60 mmHg) with normal or low $PaCO_2$, while type II respiratory failure *or hypercapnic respiratory failure* is defined as the presence of hypercarbia ($PaCO_2$ >46 mmHg) with or without coexistent hypoxaemia. Using the pathophysiologic approach, respiratory failure is classified into four types. In type I respiratory failure, the pathophysiologic abnormality is *alveolar flooding* resulting in intra-pulmonary shunting. These patients have a predominant hypoxaemic respiratory failure, although in very severe cases, CO_2 retention may supervene. Common aetiologies include cardiogenic and non-cardiogenic pulmonary oedema, pneumonia and alveolar haemorrhage

(Table 13.1). Type II respiratory failure is due to *alveolar hypoventilation*. In this type of respiratory failure, the pathophysiologic abnormality is hypoventilation either due to a process in the central nervous system (cortical, subcortical, brainstem or spinal cord), peripheral nerves, muscle, neuromuscular junction or the alveoli (alveolar hypoventilation). These patients typically manifest hypercapnic respiratory failure with or without hypoxaemia. Type III respiratory failure occurs due to *lung atelectasis*. Since this is common in the post-operative setting, it is also termed *perioperative respiratory failure*. Patients manifest hypoxaemic respiratory failure. Type IV respiratory failure occurs due to *hypoperfusion of respiratory muscles* as in circulatory shock. In normal individuals <5 % of the cardiac output is utilised for the work of breathing. In patients with shock, due to increased work of breathing,

Table 13.1 Classification of respiratory failure and causes

Pathophysiologic type of respiratory failure	Physiologic type of respiratory failure	Causes
Type I respiratory failure – alveolar flooding	Hypoxaemic respiratory failure[a]	Fluid – alveolar and interstitial oedema (cardiac and non-cardiogenic pulmonary oedema, ARDS)
		Pus/infection – alveolar and interstitial infection (pneumonia, interstitial pneumonitis)
		Blood – alveolar haemorrhage
		Protein – alveolar proteinosis (rare)
Type II respiratory failure – alveolar hypoventilation	Hypercapnic respiratory failure	CNS depression – drug overdose and poisoning, infection, trauma, stroke
		Spinal cord – poliomyelitis, transection, myelitis
		Peripheral nerves – Guillain-Barre syndrome, phrenic nerve injury, amyotrophic lateral sclerosis
		Chest wall – kyphoscoliosis, chest wall injuries, ankylosing spondylitis
		Muscle – myasthenia gravis, myopathies, hypokalaemia, hypophosphataemia, polymyositis
		Alveolar hypoventilation – COPD, severe cystic fibrosis, end-stage pulmonary fibrosis, airway obstruction
Type III respiratory failure – lung atelectasis	Hypoxaemic respiratory failure	Post-operative atelectasis (intra-pulmonary shunting), basal atelectasis due to intra-abdominal pathology, pulmonary embolism[b]
Type IV respiratory failure – hypoperfusion of respiratory muscles	Hypercapnic respiratory failure	Cardiogenic shock, hypovolaemic shock, septic shock

[a]Hypoxaemic respiratory failure also occurs in high altitude due to a low inspired oxygen concentration
[b]Ventilation/perfusion mismatch is also an important contributor of hypoxaemia in patients with pulmonary embolism

up to 40 % of the cardiac output may be utilised for breathing. These patients manifest hypercapnic respiratory failure due to ventilatory fatigue.

Approach to Hypoxaemic Respiratory Failure

The pathophysiologic mechanisms that may contribute or result in hypoxaemia are (a) low inspired oxygen, (b) ventilation/perfusion (*V*/*Q*) mismatch, (c) shunt, (d) hypoventilation, (e) diffusion abnormality and (f) reduced mixed venous oxygen. In the clinical setting, the common pathophysiologic abnormalities that cause hypoxaemia include *V*/*Q* mismatch, shunting and hypoventilation. More than one pathophysiologic process may coexist in the same patient. Pure diffusion abnormalities are uncommon. A marked reduction in the oxygen content of the blood returning to the lungs (mixed venous oxygen), as occurs with reduced oxygen delivery or increased tissue consumption, may also result in the need for more oxygen to be transported from the inspired gas to the blood to normalise the PaO_2. If the lungs are normal, this does not have a significant effect. However, in the presence of a *V*/*Q* abnormality or a shunt, the effect is magnified as the shunted blood has a lower than normal oxygen content.

The alveolar-arterial oxygen difference ($PAO_2 - PaO_2$) and response to oxygen therapy help in ascertaining the cause of hypoxaemic respiratory failure (Fig. 13.1). The alveolar-arterial (A-a) oxygen gradient (difference) is calculated using the formula given below. It must be noted that the term 'alveolar gradient', although commonly used, is a misnomer since what is calculated is the gap between the alveolar and arterial O_2 and not a true gradient in PaO_2 from the alveolar space to the blood.

$$\text{A-a difference} = \left[FiO_2 \left(P_{atm} - P_{H_2O} \right) - PaCO_2 / 0.8 \right] - PaO_2$$

FiO_2, fixed inspired oxygen concentration; P_{atm}, atmospheric pressure; P_{H2O}, partial pressure of water at body temperature; $PaCO_2$, partial pressure of carbon dioxide; and PaO_2, partial pressure of oxygen in the arterial blood: Normal A-a difference is 5–15 mmHg. The formula [Age (in years)/4] + 4 may be used to calculate the A-a difference adjusted for age.

An increased A-a difference is the result of abnormalities of gas exchange within the lung (intra-pulmonary processes). Thus, intra-pulmonary processes such as *V*/*Q* mismatch, shunt and diffusion abnormalities would increase the A-a difference. The extent of increase is usually more pronounced with pure pulmonary processes than with mixed pulmonary and extra-pulmonary processes.

In the evaluation of a hypoxaemic patient, the first step is to ascertain the CO_2 level. A high CO_2 (>46 mmHg), in the absence of metabolic alkalosis as the cause for a compensatory increase in CO_2, suggests hypoventilation. In such patients, the A-a difference helps differentiate pure hypoventilation from a mixed process (Fig. 13.1). In the absence of hypercarbia, an increase in the A-a difference suggests either an increase in the A-a difference suggests either a shunt, *V*/*Q* mismatch or diffusion abnormality. Hypoxaemia due to low inspired oxygen concentration does not increase

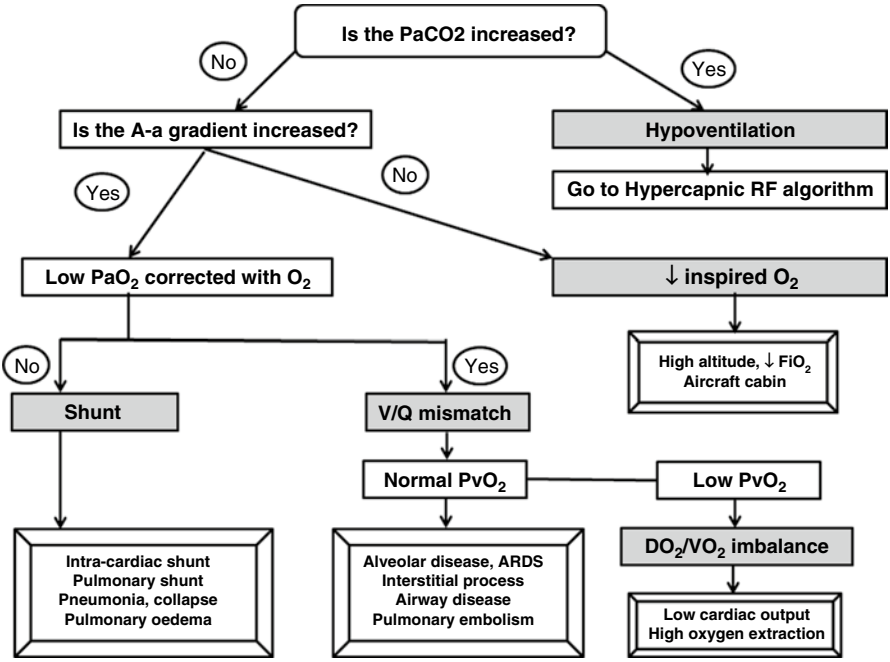

Fig. 13.1 Approach to hypoxaemic respiratory failure. The alveolar-arterial (A-a) oxygen difference ($PAO_2 - PaO_2$) and response to oxygen therapy help in the assessment of the cause of hypoxaemic respiratory failure (RF) as shown in the diagram. *V/Q* ventilation/perfusion, PaO_2 arterial partial pressure of oxygen, PvO_2 venous partial pressure of oxygen, DO_2/VO_2 oxygen supply/oxygen utilisation ratio

A-a difference and responds to supplemental oxygen therapy. In the setting of a high A-a gradient, improvement in oxygenation with supplemental oxygen would suggest *V/Q* mismatch, while lack of improvement would suggest a shunt (Fig. 13.1).

Aetiology of Acute Hypoxaemic Respiratory Failure

The aetiology of acute hypoxaemic respiratory failure can be broadly classified as:

(a) Parenchymal pathology

1. Increased capillary pressure: cardiogenic pulmonary oedema and fluid overload
2. Increased capillary permeability: acute respiratory distress syndrome (ARDS) due to pulmonary and extra-pulmonary causes
3. Inflammatory: infection (lobar and bronchopneumonia, interstitial pneumonitis), alveolitis (acute interstitial pneumonitis, acute vasculitis), and haemorrhage (alveolar)
4. Atelectasis

(b) Pleural: pneumothorax and pleural effusion
(c) Airway related: acute severe asthma
(d) Vascular: pulmonary embolism and circulatory shock

Management of Acute Hypoxaemic Respiratory Failure

The principles of management of acute hypoxaemic respiratory failure include (a) treatment of the underlying cause (specific treatment), (b) improving oxygen delivery to the tissues, (c) limiting potentially damaging therapies and (d) reducing tissue oxygen demand.

Specific therapy involves the treatment of the cause that precipitated respiratory failure. Examples of this would include antibiotic therapy for sepsis, bronchodilators for acute asthma, thrombolysis for pulmonary embolism, paracentesis for pleural effusion or diuretic and vasodilator therapy for heart failure.

Oxygen delivery to the tissues can be increased by improving oxygenation, maintaining haemoglobin and by optimising cardiac output. Oxygenation can be improved by increasing the FiO_2 (up to 1.0) or by adding positive end-expiratory pressure (PEEP). PEEP can be provided by non-invasive ventilation or through invasive mechanical ventilation. Tissue oxygen demand can be reduced by control of fever, sepsis or seizures. Increased WOB can also increase oxygen demand significantly, and in certain situations, particularly in patients with shock, it may be prudent to intubate and ventilate these patients. Potentially damaging therapy should be limited by minimising the use of high oxygen concentration for protracted periods and by adopting lung protective ventilatory strategies.

Oxygen Delivery Devices

Oxygen delivery devices should be able to deliver controlled and consistent oxygen concentrations. Oxygen delivery devices are classified based on flow (low flow or high flow), performance (variable or fixed) and whether they are non-rebreathing or rebreathing systems (Table 13.2). Rebreathing systems allow some mixture of exhaled gases, while non-rebreathing systems have one-way valves. Closed mask systems connected to non-breathing devices ensure the delivery of set volumes (e.g. continuous positive airway pressure (CPAP) devices).

Low flow devices are so called as they deliver oxygen at less than the peak inspiratory flow rate (PIFR). Examples include nasal cannula, simple face mask and partial rebreather masks. High-flow devices deliver oxygen at flow rates higher than the PIFR. These systems have adequate reservoir capacity that enables the delivery of adequate flow. Examples include venturi devices, T-piece or breathing circuits (e.g. CPAP circuits) with reservoir bags or connected to high-flow oxygen source.

Table 13.2 Oxygen delivery devices

Categorisation based on flow	Example	Performance	Oxygen flow rate (per min)	FiO_2 delivered
Low-flow device	Nasal cannula	Variable	2–4 l[a]	24–35 %
	Simple face mask	Variable	5–10 l	40–60 %
	Tracheal mask	Variable	5–10 l	40–60 %
	Partial rebreathing mask with reservoir bag	Variable	4–10 l	35–60 %
High-flow device	Venturi	Fixed	3–15 l	24–60 %
	High-flow warmed nasal devices	Fixed using blenders	10–40 l	40–100 %
	Non-rebreather mask with reservoir bag	Variable	8–10 l	60–90 %

[a]Higher flow rates are uncomfortable

Table 13.3 Example of a variable performance device

Parameter	Patient 1	Patient 2
Tidal volume	400 ml	400 ml
Respiratory rate	10	20
Minute ventilation	4000 ml	8000 ml
I:E ratio	1: 2	1: 2
Inspiratory time	2 s	1 s
Oxygen through cannula	2 l/min (2000 ml)	2 l/min (2000 ml)
Additional air mix	2000 ml	6000 ml
Ratio of oxygen: air mix	1: 1	1: 3

In a variable performance device, the oxygen concentration of the air-oxygen mix reaching the alveoli is not constant; the final O_2 concentration is dependent on the oxygen flow rate, size of the reservoir and the respiratory rate of the patient. For a fixed tidal volume, when the respiratory rate increases, since the amount of oxygen given through the device (e.g. nasal cannula) is fixed (e.g. 2 l), the resultant air-oxygen mixture at the higher respiratory rate contains less oxygen than when the rate is lower (see example in Table 13.3). A fixed performance device on the other hand is not influenced by these factors and is able to provide a fixed inspired oxygen concentration irrespective of the patient's respiratory rate (e.g. a venturi device).

The choice of the device is based on the severity of hypoxaemia and whether a fixed performance device is essential. In patients with mild hypoxaemia (PaO_2 60–70 mmHg on room air), a nasal cannula or a simple mask may be sufficient. Nasal cannula is well tolerated and patients are able to eat and drink while on this device. However, delivery of oxygen through a nasal device can be associated with drying of the nasal mucosa. With moderate hypoxaemia (PaO_2 50–60 mmHg), a partial rebreather mask or venturi device may be used; the latter is preferred for COPD patients. In patients with severe hypoxaemia (PaO_2 <50 mmHg) and those not respond-

ing to simpler devices, non-rebreather systems (e.g. CPAP, non-invasive ventilation, Ambu bag, Bains) or invasive mechanical ventilation may be considered.

Intubation and mechanical ventilation are sometimes required for patients with severe or persistent hypoxaemic respiratory failure. Ventilatory support offloads the respiratory muscles, reduces the WOB and reduces oxygen demand. In addition, ventilation (invasively or non-invasively) allows the application of PEEP. Several studies have demonstrated the beneficial effect of PEEP. PEEP helps by improving oxygenation (by increasing functional residual capacity and increasing alveolar volumes), improving lung compliance (by preventing alveolar de-recruitment and reducing pulmonary venous congestion in heart failure patients), reducing dead space (keeping the alveoli open), improving cardiovascular function (by reducing afterload) and reducing the work of breathing. The usual PEEP level in the intensive care unit (ICU) is 5–15 cm H_2O; higher levels have been used in severe ARDS.

Newer methods of oxygen delivery in severe ARDS with refractory hypoxaemia have been with the use of extracorporeal membrane oxygenators (ECMO).

Approach to Hypercapnic Respiratory Failure

Hypercapnia results either from increased CO_2 production or reduced CO_2 elimination or a combination of both. Increased CO_2 production (Fig. 13.2) may occur with increased muscle activity (spasms, convulsions), hypermetabolic states (fever, sepsis) and carbohydrate-rich feeds. In this setting, hypercapnia occurs if CO_2 elimination does not keep pace with CO_2 production. Reduced CO_2 elimination occurs due to reduced pacemaker function, impaired respiratory pump function, airway problems and abnormalities of the gas exchanger. Generally, pure abnormalities of the pulmonary parenchyma result in low *V*/*Q* units with hypoxaemia without hypercapnia. However, when *V*/*Q* abnormalities are very severe or when there is coexistent respiratory muscle fatigue, hypercapnia may ensue. Hypercapnia may also occur when breathing a gas containing CO_2. This may occur due to rebreathing exhaled gases as a result of improper ventilatory expiratory connections (tube or expiratory port).

Hypercapnia may be approached as pulmonary or extra-pulmonary causes or a combination of both. Extra-pulmonary causes include CNS and peripheral nervous system (PNS) disorders, respiratory muscle dysfunction (due to a primary muscle disease or neuromuscular dysfunction) or due to chest wall abnormalities (Table 13.1). Pulmonary causes include airway obstruction (foreign body, epiglottitis, obstructive sleep apnoea), severe COPD and end-stage lung disease due to other parenchymal processes. An increase in the A-a difference would suggest a coexisting *V*/*Q* abnormality or a shunt (Fig. 13.2). In the absence of an increased A-a gradient, assessment of maximal inspiratory pressure (MIP or PI max) and/or maximal expiratory pressure (MEP or PE max) would help diagnose respiratory muscle weakness. MIP primarily reflects the strength of the diaphragm and other inspiratory muscles, while MEP reflects the strength of the abdominal muscles and other expiratory muscles. The

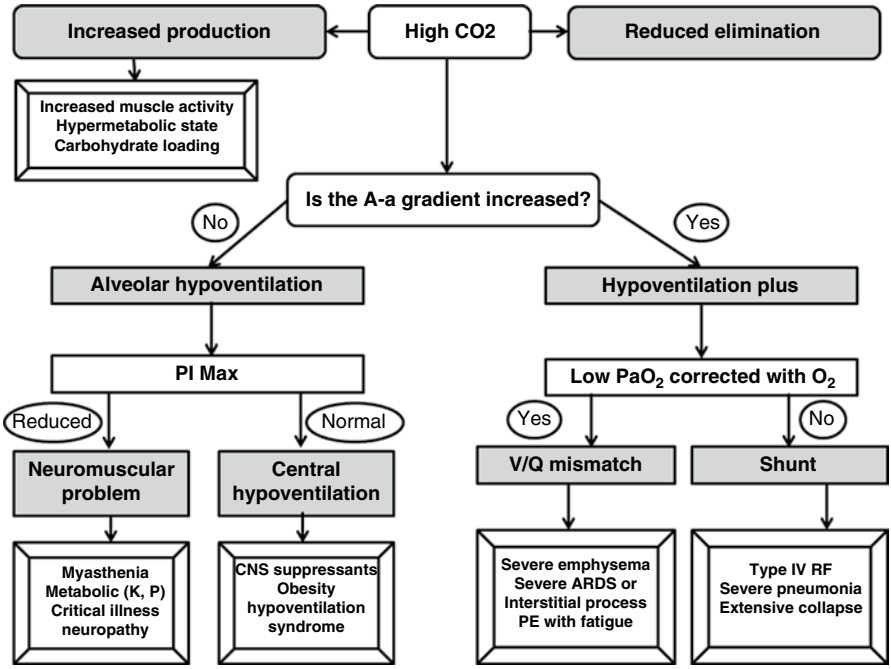

Fig. 13.2 Approach to hypercapnic respiratory failure. Hypercapnic respiratory failure may be due to increased CO_2 production or reduced CO_2 elimination of a combination of both. The alveolar-arterial (A-a) oxygen difference ($PAO_2 - PaO_2$) helps to ascertain if alveolar hypoventilation is occurring independently or in conjunction with a *V/Q* (ventilation/perfusion) mismatch or shunt. *PI max* maximal inspiratory pressure

sniff nasal inspiratory pressure (SNIP), an easy-to-use first-line tool, may be used as an alternative diagnostic test for respiratory muscle weakness. If these tests suggest respiratory muscle weakness, further evaluation is warranted to ascertain the cause. These include primary muscle diseases (myopathies, polymyositis), neuromuscular transmission defect (myasthenia gravis), metabolic disorders (hypokalaemia, hypophosphataemia) and critical illness polymyoneuropathy. Normal respiratory muscle function would suggest a central cause for hypercapnia. This includes obesity-hypoventilation syndrome and respiratory centre depression due to overdose, CNS infection, trauma, tumour or stroke (Table 13.1).

The $PaCO_2$ must always be considered in relation to the pH. This is particularly helpful in distinguishing acute and chronic hypercapnic respiratory failure as well as stable chronic hypercapnic respiratory failure and acute-on-chronic hypercapnic respiratory failure. In acute hypercapnic respiratory failure, there is always a shift in the pH, since compensatory mechanisms take time, unless the respiratory failure is mild. However, in chronic hypercapnic respiratory failure, since metabolic compensation occurs, the pH is usually close to normal, often >7.32 and sometimes even normal. Thus, the distinction between chronic respiratory failure and acute-on-chronic respiratory failure is not made on the CO_2 level but on the pH, where any

acute process superimposed on a chronic stable state would shift the pH. Thus, a drop in pH to <7.30 in such patients would be diagnostic of acute CO_2 retention.

Aetiology of Hypercapnic Respiratory Failure

The aetiology of acute hypoxaemic respiratory failure can be broadly classified as:

(a) Central nervous system pathology:

1. Cortical: stroke, infection, trauma, drug overdose and acute disseminated encephalomyelitis
2. Brainstem depression: stroke, basal meningitis, trauma and obesity-hypoventilation syndrome
3. Spinal cord: trauma, infectious and post-vaccine myelitis and poliomyelitis

(b) Peripheral nervous system pathology: Guillain-Barre syndrome, phrenic nerve injury, amyotrophic lateral sclerosis and critical illness polyneuropathy
(c) Neuromuscular: myasthenia gravis
(d) Muscle: critical illness myopathy, metabolic (hypokalaemia, hypophosphataemia, magnesium depletion) and polymyositis
(e) Chest wall: flail chest, kyphoscoliosis and ankylosing spondylitis
(f) Alveolar hypoventilation due to pulmonary causes: COPD, severe cystic fibrosis, end-stage pulmonary fibrosis and airway obstruction

Management of Acute Hypercapnic Respiratory Failure

As with acute hypoxaemic respiratory failure, the goals of treatment of acute hypercapnic respiratory failure include (a) treatment of the underlying cause (specific treatment), (b) reducing CO_2 production, (c) improving CO_2 elimination and (d) limiting potentially damaging therapies.

Specific therapy involves treating the precipitating cause. This would include antibiotics to treat infection, bronchodilators and steroids for exacerbation of COPD or the reversal of the central or peripheral nervous system problem that resulted in hypercapnic respiratory failure. CO_2 production may be reduced by controlling fever and excess motor activity (convulsions) and by reducing carbohydrate intake. Since the respiratory quotient for carbohydrate is 1.0 and for fat is 0.7, this is particularly important in the setting of COPD exacerbation with difficulty in weaning where reduction in the carbohydrate intake may translate to easier weaning.

CO_2 elimination can be enhanced by increasing the respiratory drive and by improving lung mechanics. Respiratory drive can be increased by reducing or minimising the use of sedation and by using drugs that increase respiratory drive, particularly in the context of COPD. Although the benefit has not been proven in

randomised trials, drugs such as acetazolamide, medroxyprogesterone acetate and other centrally acting CNS stimulants have been used in COPD exacerbations. Lung mechanics can be improved by manoeuvres such as propping up the patient, use of analgesics to reduce chest pain as in chest wall injuries, reducing airway resistance (use of bronchodilators and bronchial hygiene), improving lung compliance (by reducing abdominal distension or pleurocentesis), improving respiratory muscle performance (by ensuring adequate oxygenation, tissue perfusion) and correcting electrolyte abnormalities (such as hypokalaemia, hypophosphataemia). Drugs such as xanthines (theophylline) which improve diaphragmatic contractility may be considered. However, given the narrow therapeutic window and toxicity profile, its use is limited.

Ventilatory support, either using non-invasive ventilation or invasive ventilation, may be required in patients with respiratory fatigue and persistent hypercapnic respiratory failure. Ventilatory support offloads the respiratory muscles, reduces the work of breathing and rests the muscles. Since CO_2 elimination is dependent on minute ventilation, appropriate targets should be set for tidal volume and respiratory rate in order to achieve minute ventilation that would correct the physiologic abnormality while the underlying problem is dealt with. Care should be taken during ventilation to limit lung injury due to high pressures (barotrauma) or high volume (volutrauma) and use of an appropriate level of PEEP to reduce atelectrauma. In patients where conventional ventilatory strategies are not sufficient to ensure CO_2 elimination and improvement in pH, extracorporeal CO_2 removal devices can be considered.

Conclusions

A systematic approach to respiratory failure is important in ascertaining the cause of respiratory failure. Since the respiratory treatment of the two physiologic types of respiratory failure is different, knowledge of the mechanisms of respiratory failure and the basis of supportive treatment is crucial. All such respiratory treatment and support would only be beneficial if the underlying disease process that resulted in respiratory failure is adequately and appropriately managed.

Further Reading

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Chapter 14
Hypotension and Shock

John Victor Peter and Mathew Pulicken

Key Points

- Shock is a life-threatening, generalised form of acute circulatory failure associated with inadequate oxygen utilisation by the cells.
- Shock may result in macrocirculatory and microcirculatory abnormalities.
- Management components include recognition of pattern of shock, selecting appropriate treatment, specific therapy for the underlying problem and monitoring clinical response.
- Resuscitation goals are based on 'VIP' rule: V for ventilate, I for infuse and P for pump.
- Lactate, mixed venous oxygen saturation and serial cardiac output measurements may help monitor response to therapy.

Introduction

Traditionally shock, or more precisely circulatory shock, was defined as an acute clinical syndrome initiated by ineffective perfusion resulting in severe dysfunction of organs vital to survival. More recently, the European Society of Intensive Care Medicine (ESICM) has defined shock as a life-threatening, generalised form of acute circulatory failure associated with inadequate oxygen utilisation by the cells [1]. The latter definition is more appropriate since inadequate cellular oxygen

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_14

utilisation may be the result of either a low cardiac output state with reduced oxygen transport (e.g. cardiogenic shock) or altered oxygen extraction (e.g. mitochondrial dysfunction) with normal or increased cardiac output (e.g. septic shock). Inadequate cellular oxygen utilisation leads to cellular dysoxia with resultant increase in blood lactate levels.

Diagnosis of Shock

The diagnosis of shock is based on a triad of features [2] that include arterial hypotension (haemodynamic), evidence of tissue hypoperfusion (clinical) and hyperlactataemia (biochemical). Although clinically arterial hypotension has been considered a cardinal sign of shock, this may not be always present as hypotension can be masked by a sympathetic vasoconstriction response [3]. A systolic blood pressure of <90 mmHg is considered as an arbitrary value for hypotension. However younger patients may tolerate lower blood pressures without any clinical evidence of tissue hypoperfusion or hyperlactataemia. Conversely, in older patients, tissue hypoperfusion and hyperlactataemia may occur even with a higher blood pressure.

The clinical signs of tissue hypoperfusion have been described through three 'windows' [1–3]. The cutaneous window (the skin) responds to circulatory shock, in low-flow states, with sympathetic activation resulting in vasoconstriction and manifests as cold, clammy, pale or dusky-coloured skin. It is important to remember that the skin may be warm and appear well perfused in distributive shock (e.g. warm phase of septic shock), even in the presence of significant hypotension, tissue hypoperfusion and organ dysfunction. The second window, the neurological window, is characterised by drowsiness, disorientation or confusion. The renal window presents as reduced (typically <0.5 ml/kg/h) urine output (in the absence of tubular absorptive dysfunction).

The biochemical marker for hypoperfusion is hyperlactataemia, which indicates abnormal cellular oxygen metabolism (cellular dysoxia). The blood lactate level is increased (>1.5 mmol/l) in acute circulatory failure. Although hyperlactataemia is generally associated with anaerobic metabolism, regional hypoperfusion (e.g. limb ischaemia, bowel ischaemia), excessive aerobic glycolysis (e.g. seizures, hyperventilation), drugs (e.g. metformin, beta-adrenergic agents) or decreased utilisation (e.g. liver failure) may also increase lactate levels [3]. In the context of altered tissue perfusion, the severity of hyperlactataemia and changes in lactate concentration over time predict outcome [3].

Pathophysiology

Circulatory shock is associated with both macrocirculatory and microcirculatory changes. Macrocirculatory parameters are called *upstream parameters*, while microcirculatory parameters are called *downstream parameters*. The upstream

parameters are cardiac output and systemic vascular resistance. Cardiac output is the product of heart rate and stroke volume, while systemic vascular resistance is determined by mean arterial pressure (MAP), central venous pressure (CVP) and cardiac output (Fig. 14.1). Macrocirculatory failure may occur either due to low cardiac output or reduced systemic vascular resistance.

Microcirculatory failure occurs either as a consequence of macrocirculatory failure (e.g. cardiogenic shock) or due to a systemic process that initiates microcirculatory abnormalities (e.g. sepsis, pancreatitis, acute liver failure). Unlike the macrocirculation which can be more easily measured (cardiac output, vascular resistance) and manipulated, it is more difficult to assess and treat microcirculatory abnormalities. Surrogate markers such as lactate, mixed venous oxygen saturation ($ScvO_2$), veno-arterial carbon dioxide ($vaCO_2$) difference and gastric tonometry have been used to study the adequacy of the microcirculation. Although microcirculatory changes in circulatory shock are global, regional vascular beds may respond differently by either shunting blood or vasodilatation. For example, regions such as the skin, muscle and splanchnic circulation may typically respond to the early phases of hypovolaemic shock by vasoconstriction in order to increase mean systemic filling pressure and maintain blood flow to more essential organs.

At a cellular level, several changes have been noted in shock. This includes endothelial dysfunction, leucocyte activation, changes in the haemorheological

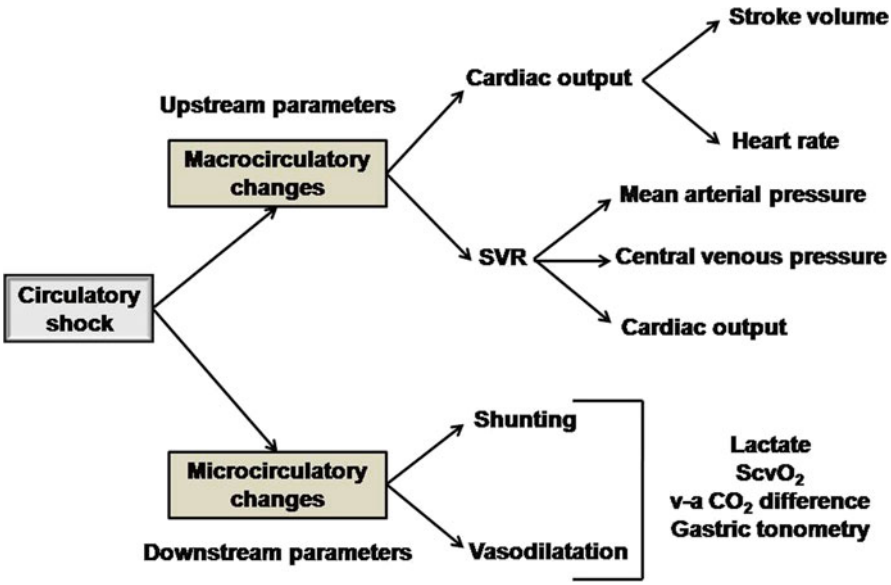

Fig. 14.1 Macrocirculatory and macrocirculatory changes. Circulatory shock is associated with macrocirculatory (upstream) and microcirculatory (downstream) changes. Macrocirculatory changes include alterations in cardiac output, reflected by stroke volume and heart rate and systemic vascular resistance reflected by changes in mean arterial pressure, central venous pressure and cardiac output. Microcirculatory changes of shunting and vasodilatation are reflected by downstream parameters such as lactate levels, mixed venous saturation (ScvO2) and veno-arterial CO2 ($vaCO_2$) difference

Table 14.1 Different types of shock

Type of shock	Pathophysiology	Haemodynamic changes		
		Central venous pressure	Cardiac output	Systemic vascular resistance
Cardiogenic	Pump failure	High	Low	High
Distributive	Vasodilatation	Low	High	Low
Hypovolaemic	Loss of volume	Low	Low	High
Obstructive	Obstruction	Variable	Low	High

The highlighted box is the primary changes. Compensatory mechanisms are the unshaded boxes

properties of red cells, coagulation abnormalities, vascular smooth muscle changes and mitochondrial dysfunction [3]. These changes result in cellular oedema, microvascular (capillary) obstruction with shunting and leaky capillaries with interstitial oedema, all of which contribute to patchy heterogeneous areas of hypoxia and microcirculatory changes, characteristic in human sepsis [3]. Technology is still being developed and evaluated to directly assess the microcirculation, and hopefully these will translate in the future to better monitoring and treatment of microcirculatory abnormalities.

Shock may result from four pathophysiological mechanisms – hypovolaemic, cardiogenic, obstructive and distributive. Mixed forms of shock may occur in the same patient. The primary pathophysiological mechanisms and compensation are outlined in Table 14.1.

Cardiogenic shock, hypovolaemic shock and obstructive shock are characterised by a low cardiac output state. Cardiogenic shock is the result of 'pump failure' either due to a myocardial pathology, valvular heart disease or cardiac arrhythmias. Hypovolaemic shock is due to volume loss (relative or absolute). Obstructive shock occurs because of obstruction to flow. In distributive shock, the primary pathophysiological process is vasodilatation as a result of many mediators including cytokines. Vasodilatation results in a compensatory increase in cardiac output, although in the later stages of shock, myocardial depression may occur due to microcirculatory abnormalities and cellular dysfunction, resulting in a fall in cardiac output. In addition, microvascular obstruction impairs blood flow and results in tissue hypoperfusion. Altered mitochondrial function with impaired oxygen extraction further compounds the problem, resulting in cellular dysoxia. The various aetiologies of the different types of shock are summarised in Table 14.2.

Management of Shock

The management of shock comprises of the following principles that include recognition of the pattern of shock, selecting appropriate treatment (resuscitation), specific therapy for the underlying problem and monitoring clinical response. Early and adequate haemodynamic support of patients in shock is essential to prevent

Table 14.2 Aetiology of shock

Type of shock	Site	Causes
Cardiogenic	Myocardial pathology	Myocardial infarction
		Myocarditis
		Cardiomyopathy
		Acute ventricular septal defect
	Valvular heart disease	Papillary muscle dysfunction
		Ruptured chordae tendineae
		Acute mitral regurgitation
		Acute aortic regurgitation
		Severe forms of valvular heart disease
	Conduction system	Arrhythmia (ventricular, supraventricular)
Distributive	–	Sepsis
		Anaphylaxis
		Multi-trauma
		Pancreatitis
		Acute liver failure
		Adrenal crisis
		Beriberi
Hypovolaemic	–	Internal haemorrhage (ruptured aneurysm)
		External haemorrhage (trauma, GI bleed)
		Fluid loss (e.g. diarrhoea, heat stroke)
		Third space loss (e.g. burns)
Obstructive	Pulmonary	Pulmonary embolism
		Tension pneumothorax
		Massive hydro-/haemothorax
		High levels of PEEP
	Cardiac	Pericardial tamponade
		Ball valve thrombus/atrial myxoma
	Abdomen	Tense ascites
		Abdominal compartment syndrome

GI gastrointestinal, *PEEP* positive end-expiratory pressure

worsening organ dysfunction and organ failure. Resuscitation and evaluation should go hand in hand with focus on rapid restoration of tissue perfusion.

Recognition of Pattern of Shock

The recognition of the pattern of shock is dependent on a careful history, thorough clinical examination and appropriate investigations. History and physical examination may provide a clue to the aetiology of shock (Fig. 14.2). For example, in a patient presenting with a diarrhoeal illness, the cause of shock is likely to be hypovolaemic. In a diabetic patient with retrosternal chest pain with hypotension, shock

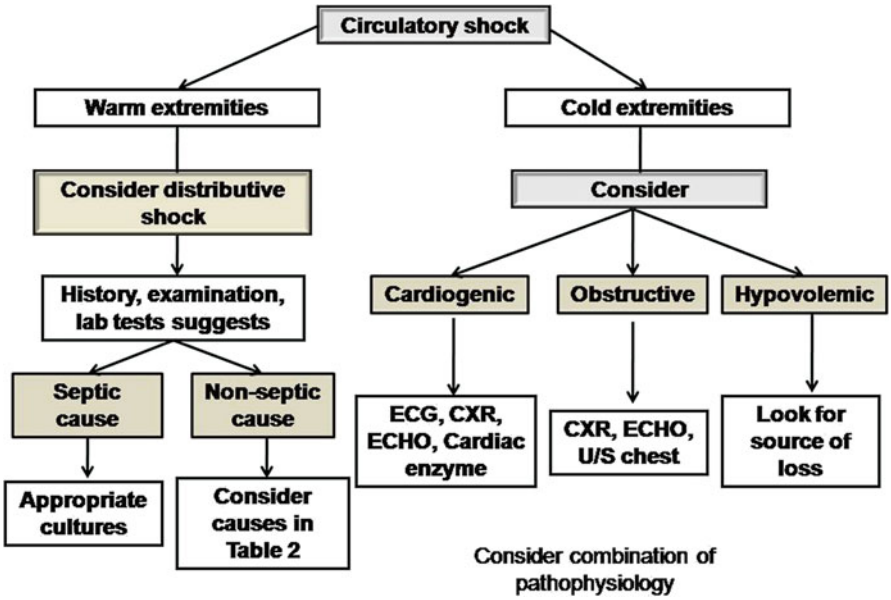

Fig. 14.2 Clinical approach to circulatory shock. The first step is to ascertain if the extremities are cold or warm. Warm shock is likely to be distributive. Detailed history, examination and appropriate laboratory tests would help differentiate between septic and non-septic causes of distributive shock. Cold shock may be due to cardiogenic or obstructive shock or due to hypovolaemia. The distinction between cardiogenic and obstructive shock can be made on the basis of test such as chest X-ray and ECHO. In hypovolaemic shock, the source of blood/fluid loss should be identified

may be due to an acute coronary syndrome. Presentation with fever and localising symptoms (e.g. cough, dysuria) may suggest distributive shock due to sepsis, while acute onset breathlessness in the setting of a venous thrombus may suggest obstructive shock due to pulmonary embolism. More than one pattern of shock may coexist in the same patient. For example, in a patient with trauma, shock may be due to hypovolaemia due to blood loss coupled with a tension pneumothorax. In sepsis, shock may be distributive and cardiogenic (due to myocardial depression).

Clinical examination should include, in addition to vital signs (pulse, respiration, temperature, blood pressure), skin colour, extremities (warm or cold, presence of oedema), jugular venous pressure and systemic examination (cardiovascular, respiratory, abdomen) looking for a focus of infection or other causes for hypotension. Appropriate investigations should be done to rule in or rule out cardiogenic (e.g. ECG, ECHO), distributive (imaging, cultures), hypovolaemic (haemoglobin, electrolytes, renal function) or obstructive (chest X-ray, ECHO) shock. Point-of-care echocardiographic evaluation has enabled the rapid assessment and diagnosis of the aetiology of shock. Focused assessment with sonography in trauma (FAST) may help localise the site of bleed and cause of shock in patients with trauma. Ultrasound examination of the chest may show absence of lung sliding suggesting a pneumothorax, while echocardiography may help diagnose pericardial disease or myocardial

disease (right or left ventricular) as the reason for circulatory shock. In hypovolaemic shock, variations in vena cava dimensions with respiration, ventricular cavity size and dynamic assessment of volume status may help assess the severity of hypovolaemia. An algorithm for the assessment of patients with shock is presented in Fig. 14.2.

The first step in the approach to circulatory shock is to ascertain if tissue hypoperfusion is present in terms of organ dysfunction with hyperlactataemia. If arterial hypotension is present without organ dysfunction or hyperlactataemia, the possibility of chronic hypotension should be considered (Fig. 14.3). If tissue hypoperfusion is evident, then assessment of cardiac output helps differentiate between high cardiac output states with shock (distributive shock) and low cardiac output states with shock (cardiogenic, hypovolaemic or distributive). Measurement of central venous pressure (CVP) helps differentiate between hypovolaemic (low CVP) and cardiogenic or obstructive shock (high CVP). An echocardiogram would help further distinguish cardiogenic from obstructive shock.

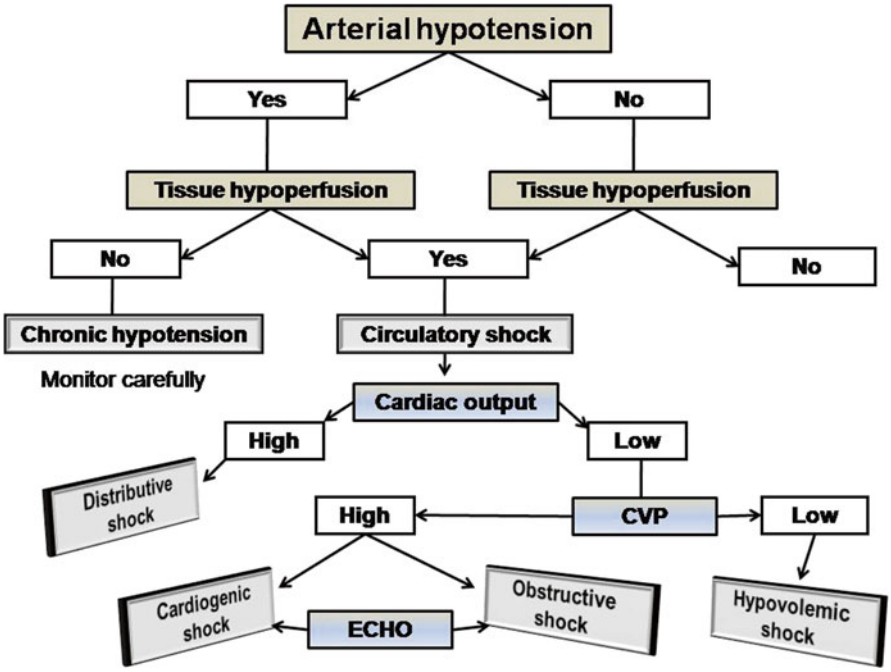

Fig. 14.3 Algorithm for approach to arterial hypotension. If arterial hypotension is not associated with tissue hypotension or hyperlactataemia, chronic hypotension should be suspected. If tissue hypoperfusion is present (even in the absence of arterial hypotension), then circulatory shock should be diagnosed. A high cardiac output (on ECHO) would suggest distributive shock, while a low cardiac output may be due to cardiogenic or obstructive shock where the central venous pressure would be high or due to hypovolaemic shock where the central venous pressure would be low

Selecting Appropriate Therapy and Resuscitation Goals

Early, appropriate and adequate management of shock is vital to limit organ dysfunction and failure. As mentioned earlier, assessment of aetiology and resuscitation should go on parallel. Resuscitation goals are focused on the 'VIP' rule; V for ventilate, I for infuse and P for pump [1, 3].

The *ventilation component* involves measures to improve oxygen delivery. Supplemental oxygen by face mask may be considered in mild shock. If shock is severe or associated with marked dyspnea, persistent hypoxaemia or worsening acidosis, endotracheal intubation and invasive mechanical ventilation must be considered. Since respiratory failure can be perpetuated by shock (see chapter on acute respiratory failure) as a result of hypoperfusion of the respiratory muscles, invasive mechanical ventilation would help by decreasing the work of breathing, reducing oxygen demand and decreasing left ventricular afterload. Improvement in oxygenation improves acidosis. It must be kept in mind that the actual process of intubation and ventilation may result in a further drop in blood pressure due to the use of sedative agents, an underfilled state (e.g. hypovolaemic shock) or increased intrathoracic pressure (e.g. use of high level of PEEP) with worsening right ventricular dysfunction

Infusion involves appropriate fluid therapy to improve cardiac output and microvascular blood flow. Three aspects are important, namely, the choice of fluid, the quantum to be administered and the end points of fluid resuscitation. Generally it is agreed that although colloids may be associated with smaller resuscitation volumes, there is no clear advantage of colloids over crystalloids. Further, colloids such as hydroxyl ethyl starch (HES) may be associated with increased need for renal replacement therapy when compared with saline. The use of albumin is precluded by cost and availability. Thus saline may be an appropriate choice for a resuscitation fluid. There is however some concern that large-volume saline resuscitation may worsen metabolic acidosis (hyperchloraemic acidosis) [3]. Suitable alternatives are balanced fluids such as lactated Ringer's or Plasmalyte® that have electrolyte compositions close to plasma and do not worsen metabolic acidosis. However it must be noted that these solutions contain potassium and so must be used with caution in the setting of renal failure.

The quantum of fluid administration is dependent on the type of shock. In hypovolaemic or distributive shock, initial fluid therapy involves the rapid administration of 20–30 ml/kg of crystalloid (see section on severe sepsis) with about 300–500 ml infused over 20–30 min. Further therapy is guided by end points of resuscitation (see below). In patients with cardiogenic shock with pulmonary oedema, fluid boluses are generally avoided. However a subset of patients with acute oedema may still benefit with cautious administration of fluids (in small aliquots, e.g. 100 ml at a time) since there may be a decrease in the effective intravascular volume. This should be done with close monitoring since oxygenation may worsen due to worsening pulmonary oedema. Patients with right ventricular myocardial infarction with shock may benefit with fluid administration.

The end points for fluid resuscitation have been the subject of much discussion. The objective of fluid resuscitation is to optimise preload in order to maximise cardiac output. Traditionally, static parameters such as a target MAP and CVP were used to guide fluid therapy. However it is well known that the targets for these parameters need to be individualised. In septic shock, although a MAP of 65 mmHg is generally recommended, in patients with a history of hypertension, maintaining a higher MAP (around 75 mmHg) is associated with a lower incidence of acute kidney injury [1]. A lower MAP may be acceptable in patients with acute bleeding in the absence of major neurological symptoms, till the source of bleeding is dealt with (permissive hypotension). In haemodynamically unstable patients and those who require vasoactive agents, it may be prudent to have an arterial line and central line for continuous haemodynamic monitoring and to administer vasoactive drugs.

More recently, dynamic parameters have been used, particularly in mechanically ventilated patients (with minimal or no spontaneous breaths), to assess fluid responsiveness. These include the assessment of pulse-pressure variation (in an arterial tracing), stroke-volume variation (using cardiac output monitors), inferior vena cava variability with respiration (using ultrasound) or increment in blood pressure or stroke volume (using ECHO) following a passive leg raise test. A fluid challenge may also be administered to assess the actual blood pressure response to the fluids.

The pump refers to the use of vasoactive agents. Three categories of vasoactive agents are available – vasoconstrictors, inotropes and vasodilators (Table 14.3). The choice of the agent depends on the cause of shock and the volume status of the patient. For example, adrenaline is the agent of choice in anaphylactic shock and cardiopulmonary resuscitation, while inotropes (e.g. dobutamine) are preferred in cardiogenic shock and vasoconstrictors (e.g. noradrenaline) in distributive shock. Adrenergic agents such as noradrenaline or adrenaline as well as dopamine and vasopressin are the commonly available vasoconstrictors. Noradrenaline is preferred since it is less arrhythmogenic when compared to adrenaline or dopamine. Noradrenaline can however reduce cardiac output due to increase in vascular tone, while adrenaline can increase myocardial oxygen demand, increase lactate levels and reduce splanchnic blood flow. However noradrenaline may also improve myocardial performance by increasing diastolic blood pressure and improving coronary perfusion. In clinical trials, dopamine has been shown to be associated with more adverse events when compared with noradrenaline and hence not generally recommended. In septic shock, noradrenaline and adrenaline were found to be equally effective. Recent trials have also shown that the addition of vasopressin to noradrenaline improved outcome in milder forms of septic shock.

In cardiogenic shock, inotropes should be used. Dobutamine is considered the agent of choice in cardiogenic shock [2]. Since dobutamine, in addition to improving cardiac contractility, causes vasodilatation, it is often combined with noradrenaline to counteract the vasodilatory effects. The vasodilatory effects of dobutamine on the peripheral circulation may help improve capillary perfusion in septic shock. In cardiogenic shock, if the patient is hypotensive, the blood pressure must be increased before initiating dobutamine therapy. Phosphodiesterase inhibitors such as milrinone and calcium-channel-sensitising drugs such as levosimendan may also

Table 14.3 Summary of vasoactive agents used in shock

Medication	Category	Action on[a]	Effect	Indication	Dose
Noradrenaline	Vasoconstrictor	Alpha	↑ SVR	Septic shock Spinal shock	0.01–0.1 mcg/kg/min
	Inotrope	Beta			
Adrenaline	Inotrope	Beta	↑ CO	Anaphylaxis	10–500 mcg bolus for anaphylaxis
	Vasodilator	Alpha	↓ SVR low dose	CPR	*Infusion*: 0.1–0.4 mcg/kg/min
	Vasoconstrictor		↑ SVR high dose	Septic shock	
Dopamine	Vasoconstrictor	Dopamine	↑ CO	Cardiogenic	0.5–2 mcg/kg/min
	Inotrope	Beta	Dose-dependent changes in SVR	Septic	2–5 mcg/kg/min – β
		Alpha			5–20 mcg/kg/min – α
Dobutamine	Inotrope	Beta	↑ CO	Cardiogenic Septic	2.5–20 mcg/kg/min
	Vasodilator		↓ SVR		
Vasopressin	Vasoconstrictor	V Receptor	↑ SVR	Septic shock	Sepsis: 0.01–0.06 U/min
				Variceal bleed	Asystole: 40 units
Isoprenaline	Chronotropic	Beta	↑ Heart rate	Heart block	0.01–0.1 mcg/kg/min
Nitroglycerin	Vasodilator	Nitric oxide	↓ SVR	Heart failure	5 mcg/min – increase based on response
Milrinone	Inotrope	PDI	↑ CO	Heart failure	*Bolus*: 50 mcg/kg bolus over
	Vasodilator				10–30 min
			↓ SVR		*Infusion*: 0.375–0.75 mcg/kg/min
Levosimendan	Inotrope	Ca-channel-sensitising drug	↑ CO	Heart failure	*Loading dose*: 12–24 mcg/kg over 10 min; *Infusion*: 0.05–0.2 mcg/kg/min
	Vasodilator		↓ SVR		

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CO cardiac output, *SVR* systemic vascular resistance, *PDI* phosphodiesterase inhibitor, *CPR* cardiopulmonary resuscitation

[a]Mechanism of action or action on specific receptor

be used in cardiogenic shock. Vasodilators such as nitrates may be used cautiously in patients with cardiogenic shock to reduce afterload. However such agents have the potential to reduce blood pressure and worsen haemodynamics.

Specific Therapy for the Underlying Problem

Investigation of the cause of shock and definitive treatment is vital for shock reversal. This may involve the rapid control of bleeding in a patient with trauma, fluid replacement in a diarrheal illness, use of thrombolytic therapy for pulmonary embolism, thrombolytic therapy or percutaneous coronary intervention and revascularisation for an acute coronary event or appropriate and early administration of antibiotic therapy (within 1 h) and source control in a patient with septic shock.

Monitoring Clinical Response

The clinical response to treatment in shock may be assessed by shock reversal, improvement of organ dysfunction and failure and by currently measurable downstream parameters. Shock reversal is characterised by improving haemodynamics with the need for reducing doses of vasoactive agents and normalisation of upstream parameters such as heart rate and blood pressure. Cardiac output can be measured serially and trends observed over time. Cardiac output response to therapy (e.g. fluid boluses) is more important than a pre-targeted cardiac output. Reversal of organ dysfunction can be clinically assessed through the three windows – the skin (improvement in peripheral perfusion), neurological system (conscious state) and the renal window (urine output) as well as through laboratory parameters (oxygenation, renal function).

Downstream parameters have also been used recently to monitor clinical response. Shock reversal is associated with a reduction in lactate level. Serial lactate levels correlate with mortality. However it must be remembered that when circulation is restored, there may be an initial paradoxical increase in lactate level despite improvement in haemodynamics. This 'lactate washout', which is a temporary state, must be distinguished from worsening hyperlactataemia due to persistent or ongoing microcirculatory abnormalities.

$ScvO_2$ monitoring, both continuous as well as intermittent, has been used extensively in studies on shock. A decrease in $ScvO_2$ may occur either due to a decrease in oxygen delivery or increase in tissue oxygen consumption or both. A low $ScvO_2$ has been used as a surrogate marker of reduced cardiac output [4] with resuscitation protocols such as the early goal-directed therapy (EGDT), focusing on improving cardiac output with a view to normalising $ScvO_2$. However in a subset of patients, although resuscitation results in normalisation of $ScvO_2$ (>70 %), some patients continue to manifest features of tissue hypoperfusion, characterised by an increase in the $vaCO_2$ difference of >6 mmHg. These patients with a $vaCO_2$ 'gap' of >6 mmHg may indicate a subset of patients who continue to remain inadequately resuscitated [5]. On the other hand, in situations such as sepsis, which is characterised by impaired mitochondrial respiration with non-utilisation of oxygen by the cell, CO_2 production may be reduced resulting in a 'narrow' $vaCO_2$ gap. These

patients are likely to have cytopathic dysoxia or regional microcirculatory abnormality [6]. The value of these downstream parameters ($ScvO_2$, $vaCO_2$) in monitoring response to therapy is still unclear.

Conclusion

Circulatory shock is associated with a high mortality. A careful history, examination and appropriate investigations would help ascertain the cause of shock. The management of shock should focus on early recognition of the pattern of shock, appropriate treatment to reverse shock, specific therapy of the underlying problem, organ support and monitoring clinical response.

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Further Reading

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Chapter 15
Mechanical Ventilation

Shivakumar S. Iyer and Jignesh Shah

Key Points

- Mechanical ventilation may have detrimental effects on the circulation and lungs and should be used appropriately.
- A mode of ventilation refers to how the ventilator performs the work of the respiratory muscles. Common ventilatory modes include volume control, pressure control and pressure support.
- The goals of mechanical ventilation are to treat hypoxia and hypercapnia and to provide rest to the respiratory muscles.
- Ventilator-associated lung injury should be minimized by avoiding volutrauma by limiting tidal volumes, barotrauma by limiting airway pressures, and atelectrauma by appropriate use of positive end expiratory pressure (PEEP).
- A stepwise approach to assessment of respiratory failure and treatment by mechanical ventilation can help improve outcomes in critically ill patients.

Differences between Normal Breathing and Mechanical Ventilation

Mechanical ventilation is positive pressure ventilation and unlike normal ventilation can have detrimental effects on the circulation and on the lungs. Table 15.1 highlights the differences between spontaneous breathing and mechanical ventilation.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_15

Table 15.1 Differences between spontaneous breathing and mechanical ventilation

Characteristic	Spontaneous breath	Ventilated breath
Intrapleural pressure	Is negative and becomes more negative during inspiration	Intrapleural pressure becomes positive during inspiration
Respiratory control	Physiological – neurochemical control through brain stem and levels of $PaCO_2$, PaO_2, and pH	Depending upon mode – fully mechanically controlled to assisted breathing
Initiation of breath and change over to exhalation	By patient	Machine initiated or patient initiated
Exhalation	Passive	Passive
Venous return	Increases during inspiration.	Decreases during inspiration

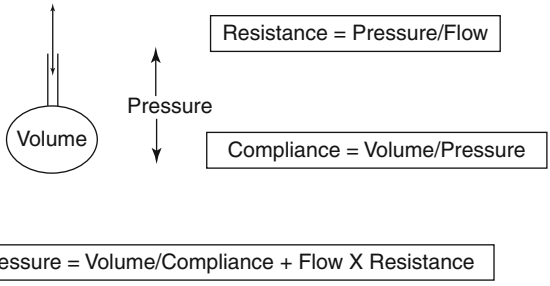

Fig. 15.1 Equation of motion for the respiratory system

The Basics of Mechanical Ventilation

What Is a Ventilator?

A ventilator is a machine that generates the pressure necessary to cause a flow of gas that increases the volume of the lungs. The relationship between pressure, flow, and volume is expressed by the equation of motion for the respiratory system (Fig. 15.1). The compliance of the lungs and chest wall determines the volume that will result because of a certain pressure, while airway resistance will determine the flow.

Pressure, volume, and flow will change with time and hence are called variables. At any given point in time, a ventilator can control only one of these variables; the other two vary according to the compliance and resistance of the underlying lungs. The compliance and resistance are called parameters and are assumed to be constant at any given point in time. Their combined effect is the load experienced by the ventilator and the ventilatory muscles. Volume/compliance represents the elastic load, i.e., the pressure necessary to expand the lungs and chest wall and resistance × flow represents the resistance load, i.e., the pressure necessary to deliver gas at a particular flow rate.

Parts of a Mechanical Ventilator

The parts of a ventilator include input power (electric or pneumatic), source of gas supply, a gas mixing unit (oxygen blender), control unit (values, electric circuits with values or microprocessors), flow sensors (inspiratory and expiratory), pressure sensors, patient circuit (with inspiratory and expiratory limbs, spacer, water-trap, and catheter mount), humidifier (heated or heat-moisture exchange filters), and a user interface (knobs, screen).

Modes of Mechanical Ventilation

The nomenclature of modes varies from ventilator to ventilator and is a common source of confusion. A mode is nothing but a short-form notation of how the ventilator performs the work of the respiratory muscles. Commonly used modes include volume control ventilation (VCV), pressure control ventilation (PCV), synchronized intermittent mandatory ventilation (SIMV), and pressure support ventilation (PSV).

Components of a Mode

The components of a mode include the type of breath, control variables, phase variables, and conditional variables

Type of Breath

A breath is said to be *mandatory* if it is initiated (triggered) and powered (as a prespecified pressure or volume) by the machine. A *spontaneous breath* is initiated and powered by the patient, while an assisted breath is triggered by the patient and powered by the machine. Accordingly in a mandatory volume control mode, the breath is triggered by the ventilator, and a prespecified volume is delivered. This mode is used in deeply sedated or paralyzed patients. In a pressure support mode of ventilation which is usually used in spontaneously breathing and reasonably awake patients, the breath is triggered by the patient, and a preset pressure support is delivered by the machine.

Control Variable

From the equation of motion (Fig. 15.1), pressure, volume, and flow are variables that can be controlled by the ventilator, and these are designated as control variables. The prespecified control variable is kept constant, while the other variables

change according to compliance and resistance. For example, in a pressure control mode, the pressure remains constant, while the volume and flow may change depending on lung compliance and resistance. Time is implicit in the equation of motion and in certain modes may act as a control variable (e.g., high-frequency ventilation)

Phase Variables

Each breath either spontaneous or mandatory goes through four phases (Fig. 15.2): the trigger phase when a breath is initiated, inspiratory phase, a plateau phase, and a baseline or expiratory phase. Each phase is controlled by a particular variable that differs from mode to mode. The *trigger variable* starts inspiration and may be triggered by changes in pressure or flow in the circuit. The *limiting variable* is that which limits inspiration and is by a preset control pressure or volume. The *cycling variable* terminates inspiration and enables cycling to expiration. In controlled modes, it is *time cycled* and thus the inspiratory time in fixed. In pressure support modes, where cycling occur when the inspiratory flow reaches a proportion of the peak flow (called *expiratory trigger sensitivity* or *cycle off*), the inspiratory time may be variable. The fourth phase which is the *baseline variable* is the variable set for the end of expiratory or baseline phase (e.g., positive end expiratory pressure – PEEP).

Conditional Variable

Conditional variables are safety mechanisms incorporated into modern ventilators and include switch from machine breaths in a SIMV mode or change from spontaneous PSV mode to control mode if apnea time exceeds the set limit.

Analysis of Basic Modes Based on the Above Terminology

Table 15.2 summarizes the modes based on the above terminology.

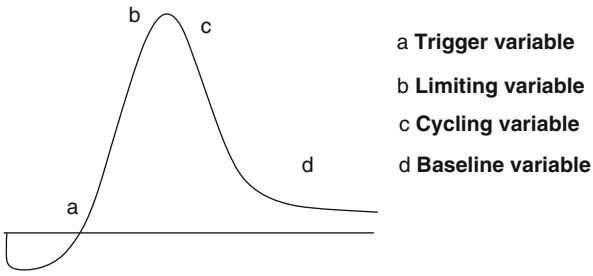

Fig. 15.2 Phase variables

Table 15.2 Analysis of basic modes

Mode/variable	Type of breath	Control variable	Trigger variable	Limiting variable	Cycling variable
VC	Assisted or mandatory	Volume	Flow or pressure	Flow or volume	Time
PC	Assisted or mandatory	Pressure	Flow or pressure	Pressure	Time
PSV	Spontaneous	Pressure	Flow or pressure	Pressure	Inspiratory flow
SIMV – VC	Mandatory	Volume	Flow or pressure	Flow or volume	Time
	Spontaneous (PS)	Pressure	Flow or pressure	Pressure	Inspiratory flow
SIMV – PC	Mandatory	Pressure	Flow or pressure	Pressure	Time
	Spontaneous (PS)	Pressure	Flow or pressure	Pressure	Inspiratory flow

VC Volume control, *PC* Pressure control, *PSV* Pressure support ventilation, *SIMV* Synchronous intermittent mandatory ventilation, *PS* Pressure support

Indications for Mechanical Ventilation

The indications for mechanical ventilation include:

1. *Type I or hypoxemic respiratory failure* where the patient is unable to meet the oxygen requirements of the body or is able to do so only at a very high cost that may result in metabolic and/or hemodynamic compromise
2. *Type II or hypercapnic respiratory failure* where there is an inability of the ventilatory pump to meet ventilatory requirements which may be due to central respiratory depression, neuromuscular weakness, severe bilateral chest wall deformities and pulmonary abnormalities or severe airway obstruction

In addition to the above, endotracheal intubation or tracheostomy may be needed for airway protection and removal of secretions.

Goals of Mechanical Ventilation

Traditionally the goals of mechanical ventilation have included:

1. Correct hypoxemia – targeting PO_2 >60 mmHg, O_2 saturation >90 %.
2. Correct hypercapnia – PCO_2 ~40 mmHg.
3. Reduce work of breathing and hence cardiac workload.
4. Provide rest to respiratory muscles and reduce oxygen cost of breathing.

It is now recognized that conventional mechanical ventilation can cause deleterious effects, termed ventilator-induced lung injury (VILI). Mechanisms for VILI

include excessive tidal volume delivered (volutrauma), high airway pressure (barotrauma), cyclical opening and closure of the alveoli (atelectrauma), and cytokine release (biotrauma). Deleterious effects of ventilation also include hemodynamic compromise due to decreased venous return and oxygen toxicity due to high FiO_2. In addition, the supine position and reduced functional residual volume during mechanical ventilation coupled with prolonged sedation and paralysis promote alveolar atelectasis.

The goals of mechanical ventilation mentioned above have therefore been modified to include strategies to reduce the risk of VILI (Table 15.3).

Common Complications of Mechanical Ventilation

1. Ventilator induced lung injury:
   - Volutrauma – due to excessive volume
   - Barotrauma – due to excessive pressure
   - Atelectrauma – due to cyclical opening and closure of alveoli
   - Biotrauma
2. Decreased venous return due to positive intrathoracic pressure. This may sometimes be very severe in patients with acute severe asthma due to excessive gas trapping and hyperinflation and may lead to a cardiac arrest like situation.
3. Ventilator-associated pneumonia.

Table 15.3 Modified goals of mechanical ventilation

Goal	Modification
Prevent ventilator-induced lung injury	Low tidal volume 6 ml/kg for ARDS and 8 ml/kg for other patients
	Limit plateau pressure <30 cm H_2O
Oxygenation – correct hypoxemia	Saturation ~90 % with minimum FiO_2<60 %.
	Recruit alveoli and keep alveoli patent
	Titrate PEEP according to PEEP/FiO_2 table (1); keep plateau <30 cm H_2O
	Prone position
Ventilation – correct hypercapnia	Accept high PCO_2 target pH >=7.2
	Permissive hypercapnia
	Avoid gas trapping and hyperinflation
	Short inspiratory time, low respiratory rate, adequate expiratory time
Reduce work of breathing using controlled mechanical ventilation and sedation and paralysis and reduce cardiac workload	Initial sedation and paralysis (if indicated) for ARDS (48 h)
Rest to respiratory muscles	Prolonged sedation and paralysis may do more harm than good. Implement spontaneous breathing early during mechanical ventilation

ARDS Acute respiratory distress syndrome, *PEEP* Positive end expiratory pressure, *FiO_2* Fixed inspired oxygen concentration

4. Airway-related complications.
5. Pressure ulcers, venous thrombosis, malnutrition, and other complications related to nonambulatory state.

A Stepwise Approach for Starting Mechanical Ventilation

A systematic approach may help in initiating and managing patients who may require mechanical ventilation (Fig. 15.3). Three steps may be considered: is ventilatory support indicated? If so, how should this support be provided? What should

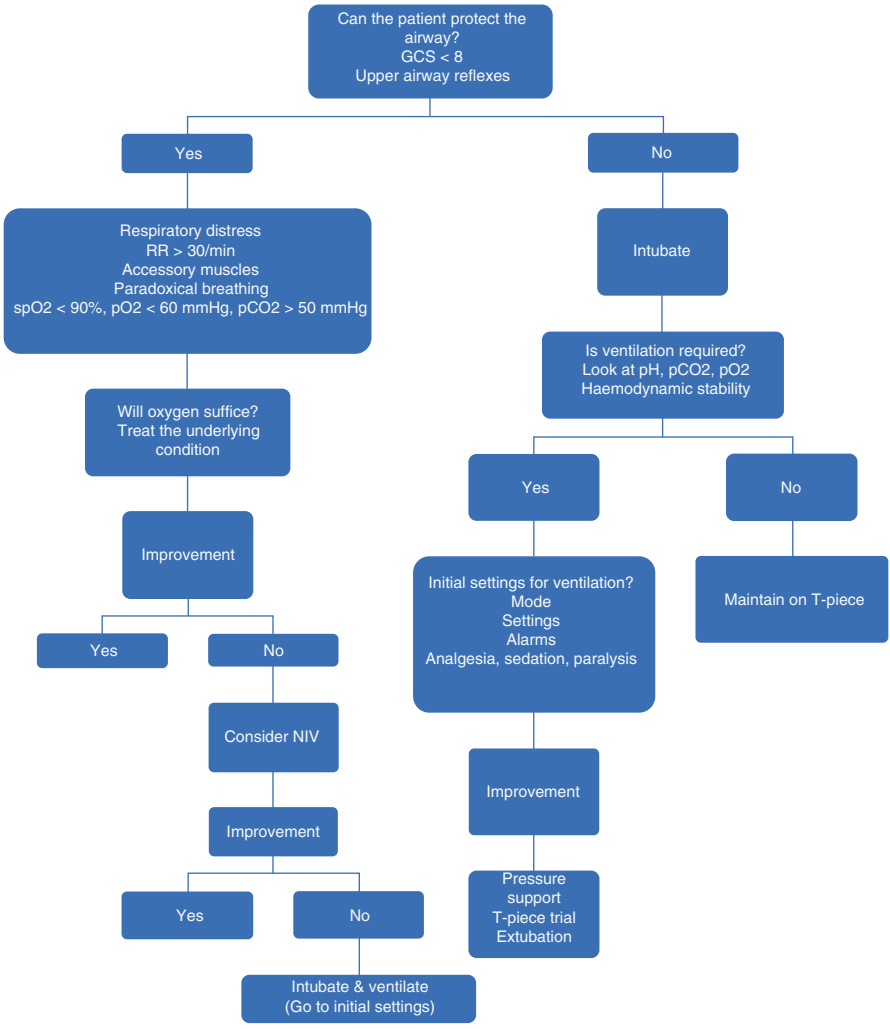

Fig. 15.3 A stepwise approach for mechanical ventilation. *GCS* Glasgow coma Scale, *RR* respiratory rate, *NIV* non-invasive ventilation

be the initial ventilator settings on someone who is initiated on mechanical ventilation?

Is Ventilatory Support Indicated?

Since mechanical ventilation is used for the management of respiratory failure (hypoxemic or hypercapnic), for airway protection, and for assisting clearance of secretions, the first step is whether mechanical ventilation is indicated. Inability to protect airway due to a low Glasgow Coma Score (<8 usually), absence of gag reflex, difficulty in swallowing, nasal regurgitation, or pooling of saliva may warrant intubation and ventilation. In the setting of hypoxemic respiratory failure without clinical evidence of severe distress (e.g., tachypnea, use of accessory muscle use), supplemental oxygen therapy may be considered (see chapter on respiratory failure) initially. In severe hypoxemic respiratory failure or in hypercapnic respiratory failure with respiratory fatigue (evidenced by paradoxical respiration, excessive use of accessory muscles, drowsiness, hypotension), ventilatory support by means of noninvasive or invasive ventilation should be considered (see below). Other features that may guide in the assessment include flap (asterixis), single breath count, or breath holding time (e.g., monitoring weakness in myasthenia gravis or Guillain-Barre syndrome) and forced vital capacity (VC) measured at the bedside using spirometry. A VC of <30 ml/kg usually indicates inability to cough well, <20 ml/kg inability to sigh and prevent atelectasis, and <10 ml/kg inability to ventilate adequately. Diaphragmatic weakness, in addition, may be assessed at the bedside by the "sniff test" performed with fluoroscopy or ultrasound. Arterial blood gas (ABG) helps confirm respiratory failure and assesses the severity of respiratory failure and response to therapy.

How Can Respiratory Support Be Provided?

Respiratory support may be provided either by means of noninvasive or noninvasive ventilation. Noninvasive ventilation refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway. Noninvasive ventilation can be provided using a comfortable, reasonably tight nasal or full face mask with ventilators that have sophisticated triggering and cycling, with the ability to compensate for leaks. Noninvasive ventilation has been shown to reduce the need for invasive mechanical ventilation in certain selected groups of patients that include acute exacerbations of chronic obstructive pulmonary disease (COPD) and acute hypoxemic respiratory failure of varied etiology, particularly cardiogenic pulmonary oedema. It is also useful in the management of post-extubation respiratory failure and reduces the need for re-intubation. Although noninvasive ventilation is used as a bridge therapy in acute etiologies of respiratory

failure (asthma, sleep apnea, acute respiratory distress syndrome, respiratory exacerbations in patients with cancer), its benefit is variable. The provision of noninvasive ventilation however requires a conscious and cooperative patient with an intact airway with hemodynamic stability and moderate respiratory failure. Severe respiratory failure (e.g., pH <7.1 and PaCO2 >100 mmHg) or an unconscious patient or a patient with copious respiratory sections is not a candidate for noninvasive ventilation.

What Should Be the Initial Settings for Invasive Ventilation?

Mode: Mandatory/Control or Spontaneous/Support Mode?

In patients with acute respiratory failure with total muscle paralysis, respiratory muscle fatigue, hemodynamic instability, raised intracranial pressure (ICP), severe metabolic acidosis, high fever, and severe sepsis, a mandatory mode is indicated. Sedation and/or paralysis may be required in the initial period to prevent patient-ventilator asynchrony, reduce cardiac work, and rest the respiratory muscles. Patients should be frequently assessed so that spontaneous breathing may be implemented as early as feasible.

Volume or Pressure Control?

Currently there is no evidence to support the superiority of one mode of ventilation over the other. VCV is usually preferred due to ease of use and familiarity. While VCV ensures the delivery of set minute ventilation, airway pressures have to be monitored to prevent barotrauma. In PCV, peak airway pressures are preset, and ventilation is more evenly distributed. The danger however is that of hypoventilation as tidal volume is not guaranteed and is dependent on lung compliance and airway resistance.

Initial settings: The default FiO_2 setting following intubation is always 100 % (or 1) unless there is preexisting COPD. However FiO_2 is titrated down based on oxygen saturation and ABG, the first one done after an hour following intubation. The tidal volume is set based on calculated minute volume (MV) and body weight. The usual minute volume is 4× body surface area (BSA) for men and 3.5 × BSA for women. This is increased by 5 % for every degree F increase above 99 °F and by 20 % for metabolic acidosis and 50–100 % if resting energy expenditure is equally increased. The tidal volume is set based on the underlying respiratory problem: 4–6 ml/kg body weight for ARDS, 8 ml/kg in the setting of "normal" lungs, and 8–10 ml/kg for COPD ventilation. Based on the tidal volume, the respiratory rate is set (usually 12–20 breaths/min). In patients with severe respiratory distress with tachypnea, a higher initial rate may be set following intubation to prevent "relative" hypoventilation and worsening acidosis due to mechanical ventilation.

Adjust tidal volume and respiratory rate after the first ABG to keep plateau pressure (alveolar pressure) below 30 cmH_2O and $PaCO_2$ ~40 mmHg and pH >7.3. Therapeutic hyperventilation may be required in head injury. This may be used only as a "bridge" prior to definitive therapy as "hypocarbia" has been shown to be deleterious. Lung-protective ventilation leading to permissive hypercapnia is acceptable in ARDS, and bicarbonate may be used to treat the ensuing acidosis due to hypoventilation. Patients with COPD or asthma may require low respiratory rate to minimize gas trapping.

The trigger variable (sensitivity) should always be set so that the patient can trigger the ventilator easily. If the trigger variable is set inappropriately high, it may increase patient effort and prevent detection of spontaneous breathing. Detection of spontaneous breathing is extremely valuable in deciding between appropriate doses of sedatives and paralyzing agents or the early implementation of a spontaneous mode. Inappropriately sensitive trigger may lead to auto triggering.

The cycling variable is set by using the I:E ratio or inspiratory flow rate or inspiratory time setting. The initial setting for I:E ratio is 1:2 or 1:3. I:E ratio changes when a patient has a high spontaneous rate, and this may cause gas trapping. Patients with COPD or asthma may require I:E ratios of 1:4 or lower. In some ventilators, the I:E ratio is indirectly set by controlling the inspiratory flow rate and /or the inspiratory time. The inspiratory rise time is dependent on the initial flow requirement of the patient and may be set from 0.05 to 0.4 s. The inspiratory pause time is usually set at 10 % of the inspiratory time. The change in inspiratory pause time also affects the I:E ratio.

The baseline PEEP is usually set at 3–5 cm in those with normal lungs. In ARDS, PEEP is sequentially increased to open closed alveoli and improve lung compliance. This is done using the $PEEP/FiO_2$ table from ARDSNet study [1] and by closely monitoring plateau pressure, blood pressure, and improvement in oxygenation.

The alarms should be set appropriately. The high pressure alarm should be initially set at <35 cm H_2O. The low and high MV alarms should be set at 10–20 % below and above the respective requirements.

Adjunctive Treatment in Patients on Mechanical Ventilation

Patients on a mechanical ventilator often receive drugs for analgesia, sedation, and paralysis at the time of intubation. Short-acting opioids like fentanyl and remifentanil are the preferred agents. Sedative drugs like midazolam or propofol are also used to prevent agitation during initiation of mechanical ventilation. Paralytic agents like succinylcholine may be required to facilitate intubation. Care should be taken to prevent a "cannot intubate" scenario becoming a "cannot ventilate, cannot intubate scenario." Expert help should always be sought for managing the airway except in dire emergencies. In patients who are already initiated on

mechanical ventilation, adequate analgo-sedation by means of a benzodiazepine (usually midazolam) along with an opioid (morphine or fentanyl) should be used.

Monitoring and Managing the Mechanically Ventilated Patient

The goals of monitoring and managing patients on the ventilator are summarized in Table 15.4. A proper airway should be ensured and secured by correct positioning of the tube and documenting the position. Tube position should be checked by five-point auscultation and confirmed by end-tidal CO_2 ($ETCO_2$) and chest X-ray. Cuff pressure should be kept at 20–25 mmHg and monitored every shift. Oxygenation should be monitored continuously by using pulse oximetry and periodic ABG. The presence of cyanosis, agitation and patient-ventilator asynchrony may suggest hypoxia. The adequacy of ventilation is difficult to monitor clinically although drowsiness, flap, or tremor may suggest this. The value of $ETCO_2$ in monitoring ICU patients is controversial, and high values of $ETCO_2$ should be confirmed by ABG. Exhaled minute ventilation on the ventilator may give an idea of hypoventilation.

Since oxygen delivery to tissues depends not only on adequate PaO_2 but also on adequate cardiac output and hemoglobin, hemodynamics should be monitored by continuous heart rate monitoring and periodic noninvasive blood pressure monitoring. In hemodynamically unstable patients, the placement of an intra-arterial line with continuous monitoring may be preferred. ABG estimation with high lactate level may suggest global hypoperfusion, and bedside ECHO may be used to assess volume status and the cause of hemodynamic instability.

Monitoring respiratory mechanics on a ventilator is now easy as all modern ventilators display scalar graphics for monitoring pressure, volume, and flow changes during the respiratory cycle. It is invaluable in detecting changes in resistance (peak pressure and peak-plateau difference), compliance (plateau pressure, measured by doing an inspiratory hold with constant flow), and auto-PEEP (by doing an expiratory hold). Patient-ventilator asynchrony may also be detected by monitoring respiratory mechanics.

Table 15.4 Goals of monitoring and managing the ventilated patient

Goals of monitoring and managing the ventilated patient
Ensure proper airway
Ensure adequate oxygenation
Ensure adequate ventilation
Maintain hemodynamic stability
Monitor respiratory mechanics
Interpret ventilator alarms and troubleshoot
Prevent infection, complications related to nonambulatory state

Troubleshooting a Patient on a Mechanical Ventilator

In the setting of respiratory distress or hypoxemia (detected on pulse oximetry) in a patient who is on mechanical ventilation, a series of steps can be undertaken to troubleshoot and identify the problem.

Step I: Is There a Problem with the Ventilator?

If the distress is severe and has caused severe hypoxia or hemodynamic instability, the first step would be to disconnect the patient from the ventilator and bag with 100 % oxygen. If the problem persists, then one should assess the three components of ABC – airway, breathing, and circulation (Fig. 15.4).

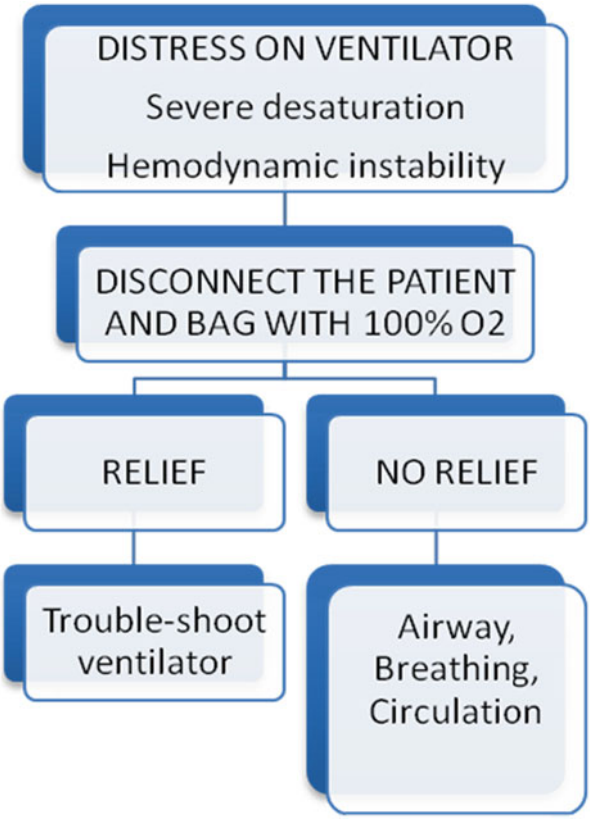

Fig. 15.4 Flow chart for troubleshooting patient distress on a ventilator

Step 2: Is It a Problem with the Airway?

This will be diagnosed by difficult bagging, which may indicate a blocked tube. If a suction catheter cannot be passed, the endotracheal tube will need to be changed immediately. If bagging results in bubbles and air leak in the mouth, the endotracheal tube may have come out into the mouth, and re-intubation will be needed (Fig. 15.5).

Step 3: Is There a Respiratory or Cardiac Problem?

An approach to managing respiratory and cardiac problems is outlined in Fig. 15.6. A careful clinical examination may give the clue to the cause for respiratory distress such as unequal movement of the chest, tympanitic percussion note, reduced or absent breath sounds and presence of adventitious sounds. Chest X-ray, ultrasound, and 2D-ECHO will help ascertain the cause. The presence of unilateral breath sounds should lead to the evaluation for endobronchial intubation, collapse, or pneumothorax. Presence of bilateral sounds with crackles or rhonchi may suggest secretions, bronchospasm, or fluid overload. If there is hypotension, appropriate hemodynamic assessment should be undertaken to ascertain cause since circulatory shock with a low cardiac output may also result in hypoxia due to an increased shunt fraction.

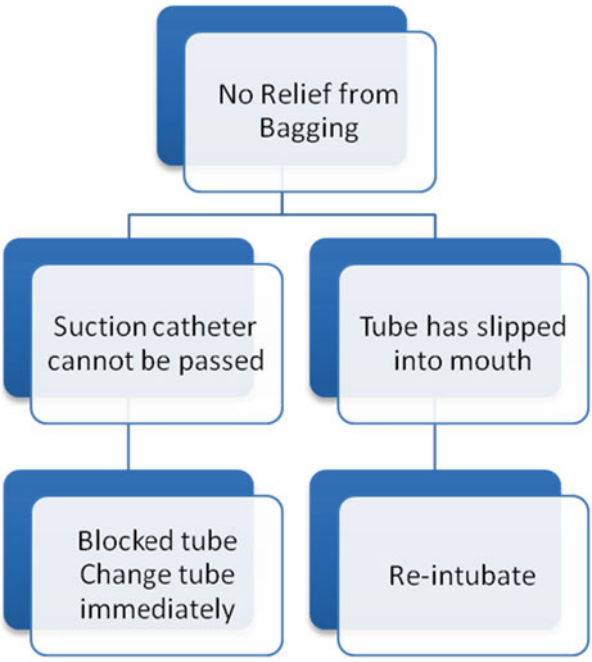

Fig. 15.5 Distress on ventilator – troubleshooting the airway

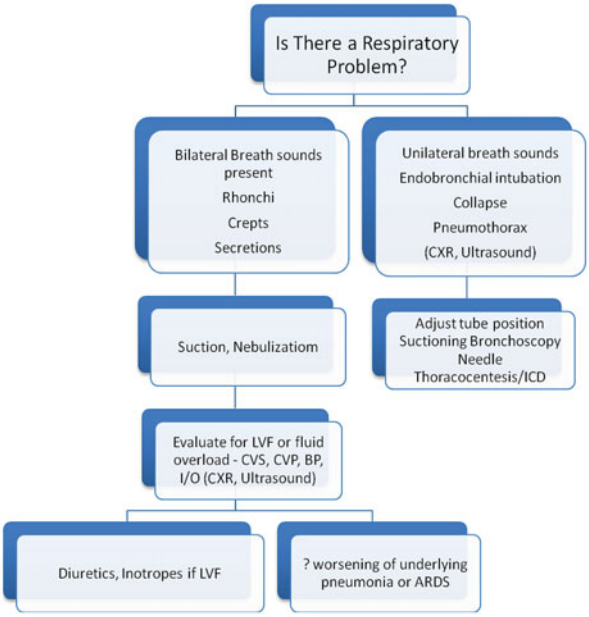

Fig. 15.6 Troubleshooting respiratory and cardiac problems. *CXR* Chest X-ray, *ICD* Intercostal drain, *LVF* left ventricular failure, *CVS* cardiovascular system, *CVP* central venous pressure', *BP* Blood pressure, *I/O* Intake/Output, *ARDS* Acute respiratory distress syndrome

Other Problems and Troubleshooting Alarms

Other problems such as obesity and abdominal distension may also contribute to hypoxia. It must also be ensured that appropriate ventilator alarm limits are set. In this context, a low pressure alarm may suggest a leak in the ventilatory system, while high pressures may suggest ventilator, airway, or patient-related factors (outlined above) as the cause of high airway pressure (Table 15.5).

Review Mode and Settings

Inappropriate mode and settings may frequently be responsible for distress on ventilator, and many factors will need to be looked at. Table 15.6 gives a few examples of how inappropriate settings may cause distress.

Ancillary Support

Managing a patient on mechanical ventilator requires careful attention to detail at the bedside. Table 15.7 highlights some of the important points in ancillary support

Table 15.5 Ventilator alarms

Alarm	Cause
Low ventilation alarm	Leak
	Low respiratory rate not triggering
	Altered settings
	Decreased compliance
	Increased resistance (concomitant high pressure alarm)
High ventilation alarm	Increased triggering, increased respiratory rate
High pressure alarm (intermittent)	Cough, asynchrony
High pressure alarm persistent	Airway obstruction
	Secretions
	Bronchospasm
	Tube in one main bronchus
	Pneumothorax
	Collapse
	Pulmonary oedema
Low pressure alarm	Leaks
	Ventilator failure
	Altered settings
Low O_2 alarm	Central O_2
	Blender problem
	O_2 sensor problem

Table 15.6 Inappropriate settings

Setting	Cause of distress
Mode	Control mode in an agitated patient
Inspiratory flow	Inadequate respiratory flow
Tidal volume	Low or excessive tidal volume
Respiratory rate	Change in respiratory rate alters I:E ratio
I:E ratio	Change in flow, tidal volume, RR alters I:E ratio
Sensitivity	High sensitivity leads to autotriggering, low sensitivity leads to increased work of breathing
Pressure level/pressure slope in pressure preset modes	Steep slope leads to overshoot of pressure, gradual slope leads to inadequate inspiratory flow
PEEP	Inadequate PEEP in COPD leads to difficult triggering

I:E ratio – inspiratory: expiratory ratio, *PEEP* Positive end expiratory pressure, *COPD* Chronic obstructive pulmonary disease, *RR* respiratory rate

Table 15.7 Ancillary support

Prevent infection	Hand hygiene, terminal disinfection, closed suction, head-up, oral decontamination
Care of the endotracheal tube	Appropriate fixing with tube holder
Ulcer prophylaxis	Prevents gastrointestinal bleeding
Suction	Using aseptic technique
Nebulization	Use metered dose inhaler in preference to nebulization
Humidification	Use humidifier-moisture exchange filter
Eye care	Tape eyes, use artificial tears
Mouth care	Decontamination with oral chlorhexidine
Bowel care	Avoid constipation/diarrhea
Bladder care	Appropriate aseptic precautions
Skin care	Back care, use of air mattress
Nutrition	Early enteral nutrition
Early mobilization and physiotherapy	Dedicated therapists for ICU

Summary

A basic understanding of mechanical ventilation and following a stepwise approach (Figs. 15.3, 15.4, 15.5 and 15.6) in the emergency department can facilitate the safe management of a patient on a mechanical ventilator. Careful attention to ancillary support right from the initiation of ventilatory support can help ensure optimal outcome for the patient.

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Chapter 16
Severe Sepsis

Suhel Al-Soufi and Vineet Nayyar

Key Points
- The cornerstones of sepsis management are recognition, haemodynamic optimisation, early and appropriate antibiotic therapy, organ-specific support and adjuvant therapy.
- Fluid management of septic patients is time sensitive.
- Mean arterial pressure (MAP) of at least 65 mmHg should be targeted in patients with septic shock.
- Timely administration of antibiotic therapy, (preferably within 1 h of recognition of severe sepsis) is associated with improved outcome in life-threatening infections.

Introduction

Sepsis is a clinical syndrome resulting from the host response to microbial invasion that is still incompletely understood. Sepsis, severe sepsis, and septic shock are commonly considered as a continuum of body's response to the presence of an infection (Table 16.1); however, severe sepsis or septic shock can be diagnosed

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_16

Table 16.1 Definitions of sepsis, severe sepsis and septic shock

Infection
The presence of pathogenic or potentially pathogenic microorganisms at a site normally considered sterile
Bacteraemia
The presence of viable bacteria in the blood
Sepsis
Host response as the result of proven or suspected infection
Host response manifested by 2 or more of the following:
Temperature >38.3 or <36 °C
Heart rate >90 per min
Respiratory rate >20 per min or pCO_2 <32 mmHg
White cell count >12,000 or <4,000 or >10 % band forms
Severe sepsis
Sepsis associated with organ dysfunction, manifested as:
Hypotension (systolic BP <90 mmHg or mean arterial pressure <70 mmHg)
Oliguria (<0.5 ml/kg per h urine output)
Hypoxaemia (PaO_2/FiO_2 ratio <250)
Lactate above upper limit of laboratory normal
Altered mental state
Septic shock
Sepsis associated with hypotension (mean arterial pressure <70 mmHg) despite adequate fluid resuscitation
Multi-organ dysfunction syndrome (**MODS**)
Presence of altered organ function in an acutely ill (often septic) patient; such homeostasis cannot be maintained without intervention

without accompanying evidence of infection. Sepsis is the most common cause of death in intensive care (ICU) patients all over the world with mortality rates of 35 % or higher amongst the worst affected cases.

Aetiology

Bacteria are the most common causative agents of septic shock, with roughly even numbers of infections due to Gram-positive and Gram-negative organisms. Sometimes, nonbacterial organisms like fungi, viruses or parasites are the cause of severe sepsis and multi-organ dysfunction. In approximately one-third of patients, causative organisms are never isolated possibly because of prior exposure to antibiotics.

Pathogenesis and Physiological Disturbances

- The hallmark of sepsis is a decrease in systemic vascular resistance that occurs despite increased levels of endogenous catecholamines. Decrease in vascular tone affects both the arterial and the venous side of circulation.
- Additionally, diffuse endothelial injury results in a vascular leak with oedema formation and intravascular fluid depletion.
- Myocardial dysfunction also occurs in patients with septic shock and takes the form of decreased myocardial compliance and stroke volume. Compensation by way of increased heart rate is sustained only in those with no pre-existing cardiac disease.
- Even before the onset of haemodynamic instability, patients manifest features of poor tissue perfusion due to maldistribution of blood and microvascular obstruction.

Clinical Features

Sepsis produces at least three categories of clinical manifestations (Table 16.2). These are sometimes superimposed on signs and symptoms of pre-existing disease or therapy-related effects.

- First, patients usually manifest signs and symptoms related to the primary focus of infection. A careful history and physical examination often leads to the probable site of infection. It is important to examine the skin, wounds, throat, nose, sinuses and optic fundi as these may hold valuable clues to the diagnosis.
- Second, patients manifest one or more non-specific signs of sepsis such as fever, tachypnoea or tachycardia. A small percentage of septic patients, particularly the elderly, present with hypothermia. Certain laboratory abnormalities are incorporated in the diagnostic criteria for sepsis (Table 16.1), but these have a poor sensitivity and specificity.
- Lastly, septic patients present with evidence of organ dysfunction or complications. Sepsis-induced hypotension is common and is associated with oliguria, metabolic acidosis, hyperlactataemia and acute kidney injury (AKI). Altered mental state can be a presenting feature in the elderly. Isolated thrombocytopaenia without overt laboratory evidence of disseminated intravascular coagulopathy (DIC) is seen in up to half of the patients. Acute respiratory distress syndrome (ARDS) develops in 30 % of patients.

Table 16.2 Clinical features of sepsis

General signs and symptoms
Fever/hypothermia
Tachypnoea
Tachycardia
Significant oedema
Hyperglycaemia
Inflammatory reaction
Altered white cell count
Increased C-reactive protein
Raised levels of biomarkers
Haemodynamic alterations
Arterial hypotension
Tachycardia
Increased cardiac output
Altered skin perfusion
Low systemic vascular resistance
Signs of organ dysfunction
Hypoxaemia
Oliguria or rise in creatinine
Coagulation abnormalities
Altered mental state
Thrombocytopaenia
Altered liver function
Intolerance to feeding
Tissue perfusion abnormalities
Hyperlactataemia (>2 mmol/L)
Decreased capillary refill or mottling

Management

Haemodynamic Management

Early Goal-Directed Therapy

Early goal-directed therapy (EGDT) targets predefined physiological goals of central venous pressure, mean arterial pressure, urine output and central venous or mixed venous oxygen saturation with protocol-driven fluid resuscitation, use of vasopressors and dobutamine and red cell transfusion [1]. International guidelines such as the Surviving Sepsis Campaign have advocated EGDT as a standard of care [2]. Two recent large, multicentre studies have led to a reappraisal of these recommendations. In the Australasian Resuscitation in Sepsis Evaluation (ARISE) study, EGDT compared with usual care, did not reduce 90-day all-cause mortality amongst patients presenting with early septic shock [3]. Similarly, in the randomised multicentre Protocolized Care for Early Septic Shock (ProCESS) trial, a

combination of EGDT and protocol-based therapy for patients in whom septic shock was diagnosed in the emergency department was not associated with a survival benefit, as compared with usual care [4]. Taken together, it appears that protocol-based resuscitation does improve outcomes of patients who were identified as having septic shock in the emergency department, but similar outcomes were also obtained by clinicians acting promptly and directing elements of patient care using their own clinical judgment.

Colloids or Crystalloids

Aggressive fluid resuscitation is the mainstay of initial haemodynamic management of severe sepsis. As the physiological volume of distribution is much larger for crystalloids compared to colloids, resuscitation with colloids requires less volume to achieve the same end points. This notwithstanding, mortality is not significantly different when unselected colloids are compared with crystalloids [5]. More than a decade ago, the Saline versus Albumin Fluid Evaluation (SAFE) study [6] compared albumin and saline in ICU patients and showed no difference in mortality. However, a subgroup analysis showed a trend towards improved survival amongst septic patients resuscitated with albumin. The Albumin Italian Outcome Sepsis (ALBIOS) study [7] demonstrated that in patients with severe sepsis, albumin replacement in addition to crystalloids did not increase survival despite improvements in haemodynamic variables. Interestingly, a post hoc subgroup analysis of patients with septic shock at the time of enrolment showed significantly lower mortality at 90 days in the albumin group compared to the crystalloid group. Therefore, albumin could be considered for patients with septic shock in whom its use might improve short-term haemodynamic indices. On the other hand, there is compelling evidence that resuscitation with hydroxyethyl starch (HES) solutions is associated with an increased use of renal replacement therapy without demonstrable benefit when compared with saline [8].

Thus, the use of crystalloids has found a revival. Balanced fluids like lactated Ringer's or Plasma-Lyte have an electrolyte composition close to plasma and do not contribute as much to the generation of metabolic acidosis as 0.9 % saline, which has in fact, a non-physiological sodium and chloride content. The optimal volume of resuscitation fluid is unknown, but approximately 30 mL/kg administered rapidly in well-defined aliquots has been recommended. Multiple studies have demonstrated potential harm with liberal fluid resuscitation, notably when given beyond the initial hours of resuscitation. Venous pooling and hypo-proteinaemia during a septic episode contribute to the formation of tissue oedema, particularly in the lungs, the myocardium and the abdominal compartment, and are considered detrimental. Unfortunately, almost all of the data on fluid accumulation in critically ill patients is retrospective in nature and points only to associative rather than causal relationships [9]. One notable exception is the Fluid and Catheter Therapy Trial (FACTT), a multicentre, randomised clinical comparison of two fluid management strategies, which showed that in the setting of acute lung injury, a more conservative

strategy reduced the duration of ventilation and length of stay in ICU, albeit without demonstration of a mortality difference [10].

Overall, it appears that early aggressive fluid resuscitation should be followed by a more restrictive fluid management to prevent excessive fluid accumulation.

Vasoactive Agents

When the mean arterial pressure (MAP) falls below the autoregulatory threshold of the heart, brain and kidneys, blood flow to organs decreases in an almost linear fashion. Observational studies have demonstrated that a MAP of less than 60–65 mmHg is associated with an increased risk of kidney injury and death. As a result of a shift in the autoregulatory range in patients with chronic hypertension, a higher MAP may be required in these patients. The recent SEPSISPAM trial targeting a MAP of 80–85 mmHg, as compared with 65–70 mmHg, did not result in significant differences in mortality at either 28 or 90 days. However, in the a priori planned subgroup analysis of patients with or without hypertension, the incidence of renal dysfunction was greater with lower MAP target amongst patients with hypertension [11].

Noradrenaline is the predominant endogenous sympathetic amine, which increases MAP by arterial vasoconstriction, augmented myocardial contractility and venoconstriction. There is no compelling evidence to substitute or even supplement the administration of noradrenaline with another vasoactive substance for the majority of patients with septic shock. Adrenaline remains popular in income-poor countries where it is widely available at a fraction of the cost of noradrenaline. Multicentre randomised controlled trials of adrenaline versus noradrenaline in septic shock have not reported a difference in primary or secondary outcomes, only a significant difference in the incidence of tachycardia, lactic acidosis and insulin requirements [12]. The Surviving Sepsis Campaign guidelines suggest that vasopressin 0.03 units/min can be added to noradrenaline with the intent of either raising MAP or decreasing noradrenaline dosage. Vasopressin may be effective in raising MAP in patients with refractory hypotension; however, the optimal time to initiate this drug is not clear. A meta-analysis that included results of the Vasopressin and Septic Shock Trial (VASST) showed reduced noradrenaline requirements in patients with septic shock but no significant survival benefit in the short term [13, 14].

Oxygen-Carrying Capacity

Liberal transfusion to a haemoglobin value of >10 g/dL has been promoted as part of the early goal-directed therapy (EGDT) to augment oxygen-caring capacity and oxygen delivery to the tissues, especially if venous O_2 saturation targets are not achieved ($SpvO_2$ <70 %) during the first 6 h of resuscitation [1]. This hypothesis was not confirmed in the recent Transfusion Requirements in Septic Shock (TRISS) trial [15]. In this trial patients with septic shock were randomised to receive transfusion at a haemoglobin threshold of either 7 g/dL or 9 g/dL. The restrictive approach

resulted in about half the amount of transfusion requirements without a significant difference in the mortality at 90 days or the rate of ischaemic events and use of life support. TRISS did not specifically address the role of blood transfusion as part of a resuscitation strategy in the first 6 h but insights gained from two early goal-directed resuscitation trials, [3, 4] which did not demonstrate a difference in overall mortality, make it likely that a restrictive transfusion strategy is the better option for septic patients.

In the absence of a demonstrable benefit from the use of a liberal transfusion strategy, a restrictive transfusion threshold with a transfusion trigger of haemoglobin of 7.0 g/dL is advocated. A higher haemoglobin level may be necessary in special circumstances such as acute coronary syndrome, life-threatening bleeding or acute burn injury.

Treatment of Infection

Along with adequate resuscitation, appropriate initial antimicrobial therapy is the critical determinant of survival in sepsis and septic shock. Beyond the issues related to infecting organisms and their sensitivity profile, optimal antimicrobial therapy in the critically ill includes consideration of host factors, site of infection and altered pharmacokinetics. In many circumstances, standard regimens require modification.

Appropriate Antimicrobial Therapy

The correct choice of antibiotics has consistently been associated with improved outcomes from septic shock. The empirical choice of therapy is determined amongst others by a number of variables including the site of infection, commonly encountered microbes and local antibiotic susceptibility patterns. Empirical coverage should include broad-spectrum antibiotics or a combination, which has Gram-negative aerobic and Gram-positive activity. Emergence of antimicrobial resistance, and occurrence of infection with nonbacterial pathogens, contributes to the increasing rates of treatment. Risk factors for infection with resistant organisms include prolonged hospital stay, residence in a long-term healthcare facility, prior colonisation or infection with multidrug-resistant organisms (MRO).

Timeliness of Antimicrobial Therapy

In their landmark study, Kumar et al. [16] showed that for every hour of delay in initiating appropriate antibiotic therapy for patients presenting with septic shock (from the onset of hypotension), there was an associated 8 % increase in mortality. A retrospective analysis of a large dataset from 28,150 patients with severe sepsis

and septic shock admitted to ICUs in Europe, the United States and South America demonstrated that each hour delay in antibiotic administration was associated with a linear increase of in-hospital mortality across all areas in the hospital and regardless of the level of illness severity [17].

Intravenous antibiotic therapy should therefore be started as early as possible, preferably within the first hour of recognition of severe sepsis. Any delay is likely to negatively impact on chances of survival.

Source Control

Appropriate and early source control reduces the load with infective pathogens. Accordingly, septic patients should be rapidly evaluated with integration of clinical history, physical examination, focused diagnostic tests and imaging for a possible source of infection resuscitation, infectious foci should be controlled as soon as possible with the least physiological insult possible (e.g. percutaneous and endoscopic versus surgical approach). Intravascular catheters or indwelling devices that are potential source of sepsis should be promptly recognised and removed. Early surgical intervention has been shown to have a significant impact on outcome in certain rapidly progressive infections such as necrotising fasciitis.

Supportive Care

Mechanical Ventilation

Lung-protective ventilation is an important aspect of management as sepsis is often complicated by acute lung injury. It consists of ventilating patients with tidal volumes of 6 ml/kg predicted body weight, trying to keep the airway plateau pressure below 30 cm H_2O and permitting a moderate grade of hypercapnia to reach this goal [18]. Positive end-expiratory pressure should be set to avoid lung alveolar collapse at end expiration.

Renal Replacement Therapy

Renal dysfunction in sepsis can be profound and may contribute to significant morbidity and mortality. Renal replacement therapy is the mainstay of supportive treatment of patients with severe acute kidney injury. Beyond this, it has been postulated that removing inflammatory molecules with continuous renal replacement therapy (CRRT) may be advantageous in sepsis. However, this hypothesis could not be confirmed in the pre-specified subgroup of septic patients in two large multicentre, randomised trials designed to assess two levels of intensity of renal replacement therapy in critically ill patients with acute kidney injury [19, 20].

Adjuvant Therapy

Steroids

Dysfunction of the hypothalamic-pituitary-adrenal axis in sepsis, which has been termed critical illness-related corticosteroid insufficiency, is a syndrome where the magnitude of adrenal response does not match the degree of stress. A meta-analysis of randomised controlled studies of low-dose hydrocortisone in patients with septic shock demonstrated earlier shock reversal but came to conflicting conclusions regarding survival of patients [21]. At the time of writing, the multicentre, double-blind, placebo-controlled ADRENAL (ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock) trial is randomising patients to determine whether hydrocortisone therapy reduces 90-day all-cause mortality of patients with septic shock [22].

Prognosis

Since the early 1990s, mortality rates of patients with severe sepsis enrolled in usual care arms of multicentre randomised trials and large retrospective, observational studies have steadily declined [23, 24]. The observed decrease in mortality over the past decade has occurred in the absence of novel therapeutic advances and is likely due to improved processes of care in the emergency department and the ICU. This has led to the use of sepsis care bundles, which on before-after studies have reported reductions in mortality, apparently justifying bundle validity and calling for widespread adoption. Several observational studies have demonstrated that patients with severe sepsis treated in hospitals with higher case volumes have lower case fatality rates. On the other hand, some studies provide compelling evidence to question the concept of bundling by pointing out that individual elements of these bundles other than timely administration of antibiotics do not improve patient outcome.

Despite optimal care, approximately 20–30 % of patients with severe sepsis and 30–40 % with septic shock do not survive hospitalisation. Those who die in the early stages do so of refractory hypotension and overwhelming multi-organ failure. Death later in the course of illness occurs as a result of nosocomial infections and complications of the underlying disease.

Conclusion

Severe sepsis is a condition as common as acute myocardial infarction and like coronary artery disease, it is a major source of short-term and long-term morbidity and mortality. Aggressive management of haemodynamic changes associated with

sepsis and early appropriate antibiotic therapy improve outcomes. It is likely that the greatest opportunity to improve patient outcome comes not from discovering new treatments but from more effective delivery of existing best practice therapies.

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Part IV
Respiratory System

Chapter 17
Acute Shortness of Breath

Seema O. Brij, Paul Bambrough, and D. Vijayasankar

Key Points
- Evaluate patients immediately for signs of clinical instability, e.g. stridor, tachypnoea or altered consciousness.
- The aim of oxygen therapy is to maintain SaO2 94–98 % although a target SaO2 88–92 % may be appropriate for a patient with COPD.
- PEFR measurement is a valid assessment of airway calibre and should be compared to best or predicted in known asthmatic patients.

Introduction

Acute shortness of breath is a common presenting problem among patients who attend the emergency department. It has been estimated that 3.5 % of patients have attended the emergency department in the United States with shortness of breath in 2003. In 2009, there were a total of 3.7 million emergency department visits with shortness of breath as a primary complaint [1, 2]. Although there is no specific data relating to shortness of breath, the epidemiology of cardiac and pulmonary diseases indicates that the magnitude of the problem is large.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_17

Shortness of breath is a normal symptom of heavy exertion but becomes pathological if it occurs in unexpected circumstances. In most cases, it is due to asthma, pneumonia, congestive cardiac failure, chronic obstructive pulmonary disease, interstitial lung disease, anaphylaxis, etc. Conditions such as asthma, COPD and PE are already discussed on its own as a separate chapter, and it won't be discussed in this chapter.

Definition

Acute breathlessness is the subjective experience of breathing discomfort for less than 48 h. The American Thoracic Society has defined dyspnoea as a term used to characterise a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity [3].

Pathophysiology

The pathophysiology of breathlessness is poorly understood. It is likely that breathlessness arises when there is a mismatch between the neural drive to breathe and the resulting ventilatory response. But whilst hypoxia and hypercarbia may induce 'air hunger', not all patients with abnormalities in gas exchange describe breathlessness. Moreover, most breathless patients have neither hypoxaemia nor hypercarbia. It is more likely that the presence of obstructive lung disease (asthma or COPD) and reduced lung compliance (lung fibrosis, pulmonary oedema, pneumonia) increase the work of breathing giving rise to symptoms.

Causes and Clinical Signs of Shortness of Breath

The duration of the onset of breathlessness usually helps to identify the likely cause of breathlessness (Table 17.1) and general clinical signs as described in Table 17.2.

Investigations

- Oxygen saturation (SaO2) measured by pulse oximetry can be used to assess the adequacy of oxygen therapy and the need for arterial blood gas (ABG) measurement.
- PEFR measurement is a valid assessment of airway calibre and should be compared to best or predicted in known asthmatic patients.
- Chest X-ray (Fig. 17.1) should be performed looking for the cause of acute breathlessness (infiltrates, consolidation, pneumothorax, pulmonary oedema, etc.).

Table 17.1 Timescale of onset of breathlessness and likely diagnosis

	Minutes to hours	Hours to days	Days to weeks	Weeks to months to years
Respiratory	Pneumothorax Pulmonary embolus Acute asthma	Pneumothorax Pulmonary embolus Acute asthma Pneumonia Pleural effusion	COPD exacerbation Pneumonia Pleural effusion	COPD/emphysema Lung cancer Lung fibrosis Pulmonary Hypertension
Cardiac	Myocardial infarction Acute heart failure Arrhythmias	Myocardial infarction Acute heart failure	Heart failure	Heart failure Valvular heart disease
Other	Anaphylactic shock Inhalation/choking Dysfunctional breathing Aspirin poisoning	Dysfunctional breathing Metabolic acidosis	Dysfunctional breathing Pregnancy Anaemia	Dysfunctional breathing Pregnancy Anaemia Neuromuscular weakness Obesity and deconditioning

Table 17.2 Clinical signs of respiratory distress and respiratory failure

Increased work of breathing	Systemic effects of inadequate respiration
Inspection	Inspection
Use of accessory muscles	Cyanosis
Need to sit upright	Cool clammy skin
Tracheal tug	Confusion or aggressive behaviour
Intercostal recession	Decreased GCS
Inability to speak in whole sentences	Exhaustion
	Chest pain
Auscultation	
Expiratory wheeze or stridor	Observations
Silent chest	Respiratory rate <10 or >25 breaths/minute
	Pulse rate >120 beats per minute
	SaO2 <92 % room air
	SaO2 <95 % high flow oxygen
	Systolic BP <90 mmHg
	Auscultation
	Silent chest
	Arterial blood gas
	pCO2 >6.0 kPa

Breathlessness: Causes and Management

Pneumothorax [4, 4a, 5] (Table 17.3)

Assessment and Treatment of Simple Pneumothorax

Controlled oxygen therapy should be administered with a target SaO2 94–98 % unless the patient has known COPD (target SaO2 85–92 %).

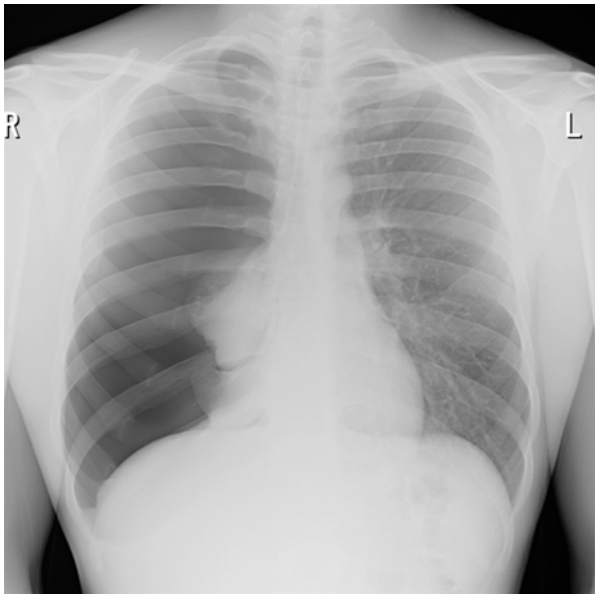

Fig. 17.1 A large spontaneous primary pneumothorax in a young man

Table 17.3 Classification of pneumothorax [4]

Spontaneous pneumothorax		Traumatic pneumothorax	
Primary (no underlying lung disease)	Secondary (underlying lung disease)	Blunt or penetrating thoracic trauma	Iatrogenic
Usually occurs in young healthy adult men 85 % patients are less than 40 years old More common in males Bilateral in 10 % of Cases Usually result of rupture of an acquired subpleural bleb – apical blebs found in 85 % of patients undergoing thoracotomy Increased frequency of spontaneous pneumothorax after each episode, but most recurrences occur within 2 years of the initial episode	10–*20 % of spontaneous pneumothorax* Can be due to: COPD (70 % cases) Asthma Interstitial lung disease Cancer including pleural metastasis Connective tissue diseases (Ehlers-Danlos syndrome, Marfan's syndrome) Infection (TB, PCP, necrotising pneumonia)	Associated rib fractures, flail chest and haemothorax	Common and occurs after: Thoracic surgery, thoracocentesis and transbronchial biopsy Other causes include: High-pressure mechanical ventilation Central venous cannulation Tracheobronchial and oesophageal injuries can cause both mediastinal emphysema and pneumothorax

Conservative Treatment

- Not all patients with small spontaneous, traumatic or iatrogenic pneumothorax are symptomatic (Fig. 17.2).
- In the case of post-procedural iatrogenic pneumothorax, a small pneumothorax may only be picked up by a routine post-procedure plain radiograph.
- If no intervention is required, patients must be followed up with a repeat radiograph to ensure that the pneumothorax has resolved and that the lung has fully expanded within 2–4 weeks.
- If the patient becomes increasingly breathless over the next few days, it is likely that the pneumothorax has increased in size and the patient must seek medical attention for an urgent assessment and chest radiograph.
- Perversely, conservative management with close observation during a hospital admission may be safer than undertaking aspiration or intercostal drainage in a patient who has a small secondary pneumothorax.

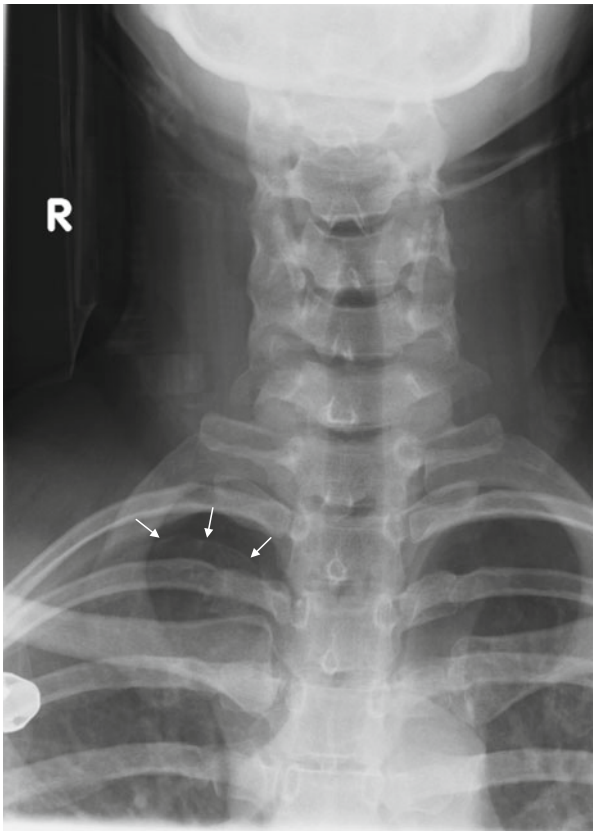

Fig. 17.2 Incidental, small traumatic pneumothorax following cervical neck injury. Pleural line is indicated by *white arrows*. This resolved without any intervention within 7 days

- Patients who have sustained a pneumothorax should be advised that they are not allowed to fly until the lung has been fully re-expanded for 1 week. Recreational sub-aqua diving is not recommended unless there has been corrective surgical repair.

Pleural Aspiration

- Even large spontaneous primary pneumothoraces (>50 %, >2 cm on plain CXR) may be treated with pleural aspiration.
- A large-bore cannula is introduced into the pleural space through a sterile field and using local anaesthesia. A three-way tap is attached to the needle and up to 2.5 L air can be aspirated.
- Aspiration can significantly reduce the size of spontaneous pneumothorax allowing the patient to have a minimally invasive intervention that reduces the risk of morbidity associated with an intercostal drain insertion and hospital admission.
- Aspiration can also be considered in small spontaneous secondary pneumothorax dependent upon the degree of symptoms and the extent of underlying lung abnormality.
- If the lung does not re-expand, it implies that the air leak is larger than the ability to aspirate air from the pleural space and an intercostal drain is required.
- It is advisable to admit patients following successful aspiration for secondary pneumothorax and to repeat the chest radiograph within 24 h.

Intercostal Drainage

- Patients with symptomatic large primary or secondary pneumothorax require intercostal drainage. If the secondary pneumothorax is small, or there is plain radiograph evidence that there is pleural adherence to a part of the chest wall, it is not safe to undertake a 'blind' procedure, and an intercostal drain placed under CT guidance by an interventional radiologist may be required.
- The intercostal drain should be placed in the 'triangle of safety' (pectoralis major anteriorly, latissimus dorsi posteriorly, and a line superior to the horizontal level of the nipple inferiorly).
- A small-bore Seldinger drain (12–18 F) is introduced into the pleural space through a sterile field and using local anaesthesia. A three-way tap is attached to the intercostal drain before being connected to an underwater seal.

Pleurodesis and Thoracic Surgery

- The definitive treatment for pneumothorax is pleurodesis which obliterates the pleural space and adheres the lung to the chest wall. Pleurodesis can be performed medically with talc slurry administered through an intercostal drain.

Other Respiratory Causes of Acute Shortness of Breath

There are some conditions, such as pneumonia, where patients may have had systemic symptoms for a while, but breathlessness occurs late in disease presentation.

Patients with chronic lung disease such as COPD/emphysema, bronchiectasis and fibrotic lung disease have exacerbations where breathlessness worsens suddenly, usually in association with infections.

Pneumonia [7]

Aetiology

- The commonest aetiology is infective, usually bacterial, although viral and fungal pneumonia is increasingly recognised especially in the immunocompromised patient.
- Inflammatory pneumonia such as eosinophilic pneumonia is not infective in aetiology and is treated with oral corticosteroid.
- Likewise, injurious pneumonia such as that caused by aspiration of gastric contents is only in part an infective process.

Risk Factors

- Increasing age
- Smoking
- Pre-existing lung disease
- Diabetes
- Chronic kidney disease
- Alcoholism
- Immunocompromise and recent influenza

Classifications

- Most widely accepted is community versus hospital-acquired pneumonia.

Community-Acquired Pneumonia (CAP) [8]

- The commonest organism identified in this group is *Streptococcus pneumoniae* (approximately 40 %). Other organisms include *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, influenza A and B, *Haemophilus influenzae* and *Legionella* species in descending order of frequency.

- The identification of *Staphylococcus aureus* or Gram-negative bacilli is infrequent and accounts for less than 2 % of organisms identified.
- The incidence of CAP is 5–11 per 1,000 population [6] and varies with age with the highest incidence in the very young and the elderly. CAP patients requiring admission have a mortality of 5–15 %, and 1–10 % will require admission to the intensive critical care unit.

Hospital-Acquired Pneumonia (HAP)

Hospital-acquired pneumonia is defined as pneumonia that develops 48 h or more after admission to hospital and was not incubating at the time of admission. HAP affects up to 1.0 % of inpatients and is thought to increase the length of stay by 7–9 days.

- The commonest organisms identified are *Staphylococcus aureus* (20–30 %), *Pseudomonas* spp. (20 %), *Escherichia coli* (5–15 %) and *Klebsiella* spp. (5–10 %). These organisms are also more likely to be highly resistant to antibiotics.

Common Symptoms

- Cough.
- Sputum production.
- Breathlessness.
- Pleurisy and fever.
- Confusion without hypoxaemia is frequently encountered in the elderly patient.
- In the young adult, breathlessness may be a late presenting feature, and myalgia and flu-like symptoms may predominate.

Assessment and Treatment of Pneumonia

Pneumonia can be diagnosed if there are symptoms and signs consistent with acute lower respiratory tract infection and new radiological findings consistent with infection that cannot be explained by another pathology such as pulmonary oedema or infarction.

Radiology

- Plain chest radiograph usually reveals focal or diffuse opacities consistent with airspace shadowing or infiltrates. The hallmark of consolidation is an air bronchogram (air-filled bronchi made visible by surrounding consolidated/infiltrated lung tissue).

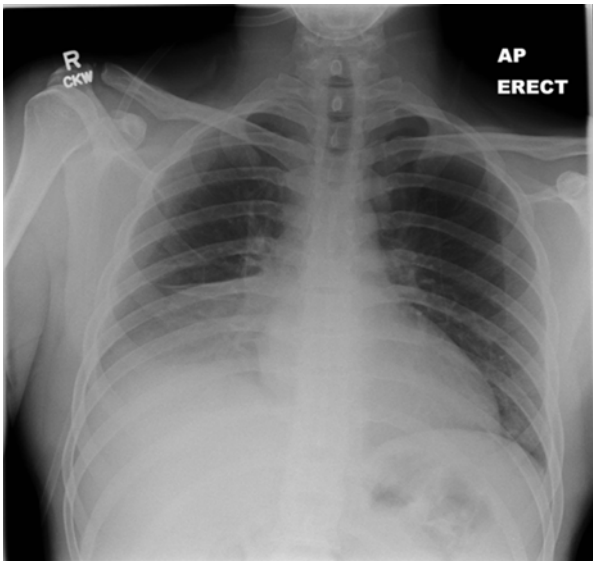

Fig. 17.3 Right lower zone shadowing with loss of the right hemi-diaphragm consistent with consolidation in a young man with community-acquired pneumonia

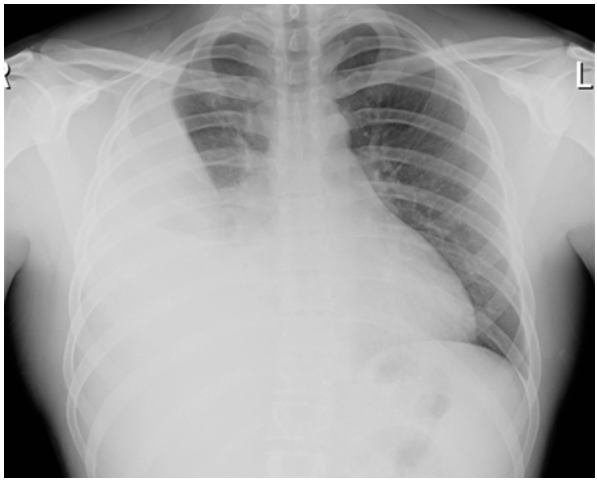

Fig. 17.4 Parapneumonic effusion secondary to community-acquired pneumonia that required intercostal drainage and surgical debridement

- Other findings on CXR that suggest the presence of pneumonia include silhouette sign (e.g. loss of outline of the right hemi-diaphragm indicates pathology in the right lower lobe) (Fig. 17.3) and pleural effusion (parapneumonic effusion) (Fig. 17.4).
- Complications of pneumonia may be apparent such as atelectasis, lung abscess and, more rarely, pneumothorax.

Laboratory

- Differential white cell count.
- Inflammatory indices such as C reactive protein.
- Electrolytes to look for acute kidney injury and urea to help in assessment of severity of pneumonia.
- Sputum as well as blood cultures to identify aetiological pathogen.
- Serological testing (*Mycoplasma*, *Chlamydophila*, *Coxiella*, influenza) should be undertaken in all cases of severe CAP.
- Urinary streptococcal and legionella antigen should be undertaken in all cases of moderate and severe CAP.
- It is recommended that HIV serology is undertaken in all adults admitted with CAP.
- If pulmonary tuberculosis is suspected, sputum examination for acid-fast bacilli is essential.

Severity Assessment

The severity of pneumonia is important to assess at presentation. The most widely used severity index for patients with CAP admitted to the hospital is the CURB-65 (Table 17.4), and increasing scores correlate with increasing mortality rates. However, clinical judgement must also be used in the interpretation of this score as younger adults can be very unwell with low CURB-65 values.

Treatment

- Antibiotic treatment for pneumonia is empirical, based on the likelihood of the aetiological pathogen and local guidelines to account for pathogenic resistance.

Table 17.4 CURB-65 [7]

Score 1 for each of the following:	
*C*onfusion (GCS <8 or new disorientation in time, manner, place)	
*U*rea (>7 mmol/L)	
*R*espiratory rate >30 per minute	
*B*lood pressure (systolic <90 mmHg and /or diastolic <60 mmHg)	
Age >*65* years	
Score	*Mortality (%)*
0	0.6
1	3.2
2	3.0
3	17.0
4	41.5
5	57.5

- Different hospitals have antibiotic guidelines specifically for CAP and HAP, including recommendations based on severity, patients with penicillin allergy or intolerance, for co-infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and in the neutropenic or immunocompromised host.
- Once the diagnosis of pneumonia is suspected or confirmed, it is important to treat with empirical antibiotic therapy and fluid resuscitation with crystalloid if appropriate.
- Supportive therapy with CPAP in patients deemed not suitable for mechanical ventilation is now widely accepted best medical practice.

Pleural Effusions

It is unusual for pleural effusions to develop rapidly and cause acute breathlessness. However, conditions such as pneumonia, heart failure and lung cancer may be complicated by pneumonia, and a therapeutic aspiration in the ED may alleviate symptoms.

Acute Aspirin Overdose

In acute aspirin overdose, as well as nausea, vomiting and tinnitus, there may be hyperventilation. This occurs because the uncoupling of cellular oxidative phosphorylation stimulates the respiratory centre in the medulla causing primary respiratory alkalosis. In addition, acute aspirin poisoning induces a metabolic acidosis which may also cause a secondary respiratory alkalosis.

Kussmaul's Breathing or Air Hunger

As metabolic acidosis worsens, respiratory compensation to 'blow off' carbon dioxide occurs and was first described by the German physician Adolph Kussmaul who recognised this phenomenon in patients suffering with severe diabetic ketoacidosis. Air hunger is observed in all forms of severe metabolic acidosis, and the arterial blood gas analysis will reveal decreased PCO2 with decreased [HCO^{3-}] and a negative base excess.

Hyperventilation Syndrome or Dysfunctional Breathing

Hyperventilation or dysfunctional breathing is a diagnosis of exclusion, and it is important to investigate acute breathlessness to ensure that another cause of breathlessness such as PE has not been missed.

Symptoms

- Breathlessness at rest without any evidence of cardiopulmonary disease
- Tingling in the extremities and perioral paraesthesia
- Chest pain
- Dizziness

Calculating the A-a gap (the difference between the alveolar concentration of oxygen and the arterial concentration of oxygen) ensures that a cause of hypoxaemia is not missed.

To further complicate matters, hyperventilation is common in persons with mild respiratory disease. A good example of this can be seen in patients with mild asthma who can reduce their inhaled therapy when they undertake Buteyko [9, 10] breathing exercises, a form of breathing control.

Treatment

- Removal of the stressor (if possible) and removal of oxygen.
- Rebreathing air (breathing in and out of a brown paper bag) resolves low end-tidal blood carbon dioxide levels. This should only be undertaken for 6–12 breaths at a time as hypoxia can be induced if undertaken for prolonged periods.
- The treatment for dysfunctional breathing is education and physical therapy (exercise and breathing control).

Cardiac Causes of Acute Dyspnoea

Acute changes in cardiac physiology can lead to breathlessness either as a result of decreased cardiac output leading to tissue hypoxia and hypercarbia thus triggering an increased respiratory rate as compensation or as a result of pulmonary oedema, which may also cause tissue hypoxia but also stimulates breathlessness by decreasing lung compliance. The underlying causes of each broad pathophysiological mechanism (i.e. pulmonary oedema or non-oedema) can overlap but can be broadly categorised as acute myocardial ischaemia or dysfunction (e.g. myocarditis), arrhythmia and mechanical valve dysfunction.

Acute Pulmonary Oedema

Any cause of acutely increased left ventricular filling pressure (LVFP) may result in pulmonary oedema. The increase in preload leads to inefficient pump function, hence reduced stroke volume and an increase in total peripheral resistance, which

further reduces stroke volume. Therefore, effective treatment strategies rely on reducing the preload or peripheral resistance.

Chest radiograph usually reveals upper lobe blood diversion with perihilar shadowing and, less commonly, small (bilateral) pleural effusions and/or Kerley B-lines.

Clearly time delayed on a lengthy history and examination approach will lead to the harm of the patient, and therefore, a treatment and simultaneous differential generation approach is advised in all guidelines [11].

Treatment of Acute Pulmonary Oedema

The primary treatment modalities are:

- Oxygen
- Diuretics
- Opiates
- Nitrates

Non-invasive Ventilation (NIV)

It has long been thought that negative intrathoracic pressure reduces left ventricular function by increasing transmural pressures and therefore afterload. Whilst there may be symptomatic benefit in dyspnoea scores using non-invasive ventilation (NIV) such as continuous positive airway pressure (CPAP), there is no definite improvement in overall mortality.

Other Cardiac Causes of Acute Breathlessness

Myocardial Infarction (MI) [12, 13]

Myocardial infarction can also cause breathlessness, likely due to an element of tissue hypoxia. The key management step is identification of the type of myocardial infarction, either with ST segment elevation (STEMI) with high risk of transmural infarction or without ST segment elevation (non-STEMI or NSTEMI).

For a STEMI presentation, the key management step is prompt administration of antithrombotic medications (dual antiplatelet medication and heparin), together with prompt revascularisation. Primary percutaneous intervention (PPCI) has been reliably demonstrated to be superior to thrombolysis for revascularisation both in terms of physiologic indices, incidence of heart failure and mortality, as long as its timing is not too prolonged when thrombolysis is a valid alternative. In addition, in those with shock or pulmonary oedema, PPCI has added benefit.

Arrhythmias

Arrhythmias can lead to decreased cardiac output and tissue hypoxia leading to increased respiratory rate and a sensation of breathlessness. In addition, arrhythmias are also a cause of pulmonary oedema, which must be screened for during the management of acute pulmonary oedema (APO).

When a tachyarrhythmia is present, a low systolic blood pressure or pulmonary oedema requires rapid conversion [14] to sinus rhythm by DC cardioversion in many cases. If more time can be taken, identification of the arrhythmia as broad or narrow and identification of its rhythm will guide further medical therapy [14].

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Chapter 18
Bronchial Asthma

G. Krishna Prasad, Prakash E. George, and Jebu A. Thomas

Key Points

- A clinical diagnosis of asthma should be suspected in patients with intermittent symptoms of wheezing, coughing, chest tightness and breathlessness.
- Objective measurements of lung function, preferably using spirometry or peak flow meters, are needed to confirm the diagnosis.
- All asthma patients presenting with an acute episode should be given a rapid-acting bronchodilator for rapid relief of symptoms.
- Other add-on therapies for acute management include systemic corticosteroids, ipratropium bromide, etc., to be instituted according to the severity of Asthma.
- Close monitoring and reassessment at frequent intervals holds the key in the proper management of acute asthma.

Introduction

Asthma is a highly prevalent disease that presents commonly to the emergency department (ED) in an acute exacerbation and is one of the five respiratory conditions that account for a great burden to the society, the others being COPD, acute respiratory infections, TB and lung cancer [1, 2].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_18

The most recent revised global estimate of asthma suggests that as many as 334 million people have asthma and that the burden of disability is high [3, 4].

The National Heart, Lung, and Blood Institute, USA, summarises the current understanding of asthma as 'Asthma is a complex disorder characterised by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation. The interaction of these features determines the clinical manifestations and severity of asthma and the response to treatment" [5].

Pathophysiology

- The pathophysiology of asthma is complex and involves the following components:
  - Airway inflammation
  - Intermittent airflow obstruction
  - Bronchial hyperresponsiveness
- In an airway there is normally a fine balance between immune cells, the epithelium and the host immune response. Airway inflammation in asthma reflects a distortion of this balance, and it's orchestrated through complex interplay between multiple effector and target compounds. Allergens and nonallergic stimuli (e.g. exercise, aspirin induced and menstrual related) induce bronchoconstriction via release of mediators and metabolic products from inflammatory cells [6, 7].
- The effector cells include mast cells, basophils, dendritic cells, T lymphocytes, eosinophils and neutrophils. Airway inflammation in asthma may represent a loss of normal balance between two 'opposing' populations of Th lymphocytes.
- Among the T lymphocytes, two types of T-helper (Th) lymphocytes have been characterised: Th1 and Th2. Th1 cells produce interleukin (IL)-2 and IFN-α, which are critical in cellular defence mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, IL-5, IL-6, IL-9 and IL-13) that can mediate allergic inflammation [6].
- The recent 'hygiene hypothesis' of asthma illustrates how Th1/Th2 cytokine imbalance may explain some of the dramatic increases in asthma prevalence in westernised countries [7].
- Subgroups of asthma patients develop airflow obstruction that is irreversible or only partially reversible and experience an accelerated rate of lung function decline. The structural changes in the airways of these patients are referred to as 'airway remodelling.'
- In airway remodelling, all elements of the airway wall are involved, and remodelled airway wall thickness is substantially increased compared to normal control airways. It is thought to contribute to the sub-phenotypes of irreversible

airflow obstruction and airway hyperresponsiveness, and it has been associated with increased disease severity [8].

Diagnosis

Diagnosis of asthma is based on [9, 10] two factors, namely:

1. *Assessment of symptoms and signs*
   - Symptoms that increase the probability of having asthma [9, 10]:
     - More than one symptom (wheeze, shortness of breath, cough, chest tightness)
     - Symptoms often worse at night or in the early morning.
     - Symptoms vary over time and in intensity.
     - Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter or irritants such as car exhaust fumes, smoke or strong smells.
   - Symptoms that decrease the probability of having asthma [9, 10]:
     - Isolated cough with no other respiratory symptoms
     - Chronic production of sputum
     - Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paraesthesia)
     - Chest pain
     - Exercise-induced dyspnoea with noisy inspiration
2. *The severity of airflow obstruction – which is measured with spirometry peak expiratory flow rate* (*PEFR*) [9, 10]:
   - Spirometry (FEV_1/FVC) is preferable rather than peak expiratory flow (PEFR), because it allows clear identification of airflow obstruction, and the results are less dependent on effort. In addition, a normal spirogram or PEFR obtained when the patient is not symptomatic doesn't exclude the diagnosis of asthma.

Differential Diagnosis

According to the presence or absence of airflow obstruction (FEV_1/FVC <0.7):

- Without airflow obstruction [10]:
  - Chronic cough syndromes
  - Hyperventilation syndrome

  - Vocal cord dysfunction
  - Rhinitis
  - Gastroesophageal reflux
  - Cardiac failure
  - Pulmonary fibrosis
- With airflow obstruction [10]:
  - COPD
  - Bronchiectasis
  - Inhaled foreign body
  - Obliterative bronchiolitis
  - Large airway stenosis
  - Lung cancer
  - Sarcoidosis

Initial Assessment of Acute Asthma

- Airway, breathing and circulation to be addressed first, if there is any compromise [9].
- After a quick assessment a brief history, physical examination and peak expiratory flow rate (PEFR).
- Measurements of airway calibre improve recognition of the degree of severity, the appropriateness or intensity of therapy and decisions about management in hospital or at home.
- PEFR should be assessed before commencing treatment, but sometimes it may be unreliable due to poor coordination and distress.
- Percentage of predicted performance values is preferable over absolute measurements to account for age, sex and height. Predicted PEF to be used only if recent personal best (within 2 years) is unknown.
- Pulse oximetry: Measure oxygen saturation (SpO_2) with a pulse oximeter to determine the adequacy of oxygen therapy and the need for arterial blood gas (ABG) measurement. The aim of oxygen therapy is to maintain SpO_2 94–98 %.
- Blood gases (ABG): Patients with SpO_2 <92 % (irrespective of whether the patient is on air or oxygen) or other features of life-threatening asthma require ABG measurement.
- Chest X-ray is not routinely recommended in patients in the absence of:
  - Suspected pneumomediastinum or pneumothorax
  - Suspected consolidation
  - Life-threatening asthma
  - Failure to respond to treatment satisfactorily
  - Requirement for ventilation

Severity of Asthma Classification (Table 18.1)

Treatment

All treatments of acute asthma are based on the severity (Appendix), and we have briefly described generic and specific treatments available for patients presenting with asthma as below:

1. *Oxygen*
   - Supplementary oxygen is administered via a nasal cannulae or face mask or non-rebreathing mask or venturi mask.
   - Controlled low-flow oxygen using pulse oximetry to maintain the saturation between 94 % and 98 % has proven to have better physiological outcome than high-flow 100 % oxygen therapy [10].
2. *Inhaled short-acting beta$_2$ agonist*
   - High-dose inhaled beta$_2$ agonist (salbutamol 5 mg in 3-ml saline repeated every 15–30 min [10, 11]) via oxygen-driven nebuliser is the first-line agent and be administered as early as possible in acute severe asthma. However, absence of supplemental oxygen should not prevent the administration of beta$_2$ agonist.

Table 18.1 Levels of severity of attacks

Moderate asthma	Increasing symptoms	
	PEF >50–75 % best or predicted	
	No features of acute severe asthma	
Acute severe asthma	Any one of:	
	PEF 33–50 % best or predicted	
	Respiratory rate ≥25/min	
	Heart rate ≥110/min	
	Inability to complete sentences in one breath	
Life-threatening asthma	Any one of the following in a patient with severe asthma	
	Clinical signs	**Measurements**
	Altered conscious level	PEF < 33 % best or predicted
	Exhaustion	SpO_2 < 92 %
	Arrhythmia	PaO_2 < 8 kPa
	Hypotension	'Normal' $PaCO_2$ (4.6–6.0 kPa)
	Cyanosis	
	Silent chest	
	Poor respiratory effort	
Near-fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures	

PaO_2 partial arterial pressure of oxygen, *kPa* kilopascals, *$PaCO_2$* partial arterial pressure of carbon dioxide

- If there is inadequate response to initial treatment, then continuous nebulisation with 5–10 mg salbutamol in 70-ml isotonic saline over an hour can be administered, but this may require an appropriate large volume nebuliser [10–12].
- Handheld pMDI (pressurised metred-dose inhaler) with an appropriate large volume spacer is as effective as nebuliser in mild to moderate exacerbation but not in severe, life-threatening, and near-fatal asthma [9, 10, 12].
- Salbutamol four puffs initially and two puffs every 2 min according to the response up to a maximum of ten puffs (pMDI 100 mcg/puff) [10, 12] is recommended in mild to moderate asthma.
- The role of intravenous $beta_2$ agonists in patients with severe asthma is questionable, and it cannot be used as a routine in managing severe asthma or as a first-line treatment [10].

3. *Ipratropium bromide*

- Short-acting anticholinergic when used along with short-acting $beta_2$ agonist has resulted in fewer hospitalisation and greater improvement in PEF and FEV_1 when compared to the administration of short-acting $beta_2$ agonist alone [9].
- Onset of action is approximately 60 min [13], and it's not as fast acting or not as potent as SABA (short-acting beta agonist) but has a longer duration of action and better side effect profile.
- Ipratropium bromide 500 mcg via oxygen-driven nebuliser at 15-min interval for three times followed by fourth hourly [10, 12].

4. *Epinephrine* [9, 14]

- Intramuscular epinephrine (0.5 mg or 0.5 ml of 1:1,000) is indicated in addition to standard therapy when associated with anaphylaxis and angioedema, which can be repeated every 5–15 min.

5. *Steroid therapy* [9, 10]

- Steroids to be utilised in all except mild exacerbation, and it requires at least 4 h to produce an initial clinical improvement.
- It decreases mortality, relapses, hospital admissions and $beta_2$ agonist requirement.
- Oral corticosteroids (OCS) are as equally effective as intravenous, so intravenous corticosteroids can be administered when patient is too dyspnoeic to swallow or is vomiting or when patient requires noninvasive ventilation or intubation.
- Prednisolone 40–50 mg per oral and it needs to be continued for a period of 5–7 days or hydrocortisone 100 mg intravenous followed by 200 mg in divided doses for 5–7 days.
- If there is concern regarding adherence to oral therapy, the patient can be given methylprednisolone 160 mg as intramuscular injection and be discharged.

6. *Magnesium sulphate* [9, 10]
   - Magnesium sulphate (2-g infusion over 20 min) is used in patient with acute severe asthma who fails to respond to initial treatment and who is having persistent hypoxaemia.
   - Single dose of intravenous magnesium sulphate is safe and may improve lung function, decrease intubation rates and reduce hospital admissions in acute severe asthma.
7. *Antibiotics* [10, 15]
   - There is no role for routine use of antibiotics.
   - Antibiotics can be used if the patient has additional signs and symptoms of lower respiratory tract infection.
8. *Intravenous fluids* [10]
   - Some patients may require rehydration and electrolyte imbalance.
   - Hypokalaemia to be corrected as it can be caused or exacerbated by beta$_2$ agonist and/or steroid treatment.
9. *Noninvasive positive pressure ventilation* [16]
   - NPPV is another treatment modality that may be beneficial in patients with severe asthma exacerbation who are at increased risk of developing respiratory failure.
   - Limited evidence suggests that it has a direct bronchodilating effect, recruits collapsed alveoli, improves ventilation/perfusion mismatch and reduces work of breathing.
   - Can be applied in patient who have or at risk of severe asthma attack.
10. *Invasive ventilation* [17]
    - Can be considered in patient with worsening hypoxia or hypercapnia, who is drowsy or unconscious and no response to medical management.
    - Parameters to be considered are severity of airflow limitation (PEF), degree of respiratory difficulty (inability to talk, respiratory rate >40/min), clinical findings (accessory muscle use, intercostal retraction, fatigue, somnolence), oxygenation, arterial tension of carbon dioxide ($PaCO_2$) and response to treatment.

Complications [9, 18]

Respiratory complications	Systemic complications
Pneumothorax	Electrolyte abnormalities (hypokalaemia, hypophosphataemia, hypomagnesaemia)
Pneumomediastinum	Lactic acidosis
Mucous plugging	Anoxic brain damage
Atelectasis	

Discharge Management

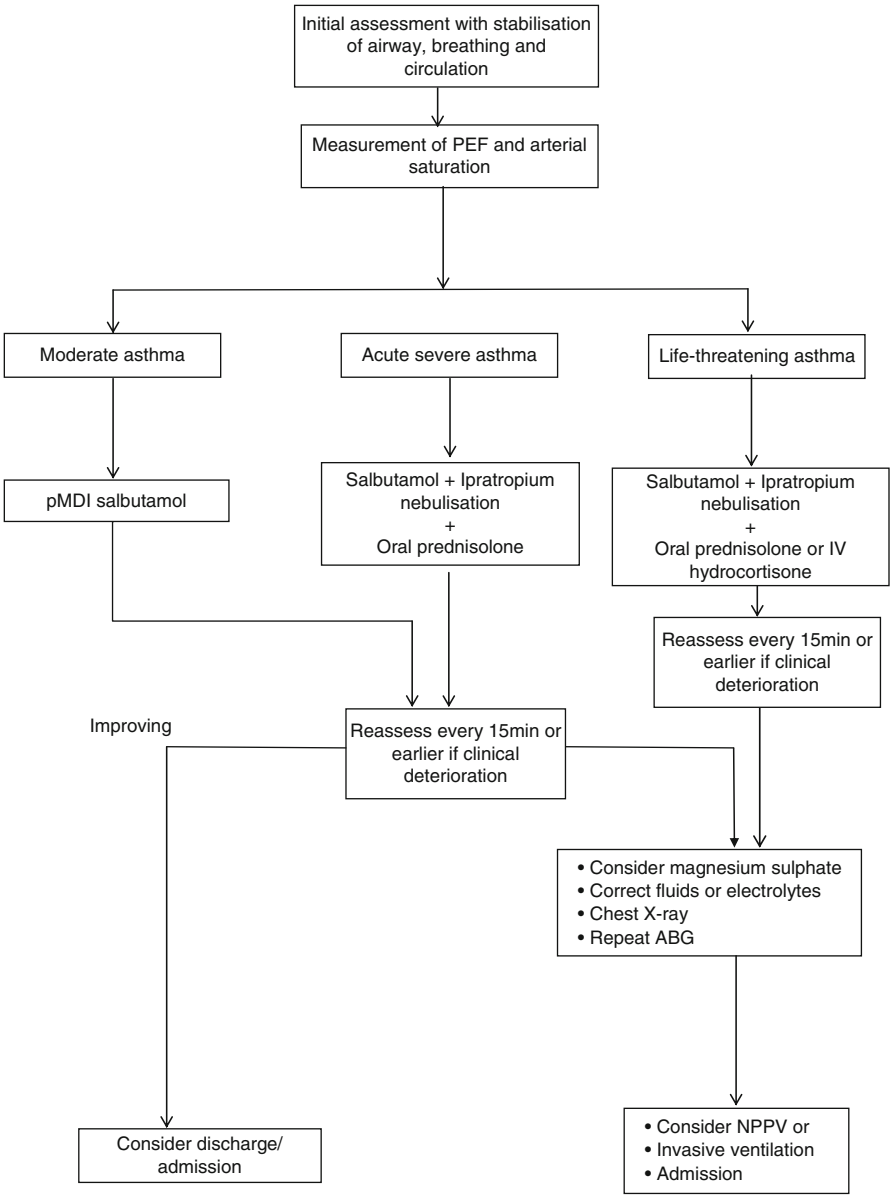
1. *Patient Education* [9]
   - Patients are to be trained in using the inhaler with spacer effectively.
   - Patients should be taught how to self-monitor his/her symptoms and how to use the peak flowmeter as an effective tool in deciding whether to escalate treatment options if necessary.
   - A written action plan is given to all patients who present with exacerbation.
   - Regular review which includes 1 week after an exacerbation, 1–3 months after commencing treatment and thereafter every 3–12 months.
2. *Nonpharmacological management* [5, 9]
   - Advise smoking cessation and to avoid exposure to tobacco smoke.
   - Breathing techniques are to be promoted as an adjuvant to pharmacotherapy.
   - Regular physical exercise are to be encouraged, but make them aware of exercise-induced asthma and, if present, should be treated promptly.
   - Advise weight reduction in patients who are obese.
   - Occupational exposure, if there is any, to be avoided.
   - Urge them to use nonpolluting cooking and heating sources to prevent exposure from indoor and outdoor pollution.
   - In confirmed food allergy, the particular food should be avoided to reduce exacerbations.
   - Medications: NSAIDs and aspirin should be avoided if the patient had previous episodes of reactions to these. In an acute coronary event, use cardioselective beta blockers.

Conclusion

Management of an acute exacerbation of asthma does not end in the ED, and it is important for the patient to be followed up as well as provided with adequate information in avoiding the triggers as well as preventing further exacerbations.

PEFR response after treatment can be used as a benchmark tool for deciding whether the patient can be sent home or not. Whenever required, patient can be admitted after initial stabilisation and treatments are continued until the symptoms are controlled.

Appendix: Clinical Pathway



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Chapter 19
Chronic Obstructive Pulmonary Disease (COPD)

Seema O. Brij, Sumit Chatterji, and Malcolm Marquette

Key Points

- COPD is a major global health problem and is predicted to be the third commonest cause of death worldwide by 2030.
- COPD is characterised by airflow obstruction that is slowly progressive and persistent. This is easily measurable with spirometry, and the rate of decline in FEV1 predicts morbidity and mortality.
- Severity of COPD is based upon a combination of factors including symptoms, functional disability, rate of decline of FEV1, presence of respiratory failure, the number of exacerbations and whether they require hospital admission.
- Stopping smoking continues to be the most cost-effective way of preventing COPD.

Introduction

COPD is characterised by airflow obstruction that is not fully reversible and is persistent and usually progressive. COPD is underdiagnosed, especially in the early stages, because symptoms may not be apparent until the development of significant airflow obstruction.

COPD produces symptoms, disability and impaired quality of life which may respond to pharmacological and other therapies that have limited or no impact on

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_19

Table 19.1 Definitions of conditions associated with airflow obstruction

Condition	Definition
Chronic obstructive pulmonary disease (COPD)	Airflow obstruction that is usually progressive, not fully reversible and does not change markedly over several months. It is usually caused by smoking
Chronic bronchitis (CB)	Presence of chronic cough productive of sputum on most days for 3 months in each of 2 consecutive years, and other causes of productive cough have been excluded
Emphysema	Abnormal, permanently enlarged distal airspaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls and without obvious fibrosis
Asthma	Airflow obstruction that is usually nonprogressive, fully reversible and changes in its severity over short periods of time either spontaneously or after treatment

the extent of airflow obstruction. COPD is now the preferred term that encompasses conditions previously known as chronic bronchitis and/or emphysema (Table 19.1).

Epidemiology

COPD is a common respiratory disorder affecting over 65 million people worldwide [2]. The prevalence of COPD increases with age, with a fivefold increased risk for those aged over 65 years compared with patients aged less than 40 years.

Mortality

According to the World Health Organization, COPD is the fourth leading cause of death in the world, with approximately 2.75 million deaths per annum, or 4.8 % of deaths [2].

Mortality from COPD is higher in males and increases with age in those over 45 yrs old.

Factors predictive of mortality:

- Severity of airflow obstruction (e.g. using GOLD [3] criteria)
- Nutritional status (body mass index)
- Exercise capacity using the 6-min walk test
- Severity of dyspnoea (using a dyspnoea functional scale such as the modified MRC scale (Table 19.2)), social status and poverty

Composite indices such as the commonly used BODE index [4] (*B*MI, severity of airflow *O*bstruction, severity of *D*yspnoea, 6-min walk *E*xercise distance) try to prognosticate using these factors and are often utilised by transplant teams to determine the timing of lung transplantation.

Table 19.2 The modified MRC Dyspnoea Scale

Grade	Degree of breathlessness related to activity
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground, *or*
	I get short of breath when walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, *or*
	I have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking about 100 yards, *or*
	I stop for breath after a few minutes on level ground
4	I am too breathless to leave the house, *or*
	I am breathless when dressing

Risk Factors

The development of COPD is dependent upon the inhalation of noxious agents in a susceptible host.

Host Factors

- Genetic mutations (e.g. α_1 anti-trypsin deficiency)
- Airway hyperresponsiveness
- Reduced lung growth

Exposures

- Smoking (cigarettes, cigars, shisha, marijuana, heroin)
- Indoor and outdoor pollution
- Occupational dusts and chemicals
- Infections

Pathological Findings

The chronic inhalation of noxious particles incites inflammation in the lungs. This becomes exaggerated and uncontrolled, resulting in mucus hypersecretion (chronic bronchitis), progressive tissue destruction (emphysema) and a disordered repair mechanism (bronchiolitis). The result is the clinical syndrome of COPD: small airways become narrowed increasing resistance to airflow; the lungs are less elastic

with increased compliance; there is air-trapping (hyperinflation); and the changes are dose dependent and persistent, even following smoking cessation.

Pathological changes are predominantly seen in the airways but can also be seen in the lung parenchyma and also in the pulmonary vasculature.

Pathogenesis of COPD

Pulmonary injury involves stages of *initiation* (through exposure to injurious agents), *progression* and *consolidation*. The underlying pathology in COPD can be summarised as mucus hypersecretion, alveolar damage caused by proteolysis and apoptosis and subepithelial airway fibrosis.

Symptoms of COPD

Common

- Exertional breathlessness
- Chronic cough
- Sputum production
- Frequent chest infections or winter bronchitis
- Wheeze

Associated Symptoms

Weight loss and tiredness

Uncommon Symptoms

Haemoptysis, chest pain and significant weight loss and other disorders such as lung cancer, bronchiectasis and TB may need to be excluded.

Unfortunately, the presence of symptoms is not a reliable indicator of COPD, and diagnosis is often missed until more severe airflow obstruction is present.

Signs of COPD

Physical examination of persons with COPD, especially early in the disease process, is often normal.

Inspection may reveal tar-stained fingers in a heavy smoker who may also smell of cigarette smoke. Other signs such as cyanosis (peripheral and central), pursed-lipped breathing (which increases expiratory airway pressure preventing premature airways collapse), use of accessory muscles of respiration (scalene and sternocleidomastoid) and barrel-shaped chest (increased anterior posterior diameter indicating hyperinflation) with reduced expansion may be present. Auscultation may reveal vesicular breath sounds. Reduced breath sounds with or without wheeze are also a feature.

Signs of advanced COPD are usually related to the presence of cor pulmonale, defined as right ventricular hypertrophy caused by any chronic lung disease and is therefore not specific to COPD. Signs of right heart failure include raised jugular venous pressure, right ventricular heave, palpable thrill or loud P_2 heart sound, tricuspid regurgitation (pulsatile liver and mild jaundice) and pitting oedema.

Investigation of COPD

Spirometry

In order to confirm the diagnosis, a post-bronchodilator FEV1/FVC ratio of less than 0.7 must be present. The severity of airflow obstruction can be assessed according to the reduction in FEV1 (Table 19.3). Thus, by performing spirometry over a long period of time, it is possible to monitor lung function decline. The rate of decline in FEV1 is a good marker of disease progression and mortality.

Spirometry should be performed in patients who are over 35, are current or ex-smokers and have a chronic cough.

Further Investigations

- A plain chest radiograph (Fig. 19.1) – hyperexpansion (greater than eight posterior or six anterior ribs clearly visible), flattened diaphragms, long thin heart, prominent hilar vessels and barrel-shaped thorax.

Table 19.3 Severity of airflow obstruction

FEV1/FVC	FEV1 % predicted	Severity
<0.7	≥80	Mild[a]
<0.7	50–79	Moderate
<0.7	30–49	Severe
<0.7	<30	Very severe[b]

[a]Symptoms should be present to diagnose COPD with mild airflow obstruction [1]

[b]Or FEV1 <50 % with respiratory failure

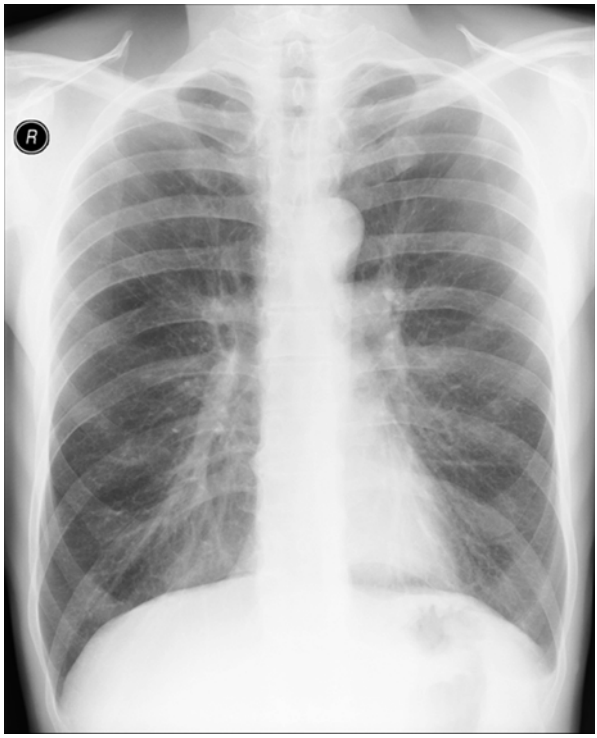

Fig. 19.1 CXR–COPD changes

- Full blood count is useful to ensure that there is not anaemia contributing to breathlessness symptoms nor polycythaemia related to hypoxaemia. A raised eosinophil count should always raise the possibility of asthma.
- Other useful investigations and their rationale are enumerated in Table 19.4.

Stable COPD Management

The management of stable COPD is a holistic approach to disease and symptom modification. The principles are outlined as four tenets of COPD management (Table 19.5).

Pharmacological Therapies for COPD

1. *Inhaled bronchodilators*
   - *Short-acting β_2-agonists* (*SABA*) such as salbutamol act on airway smooth muscle through β_2-adrenergic receptor agonism resulting in bronchial smooth muscle relaxation and therefore airway dilatation. The onset of airway dilatation is minutes with a duration of action up to 6 h. Short-acting

Table 19.4 Other useful investigations

Investigation	Rationale for testing
Peak flow diary exercise	Variable airflow obstruction is more likely to be asthma
α_1 anti-trypsin levels	Early onset COPD, minimal smoking history or family history
Transfer factor (TLCO)	To investigate symptoms that seem disproportionate to the impairment in FEV1
Chest CT	To investigate
	(a) Symptoms that seem disproportionate to the impairment in FEV1
	(b) Abnormalities seen on a chest radiograph
	(c) Extent and distribution of structural parenchymal and airways disease
ECG	Exclude arrhythmia and look for evidence of cor pulmonale
ECHO	Exclude significant LVD, valvular abnormalities and look for evidence of cor pulmonale
Pulse oximetry	Screen for hypoxaemia (suggestive if SaO_2 <92 %)
Sputum culture	Identify resistant or unusual organisms if sputum is persistent and purulent

Table 19.5 The four tenets of COPD management

Tenet	Theory	Practice
1. Stop smoking	Smoking is the most important aetiology for the development of COPD	Tobacco legislation
	Smoking cessation is the only proven way of modifying the natural course of COPD	Smoking cessation
2. Keep fit	Regular exercise training conditions the muscles and reduces the ventilatory demand of exercise	Pulmonary rehabilitation [5] should be undertaken and repeated if necessary
		COPD patients should be encouraged to keep as active and fit as possible
		Smoking cessation
3. Multidisciplinary patient-focused care	Good understanding of disease process, collaborative approaches to pharmacotherapy and regular review by highly motivated COPD team ensure high-quality care and favourable patient satisfaction	Smoking cessation
		Inhaler technique assessment
		Assess response to pharmacotherapy and amend/discontinue as required
		Yearly spirometry, BMI, flu vaccination
4. Self-management of exacerbations	Early identification of symptoms such that COPD patients are empowered to initiate empirical therapy thereby reducing severity of exacerbations	Rescue medication (antibiotics and oral corticosteroid therapy)
		SOS access to COPD team
		End of life and advanced care plan

β_2-agontists are therefore used as rescue medication to treat symptomatic breathlessness and to improve exercise tolerance on an as required basis.
- *Long-acting β2-agonists* (*LABA*) such as salmeterol and formoterol also act on airway smooth muscle with a longer duration of action, about 12 h.

2. *Anticholinergics*

- Short-acting anticholinergics such as ipratropium antagonise muscarinic receptors and therefore block reflex cholinergic bronchoconstriction. The onset of action is slower, but the duration of action is more sustained.
- Ipratropium is given regularly three to four times a day and reduces the need for rescue medication as well as improving lung function and quality of life.
- Long-acting anticholinergics such as tiotropium antagonise muscarinic receptors and block reflex cholinergic bronchoconstriction.

3. *Combination bronchodilators*

- The first combination long-acting β_2-agonists and long-acting anticholinergic.
- LABA/LAMA for the treatment of COPD has become available. Ultibro, indacaterol (LABA) and glycopyrronium (LAMA), is administered once daily using a Breezhaler device and has been shown to be comparable to treatment with Seretide.

4. *Inhaled corticosteroids* (*ICS*)

- The combination of inhaled corticosteroid and long-acting β_2-agonist (ICS/LABA) is considered standard therapy for COPD patients (with moderate or more severe airflow obstruction) who frequently exacerbate.
- Compared to placebo, Seretide (fluticasone propionate and salmeterol) and Symbicort (budesonide and formoterol) reduce exacerbation rates and improve lung function and quality of life.
- Newer treatments such as Relvar (fluticasone furoate and vilanterol) have the added advantage of being administered once daily.

5. *Methylxanthines*

- Methylxanthines, such as caffeine, theophylline and aminophylline are bronchodilators that can be administered orally.
- Only the slow-release formulations have been shown to be of benefit in stable COPD patients.

6. *Mucolytic therapy*

- Despite mucolytic therapy having no effect on lung function, there are studies demonstrating that regular usage is associated with reduced exacerbations.

7. *Antibiotic prophylaxis*

- There is growing evidence that low-dose macrolide therapy in selected COPD patients appears to have an immunomodulatory effect with reduced exacerbation rates and improved quality of life scores.

8. *Oral corticosteroid therapy*

   - If at all possible, oral corticosteroid therapy in the management of stable COPD should be avoided. However, there are some patients in whom prolonged oral corticosteroid therapy cannot be avoided, generally following exacerbations, and current guidelines advise that the lowest dose of oral corticosteroid is used.

9. *Oxygen therapy*

   Many patients with COPD will develop respiratory failure. This can either be hypoxic or hypercapnic in nature:

   (a) Type 1 respiratory failure is characterised by hypoxaemia (PaO_2 <8 kPa) secondary to impaired gas exchange in the lungs.
   (b) Type 2 respiratory failure (or ventilatory failure) is hypoxaemia accompanied by hypercapnia ($PaCO_2$ >6 kPa) and occurs as a result of impaired ventilation.

   The treatment for hypoxaemia is controlled oxygen therapy. In contrast, the treatment for hypercapnic respiratory failure is ventilatory support.

10. *Long-term oxygen therapy* (*LTOT*)

    Long-term oxygen therapy is defined as oxygen therapy administered for greater than 15 h per day and should be considered in patients with COPD who satisfy the following criteria:

    (a) PaO_2 <7.3 kPa performed on two separate occasions at least 3 weeks apart during a period of clinical stability
    (b) PaO_2 <8.0 kPa if there is stress polycythaemia, pulmonary hypertension, peripheral oedema or nocturnal hypoxaemia

11. *Ambulatory oxygen therapy* (*AOT*)

    Ambulatory oxygen therapy should be considered in two groups of COPD patients:

    (a) Patients on LTOT and have oxygen requirements not met by their concentrator, for example, when they are out of their home and during exercise
    (b) Patients, whom there is documented symptomatic exercise desaturation without the requirement for LTOT

12. *Non-invasive ventilation for chronic hypercapnic respiratory failure*

    Non-invasive ventilation should be considered in either of the following:

    - Chronic hypercapnic respiratory (ventilatory) failure.
    - Patients requiring assisted ventilation (whether invasive or non-invasive) during an exacerbation.
    - Patients who are hypercapnic or acidotic on LTOT should be considered for long-term non-invasive ventilation.

13. *Immunisation*

    - Although clinical trial data are limited, there is evidence that influenza and to a lesser extent pneumococcal vaccination can prevent some of the infections that cause COPD exacerbations and therefore should be administered to all patients with COPD.

14. *Surgical therapy*

- Surgical intervention is normally only considered in non-smokers and ex-smokers when maximal medical therapy has failed.
- The aim of surgery is to restore quality of life and alleviate symptomatology.
- NICE recommend that patients below the age of 65 with severe COPD who remain breathless with marked restrictions of their activities of daily living despite maximal medical therapy should be considered for referral for assessment for lung transplantation.

Acute Exacerbations of COPD

COPD exacerbations are defined as an acute worsening of patient symptoms and respiratory function, which is not explained by normal day-to-day variation in symptoms and which requires alteration in the pharmacological treatment.

The most common pathogens causing COPD in United Kingdom are *Haemophilus influenzae* and Rhinovirus. Less common pathogens such as *Streptococcus*, *Moraxella catarrhalis*, parainfluenza virus, respiratory syncytial virus and *Pseudomonas aeruginosa* cause exacerbation of COPD.

Management of Acute Exacerbation

- Oxygenation – controlled oxygen therapy to maintain SaO_2 88–92 %
- Nebulised bronchodilators
- Intravenous aminophylline, although the evidence for additional benefit is lacking.
- Corticosteroid (prednisolone 30–40 mg per day) or if unable to swallow then intravenous hydrocortisone (100–200 mg).
- Antibiotic therapy is most likely to be useful if the sputum is purulent.
- Chest clearance may be facilitated with the use of mucolytic agents such as carbocysteine, nebulised saline and chest physiotherapy.
- Acute hypercapnic respiratory failure is an indication for non-invasive ventilation.
- Venous thromboembolism prophylaxis unless contraindicated.
- Adequate hydration and nutrition.

Hospitalisation Criteria

The majority of patients experiencing an exacerbation of COPD do not require hospitalisation (Table 19.6), but more than 50 % of the total cost of COPD is accounted for by services related to exacerbations.

Non-invasive Ventilation (NIV) for COPD in the Acute Setting

NIV used appropriately reduces mortality, escalation to invasive ventilation, days in hospital and nosocomial pneumonia [6–8].

Table 19.6 Factors that may determine where COPD exacerbations are treated

Factor	Treat at home	Treat in hospital
Social factors		
Social circumstances	Good	Living alone or not coping
Able to cope at home	Yes	No
Severity of stable COPD		
Breathlessness	Mild	Severe
LTOT	No	Yes
Level of physical activity	Good	Poor or confined to bed
General condition	Good	Poor or deteriorating
Significant co-morbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes
Severity of the exacerbation		
Rapid rate of onset	No	Yes
Breathlessness	Mild	Severe
Worsening peripheral oedema	No	Yes
Acute confusion	No	Yes
Level of consciousness	Normal	Impaired
Cyanosis	No	Yes
SaO_2 <90 %	No	Yes
Arterial pO_2	≥7 kPa	<7 kPa
Arterial pH level	≥7.35	<7.35
Changes on CXR	No	Yes

Equipment

NIV machines are typically bilevel positive airway pressure (BIPAP) ventilators.

Patient Selection

- NIV should be considered in patients with an acute exacerbation of COPD who have a respiratory acidosis (pH <7.35) and hypercapnia ($PaCO_2$ >6 kPa) despite intensive medical management for a maximum of 1 h from admission.
- There are relative contraindications to NIV (Table 19.7).
- The decision to proceed with NIV should be made on an individual basis considering all these potential factors.

Treatment Success and Failure

Success of NIV in the acute setting is defined by improvement in clinical parameters, normalisation of blood pH and a progressive return of respiratory rate to normality.

Table 19.7 Relative contraindications to NIV

Facial trauma/burns
Recent facial, upper airway or upper gastrointestinal tract surgery[a]
Fixed obstruction of the upper airway
Inability to protect the airway[a]
Life-threatening hypoxaemia[a]
Haemodynamic instability[a]
Severe co-morbidity[a]
Glasgow coma score <10[a]
Confusion/agitation[a]
Vomiting
Bowel obstruction[a]
Copious respiratory secretions or pneumonia[a]
Pneumothorax[a]

[a]NIV can be used as a ceiling of treatment in these circumstances

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Chapter 20
Pulmonary Embolism

Dhakshinamoorthy Vijayasankar

Key Points

- Deep venous thrombosis (DVT) probably accounts for the majority of detached thrombus that becomes lodged in the pulmonary arteries giving rise to pulmonary embolism (PE).
- Negative highly sensitive D-dimer test with a low or indeterminate pretest probability essentially excludes VTE.
- High-risk or massive PE is defined by the American Heart Association as 'sustained hypotension (systolic blood pressure of <90 mmHg for more than 15 min) or the requirement for inotropes or signs of shock'.
- Thrombolysis is only recommended for patients who have a diagnosis of massive PE.

Introduction

Venous thromboembolism includes deep vein thrombosis (DVT) and pulmonary embolism (PE), and it is the third most frequent cardiovascular disease with an annual incidence of 74.5 per 100,000 person-years in hospitalised patients [1, 2]. The quality of life in patients with history of acute PE tends to have moderate to severe impairment of social activities and physical performance. In addition, recurrent thromboembolic events were associated with increased body pain and decreased health change and health functioning [3]. Pulmonary embolism is a major cause of mortality and morbidity in Europe with reported 317,000 deaths in six countries of the European Union in 2004 [4]. The mortality rate is relatively

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_20

lower in patients with haemodynamic stability and higher in patients presenting after a cardiorespiratory arrest. If PE is left untreated, the prognosis remains poor, even for treated patients who might develop thromboembolic pulmonary hypertension.

The rate of PE in pregnancy is 1–2/7,000 births [5] and usually occurs postpartum, particularly associated with preeclampsia, caesarean section and multiple births. Current smoking used to be regarded as a minor risk factor for VTE but this has not been conclusively demonstrated.

Definition

Mechanical obstruction of pulmonary artery which is usually due to blood clot from venous thromboembolism.

Classification

American Heart Association classification of pulmonary embolism [6]

- Massive pulmonary embolism
  - Sustained hypotension

    Systolic blood pressure <90 mmHg for >15 min or requiring inotropic support
  - Persistent profound bradycardia
  - Pulselessness
- Submassive PE – acute PE without systemic hypotension but with either right ventricular dysfunction or myocardial necrosis
- Low-risk PE
  - Acute PE without clinical markers of adverse prognosis

European Society of Cardiology (ESC) classification of pulmonary embolism [7]

- High-risk pulmonary embolism – haemodynamic instability with shock or hypotension
- Intermediate risk (without shock or hypotension)
  - Pulmonary embolism index (PESI) class 3–5 or sPESI >1
- Intermediate low-risk pulmonary embolism
  - PESI class 1–2 or sPESI = 0
- Low risk – absence of all the above factors

Pathogenesis

VTE develops when there is stasis, endothelial damage and hypercoagulability (Virchow's triad). This can occur in any part of the venous system, although most thrombus formation occurs in lower extremity deep veins [8]. Deep venous thrombosis (DVT) probably accounts for the majority of detached thrombus that becomes lodged in the pulmonary arteries giving rise to pulmonary embolism.

Risk Factors (Table 20.1)

Table 20.1 Risk factors for venous thromboembolism (VTE)

Major risk factors (relative risk 5–20)	
Surgery[a]	Major abdominal/pelvic surgery
	Hip/knee replacement
	Postoperative intensive care
Obstetrics	Late pregnancy
	Caesarian section
	Postpartum
Lower limb problems	Fracture
	Varicose veins
Malignancy	Abdominal/pelvic disease
	Advanced or metastatic cancer
Reduced mobility	Hospitalisation
	Institutional care
Miscellaneous	Previous proven VTE
Minor risk factor (relative risk 2–4)	
Cardiovascular	Congenital heart disease
	Congestive cardiac failure
	Hypertension
	Superficial venous thrombosis
	Indwelling central venous catheter
Oestrogens	OCP, HRT
Miscellaneous	COPD
	Neurological disability
	Occult malignancy
	Thrombotic disorders
	Long-distance sedentary travel
	Obesity
	Other[b]

VTE venous thromboembolism, *OCP* oral contraceptive pill, *HRT* hormone replacement therapy, *COPD* chronic obstructive pulmonary disease

[a]Where appropriate prophylaxis is used, relative risk is much lower

[b]Inflammatory bowel disease, nephrotic syndrome, chronic dialysis, myeloproliferative disorders, paroxysmal nocturnal haemoglobinuria, Behçet's disease

History [4, 6, 7]

Consider history of

- Thrombophilia
  - Factor V Leiden mutation
  - Antithrombin deficiency
  - Protein C and S deficiency
  - Antiphospholipid antibody syndrome
  - Dysfibrinogenaemia
- Risk factors – Table 20.1
- Symptoms
  - Dyspnoea
  - Tachypnoea
  - Pleuritic chest pain
  - Cough
  - Fever
  - Symptoms of shock in patients with massive pulmonary embolism

  Less common symptoms
- Haemoptysis
- Leg pain or swelling
- Syncope
- Symptoms of encephalopathy
- Seizure

Examination

- Sinus tachycardia may be present.
- Persistent bradycardia or pulselessness may be present in massive pulmonary embolism.
- Sustained hypotension may be present in massive hypotension.
- Respiratory signs may not be more common in patients with PE than in other patients [9].
- Chest pain on palpation does not rule out PE in patients with suspected PE [10].
- Signs of deep vein thrombosis may be present.

Making the Diagnosis

- *Pretest probability of PE*

D-dimer is a circulating fibrin degradation product that is elevated in the presence of clot formation. It is not specific to VTE and can be elevated in sepsis, pregnancy, chronic kidney disease, trauma and post-surgery. However, a negative highly sensitive D-dimer test with a low or indeterminate pretest probability essentially excludes VTE. The D-dimer test should not be undertaken if the pretest probability is high as a diagnostic investigation is required. There are many validated scores that can be used to assess the likelihood of PE including Wells and Geneva (Table 20.2).

Table 20.2 Scoring scales for grading the clinical likelihood of acute symptomatic PE

Wells score	Score
Alternative diagnosis less likely than PE	3.0
Signs or symptoms of DVT	3.0
History of PE or DVT	1.5
Immobilisation for at least 3 days or surgery in the previous month	1.5
Heart rate >100 beats/min	1.5
Haemoptysis	1.0
Active cancer (treatment ongoing, within previous 6 months or palliative)	1.0
Risk stratification	
For high sensitivity D-dimer:	
Low probability: <2 points	
Intermediate probability: 2–6 points	
High probability: ≥6 points	
For lower sensitivity D-dimer:	
PE unlikely: ≤4 points	
PE likely: >4 points	
Geneva score	
Age >65 years	1.0
Previous DVT or PE	3.0
Surgery under general anaesthesia or fracture ≤1 month	2.0
Active cancer, solid or haematologic, or considered cured ≤1 year	2.0
Unilateral lower limb pain	3.0
Haemoptysis	2.0
Heart rate 75–94 beats/min	3.0
Heart rate ≥95 beats/min	5.0
Painful lower extremity on palpation and unilateral oedema	4.0
Risk stratification	
Low probability: 0–3 points	
Intermediate probability: 4–10 points	
High probability: ≥11 points	

Investigations

- Hypoxia is common in PE but up to a fifth of patients with PE will have normal oxygenation.
- Chest radiograph is often normal but may reveal a small pleural effusion, plate atelectasis or a slight elevation of hemi-diaphragm. Local oligaemia (Westermark's sign) or Hampton's hump (a wedge-shaped, pleural-based consolidation associated with pulmonary infarction) is rarely seen.
- Electrocardiograph (ECG) often reveals sinus tachycardia but there may be evidence of right heart strain as evidenced by atrial fibrillation, right bundle branch block or inverted T waves V1-3. The classic SI QIII TIII strain pattern is rare and non-specific.
- Urgent CT pulmonary angiography is the investigation of choice to demonstrate filling defects within the pulmonary arterial circulation (Fig. 20.1).

Treatment [7, 8, 11]

Low-Risk PE

- Patients with PE should be started on low molecular weight heparin for a minimum of 5 days.
- Concomitant warfarin therapy should also be administered until the INR is within therapeutic range. Anticoagulation with warfarin or other novel therapies such as rivaroxaban (oral factor Xa inhibitor) should be continued for a duration dependent upon the likely cause.
- VTE with temporary risk factors may only require 3 months anticoagulation.

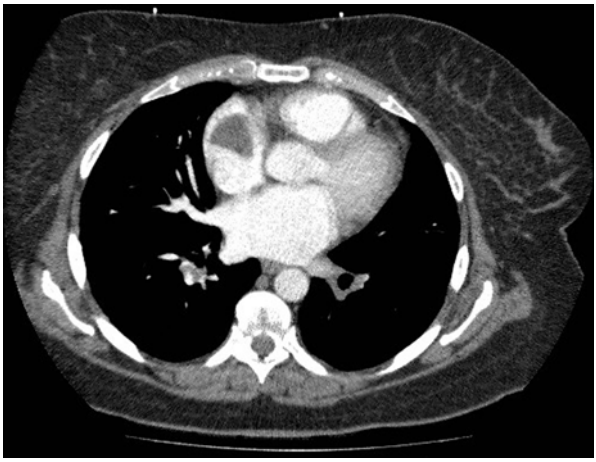

Fig. 20.1 Pulmonary emboli in the right lower lobe pulmonary arteries with right atrial thrombus demonstrated on computed tomography pulmonary angiogram (CTPA)

- A first episode of unprovoked PE is treated for a duration of 6 months, and recurrent VTE should be treated for as long as the benefit of anticoagulation outweighs the risk of severe bleeding.

High-Risk PE

This group of patients have improved mortality with thrombolysis; the earlier given the better. In most treatment algorithms, imminent cardiac arrest in massive PE should be treated with half-dose thrombolysis. The most widely used thrombolytic agent is alteplase using the same treatment as for acute myocardial infarction.

Other Treatments for PE

Occasionally, conventional angiography or CTPA examination may be contraindicated and another modality of investigation is required.

- Isotope lung scanning should only be considered if the chest radiograph is normal. If isotope lung scanning is normal, PE can be reliably excluded. Lower limb examination with USS Doppler or venography in this situation may confirm DVT and thus the increased likelihood of PE.
- Occasionally, the CTPA is negative despite a high probability of PE. Isotope lung scanning may identify areas of ventilation-perfusion mismatch presumably secondary to multiple small sub-segmental peripheral PE. The disadvantage of isotope lung scanning is the high number of indeterminate examinations and that other diagnosis such as infarction, pneumonia and cancer cannot be confirmed or excluded.
- In high-risk PE, surgical interventions should be considered if the risk of anticoagulation is too great. Thromboendarterectomy, right atrial appendage resection of thrombus and the insertion of vena caval filters can successfully treat PE and VTE in acute and chronic disease.

Complications

- Sudden cardiac death
- Obstructive shock
- Pulseless electrical activity
- Atrial or ventricular arrhythmias
- Secondary pulmonary hypertension
- Cor pulmonale

- Severe hypoxaemia
- Right to left intracardiac shunt
- Lung infarction
- Pleural effusion
- Paradoxical embolism
- Heparin-induced thrombocytopaenia
- Thrombophlebitis

Prognosis

- Prognosis depends upon clinical severity at diagnosis and response to treatment.
- Poor prognostic factors include

Table 20.3 Prognostic scores in patients with acute symptomatic PE

Variable	Score
PESI score (Pulmonary Embolism Severity Index)	
Age	1/year
Male gender	10
Cancer	30
Heart failure	10
Chronic lung disease	10
Heart rate ≥110 beats/min	20
Systolic blood pressure <100 mmHg	30
Respiratory rate ≥30 breaths/min	20
Temperature <36 °C	20
Altered mental status	60
O_2 saturation <90 %	20
Risk stratification	
Class I (very low risk): <65 points	
Class II (low risk): 66–85 points	
Class III (intermediate risk): 86–105 points	
Class IV (high risk): 106–125 points	
Class V (very high risk): >125 points	
Simplified PESI score	
Age >80 years	1
Cancer	1
Chronic cardiopulmonary disease	1
Heart rate ≥110 beats/min	1
Systolic blood pressure <100 mmHg	1
O_2 saturation <90 %	1
Risk stratification	
Low risk: 0 points	
High risk: ≥1 point(s)	

- Major embolism (hypotension and evidence right heart strain)
- Co-morbidities (congestive cardiac failure, COPD, malignancy)
- Previous or current DVT

Non-fatal recurrence is least likely in those patients with a temporary risk factor. To further complicate prognosis, there is an increased chance of cancer being diagnosed within 6–12 months of the first episode of VTE (Table 20.3).

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Part V
Environmental Medicine

Chapter 21
Accidental Hypothermia and Cold Injury

Seelan Pillay

Key Points
- The clinical features of hypothermia vary among patients and core temperatures are often unreliable; therefore, prompt recognition of each stage of hypothermia is crucial in its management.
- Gentle handling of the patient is paramount since manipulation can precipitate arrhythmias in the irritable myocardium.
- With failure to rewarm a clinician should consider underlying sepsis or non-infectious causes of impaired thermogenesis.
- With regard to frostbite rewarming is an essential component of therapy but should be delayed until definitive care is imminent since refreezing following rewarming results in worsening tissue damage.

Introduction

Accidental hypothermia is the involuntary drop in core temperature below 35 °C [1]. Death from accidental hypothermia occurs throughout the world, and although more commonly seen in cold climates, hypothermia may develop without exposure to extreme environmental conditions [1]. In spite of current advances in rescue, prehospital and supportive care, the in-hospital mortality of patients with moderate or severe hypothermia is approximately 40 % [1].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_21

Table 21.1 Staging of accidental hypothermia [4]

Stage	Clinical symptoms	Core temperature
HT 1	Conscious	32–35 °C
	Shivering	
HT 2	Impaired consciousness	28–32 °C
	Not shivering	
HT 3	Unconscious	24–28 °C
	Not shivering	
	Vital signs present	
HT 4	No vital signs	

HT hypothermia

Classification

The stage of hypothermia impacts directly on both recognition and management. The most widely used definitions in the literature are as follows [2]:

- Mild hypothermia: Core temperature 32–35 °C
- Moderate hypothermia: Core temperature 28–32 °C
- Severe hypothermia: Core temperature <28 °C, although some experts regard a core temperature <24 °C as profound hypothermia [3].

Because the clinical features of hypothermia vary among patients and core temperatures are often unreliable, the appreciation of each stage is more important than the absolute temperature when managing hypothermia. Other published temperature ranges are similar.

Prehospital personnel may also refer to the clinical staging defined by the International Commission for Mountain Emergency Medicine also known as the Swiss System (Tables 21.1).

Pathophysiology

The body maintains homeostasis of normal core temperature by a balance between heat production and heat loss. Heat is generated by cellular metabolism and lost via skin and lungs via four main mechanisms [5]:

- Evaporation: vaporisation of water through insensible losses and sweat
- Radiation: emission of infrared electromagnetic energy
- Conduction: direct transfer of heat to an adjacent cooler object
- Convection: direct transfer of heat to convective currents of air and water

Convective heat loss to cold air and conductive heat loss to water are the most prevalent mechanisms of accidental hypothermia [5].

The preoptic nucleus of the anterior hypothalamus is responsible for thermoregulation at a set point core temperature of 37±0.5 °C. In response to cold stress, the

hypothalamus endeavours to stimulate heat production through shivering and increased thyroid, catecholamine and adrenal activity. Sympathetically mediated vasoconstriction decreases heat loss by reducing blood flow to the peripheral tissues. Peripheral blood vessels (where cooling is greatest) also vasoconstrict in direct response to cold [5].

Cooling also decreases neural activity and tissue metabolism. Initially, however, shivering in response to cooling skin produces heat and increased metabolism, cardiac output and ventilation. Once core temperature reaches 32 °C cardiac output, ventilation and shivering becomes ineffective and finally ceases as core temperature plummets [2].

The human body has therefore limited physiological capacity to maintain a narrow temperature homeostasis. Thus, behavioural responses like clothing and shelter are critical to avert hypothermia.

Clinical Features

Patients will present with:

- Mild hypothermia: tachypnoea, tachycardia, hyperventilation, ataxia, impaired level of consciousness, shivering and cold diuresis
- Moderate hypothermia: bradycardia, reduced cardiac output, arrhythmias, hypoventilation, CNS depression, hyporeflexia and loss of shivering
- Severe hypothermia: pulmonary oedema, oliguria, areflexia, ventricular arrhythmias and asystole [5]

Neurological features vary widely but the level of consciousness should correlate with core temperature. An alternative diagnosis should be considered if a significant discrepancy exists.

Risk factors associated with increased mortality of accidental hypothermia include: [6]

- Ethanol use
- Older age
- Psychiatric illness
- Homelessness
- Malnutrition

Investigations

Investigations should be guided by thorough history and clinical examination. The goal of laboratory evaluation should be to identify potential co-morbidities and complications including lactic acidosis, bleeding tendency and infection. Previously healthy patients with mild accidental hypothermia may not require

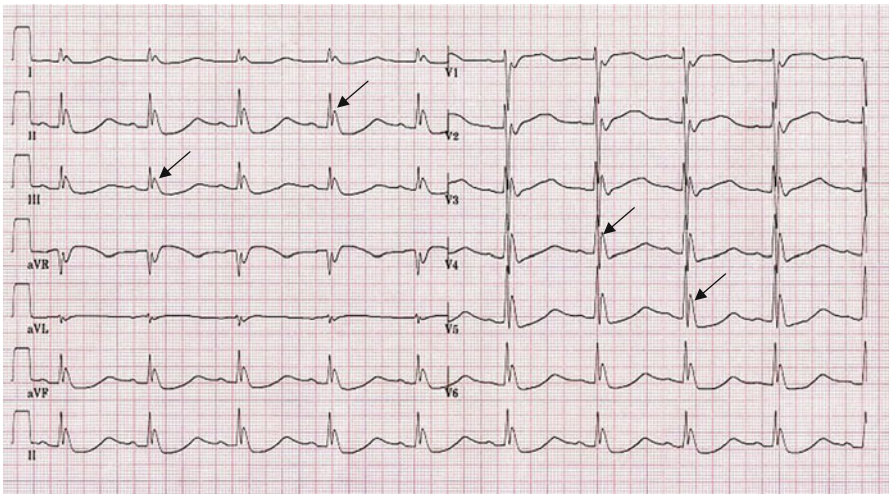


Fig. 21.1 J wave or Osborne wave

investigation. The following evaluation is suggested in cases of moderate to severe hypothermia [2]:

- Bedside glucose determination
- ECG (Fig. 21.1)
- Urine dipstick
- Serum electrolytes and urea, creatinine
- Serum haemoglobin, white cell count and platelets
- Serum lactate
- Creatine phosphokinase
- Arterial blood gas (uncorrected for temperature) in ventilated patients
- Chest radiograph

Treatment

Both general supportive measures and specific rewarming techniques remain the cornerstone in the management of hypothermia. Gentle handling of the patient is paramount since manipulation can precipitate arrhythmias in the irritable myocardium. Detection of pulses may be challenging and chest compressions may potentiate ventricular fibrillation. Inappropriate chest compressions should be avoided by examining the patient carefully for any respiratory activity, signs of life or cardiac contractility on ultrasound, suggesting a perfusing rhythm.

Management of cardiac arrest according to standard ACLS protocols is advised but electrical defibrillation is rarely successful until core temperature is greater than 30 °C. Oxygen and intravenous fluids should be warmed, and patients should have continuous monitoring of core temperature (low reading), cardiac rhythm and oxygen saturation.

Rewarming Approaches

1. Passive rewarming: remove cold damp clothes and wrap with blankets in a warm room.
2. Active external rewarming: apply heat to skin.
   - Heating blanket or radiant heat
   - Hot water bottles or heating pads to trunk (caution can burn skin)
   - Risk of *core temperature after-drop*: vasodilation with active external rewarming which causes:
     - Cold peripheral blood to return to heart
     - Decreased systemic vascular resistance and hypotension
     - Wide pulse pressure
   - Risk of rewarming acidosis: lactate from periphery returns to core circulation which may cause transient shock
3. Active core rewarming:
   - Humidified air at 40 °C
   - Warm intravenous fluids at 40–45 °C
   - Warm fluid lavage of stomach, bladder, colon or pleural space
   - Cardiopulmonary bypass (CPB), haemodialysis (HD) or extracorporeal membrane oxygenation (ECMO)
   - Peritoneal dialysis with normal saline at 40–45 °C at 6–10 L/h
   - Mediastinal lavage through open thoracotomy [7]

Choosing a Rewarming Approach

General approach:

- Check glucose.
- Give thiamine 100 mg IVI especially in known or suspected alcoholics.
- Treat underlying aetiology of hypothermia.
- Give antibiotics +/− steroids as indicated only.

If patient in cardiopulmonary arrest:

- CPR, ACLS protocol, intubate
- Warm intravenous fluid
- Heated humidified oxygen
- Extracorporeal rewarming technique (e.g. CPB, ECMO)
  - If not available then, active core rewarming
- Rewarm to target of >30 °C

If *not* in cardiopulmonary arrest and temperature <32 °C:

- Active external rewarming (e.g. Bair Hugger or other similar external warming device)
- Minimally invasive active core rewarming (e.g. warm air, IV fluids)

If *not* in cardiopulmonary arrest and temperature >32 °C

- Passive external rewarming measures

Rewarming Pearls and Pitfalls

No prospective, randomised controlled studies comparing the various rewarming modalities have been done in humans. Therefore, firm guidelines for therapy cannot be given.

Fluid

- Although warmed intravenous fluids are essential, they are not an effective means of treating hypothermia because of the small temperature differential or gradient and large difference in mass between body and infused fluid. Their use becomes more apparent when large volumes of fluid in a hypovolaemic patient are used for resuscitation [7].
- One litre of crystalloid at room temperature can be heated in a microwave (1,000 W) to 40 °C for 2.5 min.
- Glucose containing fluids and blood should not be microwaved.

Body Cavity Rewarming Techniques

- Pleural irrigation results in cardiac rewarming and may be the technique of choice if an arrhythmia is present.
- Direct irrigation of liver through peritoneal lavage may restore its ability to clear toxins and lactate.
- Stomach, colon and bladder are poor sites for body cavity lavage because of their small surface area for heat exchange.

Temperature Measurement

- A rectal probe thermometer is practical in conscious patients.
- Rectal and bladder probes should not be used in critical patients during rewarming because a significant lag exists with core temperature.
- Oesophageal temperature is the most accurate in rewarming.
- An oesophageal probe placed in the lower third of the oesophagus provides near approximation of cardiac temperature.
- The effectiveness of rewarming depends on the technique used and the clinical indication based on severity of the presenting problem (Table 21.2)

Table 21.2 Effectiveness of rewarming [8]

Technique	Rewarming rate (°C/h)	Indication
Warm environment and clothing, warm sweet drinks and active movements	2	HT 1
Active external and minimally invasive rewarming, e.g. forced heated air	0.1–3.4	HT 2 or HT 3 with haemodynamic stability
Peritoneal dialysis	1–3	Uncertain
Haemodialysis	2–4	Uncertain
Thoracic lavage	3	HT 4 when ECMO or cardiac bypass not available
Venovenous ECMO	3	Uncertain
Venoarterial ECMO	6	HT 3 with cardiac instability or HT 4
Cardiopulmonary bypass	9	HT 3 with cardiac instability or HT 4 when ECMO not available

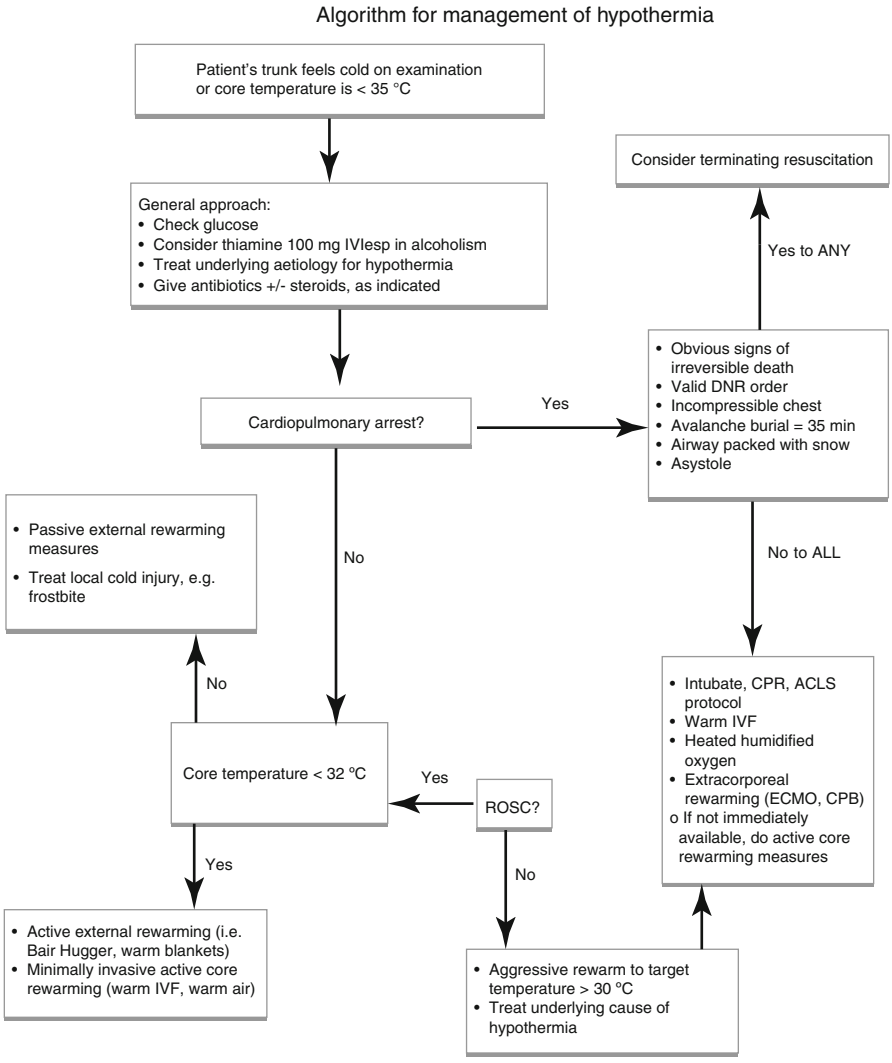
Failure to Rewarm

- First ensure that appropriate aggressive rewarming techniques are in progress with all equipment functioning optimally.
- Failure to rewarm may be due to the possibility of core temperature after-drop. However, its incidence, magnitude and clinical significance are unclear.
- Consider impaired thermogenesis from underlying sepsis.
- Consider non-infectious causes of impaired thermogenesis:
  - Toxins
  - Hypothyroidism
  - Adrenal insufficiency

Disposition

Provided they are asymptomatic and can return to a warm environment, patients with mild accidental hypothermia can be discharged. Most other patients require admission for treatment of hypothermia and investigation of the underlying cause.

- The Osborn wave (J wave) is a positive deflection at the J point (negative in aVR and V_1) and is usually most prominent in the precordial leads.
- Usually seen with hypothermia <30 °C but they are not pathognomonic.
- Hypothermia-associated ECG changes are significantly more frequent in patients with fortunate prognosis.
- Other ECG changes may include:
  - Muscle tremor artefact
  - T wave inversion
  - PR, QRS and QT prolongation [9]
  - Dysrhythmias – sinus bradycardia, atrial fibrillation, AV block and nodal rhythms



Cold Injury

Introduction

The concept of localised cold injuries extends as far into history as the 1700s when the Swedish Army invaded Russia. The Swedes were defeated, with cold injury being a major contributory factor to their loss. It has also been described during Napoleon's Franco-Russian War, nineteenth-century military conflicts and World Wars I and II.

However, cold-related injury is not limited to military personnel [10]. The homeless together with people who spend prolonged periods in freezing temperatures or engage in outdoor winter sports, are also at risk.

Pathophysiology

Cold exposure triggers a thermoregulatory response where the core body temperature is maintained at the expense of the extremities and skin. Freezing of the extremities is best described in four phases.

Phase 1: Cooling and Freezing

The initial response to cold temperature is vasospasm. This is followed by the 'hunting response' which is an alternation in vasodilation and vasoconstriction, occurring every 5–10 min. During persistently cold temperature exposure, the body attempts to maintain core body temperature by shutting off blood flow to the coldest limbs. Extracellular ice crystals form in the plasma and interstitium at a temperature of −2 °C causing stasis. The crystals produce an osmotic gradient resulting in intracellular dehydration. Intracellular crystals form and there is cellular membrane destruction.

Phase 2: Rewarming

Exposure to warmth reverses the freezing process. The crystals melt and the vulnerable endothelium of the small capillaries becomes highly permeable. Fluid extravasates with resultant oedema and blister formation.

Phase 3: Tissue Injury

This phase is similar to that of burns. An arachidonic acid cascade forms and the metabolites, prostaglandins and thromboxane are liberated. These inflammatory mediators initiate an inflammatory cascade with resultant vasoconstriction and platelet aggregation.

Phase 4: Resolution

The result of frostbite may culminate into gangrene, complete tissue recovery or later sequelae.

Clinical Features

Chilblain or pernio occurs on bare body surfaces which are chronically or repeatedly exposed to cold, but non-freezing temperatures. Acute exposure to cold may trigger symptoms of burning paraesthesiae, erythema, localised swelling and nodules on these areas. The lesions have the potential to progress to ulcerations and form bullae.

Trench foot progresses over hours to days following immersion in cold, stagnant water. Involvement of peripheral nerves causes paraesthesiae. The foot appears pale and cyanotic and is painless or extremely painful with or without a pulse. Tissue loss or permanent disability may result.

Frostnip presents as paraesthesiae that is localised and resolves with rewarming.

Frostbite most commonly occurs, but is not limited to the nose, ears, face, hands and feet. It may also present as a freezing keratitis of the cornea in skiers without eye protection.

The clinical features of frostbite is classified into first to fourth degree with first and second degrees being superficial and third and fourth degrees being deep (Table 21.3).

Table 21.3 Classification of frostbite [11]

Classification	Symptoms	Prognosis
Superficial		
First degree	Burning or stinging. May have hyperhidrosis	Excellent
White area with surrounding erythema and oedema. No blisters/necrosis		
Second degree	Numbness	Good
Clear fluid-filled blisters. Oedema and erythema	Vasomotor disturbances	
Deep		
Third degree	No sensation	Often poor
Haemorrhagic blisters	Later, painful, throbbing, aching	
Skin necrosis		
Blue – grey discolouration		
Black eschar formation after 1 to several weeks		
Fourth degree	Possible joint pains	Extremely poor
Mottled skin		
Extension into muscle and bone		
Mummification in 4–10 days		

Investigations

The diagnosis is usually clinical. The following investigations may be used to determine the prognosis, extent of injury and associated co-morbidities.

- Plain radiographs: To assess for fractures or growth plate destruction in children
- Technetium scintigraphy: May be used to assess long-term tissue viability but is not superior to clinical examination
- MRI: May demonstrate the boundaries of ischaemic and non-ischaemic tissue

Treatment

Chilblain

Therapy is mostly supportive. Affected areas should initially be rewarmed, then bandaged and elevated.

Trench Foot

Management is supportive, as with chilblain. In addition, pentoxifylline 400 mg three times a day may be considered. Wounds are to be inspected for onset of sepsis. Preventative measures should be encouraged. This includes ensuring the use of dry socks, correct boot size and keeping warm.

Frostbite

Prehospital Management

The initial aim is to treat the presenting problems and prevent further injury. All wet, constricting clothing and boots must be removed and changed to dry garments. Patients should be removed from the freezing environment as soon as possible. The affected limbs ought to be splinted, padded and elevated. Rewarming is an essential component of therapy but should be delayed until definitive care is imminent. Refreezing following rewarming results in worsening tissue damage. The use of stoves and open fires for rewarming is strongly discouraged [12].

Emergency Department Management

Hypothermia can be life threatening and should be excluded or treated, if present. Further management should focus on rewarming, analgesia, wound care and preventing complications.

- Rewarming: Initiate only when the core body temperature is greater than or equal to 35 °C. The injured extremity should be soaked in circulating water for 10–30 min. The water temperature ought to be maintained at 40–42 °C. Successful rewarming is suggested when the tissue becomes red and pliable [13].
- Analgesia: Opioids are an effective choice for analgesia. Morphine, 0.1 mg/kg, is recommended.
- Anti-inflammatories: Ibuprofen 12 mg/kg/day dampens the arachidonic acid cascade.
- Wound care:
  - Tetanus may be a complication. Tetanus prophylaxis is advisable.
  - Maintain sterility when examining or treating wounds.
  - Clear blisters contain thromboxane and prostaglandins. They should be aspirated and debrided.
  - Haemorrhagic blisters suggest injury to the microvasculature. They may be aspirated but not debrided.
  - Aloe vera cream is recommended as a topical application, 6 hourly. It aids in the inhibition of the arachidonic acid cascade.
  - Patients are predisposed to infection by various pathogens. *Staphylococcus aureus*, *S. epidermidis*, beta-haemolytic streptococci and anaerobes may be culprits. Prophylactic penicillin G, 500 000 units IVI 6 hourly or clindamycin 600 mg IVI, 6 hourly for 48–72 h is recommended.
  - An early surgical consult is needed, but intervention may be indicated at a later stage when there is adequate demarcation of dead tissue [14]. Early surgical intervention is indicated in the presence of a constricting eschar or very rarely a fasciotomy in the presence of compartment syndrome.

Various other treatment modalities are currently being researched and may prove beneficial in the treatment of cold extremity injuries in the future.

Hyperbaric oxygen therapy (HBOT) may aid in repairing vasculature and healing tissue. Anticoagulants, vasodilators, thrombolytics and sympathetic-blocking drugs are also being researched.

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Chapter 22
Altitude Medicine

Jaybalan Allan Matthew

Key Points
- Increasing altitude exposes one to a hypobaric hypoxic environment.
- Without acclimatisation, people are at risk of high-altitude syndromes, predominantly acute mountain sickness, high-altitude pulmonary oedema or high-altitude cerebral oedema.
- Therapy for each of these is descent to a lower altitude and supplemental oxygen.
- Acetazolamide and dexamethasone have a role to play in prevention and treatment.
- Hyperbaric therapy can be considered if there is a delay in evacuating the patient to a lower altitude.

Introduction

The incidence of acute mountain sickness (AMS) is 23–67 % and depends on multiple risk factors. The incidence of high-altitude pulmonary oedema (HAPO) is 2 %, whilst the incidence of high-altitude cerebral oedema (HACO) is much lower [1].

The incidence of altitude illnesses depends on the rate of ascent, previous altitude exposure and illnesses, individual susceptibility, final altitude reached, sleeping altitude, duration at altitude and exertion at altitude [1].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_22

Fitness and gender have not been shown to be associated with the development of altitude-related illness [1, 2].

Whilst relatively few people live at altitude, participation in recreational activities at high altitude is on the increase, and emergency health-care workers should be aware of these problems.

Pathophysiology of Altitude-Related Illnesses

- With increasing altitude, atmospheric pressure decreases. This results in decreasing partial pressures of inspired oxygen.
- A hypobaric hypoxic environment results in many physiologic changes.
- Carotid body chemoreceptors stimulate the apneustic and pneumotaxic centres in the medulla, with an increased minute ventilation. This is called the *hypoxic ventilatory response* (*HVR*), which causes hypocarbia and respiratory alkalosis [1, 2].
- This respiratory alkalosis causes the kidneys to excrete bicarbonate ions, moving the pH back to normal, which further stimulates increased ventilation.
- This is a mechanism to improve oxygenation.
- Hypoxia also stimulates renal production of erythropoietin, which increases erythrocyte counts and haemoglobin [1].
- Hypoxia further causes the increased production of 2,3-diphosphoglycerate, which pushes the oxygen-haemoglobin dissociation curve to the right, with oxygen released more freely to tissues [1].
- Altitude hypoxia also causes a catecholamine release with a resultant increase in cardiac output.
- Cerebral hypoxaemia results in mediator-induced vascular permeability with resultant vasogenic oedema. Without counteracting mechanisms to buffer brain volume, AMS develops. If the cerebral oedema worsens and intracranial pressure increases, HACO develops [1–3].
- Pulmonary vasoconstriction increases pulmonary arterial pressure and, when combined with decreased alveolar clearance, constitutes the mechanism of HAPO. Increased pulmonary arterial pressure also places strain on the right side of the heart [1, 2].

Clinical Features

- Risk factors for high-altitude disease are shown in Table 22.1 [4, 5].

Table 22.1 Risk factors for high-altitude diseases [4, 5]

Rate of ascent
Altitude attained
Time at maximal altitude
Sleeping altitude
Extent of physical exertion at altitude
Personal susceptibility

Table 22.2 Diagnosis of acute mountain sickness (AMS) [1, 4]

Recent gain in altitude
Exposure to the new altitude for several hours
Headache *plus at least one of the following:*
Gastrointestinal upset (anorexia, nausea, vomiting)
General weakness or fatigue
Dizziness or light-headedness
Difficulty sleeping

Acute Mountain Sickness

- Acute mountain sickness (AMS) is defined as the presence of the following [4]:
  - Recent gain in altitude
  - Headache
  - *Any one of the following*:

    Gastrointestinal disturbances (nausea/vomiting/anorexia)
    Fatigue/weakness
    Dizziness/light-headedness
    Difficulty sleeping
- Symptoms of mild AMS are similar to a non-specific viraemia, physical exhaustion or a 'hangover' from excess alcohol use [1, 4].
- Diagnosis of AMS is based on specific symptoms as shown in Table 22.2 [1, 4].
- The headache described for AMS is usually mild to severe and throbbing in nature. It can be unilateral but is usually bilateral. It is worse with postural changes, like sitting upright quickly, and is temporally related to early morning or occurs during the night [1].
- The International Hypoxia Symposium created the criteria for high-altitude diseases known collectively as the *Lake Louise Consensus Definitions* [4, 5].

High-Altitude Pulmonary Oedema (HAPO)

- HAPO, according to the *Lake Louise Consensus Definitions*, is defined by [4, 5]:
  - Recent gain in altitude
  - *At least two of the following*:

    Dyspnoea at rest
    Cough
    Weakness or decreased exercise tolerance
    Chest tightness or congestion

  - *At least two of the following*:

    Crackles or wheezes in at least one lung field
    Central cyanosis
    Tachypnoea
    Tachycardia

- HAPO presents with worsening dyspnoea at rest, dry cough and eventually cyanosis and rales [6].
- The patient is initially tachypnoeic and tachycardic.
- Constitutional symptoms of fatigue, anorexia and headache may also be present [1].

High-Altitude Cerebral Oedema (HACO)

- HACO, according to the *Lake Louise Consensus Definitions*, is defined by [4, 5]:
  - Recent gain in altitude
  - *Either of the following*:

    Change in mental status *or* ataxia *with* AMS
    Change in mental status *and* ataxia *without* AMS

- HACO rarely occurs alone and is usually associated with AMS and/or HAPO.
- Ataxia and depressed level of consciousness are two of the main signs, which are the most sensitive for early HACO.
- Other symptoms or signs include severe headache, nausea/vomiting, seizures, slurred speech, coma or altered mentation manifesting as emotional lability, confusion or hallucinations [1].

Differential Diagnoses

The differential diagnoses of high-altitude emergencies are many and the salient ones are compiled in Box 22.1.

Box 22.1 Differential Diagnoses: High-Altitude Emergencies

AMS	*HACO*
Dehydration	Dehydration
Viraemia	Other causes of a depressed level of consciousness
Exhaustion	Seizure disorders
Substance use	Intracranial sepsis and meningitis
HAPO	Cerebrovascular events
Dehydration	Psychiatric disorders
Pneumonia	Hypoglycaemia
High-altitude bronchitis	
High-altitude pharyngitis	
Pulmonary embolism	

Investigations

- There are no specific investigations for altitude-related illnesses.
- Hypoxia can manifest as a decreased pulse oximetry value, but this may be unreliable in the presence of vasoconstriction due to cold weather.
- Arterial blood gas analysis would be more valuable.
- Basic monitoring (pulse oximetry, waveform capnography, cardiac monitoring) is needed at all times.
- Chest x-rays (CXR) (Fig. 22.1) are potentially useful for HAPO, as they may show patchy, alveolar infiltrates bilaterally similar to cardiogenic pulmonary oedema (other findings of cardiogenic pulmonary oedema are not usually present, i.e. cardiomegaly, batwing infiltrates and Kerley B lines) [1, 2].
- The electrocardiogram (ECG) may show features of hypothermia, with J or Osborne waves. Features of right heart strain due to increased pulmonary pressures may be seen, as shown in Fig. 22.2 [1, 2].
- Patients with HACO will require computed tomography (CT) imaging of the head to assess for raised intracranial pressure or rule out other causes of depressed level of consciousness.
- Other imaging may be required if concomitant trauma is suspected.
- Basic laboratory investigations must be guided by the clinical assessment:
  - Blood glucose for all patients with altered mental status and depressed level of consciousness, or where clinically indicated.
  - Electrolytes, renal functions and liver function tests, as indicated.
  - A complete blood count may reveal a non-specific leukocytosis. Coagulation studies may be normal.

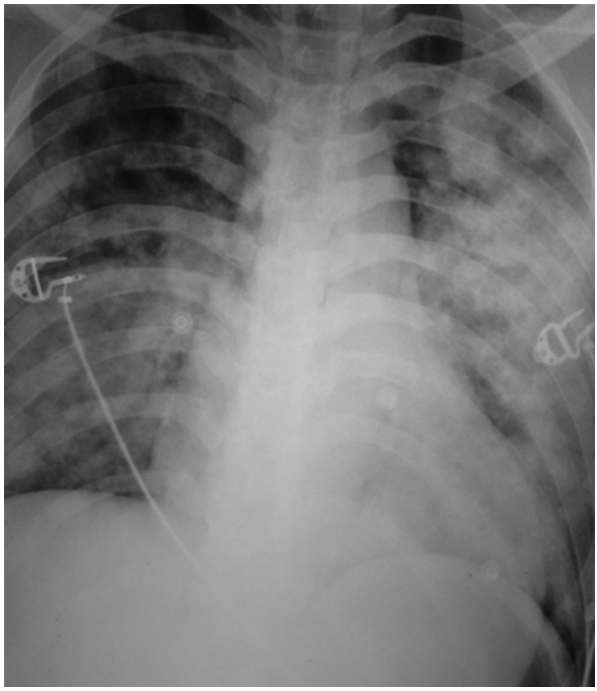


Fig. 22.1 CXR showing features of pulmonary oedema due to high altitude

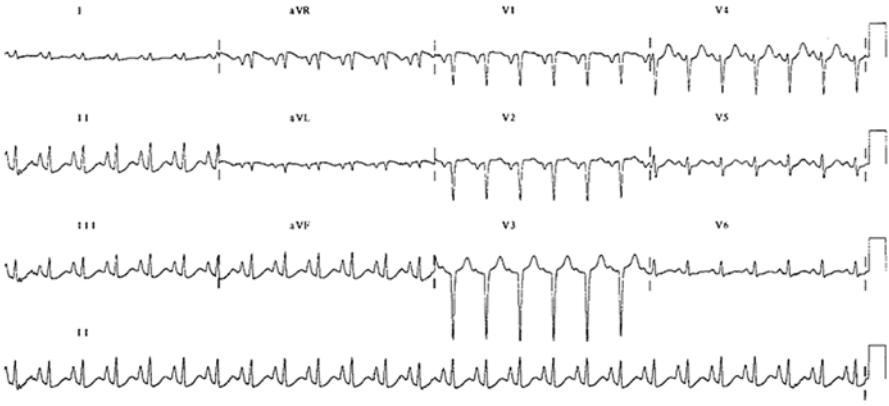


Fig. 22.2 ECG showing possible pulmonary hypertension and right heart strain that may occur with HAPO

Management

- Altitude-related illnesses may occur at <2,500 m and actual altitude should not be used to exclude this [7].

- Mild AMS is usually self-limiting and does not normally require any treatment [1, 2].
- Manage the patient initially as per ACLS guidelines and, if suspected, then ATLS guidelines for trauma.
- Moderate to severe forms require descent and supplemental oxygenation [1, 2, 4].
- Obtain intravenous access and provide isotonic crystalloid to ensure a urine output of 1–2 ml/kg/h.
- Acetazolamide 250 mg 12 hourly PO (2.5 mg/kg/dose 12 hourly PO in children, maximum 250 mg) can relieve symptoms [1, 2, 7–9].
- The headache can be treated with either aspirin (not in children), ibuprofen or paracetamol PO. Avoid opioid analgesics as they decrease the HVR [1, 2, 4].
- Prochlorperazine can be used for emesis [4].
- Severe symptoms respond to dexamethasone 8 mg STAT and then 4 mg 6 hourly PO/IV/IM (0.15 mg/kg/dose 6 hourly, in children) [1, 2, 7–9].
- Severe symptoms, where descent is delayed, may be managed with hyperbaric therapy in a Gamow or Certec Bag [1, 2, 5].
- Management of HAPO is similar to that for AMS, with descent and supplemental oxygenation the mainstay of management [1, 2, 5].
- Hyperbaric therapy can be considered, if there is a delay in descent.
- Adjunctive therapy to reduce pulmonary vasoconstriction and pressure are:
  - Nifedipine 10 mg 4–6 hourly PO *or* 10 mg *stat* and then 30 mg SR 12 hourly PO *or* 30 mg SR 12 hourly PO [1, 2, 4, 7, 8]
  - Tadalafil 10 mg 12 hourly PO
- Avoid multiple pulmonary vasodilators when treating HAPO.
- Consider also dexamethasone and acetazolamide.
- Severe forms of HAPO may not respond to this. Provide appropriate oxygenation and ventilation, and support this mechanically, if necessary.
- There is *no* role for diuretics in the management of HAPO [7].
- A patient with HACO requires immediate evacuation to a lower altitude.
- Oxygen therapy must be provided.
- Hyperbaric therapy may be considered, but should not be used as an alternative or delay descent.
- Dexamethasone 8 mg *stat* IV/IM/PO followed by 4 mg 6 hourly IV/IM/PO.
- Advanced life support measures should be considered, including intubation and ventilation and measures to decrease intracranial pressure [1, 2, 5].
- Prevent and manage hypothermia in these patients.
- Obtain a 12-lead electrocardiogram (ECG), looking for cold-related dysrhythmia, features of electrolyte abnormalities or intracranial catastrophes.
- Check glucose level and address abnormalities.
- Ensure periodic assessment of the Glasgow Coma Scale (GCS) and document findings thoroughly.
- Manage seizures as appropriate.

Disposition

- Patients with mild symptoms of AMS can be treated in the field and allowed to acclimatise. Failure to acclimatise, with ongoing symptoms, or patients with moderate to severe AMS require descent with supplemental oxygenation.
- In-hospital management of AMS depends on the severity and resolution of symptoms.
- Mild AMS, who remains symptom-free after 6 h in the emergency department (ED), with normal pulse oximetry levels on room air, can probably be discharged with advice on gradual ascent and acetazolamide prophylaxis.
- Moderate to severe AMS should be admitted until resolution of symptoms, and assessment for other possible differential diagnosis, whilst being provided with supplemental oxygen. Acetazolamide and dexamethasone may be considered.
- Patients with HACO/HAPO require admission and further assessment and management.

Prognosis

- Mild AMS is self-limiting and usually has no sequelae.
- Moderate to severe AMS may result in short-term to medium-term restriction of activity levels, but do not result in long-term complications.
- HAPO may resolve with complete normal pulmonary function. Cases of long-term restricted pulmonary function have been reported.
- HACO results invariably in neurocognitive impairment, although these may be insignificant and not clinically obvious. Psychiatric symptoms may result.

Prevention

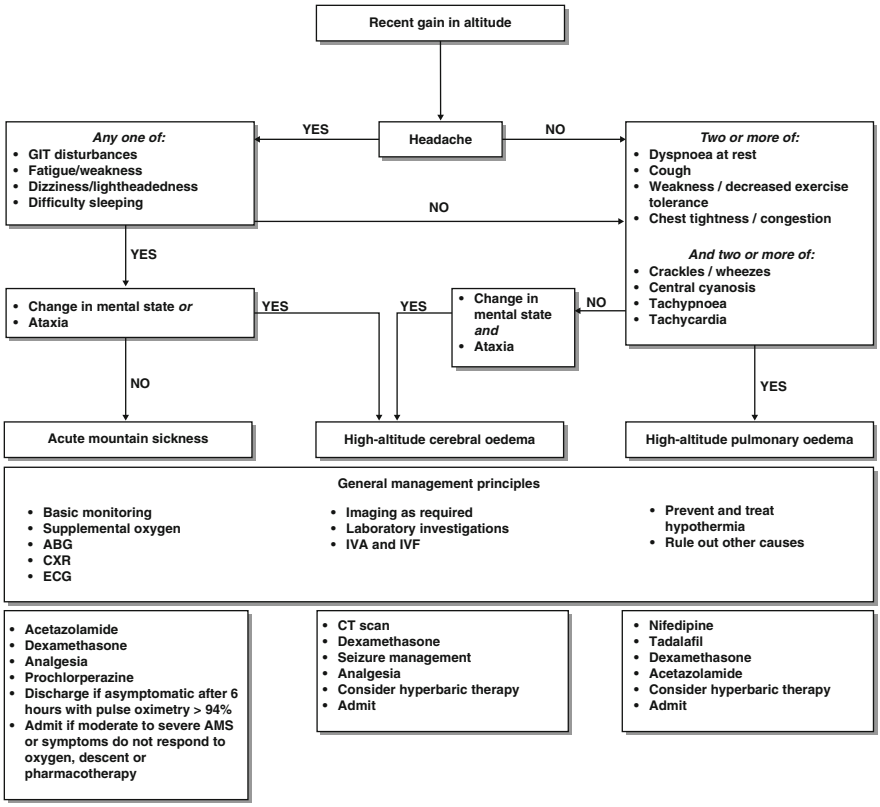
- Gradual ascent may help prevent AMS/HACO [1, 2].
- Other strategies that have been shown to work include:
  - High-carbohydrate diet prior to ascent
  - Avoiding ethanol and smoking
  - Avoiding narcotics and sedatives
- The first night spent at altitude should not be >2,800 m.
- Do not increase your altitude by >500 m/night.
- At an altitude >3,000 m, add one night for every 900–1,200 m gain in altitude.
- If your journey begins at 3,000 m, then spend three nights at this altitude before further ascent.

- There is a possible role for pre-acclimatisation and staged ascent, but logistics might preclude this as a strategy [7].
  - Pre-acclimatisation refers to repeated exposure to low-pressure or normal-pressure hypoxic environments, prior to ascent.
  - Staged ascent occurs by spending 6–7 days at a moderate altitude (2,200–3,000 m) before a high-altitude ascent.
- Preventative strategies for HAPO are similar to that for AMS, with gradual ascent being a priority.
- Where a climber has had a previous episode of HAPO, the following may be useful [1, 2, 4, 7, 8]:
  - Nifedipine 30 mg SR 12 hourly PO up to 4 days at altitude or until descent if this occurs earlier
  - Tadalafil 10 mg 12 hourly PO *or* sildenafil 50 mg 8 hourly PO
  - Dexamethasone 2 mg 6 hourly PO *or* 4 mg 12 hourly (4 mg 6 hourly in very high-risk situations) starting 2 days before ascent (not in children)
  - Acetazolamide 125 mg 12 hourly PO (2.5 mg/kg/dose 12 hourly PO, maximum 125 mg, in children)
  - Salmeterol 125 μg 12 hourly
- Patients with co-morbidities should seek expert medical advice regarding their fitness to travel to high-altitude environments [1, 2, 10].
- Uncompensated congestive cardiac failure (CCF), symptomatic pulmonary hypertension, severe chronic obstructive pulmonary disease (COPD) and sickle cell anaemia with previous sickle cell crises are contraindicated for high-altitude ascent [1, 2].
- Moderate risk factors include [1, 2, 10]:
  - Moderate COPD
  - Asymptomatic pulmonary hypertension
  - Compensated CCF
  - Morbid obesity
  - Sleep apnoea syndromes
  - Moderate to severe arrhythmias
  - Stable angina or coronary artery disease
  - High-risk pregnancy
  - Sickle cell trait
  - Cerebrovascular disease
  - Restricted pulmonary circulation
  - Seizure disorders not on medication or poorly controlled
- Little risk exists with the following problems (although it is still advisable to seek medical advice) [1, 2, 10]:
  - Extremes of age
  - Mild obesity

- Diabetes
- Coronary artery bypass graft (without angina)
- Mild COPD or asthma (well controlled)
- Low-risk pregnancy
- Hypertension (controlled)
- Seizure disorders (controlled)
- Psychiatric disorders (controlled)
- Neoplastic diseases (without lung or cerebral involvement)
- Musculoskeletal and other derma-inflammatory syndromes

- There is some role for ibuprofen 600 mg every 8 h PO for prevention of AMS but only when other measures are *not* immediately available [7].

Algorithm for the management of high-altitude illnesses



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Chapter 23
Electrical Injuries

Roshen Maharaj

Key Points

- The type and severity of electrical injury are dependent on the voltage, type and strength of current, resistance to flow, duration of contact and pathway of electrical current.
- Alternating current (AC) is more dangerous than direct current (DC) at the same voltage, because of the risk of muscle tetany and prolonged contact.
- Patients who sustain low voltage electrocution and are asymptomatic with a normal physical exam and electrocardiography (ECG) can be safely discharged from the emergency department (ED) without ancillary testing.

Introduction

Electrical injuries present with a broad spectrum of pathology ranging from a simple burn to multi-organ involvement to death. Injuries due to lightning strikes are also included in the spectrum of electrical injuries and will be discussed later in the chapter. A review of deaths from electrocution was predominantly as a result of accidental electrocution and has demonstrated a mortality rate of 4.4 per 100,000 population [1].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_23

Pathophysiology of Electrical Injuries

- The generation of electricity is dependent on the flow of electrons across a potential gradient. The following variables influence the flow of electrons:
  - Voltage (V)
  - Current (I)
  - Resistance (R)
- These variables are expressed as the following equation:

$$V = I * R \left(\text{Ohm s Law}\right)$$

- The type and severity of electrical injuries are thus dependent on the above variables, as well as the type of current, duration of contact and pathway taken by the electrical current [2].

Voltage (Volts)

- General household appliances are low voltage (110 V or 240 V). However, high-tension power lines and industrial equipment are considered high voltage (>600 V) and are associated with higher morbidity and mortality [2].

Current (Amperes)

- Currents of 1 mA are perceptible to human touch. Household current ranges from 15 to 30 A.
- The maximum current a person can grasp and release is termed 'let go' current. This ranges from 3 to 9 mA [3].
- Muscle tetany occurs approximately between 16 and 30 mA. However, ventricular fibrillation occurs between 50 and 100 mA.

Resistance (Ohms)

- Resistance is defined as the impedance to the flow of current in a conductor.
- Organs in the human body have varying degrees of resistance.
- Bone, cartilage and skin have higher resistance compared to blood vessels, muscle and nerves [4].

Types of Current

- Direct current (DC) produces a single muscle contraction and tends to throw the victim away from the source.
- Alternating current (AC) produces muscle tetany and can result in prolonged contact with the source [4].

Mechanisms of Electrical Injury

- Direct contact – current passes through the body. This commonly results in burns at the point of entry and exit. There could be extensive necrosis of the intervening tissue (Fig. 23.1).
- Arc – current 'jumps' from one point to another due to an electrical potential difference. Arcs cause thermal and flash burns (Fig. 23.2).
- Flash – there is no transfer of current but heat from an arc causes burns [5].

Clinical Presentation

Electrical injuries can result in multisystemic dysfunction. The common systems involved are the cardiovascular, neurological, skin and musculoskeletal systems.

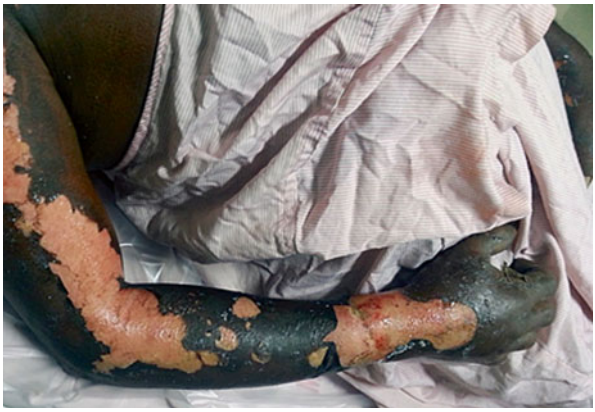


Fig. 23.1 Thermal burns following electrocution (Courtesy of Dr. Krishnaprasad, Emergency Medicine, Pushpagiri Medical College Hospital, Tiruvalla, Kerala-India)

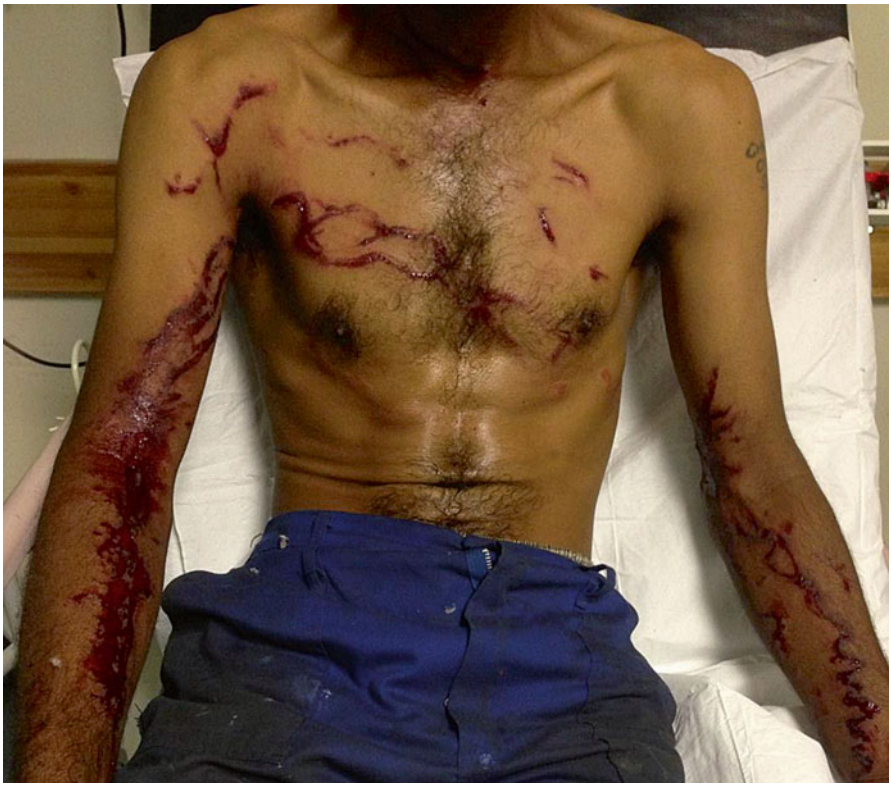


Fig. 23.2 Arc injuries

Cardiovascular Complications

- Common findings on ECG include premature ventricular contractions (PVCs), sinus tachycardia, ST changes, QT prolongation, atrial fibrillation and bundle branch blocks [4, 6].
- Cardiac arrest – asystole or secondary to ventricular fibrillation. Ventricular fibrillation is more common with low voltage AC electrocution, whilst asystole is associated with high voltage AC or DC electrocution [7].

Neurological Complications

- Short-term problems include transient confusion, amnesia, seizures and coma.
- Respiratory arrest can occur if the brainstem is involved.
- Spinal and head injury can occur due to blunt trauma sustained in high voltage electrocution.

- Long-term complications include psychiatric disorders, peripheral neuropathies and seizures [4].

Skin and Musculoskeletal Complications

- Burns to the skin may initially appear minor, but may mask deeper soft tissue injury.
- Most burns occur at the source and ground contact points.
- The duration of contact and the strength of the electrical current determine the severity of tissue damage [4, 8].
- Oral burns are common in paediatric patients who tend to bite or suck on electrical cords.
- Other important injuries include fractures from blunt trauma, compartment syndrome and rhabdomyolysis [9].

Lightning Injury

- The incidence of injury and death from lightning strikes is unknown, due to no formal reporting system [10].
- Studies from the United States estimate that lightning accounts for 50–300 deaths per year [10, 11].
- Lightning is described as a brief, massive, unidirectional flow of an electrical impulse.

Pathophysiology of Lightning Injury

- Mechanisms of injury from lightning strikes are as follows:
  - Direct strikes: victim is hit directly by the lightning strike.
  - Contact: victim is touching an object that is struck by lightning.
  - Sideflash/side splash: lightning arcs from the primary strike object to the victim.
  - Ground current/step voltage: a potential difference is created when the victim walks. The lightning current tends to go up the leg and down the other leg of the victim [12].
  - Blunt trauma: injury is sustained by either being thrown by the lightning strike or secondary to an implosive or explosive force created by rapid heating and cooling along the pathway of the lightning current in the body.
- Lightning injuries are also multisystemic.

- Head and neck injuries are common and include tympanic membrane rupture, middle ear disruption, corneal lesions, uveitis, retinal detachment and optic nerve injury. Cataracts are a late complication [13].
- Cardiac arrest may occur due to the electrical shock or secondary to coronary vascular spasm. The ECG may show dysrhythmias, ST and T wave changes and QT prolongation. Cardiac enzymes can be elevated [13, 14].
- Skin changes include thermal burns which may be linear, occurring where sweat and water accumulates, or punctate burns. Feathering or ferning is pathognomonic of lightning injury. These patterns are due to electron showers induced by lightning. They are also called Lichtenberg figures [13].
- Extremity injuries include fractures, shoulder dislocations due to tetany of the rotator cuff muscles and transient vasospasm of the extremities.
- Keraunoparalysis – temporary paralysis of the extremities which become blue and mottled, occurs in most of the severe lightning strikes. Peripheral nerve damage, seizures, amnesia and confusion are other neurological sequelae [13, 14].

Management of Electrical and Lightning Injuries

Prehospital Management

- Ensure scene safety before trying to rescue individuals. Live electrical points should be turned off. The local electricity authority may be required to turn off high voltage sources [4].
- There may be multiple victims, for example, in lightning strikes, requiring field triage. Patients in cardiac arrest are usually given priority over others. Patients may need basic and advanced cardiac and trauma life support [4, 8, 9].
- Attention should be paid to the airway, cervical spine, breathing and circulation.
- In cardiac arrest patients, CPR should be initiated in the field and prolonged CPR may be needed [4, 8, 9].

Emergency Department Care

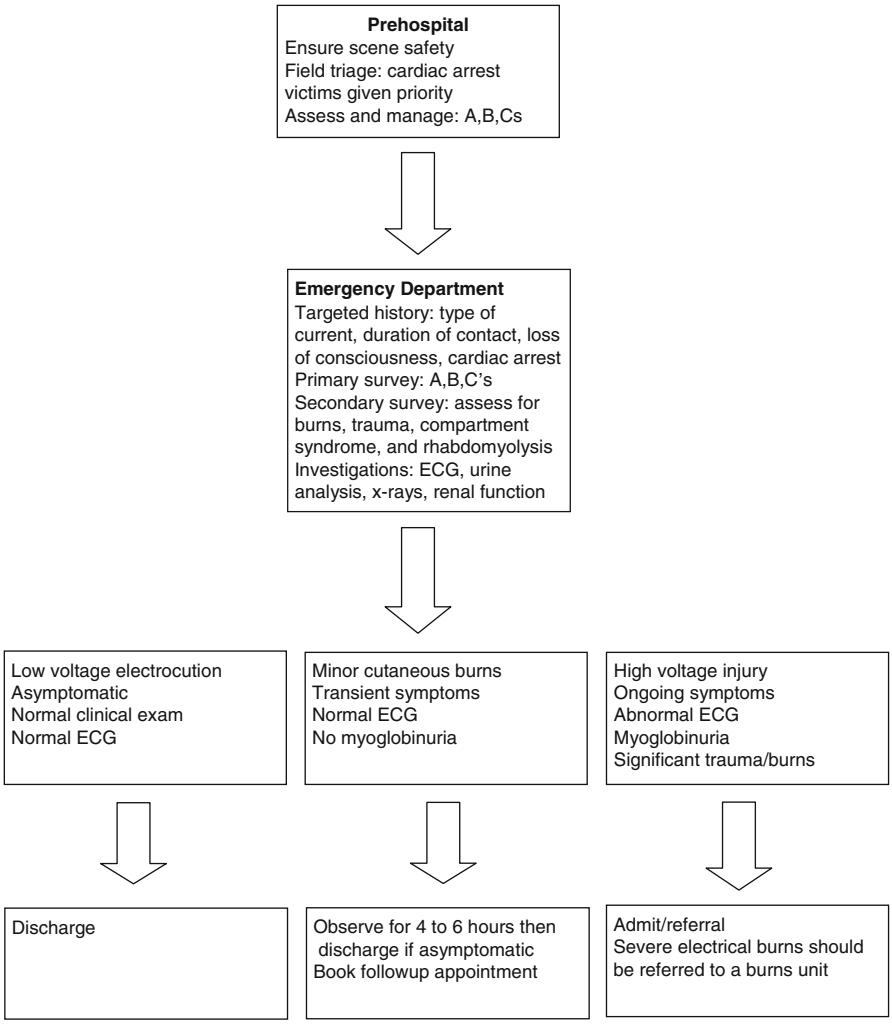
- A rapid primary survey and, once stabilised, a thorough secondary survey should be done.
- Give supplemental oxygen to hypoxic patients. Ventilatory support may be needed.

- A targeted history should be obtained regarding the type of electrical source, duration of exposure, history of cardiac arrest and the initial resuscitative measures initiated by prehospital staff and bystanders [4, 9].
- Early intubation may be required in patients presenting with facial injuries and burns and in those with already established airway compromise.
- ECG and cardiac monitoring are required for most electrical injuries. Indications for ongoing cardiac monitoring are a history of cardiac disease, initial abnormal ECG, history of cardiac arrest or dysrhythmias either prehospital or in the ED, history of loss of consciousness, ongoing chest pain and presence of hypoxia [4, 8].
- Intravenous fluids should be initiated early in patients presenting with severe burns or suspicion of rhabdomyolysis.
- Shock in electrical injuries can be multifactorial – hypovolaemic secondary to trauma, cardiogenic due to cardiac dysfunction, neurogenic in patients with spinal trauma and obstructive due to tension pneumothorax.
- The secondary survey should focus on assessing for traumatic injuries, compartment syndrome and burn extent estimation.
- Investigations in the ED are tailored to the type and severity of electrical injury and include ECG, urine analysis (check for haematuria/myoglobinuria), electrolytes, creatinine, arterial blood gas and cardiac enzymes [8, 9, 14].
- Imaging studies include point-of-care ultrasound (EFAST), X-rays and computed tomography (CT) scan as indicated [4, 8].

Disposition

- Patients sustaining low voltage electrocution who are asymptomatic and have a normal physical exam and ECG can be discharged [4].
- Patients with minor cutaneous burns or mild transient symptoms can be discharged if they have a normal ECG and urine analysis for haematuria/myoglobinuria [4, 8].
- All patients with history of high voltage electrocution, ECG changes, ongoing symptoms and significant injuries need to be admitted [9, 14].
- Severe electrical burns are best treated in a burns centre and should be appropriately transferred [14].

Summary



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Chapter 24
Heat-Related Illnesses

Ruvendra D. Shah

Key Points
- Regulation of body temperature involves thermosensors, the central nervous system (CNS) and thermoregulatory effectors.
- Heat exhaustion and heatstroke should be considered extremes of a spectrum of response to heat stress.
- Immediate cooling is the cornerstone of management of heatstroke.

Introduction

Climate change is a growing international concern with current and future global effects [1]. The warming of climate systems has seen an increase in heat-related illness morbidity and mortality globally [1].

- In May 2010, in Ahmedabad, India, 1344 excess deaths occurred when the ambient temperature reached a high of 46.8 °C [1, 2].
- More than 700 excess deaths were caused by the 1995 heat wave in Chicago [3, 4].
- In France, the 2003 summer heat wave claimed 14,800 lives [5].

In order to deal with this increasing morbidity and mortality, the emergency physician must understand the pathophysiology of heat-related illnesses and promptly recognise and manage potentially fatal heat-related illnesses in the emergency department.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_24

Physiology of Heat Transfer

Conduction, evaporation, radiation and convection play an important part in human physiological heat transfer [3, 6, 7].

- *Conduction* is the direct transfer of heat energy from warmer to cooler objects. Air is a poor conductor, while water has 25 times more thermal conductivity. This is the basis of treatment of severe heat illness with cold water immersion – as more body surface area is immersed in cold water, more heat is transferred and effective cooling occurs.
- *Evaporation* in humans is facilitated by perspiration. Perspiration is dependent on sweat production and water vapour pressure gradient. Therefore, as humidity increases, evaporation decreases and perspiration becomes the main modality of heat loss.
- *Radiation* is heat transfer by electromagnetic waves. Radiant energy is resorbed and reflected. Hence, light-coloured clothing can prevent heat illness by reducing heat absorption.
- *Convection* occurs when the body exchanges heat with the surrounding air. Heat is gained from hot air coming into contact with the skin. Convective heat exchange can be increased by fans, air-conditioning and loose-fitting clothing.

Physiology of Heat Regulation

The regulation of body temperature involves three distinct aspects, i.e. thermosensors, central nervous system and thermoregulatory effectors [3, 6–8].

- Thermosensors are temperature-sensitive structures located peripherally in the skin and centrally in the body and are activated when the temperature of blood exceeds a ‘set point’.
- The central nervous system (central integrative area) interprets information received from thermosensors to instruct thermoregulatory effectors.
- The thermoregulatory effectors consist of sweating and the vascular response.
- Sweating is facilitated via apocrine and eccrine sweat glands.
- The vascular response consists of peripheral cutaneous vasodilatation and compensatory splanchnic and renal vasoconstriction.

Risk Factors for Heat-Related Illnesses

- The body’s ability to dissipate heat can be adversely affected by certain conditions and medications (*refer to* Table 24.1).

Table 24.1 Risk factors for heat-related illnesses [3, 6, 7]

Extremes of age
Cognitive impairment
Heart and lung diseases
Limited access to air-conditioning
Mental illness
Obesity
Physical disabilities/impaired mobility
Poor fitness level
Sickle cell trait
Strenuous outdoor activity during hottest daytime hours
Urban residence or living on higher floors
Chronic medications that inhibit effective thermoregulation or illicit drugs that increase endogenous heat production

- The elderly are at risk because of co-morbidities, immobility and diminished physiological reserves.
- Young, healthy people who engage in prolonged strenuous activity in hot and humid conditions are at an increased risk of heat illnesses [7–9].
- Studies have shown that people who work outdoors have a 20-fold increase in heat-related death compared with persons in other forms of employment [3, 8, 9].
- Heat-related illnesses can be divided into minor and major heat illnesses [6–8].
- Minor heat illnesses emanate from excessive physiological responses to heat stress and are usually self-limiting.
- The two major heat illnesses, namely, heat exhaustion and heatstroke, should be considered as disorders of either extreme of a continuum of heat stress response [3, 6].
- Major heat illnesses require urgent management.

Heat Exhaustion

Pathophysiology

- Heat exhaustion is a clinical syndrome characterised by volume depletion resulting from exposure to excessive environmental heat.
- There are two types, namely, water depletion and salt depletion [3, 6–8].
- Water depletion results from inadequate replacement of fluid and can lead to progressive hypovolaemia and ultimately heatstroke.
- Salt depletion heat exhaustion results when large volumes of sweat are replaced by water only and not enough salt.
- The biochemical presentation is one of hyponatraemia, hypochloraemia and decreased urinary sodium and decreased urinary chloride [7, 8].

Clinical Features

- Patients present with a normal core temperature, or if raised, it is less than 40 °C.
- Vague malaise, fatigue and headaches may occur.
- Mental function remains intact with no coma and seizures.
- Tachycardia, orthostatic hypotension and clinical dehydration may occur.
- Hepatic transaminases may be increased to several thousand, whereas in heatstroke hepatic transaminases are increased to tens of thousands.
- If there is any uncertainty about the diagnosis, treat as heatstroke.

Management

- Ensure the patient rests in a cool environment [9–11].
- Assess the volume status of the patient by measuring orthostatic blood pressure changes, blood urea and haematocrit and serum sodium levels.
- Replace fluid losses slowly with normal saline, being careful to avoid cerebral oedema.
- Admit patients if extremes of age, if there are significant electrolyte abnormalities or if there is a high risk of recurrence.

Heatstroke

Pathophysiology

- Heatstroke is a catastrophic life-threatening emergency that occurs when homeostatic thermoregulatory mechanisms fail, in the setting of excessive endogenous or exogenous heat exposure [3, 6–8].
- This results in an extreme elevation of core body temperature to more than 40.5 °C, producing multi-organ dysfunction.
- Neurological dysfunction is the hallmark of heatstroke [3, 6–8].
- Failure of compensatory splanchnic vasoconstriction results in an increased rate of heat storage which in turn causes an elevation in intracranial pressure.
- This combined with a decrease in mean arterial pressures and a concomitant reduction in cerebral blood flow causes major central nervous system dysfunction.
- Heat stress also creates great physiological demands on the cardiovascular system, and patients exhibit signs of circulatory failure.
- Hepatic damage is also a consistent feature of heatstroke.

Clinical Features

- Patients present with a sudden onset of an altered level of consciousness after being exposed to heat stress.
- The core temperature exceeds 40.5°.
- There are signs of central nervous system dysfunction, namely, coma, seizures or delirium.
- Patients present with hot skin, and sweating may persist.
- Biochemically, there is a marked elevation of hepatic transaminases.

Differential Diagnosis

- Intracranial haemorrhage
- Toxins
- Drugs
- Seizures
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Thyroid storm
- Sepsis and meningoencephalitis

Two forms of heatstroke have been described [7–9, 11].

- Classic heatstroke occurs during heat waves.
- Exertional heatstroke results from overwhelming endogenous heat production.

Management

- Attend to the airway, breathing and circulation as priorities.
- Insert wide-bore intravenous lines, and attach the patient to monitors and face mask oxygen.
- Confirm core temperature rectally.
- Take blood for full blood count, urea and electrolytes, hepatic transaminases, clotting profile, blood sugar, cardiac enzymes, serum lactate and venous blood gas.
- Commence immediate cooling by evaporative cooling using fans and skin wetting or ice water immersion [6, 8, 10, 11].
- Adjuncts to cooling include ice packs to axillae and groin, cooling blankets, rectal lavage, gastric lavage and cardiopulmonary bypass [10, 11].

- If the patient is hypotensive or has signs of rhabdomyolysis, a central venous catheter should be inserted to guide the fluid resuscitation.
- A urine output of 2 mL/kg/h should be maintained.
- Short-acting benzodiazepines can be used for sedation and seizure control or to counteract shivering.
- Consider fresh frozen plasma and platelet transfusion after cooling to manage coagulopathies.
- Antipyretics are ineffective and should not be used in heatstroke.

Minor Heat Illnesses

Heat Cramps

- Are episodic severe muscular cramps in exertional muscles related to salt deficiency.
- Occur typically when patient has stopped strenuous activity and is at rest.
- They are rapidly relieved by oral salt solution in mild cases and intravenous isotonic solution in severe cases.

Heat Oedema

- Patients present with swollen feet and ankles, especially the elderly, who are unacclimatised to warm climatic stress.
- No underlying cardiac, hepatic, venous or lymphatic disease is present.
- Treatment is simple leg elevation or thigh-high support stockings.

Heat Syncope

- This is a temporary loss of consciousness due to pooling of blood in the lower extremities.
- Heat syncope is common in patients who stand for protracted periods in hot humid conditions.
- It is self-limiting as resumption of a horizontal position is curative.

Heat Rash

- This is an acute inflammatory disorder of the skin in tropical climates arising from blockage of sweat gland pores [6–8].

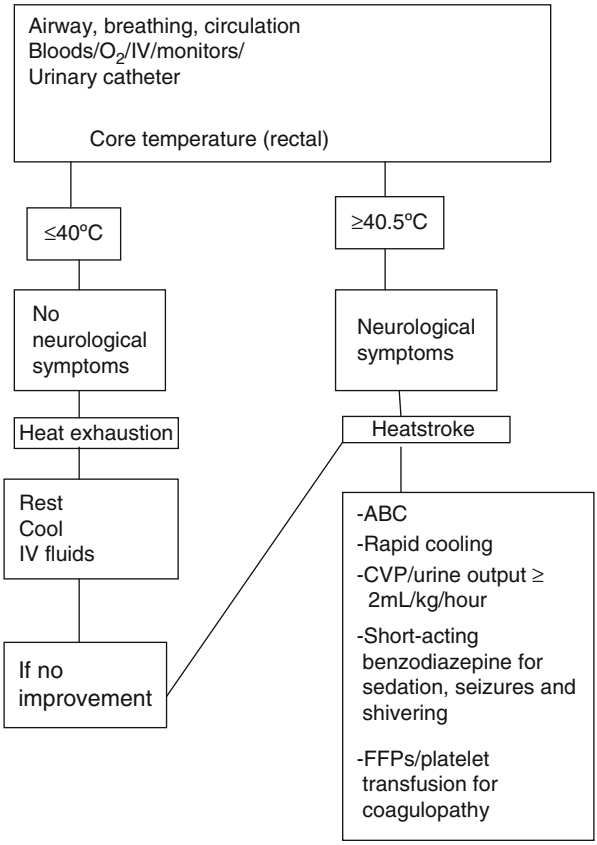

Fig. 24.1 Algorithm for management of major heat illnesses

- It is characterised by pruritic vesicles on an erythematous base confined to clothed areas.
- Treatment includes topical chlorhexidine cream, 1 % salicylic acid or erythromycin for diffuse pustular lesions [6, 7] (Fig. 24.1).

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Chapter 25
Submersion and Diving-Related Illnesses

Jaybalan Allan Matthew

Key Points

- The underlying pathophysiology of submersion injury is aspiration and laryngospasm, which results in ventilation (V)/perfusion (Q) mismatching and hypoxia.
- Hypothermia is an associated problem in submersion, and its effects must be considered.
- Management of the submersion injury patient is usually resuscitative and supportive.
- Diving-related illness can also be related to toxicities of various gases that the diver is exposed to.

Introduction

It is estimated that approximately 500,000 people die from drowning each year, with the majority of people being toddlers and teenagers [1]. The Center for Disease Control and Prevention further estimates that there are four to five people seeking medical care with nonfatal problems for every person dying from drowning [1].

Unfortunately, the disease profile is not just one presentation, and both submersion injuries and diving-related problems potentially present in multiple different

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_25

ways. These can be further compounded by hypothermia associated with the exposure to an aquatic environment. Submersion and diving-related injuries pose unique challenges to emergency physicians across the world, with very little training and experience available to address these presentations.

Pathophysiology of Submersion and Diving-Related Illnesses

- *Drowning* is defined as the process of experiencing respiratory impairment from submersion or immersion in liquid [2, 3].
- *Submersion* refers to the process whereby the person's airway is exposed to liquid, usually with the head under the surface of a body of liquid.
- *Immersion* refers to the process whereby the person's airway is not exposed to liquid, despite them being exposed to a body of fluid.
- Drowning outcomes are subsequently defined as:
  - Death
  - Morbidity
  - No morbidity [1]
- Morbidity outcomes are further classified as:
  - Moderately disabled
  - Severely disabled
  - Vegetative state or coma
  - Brain death [3]
- Therefore, older terminology to define drowning-related problems has been abandoned. A patient presenting to the emergency department (ED) alive can be classified as drowning by submersion with morbidity/no morbidity, depending on signs and symptoms.

Immersion syndrome refers to a syncopal episode due to cardiac dysrhythmia(s) because of sudden contact with cold water, at least 5 °C less than the person's core body temperature [1]. This syndrome has been postulated to result from either vagal stimulation or prolonging of the QT interval, because of the rapid exposure to cold temperature [1].

- Potential risk factors for drowning are:
  - Ethanol consumption
  - Seizure disorders
  - Developmental disorders
  - Prolonged QT syndrome [4]
- Submersion acutely involves the victim holding their breath, which leads to asphyxia and resultant hypoxia.

- When the person gasps, they swallow water, which is subsequently aspirated. There may be an initial element of laryngospasm [3].
- Most drowning victims aspirate <4 ml/kg of water, and only when volumes >11 ml/kg[1] to >22 ml/kg[3] are aspirated can one begin to consider the effects of freshwater versus salt water aspiration, and the resultant electrolyte abnormalities, along with fluid shifts and haemolysis [1].
- Aspiration disrupts the integrity of the alveolar surfactant and subsequent dysfunction of the alveolar-capillary unit.
- This results in alveolar collapse and fluid accumulation inside the alveolus and subsequent non-cardiogenic pulmonary oedema.
- This atelectasis and oedema result in intrapulmonary shunting and a subsequent ventilation (V)/perfusion (Q) mismatch, with resultant hypoxia [3].
- Diving-related illnesses include *dysbarism*. This refers to illnesses resulting from the diver exposed to an environment of increasing ambient pressure [5].
- Increasing depth increases the ambient pressure that the diver is exposed to.
- This affects air-filled cavities as well as the physicochemical properties of gases within the body.
- The important gas laws that affect this behaviour of gases are:
  - *Henry's Law:*

    The amount of gas that will dissolve in liquid at a given temperature is proportional to the partial pressure of that gas.
  - *Boyle's Law:*

    The volume of a gas is inversely proportional to the pressure the gas is exposed to, at constant temperature [6].
- Increasing depth, with its resultant increasing pressure, and decreasing volumes have an effect on air-filled spaces on or in the human body, and the increasing pressure affects dissolution of gases in the human body.
- During ascent, the pressure the diver is exposed to decreases, with a subsequent increase in volumes on spaces on or in the human body, and the decreasing pressure causes gases to come out of solution, forming bubbles in the blood and body tissues [5].

Clinical Features

- Fluid in the airway can initially present to the first responder as choking or coughing, with possible vomiting.
- Respiratory signs – tachypnoea, cyanosis, wheezing and crepitations.
- Increased risk of vomiting and aspiration due to gastric distention from swallowing large amounts of water.
- Aspiration complicates into acute respiratory distress syndrome (ARDS).

- Submersion could result in or be the result of cardiac dysrhythmias, aggravated by hypoxia, hypothermia and acidosis.
- Hypoperfusion of the kidneys could result in acute renal impairment.
- Hypothermia affects platelet activity, and there could be evidence of coagulation problems. A frank disseminated intravascular coagulopathy could result.
- Central nervous system (CNS) effects are altered mental status with a depressed level of consciousness and coma. Seizures may occur.
- During rapid ascent, pressure decreases rapidly and volume increases quickly, as shown in Fig. 25.1. Air-filled spaces in the body may expand rapidly causing pain. Gastrointestinal barotrauma results in abdominal pain due to increase in the lumen of the tract. This could result in vomiting, with the risk of aspiration. Patients usually have increased eructation and flatulence.
- Air spaces in dental cavities result in pain. This is called barodontalgia.
- More sinister increases in volume affect the pulmonary system resulting in pneumothorax, pneumomediastinum or arterial gas embolism (AGE).
- AGE is a potentially life-threatening problem. Gas bubbles increase in volume and are forced out of alveoli and into the pulmonary veins, making their way back to the heart. Here they can cause coronary gas embolism, which could manifest as cardiac ischaemic pain, or embolise to the cerebral arteries, where they could manifest as an acute cerebrovascular event.
- If the dive was deep, close to the decompression limits, or prolonged and there were few adequate compulsory stops on ascent, the patient could develop a decompression sickness (DCS) [5].

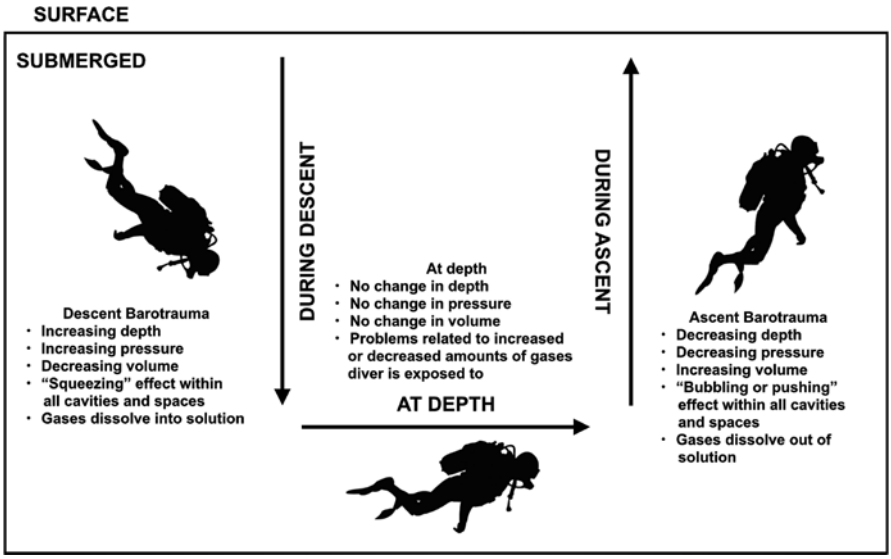


Fig. 25.1 Stages of the diving profile and the potential pathophysiological problems that could occur

- The Golding Classification categorises these as follows [7]:
  - Type I: Dermo-arthralgic
  - Type II: Nervous or cardiac/pulmonary
  - Type III: Considered by some authors as the most devastating when type II is present with AGE and its complications
- Risk factors for the development of DCS are shown in Table 25.1, and general risk factors for drowning are shown in Table 25.2.
- Under pressure, nitrogen dissolves into blood and tissues, and when ambient pressure decreases, nitrogen 'bubbles' back out of solution. These bubbles coalesce and progress to the lungs or other areas, where they cause | symptoms [5].
- Type I or dermo-arthralgic DCS results in periarticular pain ('bends'), itching and erythema with marbling of skin (cutis marmorata).
- Type II or neurosystemic DCS affects other organ systems, and depending on the affected system, the symptoms are diverse:
  - CNS manifestations could be spinal (limb weakness and backache with patchy motor/sensory fallout) or cerebral (headache, blurred vision/diplopia, malaise or altered behaviour).

Table 25.1 Risk factors for decompression sickness [1, 3]

Length of dive
Depth of dive
Obesity
Fatigue
Exertion
Dehydration
Fever
Smoking and alcohol
Male gender
Cold ambient temperature post-dive
Diving at altitude
Flying immediately after diving
Patent foramen ovale or other congenital abnormality creating a right-to-left shunt

Table 25.2 General risk factors for drowning [3]

Age: bimodal (toddlers and teenagers)
Location: home pools, buckets, bathtubs, community pools, open bodies of water
Gender: males > females
Race: blacks > whites
Substance use
Pre-existing disease

  - Inner ear manifestations ('staggers') are similar to inner ear barotrauma and need careful evaluation to differentiate the two. The distinction is based on the stage of the dive symptoms developed.
  - Pulmonary manifestations ('chokes') are non-specific and include dyspnoea, cough and pleuritic pain.
- Hypothermia remains a problem at depth, and these will be addressed in another chapter [5].
- There could also be concomitant signs of trauma depending on the mechanism [5].

Differential Diagnosis

- Drug or alcohol intoxication
- Hypoglycaemia
- Seizure disorders
- Suicide or homicide (differential for drowning)
- Other causes of cardiac arrest
- Respiratory tract infections for oto-barotrauma
- Lower respiratory tract infections for lower respiratory tract barotrauma
- Other medical problems mimicking DCS or AGE

Investigations

- There are no specific investigations for drowning or diving-related illnesses.
- Chest x-rays is essential, especially when pulmonary barotrauma is suspected. However, they may be initially clear and should be requested based on clinical expectation.
- Arterial blood gases (ABG) are more sensitive for hypoxia, and the patient may even require serial ABGs to be done.
- If the patient remains comatose, a computed tomography (CT) scan of the head may be useful to rule out other causes of depressed level of consciousness, but the CT is usually normal initially in a drowning/diving victim.
- Cervical spine requires imaging if cervical spine injury is suspected.
- Blood glucose determinations must be done for all patients with altered mental status, a depressed level of consciousness, or where clinically indicated.
- Electrolytes, renal functions and liver function tests must be requested, indicated.
- Toxicology screens may be requested where a clinical suspicion exists. This must include a blood alcohol level, where intoxication is suspected.
- A complete blood count may reveal a non-specific leukocytosis. Coagulation studies may be normal.

Management

- If the patient is in cardiac arrest, advanced life support interventions must be initiated immediately, with particular emphasis on airway management, oxygenation and ventilation, chest compressions, electrical therapy and rewarming. Continue CPR at least until the patients' body temperature is 30–35 °C.
  Try to remove the victim's wet clothes off quickly, but do not delay assessment of pulses, and commencement of CPR, if indicated.
- If utilising aeromedical resources to transport a patient with a diving-related problem, consider the following:
  - Pressurise the cabin to 304.8 m if possible.
  - Helicopters should fly at no more than 152.4 m above the departure facility altitude.
- If trauma is suspected, then advanced trauma life support (ATLS) measures must be implemented.
- If hypoxia, DCS or AGE is not suspected, and the patient's oximetry is >94 % and then oxygen can be delivered as a titrated dose to effect. If in doubt in these patients, provide supplemental oxygen.
- If an ascent-related problem is suspected, consider the possibility of DCS or AGE, and contact the nearest hyperbaric chamber facility to arrange for the transport of the patient there.
- At all times, provide the patient with 100 % oxygen, especially if a decompression problem is suspected, to facilitate nitrogen washout and to treat hypoxia.
- If hypoxia or a decompression sickness or arterial gas embolisation is not suspected and the patient's oximetry is >94 %, then oxygen can be delivered as a titrated dose to effect. If in doubt in these patients, provide supplemental oxygen.
- Obtain a 12-lead electrocardiogram (ECG), looking for cold-related dysrhythmias, features of electrolyte abnormalities and long QT syndrome.
- Check the patient's glucose level and treat if not normal.
- Ensure periodic assessment of the Glasgow Coma Scale (GCS) and document findings thoroughly.
- Measure the core temperature of the patient, and maintain thermoregulation.
- Aspirin 325–650 mg may be given PO to prevent platelet clumping.
- Decompress the stomach by inserting a nasogastric/orogastric tube.
- There is no role for routine steroid use.
- Treat cardiac dysrhythmias, according to standard ACLS protocols.
- Manage seizures as appropriate.
- Avoid the Trendelenburg position in the patient as it increases intracranial pressure and increases the risk of coronary gas embolisation.
- Recompression therapy is indicated in severe cases of decompression states. It should be provided at least within the first 24 h, but there has been benefit in offering it 10–14 days after exposure.

- The goals of recompression are to reduce the mechanical obstruction caused by the air bubbles, facilitate the washout of nitrogen gas bubbles, and deliver oxygen to ischaemic tissues.
- Traditional 'HYPER' therapy (hypothermia, hyperventilation, steroid, dehydration, barbiturate coma, neuromuscular blockade) has been proven to be detrimental to the submersion patient outcome [8].

Disposition

- *Patients require admission if they:*
  - Required CPR at any time
  - Were apnoeic at any time
  - Had a depressed level of consciousness or altered mental status at any time
  - Showed signs or symptoms of hypoxia at any time
  - Had any dysrhythmia at any time
  - Had abnormal chest X-ray or arterial blood gas determination at any time
  - Require recompression therapy for any length of time.

  Patients may be considered for discharge if they have remained asymptomatic after 6 h of observation in the ED *and* have a normal room air oxygen saturation *and* have a normal chest x-ray *and* have a normal arterial blood gas.
- For patients with decompression illness, they should delay flying for 12 h, if they have a total dive time of less than 2 h in the last 48 h.
- For multi-day or unlimited diving, patients should delay flying for 24 h.
- Patients recompressed for DCS or AGE should not fly for 72 h.
- Any patient suspected of having a diving-related illness should not go diving for 7 days after recompression for DCS type I and for 4 weeks for DCS type II.

Prognosis

- Patients with drowning usually have a good prognosis unless the following criteria are present: [9]
  - Age <3 years
  - Submersion >5 min
  - Asystolic cardiac arrest
  - Cardiac arrest with no return of spontaneous circulation in 10 min
  - Time to initiate CPR >10 min
  - Hypothermia (water temperature <10 °C, core temperature <35 °C)
  - Acidosis, ph <7.1

Table 25.3 Modell, Conn and Barker classification of drowning patients (describing the patients' condition within 1 h of ED arrival) [3]

Category	Description
A	Awake
	Fully orientated
B	Blunted
	Arousable
	Purposeful response to pain
C	Comatose
	Not arousable
	Abnormal response to pain
C1	Flexor response to pain
C2	Extensor response to pain
C3	Flaccid
C4	Cardiac arrest

  - GCS 3/15
  - Unreactive pupils
  - Aspiration
- Patients with diving-related illness usually have self-limiting problems or respond well to symptomatic therapy, with little or no residual sequelae.
- Poor prognosis with morbidity/mortality is expected in the following:
  - Oxygen toxicity with seizures
  - Nitrogen narcosis with decrease higher-centre function and secondary injury due to lack of judgement
  - Any form of type I or II DCS or AGE without recompression
  - AGE with coronary or cerebral vessel occlusion
  - DCS type II with neurologic symptoms

Table 25.3 shows a useful classification system to assist with prognostication for a patient arriving at an emergency department.

- Paediatric drowning victims may present at their worst, in respiratory arrest (65 %) or cardiac arrest (35 %) [10]. This is probably the same for adults with drowning morbidity.
- Of those children in any form of arrest, 66 % complicate with multi-organ dysfunction, 12 % end up with single organ dysfunction, and 22 % have no organ failure [10].

Prevention

- Prevention of drowning can be achieved with vigilance around children, reducing alcohol consumption near aquatic environments or during water sport activities.
- Injury from drowning can also be mitigated against by layperson CPR; therefore, it is important for people to learn CPR to assist family members.

- Prevention of diving-related illness involves conscious efforts to reduce the effects of pressure on the human body.
- Steps to equalise pressure during descent should help reduce descent barotrauma.
- Avoid factors that increase your risk for barotrauma and other diving-related illnesses.
- Ensure the safe set-up and usage of diving equipment.
- Ensure that you stick to appropriate and safe diving schedules to limit your bottom time.
- Ensuring safe and gradual ascent will reduce your risk of ascent barotrauma.
- Steps are being made to create awareness of drowning using a similar approach for cardiac arrest, and a *drowning chain of survival* has been proposed (Fig. 25.2) [11].

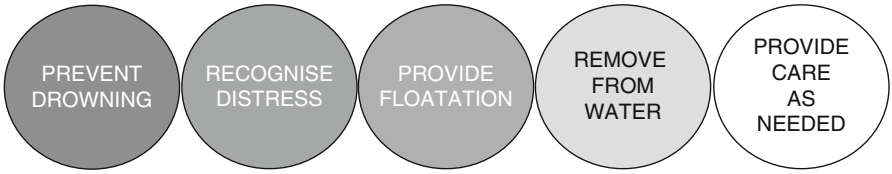
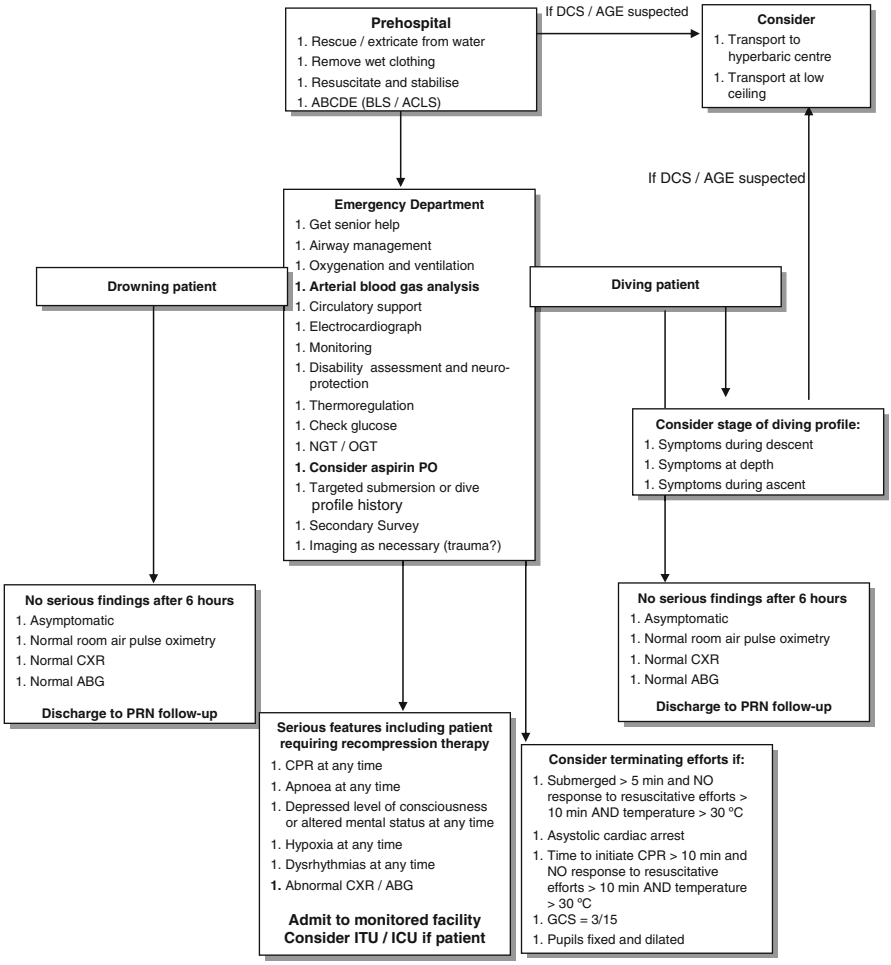


Fig. 25.2 Drowning chain of survival [11]

Algorithm for the Management of Diving-Related and Submersion Injuries



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Part VI
Gastrointestinal System

Chapter 26
Abdominal Pain

Harshil Mehta

Key Points
- Wide range of pathologies may present with abdominal pain.
- Key to reach proper diagnosis is adequate history and physical examination along with laboratory tests and imaging.
- Disposition of patients with abdominal pain is as difficult as its diagnosis.
- Low threshold should be kept for high-risk patients.
- Life-threatening diseases should not be missed in emergency.

Introduction

- Abdominal pain is one of the most common reasons for emergency department visits. Incidence is around 10–12 % globally. Demographic factors like age, gender, ethnicity and family history affect its presentation.
- It is paramount for emergency physicians to have methodical approach in history, physical examination, investigation and treatment. Clinical suspicion of life-threatening diseases in high-risk patients is utmost important.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_26

Pathophysiology

- Many intra-abdominal and extra-abdominal diseases are responsible for abdominal pain.
- Nature of abdominal pain can be divided into three categories based on neurological pathways:
  - Somatic (parietal) pain:
    It results from irritation of parietal peritoneum caused by inflammation, infection or chemical reaction. It is supplied by myelinated nerve fibres. It is localised and constant. As the disease process evolves and irritates parietal peritoneum, we can elicit tenderness, guarding and rigidity. The patient prefers to lie immobile.
  - Visceral pain:
    It is caused by stretching of walls of hollow viscera, innervated by unmyelinated fibres. It is diffuse and intermittent, dull aching and colicky in nature. Patients keep tossing on the bed. It is felt in the abdominal region which correlates to the somatic segment of embryonic region. Foregut, midgut and hindgut structures (Table 26.1) relate to upper, middle and lower abdomen, respectively. Visceral pain can be perceived away from actual disease process, i.e. pain of acute appendicitis is felt around umbilicus initially as it corresponds to T10 somatic distribution.
  - Referred pain:
    It is defined as a pain that is felt away from the site of origin. Common anatomical origin or same nerve root innervations are primary reasons for such pain (Fig. 26.1).

Clinical Features

- History:
  - Age and gender are important history points. Elderly patients with nonspecific complaints may have serious pathology. In females, obstetrics and gynaecological causes should be considered.

Table 26.1 Abdominal structures and its origin

Foregut	Stomach, liver, gall bladder, pancreas, first/second part of duodenum
Midgut	Third/forth part of duodenum, jejunum, ileum, appendix, caecum, ascending colon, transverse colon (proximal two thirds)
Hindgut	Transverse colon (distal one third), descending colon, sigmoid, rectum, genitourinary organs

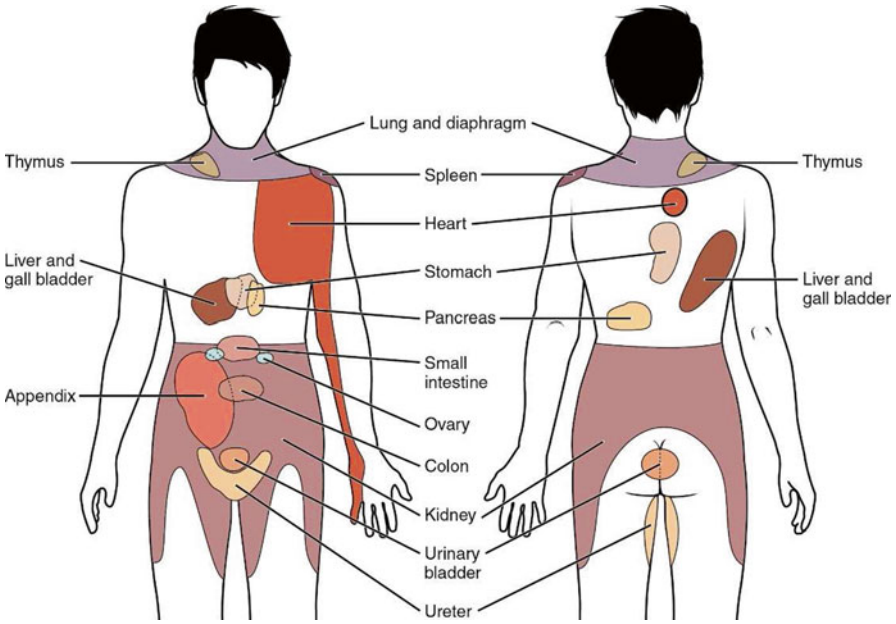

Fig. 26.1 Common locations for referred pain

– Pain can be described as (SCRIPT FADO):

  *S*ite
  *C*haracter
  *R*adiation
  *I*ntensity
  *P*recipitating/relieving factors
  *T*ime duration
  *F*requency
  *A*ssociated features
  *D*iurnal variation
  *O*nset

– *Gastrointestinal* complaints (anorexia, nausea, vomiting, altered bowel habits, haematemesis, haematochezia, abdominal distension, back pain), *genitourinary* problems (urinary complains, foul discharge), *thoracic* complaints (chest pain, breathlessness, palpitation) and *constitutional* symptoms (fever, weight loss)
– *Past history*: Regarding previous similar episodes, admissions, investigations and treatment
– *Pre-existing medical illness*: Diabetes, hypertension, heart diseases, liver/renal diseases, HIV, STD and tuberculosis
– *Medication history*: Antibiotics, antiplatelets/anticoagulants, steroids, beta-blockers/calcium channel blockers, NSAIDs, chemotherapeutic agents, etc.
– *Surgical history*: Laparotomy, caesarean sections, etc.

Table 26.2 Physical examination correlation

Respiratory	
Restriction	Pleural effusion
Crackles	Pneumonia
Cardiovascular	
Gallop rhythm, arrhythmia	Myocardial infarction
Abdomen	
Caput medusa	Portal hypertension
Bulging flanks	Ascites
Visible hernia	Strangulated hernia
Tenderness, guarding, rigidity	Peritonitis
Shifting dullness	Ascites
Absent bowel sounds	Ileus, late sign of bowel obstruction
Psoas sign	Retrocaecal appendicitis
Obturator sign	Retrocaecal appendicitis, local abscess
Rovsing's sign	Appendicitis
Murphy's sign	Cholecystitis
Kehr's sign	Cholecystitis, perforation
Cullen's sign	Pancreatitis, retroperitoneal bleed
Renal angle tenderness	Renal stones
Grey Turner sign	Pancreatitis, ruptured abdominal aortic aneurysm
Rectal	
Tenderness	Prostatitis, anal fissure
Mass	Anorectal carcinoma, haemorrhoids
Empty PR examination	Intestinal obstruction
Pelvic	
Tenderness	Ectopic pregnancy, PID, ovarian cyst
Mass	Ovarian cyst, tumour, abscess

PID pelvic inflammatory disease, *PR* per rectal

  - *Obstetric history*: Last menstrual period, previous pregnancies/deliveries, abortions, ectopic, IVF, IUCDs and other contraceptive measures
  - Allergies, social history (alcohol/drug addiction), history of last meal and history of trauma

- *Physical examination*:
  - Despite the development of newer imaging modalities, i.e. ultrasound, CT scan and MRI, physical examination holds a key role in patient evaluation. Some specific signs are summarised in Table 26.2.
  - *General examination and vital signs*: Appearance, temperature, pulse, blood pressure, respiratory rate, oxygen saturation, GCS, blood glucose measurement and pain score.

- *Inspection*: With consent, inspect abdominal skin for scars (adhesions), dilated tortuous vein (spider angiomata, caput medusa), skin eruptions (herpes zoster), haemorrhage or signs of trauma (ecchymosis), foreign body and entry/exit wounds. Distension of abdomen (ascites, intestinal obstruction, ileus) and obvious masses (tumour, hernia, pregnancy, distended bladder, aneurysm) should be examined. Hernia orifices and external genitalia should not be forgotten.
- *Palpation*: Focus on locating the site of tenderness, signs of peritonism and palpation of masses. Abdomen is divided into right upper, right lower, left upper and left lower quadrants. Localisation of tenderness guides physician to generate differential diagnosis pertaining to that area. However, one can have diffuse abdominal pain spreading to more than one quadrant, i.e. pain of renal calculus extends from lumbar region to the iliac fossa and groin.

  Patients with peritoneal irritation show tenderness, guarding/rigidity and pain with coughing. Guarding could be voluntary or involuntary. Due to lax abdominal wall musculature, guarding and rigidity may be absent in the elderly. Typical rebound tenderness is no longer considered an important examination tool due to painful procedure [1].

  Abdominal aorta, liver and spleen sizes can be evaluated by palpation. Elderly patients with history of recent abdominal/flank/low back pain, known hypertension, pulsatile abdominal mass and feeble/absent distal pulses are suggestive of abdominal aortic aneurysm/dissection. Bedside ultrasound facilitates visualisation of increased abdominal aortic diameter and determines further surgical/medical management.
- *Percussion*: Helpful to assess free air intraperitoneum, degree of ascites, gas-filled bowel loops and peritonitis. It is not very useful in noisy ED.
- *Auscultation*: It gives information regarding bowel and vascular status. Absent or diminished bowel sound indicates ileus, mesenteric ischaemia, narcotic use or peritonitis. Hyperactive bowel sounds suggest small bowel obstruction, enteritis or early ischaemic intestine. High pitched tinkling sound reflects mechanical obstruction.
- *Digital rectal examination*: Useful for detection of perianal and rectal pathologies (haemorrhoids, fissure and fistula), intraluminal intestinal haemorrhage (dark maroon/red stool), proctitis and constipation (faecal impaction and intestinal obstruction). It is no more useful in diagnosing acute appendicitis [2].
- Emergency physicians should be vigilant and think of serious pathology in presence of any of the following clinical features:

  Abdominal pain prior to vomiting
  Haematemesis/haematochezia
  Confusion

Toxic appearance
Signs of shock/dehydration
Localised/generalised tenderness
Guarding/rigidity
Absent bowel sound

Differential Diagnosis

Extensive differential considerations ranging from simple nonspecific abdominal pain to severe life-threatening conditions are mentioned in Table 26.3.

It is essential to suspect life-threatening conditions (Box 26.1) in haemodynamically unstable. Early resuscitation and stabilisation should be followed by investigations and hospitalisation of such patients.

Box 26.1 Life-Threatening Conditions

Acute intestinal obstruction
Viscus perforation
Traumatic rupture of the spleen/liver/bowel
Acute pancreatitis
Mesenteric ischaemia
Ruptured abdominal aortic aneurysm
Ruptured ectopic pregnancy
Myocardial infarction

Women of reproductive age group with abdominal pain should undergo pregnancy test and seek gynaecological consult and bedside ultrasonography if necessary. Consider ectopic pregnancy in such patients unless proven otherwise.

It is not necessary to reach proper diagnosis despite availability of various tests. It is incumbent to consider extra-abdominal causes (Table 26.4) in such patients before considering it as nonspecific.

Investigations

Laboratory evaluation in addition to history and clinical findings aid in diagnosis (Box 26.2).

Table 26.3 Important differential diagnosis

Condition	Epidemiology	Clinical features	Laboratory tests	Imaging	Complications
Acute gastritis	Any age	Epigastric burning pain, associated with food, increases on supine position	–	Upper GI endoscopy, biopsy for *H. pylori*	Gastro-oesophageal reflux disease, perforation
		Epigastric tenderness, no rebound tenderness			
Peptic ulcer disease	Age >50 years, M>F, RF: *H. pylori*, NSAIDS use, smoking, alcohol	Severe epigastric pain 2–5 h after meals or at night, nausea, vomiting, early satiety	Stool for occult blood (bleeding ulcer)	Upper GI endoscopy	Perforation, bleeding
		Epigastric tenderness			
Biliary tract disease	Age: 40–60 years, F>M, RF: childbearing age, obese, alcohol, OC pills	Epigastric/RUQ pain, radiating to right shoulder/ subscapular, postprandial pain, nausea, fever	CBC, liver function test	Ultrasonography – most sensitive, CT scan in extrahepatic biliary obstruction, hepatobiliary scintigraphy	Septicaemia, pancreatitis
		Jaundice, RUQ tenderness, rebound tenderness, Murphy's sign			
Acute pancreatitis	Age: 45–60 years, varies with aetiology; M>F, aetiology: gallstones, alcohol	Severe epigastric pain following meal, radiating to back, nausea, vomiting, fever, tachycardia, tachypnoea, hypotension, hyperthermia, epigastric tenderness, guarding, Cullen's sign, Grey Turner's sign	CBC, S. lipase, S. amylase, liver function test	Helical CT with contrast, ultrasonography for biliary tract pathology	Local complications: acute local fluid collection, pseudocyst, necrosis, abscess
					Systemic: septicaemia, ARDS

(continued)

Table 26.3 (continued)

Condition	Epidemiology	Clinical features	Laboratory tests	Imaging	Complications
Bowel obstruction	Any age, RF: h/o previous abdominal surgery	Crampy abdominal pain, nausea, vomiting, constipation, abdominal distension	CBC, S. electrolytes	X-ray abdomen standing, CT abdomen	Strangulation, incarceration
		Tachycardia, diffuse tenderness, tympanic note, hyperactive bowel sound, PR examination – empty			
Viscus perforation	Elderly age, RF: peptic ulcer, intestinal ulcers, carcinoma	Severe abdominal pain, lies still in bed, abdominal distension, vomiting, fever	CBC, S. electrolytes	X-ray chest, abdomen standing	Septicaemia
		Signs of shock, generalized abdominal tenderness, rigidity, signs of peritonitis			
Mesenteric ischaemia	Elderly population, M>F, RF: atherosclerosis, arrhythmia, CHF, recent MI, valvular diseases	Diffuse abdominal pain out of proportion, vomiting, diarrhoea	CBC, S. lactate, blood pH, S. amylase, S. creatinine kinase	CT abdominal angiography	Intestinal necrosis, metabolic acidosis
		Tachycardia, tachypnoea, hypotension, silent abdomen initially, signs of peritonitis			
Diverticulitis	Mean age: 60 years, M=F, sigmoid colon – most common site	Left lower quadrant pain, fever, change in bowel habits	CBC, stool for occult blood	CT abdomen	Perforation, fistula, obstruction, haemorrhage
		Abdominal tenderness, guarding, signs of peritonitis			

Appendicitis	Young adulthood, M>F	Periumbilical pain migrates to RLQ, nausea, vomiting, fever	CBC, S. electrolytes, urine examination	CT in adult and non-pregnant patients	Perforation, peritonitis, septicaemia, abscess
		RLQ tenderness, guarding, rebound tenderness, psoas sign, obturator sign			
Ureteric colic	Age: 30–40 years, M>F	Severe colicky flank pain radiating to groin, nausea, vomiting, haematuria, tossing up in bed	Urine examination, CBC	Spiral CT, ultrasonography in pregnancy	UTI
		Flank tenderness			
Ruptured abdominal aortic aneurysm	Age >50 years, M>F, RF: hypertension, atherosclerotic disease, DM, smoking family history	Severe sudden onset abdominal pain radiating to back, syncope, GI bleeding, shock	–	Bedside ultrasonography, CT aortogram	Shock, limb ischaemia
		Tachycardia, hypotension, palpable abdominal mass, unequal femoral pulses			
Traumatic organ rupture	Age:15–35 years; M>F	Abdominal pain, vomiting	CBC	EFAST, abdominal sonography, CT abdomen	Shock, peritonitis, DIC
		Signs of shock, injury marks			
Ruptured ectopic pregnancy	Female of childbearing age, RF: IUCD, previous ectopic, PID	Sudden, severe pain, spotting, amenorrhoea	UPT, S.HCG, CBC	FAST, transvaginal and transabdominal ultrasonography	Shock, septicaemia, DIC
		Tachycardia, hypotension, peritoneal signs, adnexal mass and tenderness, cervical motion tenderness, blood in vaginal vault			

(continued)

Table 26.3 (continued)

Condition	Epidemiology	Clinical features	Laboratory tests	Imaging	Complications
PID	Age: 15–49 years; RF: multiple partners, previous PID	Lower abdominal pain, fever, nausea, vomiting, vaginal discharge	UPT, CBC, vaginal swab test for gonorrhoea/ chlamydia	Transvaginal ultrasonography	Tubo-ovarian abscess, ectopic pregnancy
		Cervical motion/uterine/ adnexal tenderness, rebound tenderness			
C. difficile colitis	Elderly population, RF: antibiotics (fluoroquinolones, penicillin, clindamycin)	Crampy abdominal pain, watery diarrhoea, fever	CBC, Stool culture	CT scan	Pseudomembranous colitis, toxic megacolon, perforation
		Signs of dehydration, abdominal tenderness, distension, rebound tenderness, marked rigidity, decreased bowel sound			

> – more, = – equal, *ARDS* acute respiratory distress syndrome, *CBC* complete blood count *CHF* congestive heart failure, *CT* computed tomography, *DIC* disseminated intravascular coagulation, *EFAST* extended focused abdominal sonography in trauma, *F* female, *HCG* human chorionic gonadotropin, *HIV* human immunodeficiency virus, *IUCD* intrauterine copper device, *M* male, *MI* myocardial infarction, *NSAIDs* non-steroidal anti-inflammatory drugs, *PID* pelvic inflammatory disease, *PR* per rectum, *RF* risk factors, *RLQ* right lower quadrant, *RUQ* right upper quadrant, *UPT* urinary pregnancy test, *UTI* urinary tract infection

Table 26.4 Extra abdominal causes [3]

Abdominal wall	Muscle spasm/haematoma
	Herpes zoster
Systemic	Alcoholic/diabetic ketoacidosis
	Sickle cell disease
	Porphyria
	Systemic lupus erythematosus
	Uraemia
Thoracic	Myocardial infarction myocarditis/pericarditis
	Pulmonary embolism
	Pneumonia
Toxicology	Lead/iron poisoning
	Snake/scorpion bite
	Black widow spider bite
Genitourinary	Testicular torsion
Infections	Mononucleosis
	Rocky mountain spotted fever
	Streptococcal pharyngitis

Box 26.2 Routine Laboratory Workup

Haematocrit: GI bleed
WBC count: infection/inflammation, though of limited value [4, 5]
Platelet count: bleeding disorders
Liver profile: hepatitis, cholecystitis, post hepatic biliary tract obstruction
Coagulation profile: status of coagulopathy, bleeding disorders, trauma
Renal profile: prerenal, renal or post renal failure, degree of dehydration, renal insufficiency, electrolyte imbalance
Pancreatic enzymes: pancreatitis, other pancreatic pathologies. Lipase is more sensitive when it is 3 times higher than normal value [6]
Serum lactate level: mesenteric ischaemia, bowel infarction. May be normal in 25 % of patients with intestinal ischaemia [7]
Serum glucose: pancreatitis, diabetic/alcoholic ketoacidosis
Urine analysis: UTI, nephrolithiasis, pyelonephritis, cystitis, renal parenchymal disorders
Urine sugar/ketone dipstick: diabetic ketoacidosis
Urine culture: UTI
Urine pregnancy test: females in reproductive age group
Stool for occult blood: upper GI bleed
Stool culture, stool for ova and hanging drop test: diarrhoea

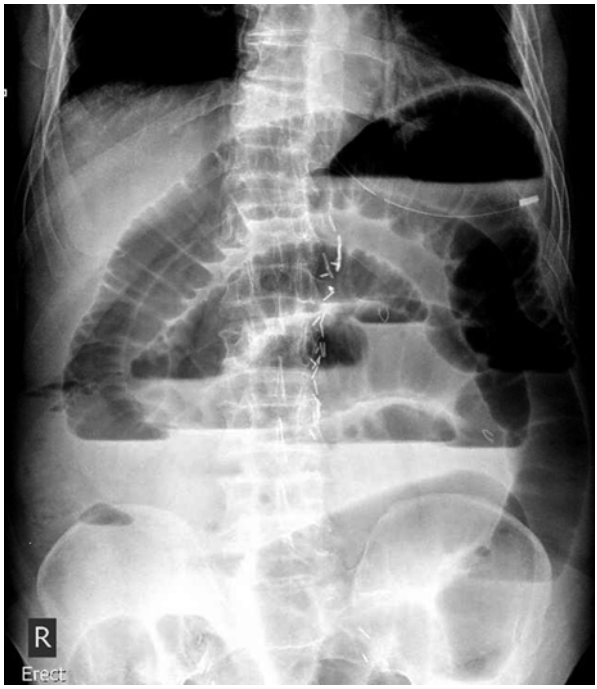

Fig. 26.2 Step-ladder pattern in cases of bowel obstruction

– Diagnostic imaging: Traditional x-rays, ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI) are available modalities.
Upright chest and abdomen x-rays: An upright chest x-ray detects 1 ml of air in peritoneal cavity [8]. Lateral decubitus x-ray shows 5–10 ml of intraperitoneal air (pneumoperitoneum) in bedridden patients.
Indications (Fig. 26.2):

Small/large bowel obstruction
Hollow viscus perforation
Sigmoid/caecal volvulus
Foreign body
Ingested metal (e.g. mercury)

Ultrasonography: Ultrasound probe is emergency physician's stethoscope in recent times. It has 94 % sensitivity and 78 % specificity for detecting acute cholecystitis [9]. It is efficient in detecting gallstones and intrahepatic and extrahepatic biliary tract diameter. Abdominal/transvaginal sonography is useful in detecting ovarian, uterine and adnexal abnormalities.
Intraperitoneal free fluid can be visualised on US scan in trauma (FAST) and nontrauma patients.
Bedside sonography is useful in following conditions:

- Intraperitoneal free fluid
- Hydronephrosis/hydroureter

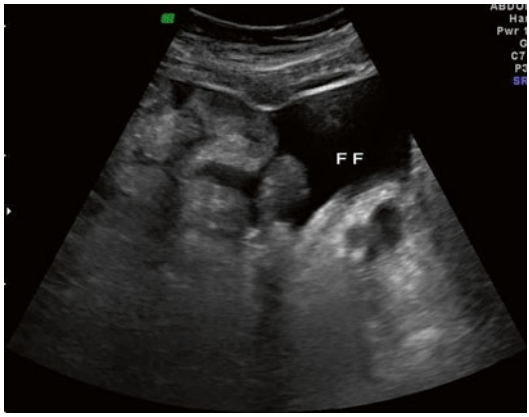

Fig. 26.3 Intraperitoneal free fluid (FF) in cases of ascites or trauma

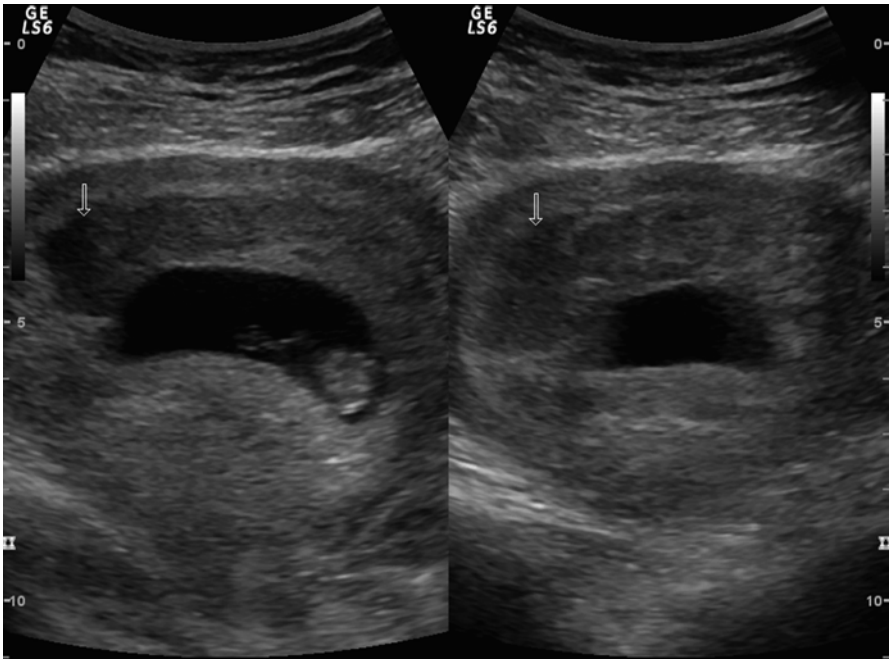

Fig. 26.4 Intrauterine gestational sac with sub-chorionic haemorrhage (marked as *arrow*)

- Intrauterine pregnancy
- Abdominal aorta diameter (aneurysm)
- Volume status with IVC diameter (RUSH protocol)
- Bladder volume (urinary retention)

Disadvantages: Operator dependent

- Distortion of anatomy gives false results.
- Requires proper training (Figs. 26.3 and 26.4).

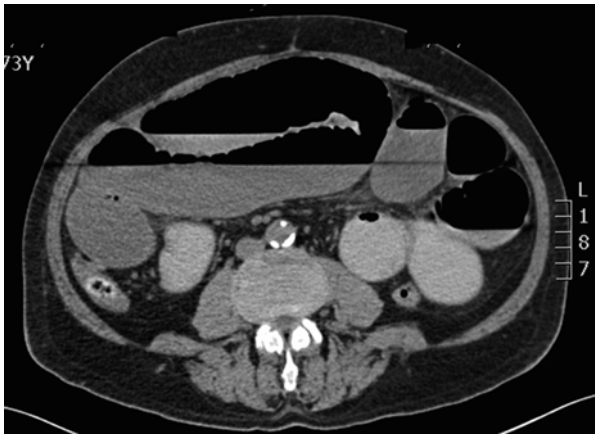

Fig. 26.5 CT abdomen with contrast film showing multiple air fluid levels suggestive of intestinal obstruction

Table 26.5 Recommended imaging test depending on the site of abdominal pain

Right upper quadrant [12]	Ultrasonography
Left upper quadrant	CT scan
Right lower quadrant [13]	CT scan with contrast
Left lower quadrant [14]	CT scan with contrast
Suprapubic	Ultrasonography

CT computed tomography

Computed tomography: It is sensitive and accurate in diagnosing acute appendicitis, bowel wall diseases, solid organs, urinary tract calculi, mesenteric ischaemia and retroperitoneal structures. It is useful in differentiating mechanical vs. paralytic bowel obstruction.

CT scan of abdomen has become an imaging modality of choice. Intraperitoneal and extraperitoneal structures can be visualised through CT scan. It helps to reduce morbidity and mortality. Elderly people are more prone to undergo surgery and have higher mortality than young patients. Moreover, history, vital signs and physical examination are not reliable in elderly due to comorbid conditions and medication use [10].

CT scan is associated with radiation risk. Improved technology and better image resolution have made oral contrast obsolete, and pathologies of solid organ and bowel wall are detected with intravenous contrast only [11] (Fig. 26.5).

Recommended imaging studies based on location of abdominal pain is shown in Table 26.5.

Electrocardiogram is essential especially in elderly people with risk factors.

Treatment

Therapeutic goals for acute abdominal pain patients are primary stabilisation, mitigation from symptoms, diagnosis and treatment of cause.

Primary Stabilisation

Haemodynamic instability may be present in patients with following features:

Extremes of age
Immunocompromised state
Abnormal vital signs
Signs of dehydration

Early resuscitation and identification of primary cause are the mainstay of treatment. This includes (OMIV): *O*, oxygen; *M*, cardiac monitor; *IV*, large bore IV lines; and *V*, vitals. Blood samples should be collected for routine investigations. Blood transfusion should be anticipated in haemorrhagic conditions (ruptured abdominal aortic aneurysm, massive GI haemorrhage, ruptured ectopic pregnancy, traumatic spleen rupture). Bedside ultrasound helps in identification of undifferentiated shock. These patients require prompt surgical consultation.

Analgesics

Early pain management doesn't mask physical findings, delay diagnosis or increase morbidity and mortality. Analgesics in the form of paracetamol, NSAIDs and opioids like fentanyl or morphine are used depending on pain score. Cope's early diagnosis of acute abdomen [15] favours opioid analgesia in abdominal pain patients.

Antacids and Antiemetics

Antacids relieve burning pain due to gastric acid production [16]. Antiemetics like ondansetron and metoclopramide are useful in remitting nausea and vomiting. NG tube is essential in patients with small bowel obstruction to decompress stomach and provide symptomatic relief. Metoclopramide has extrapyramidal side effects.

Antibiotics

Administration of antibiotics is useful in cessation of disease process and early recovery. Antibiotics should cover gram-negative anaerobic and aerobics and extended to gram-positive pathogens too. Table 26.6 shows some commonly used regimens.

Table 26.6 Useful antibiotic regimen

Uncomplicated infective conditions	Second generation cephalosporins
	Cefotaxime 1 g IV 12 hourly
Immunocompromised, elderly, hypotensive	Aminoglycosides
	(Gentamicin/tobramycin 1.5 mg/kg IV 8 hourly)
	+
	Metronidazole 400 mg IV 8 hourly
Suspected biliary sepsis	Piperacillin tazobactam 4.5 g IV 12 hourly
Suspected bacterial peritonitis	Ceftriaxone 1 g IV 12 hourly
PID	Doxycycline 100 mg PO 12 hourly for 14 days
	Metronidazole 400 mg PO 12 hourly for 14 days
Clostridium difficile colitis	Metronidazole 400 mg PO 8 hourly for 14 days
	Vancomycin 500 mg/day PO for 4 days
H. pylori gastritis [17]	Amoxicillin 1,000 mg PO 12 hourly +
	Clarithromycin 500 mg PO 12 hourly +
	Omeprazole 20 mg PO 12 hourly for 14 days

IV intravenous, *PO* per oral

Disposition and Follow-Up

Decision to discharge is as difficult as diagnosis of acute abdominal pain. Various available options are:

Admission and surgical/nonsurgical consultation
Admission for observation
Discharge with follow-up advice

Indications for hospitalisation:

Elderly and immunocompromised
Intractable nausea, vomiting and abdominal pain
Appears ill with unclear diagnosis
Intolerable oral intake
Abnormal physical examination (signs of peritonitis)
Poor social support

Patients with less severe symptoms without specific diagnosis need laboratory/radiological evaluation and observation for 8–10 h in ED. Follow-up with primary care physician in 12 h is another valid option.

Stable asymptomatic patients can be discharged from emergency. Discharge criteria may include:

Asymptomatic
No abnormal clinical features
Normal vital signs
Tolerate oral intake
Adequate social support at home

Patients should be given proper diet advice and safety instructions.

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Chapter 27
Acute Pancreatitis

Ajay Kumar Mishra

Key Points

- Early diagnosis and treatment are crucial in the management of acute pancreatitis to prevent complications and to reduce morbidity and mortality.
- Other life-threatening conditions which mimic acute pancreatitis should also be considered and ruled out simultaneously while managing the patient.
- Prophylactic antibiotics are not indicated in sterile pancreatic necrosis.
- Consider early admission in intensive care unit after initial resuscitation in the emergency department.

Introduction

- Acute pancreatitis (AP) is an acute inflammatory process in which there is autodigestion of pancreas by its own enzyme.
- Annual incidence of AP varies between 4.9 and 73.4 cases per 100,000 worldwide with an increasing trend in the annual incidence [1, 2]. Even though the case fatality rate for AP has decreased over time, the overall population mortality rate for AP has remained unchanged [3].
- Aetiological variation has been seen depending upon the lifestyle in different population.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_27

- Generally, acute pancreatitis is more common in males than females. In males, the aetiology is more often related to alcohol; in females, it is more often related to biliary tract disease.
- The overall mortality in patients with acute pancreatitis is 10–15 %. Mortality due to biliary pancreatitis is high as compared to alcoholic pancreatitis. Twenty percent of patients present with severe disease (organ failure) in whom, mortality is approximately 30 % [4].

Pathophysiology (Fig. 27.1)

Aetiology

- The causes of acute pancreatitis have been listed in Table 27.1 [5–8].
- Cholelithiasis is the most common cause of acute pancreatitis (40–70 %), whereas alcohol is the second most common cause (25–35 %) [9–11].

Classification

- Revised Atlanta criteria 2013 (Table 27.2) defines severity of acute pancreatitis into three categories – mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis [12].
- Local complications include peripancreatic fluid collections and pancreatic/peripancreatic necrosis (sterile or infected).
- Organ failure is defined as a score of 2 or more using the modified Marshall scoring system (Table 27.3) [12, 13].
- Phases of severe pancreatitis [14, 15]:
  - Early – usually last for the first week in which patient may present with systemic inflammatory response syndrome (SIRS).
  - Late – follows the early phase and lasts from weeks to months, usually characterised by local complications and/or persistent organ failure.
- Most patients with severe pancreatitis present to emergency department during the early phase without any signs of organ failure and local complications, thus leading to errors in clinical management of this disease [16].

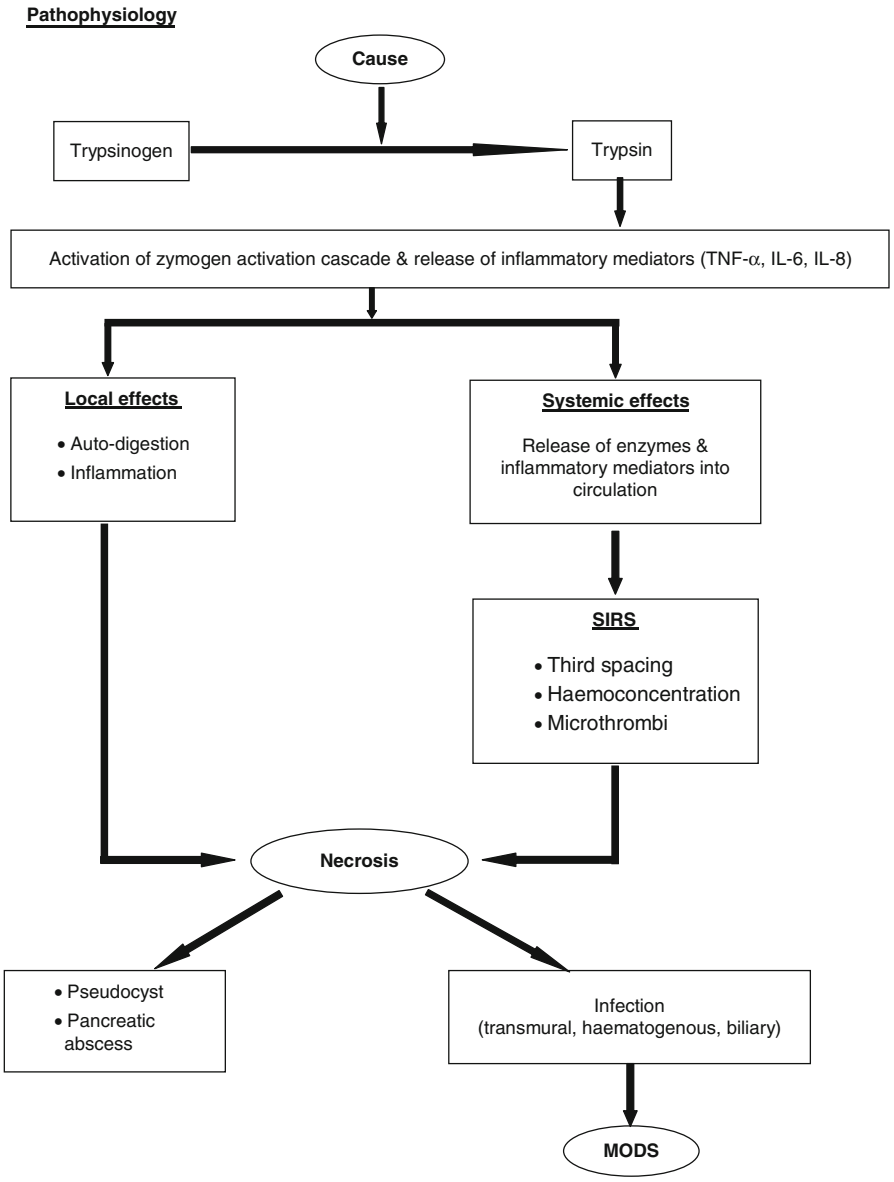

Fig. 27.1 Pathophysiology of acute pancreatitis

Table 27.1 Causes of acute pancreatitis

Cholelithiasis
Ethanol abuse
Idiopathic
Infections *Mumps*, *Coxsackie B*, *Mycoplasma*, *ascariasis*, *viral hepatitis (A, B, C)*, *HIV*, *Cytomegalovirus*, *varicella*, *Epstein-Barr virus*, *echovirus*, *adenovirus*, *legionella, leptospirosis*, *Campylobacter jejuni*, *tuberculosis*, *Mycobacterium avium*
Metabolic *Hypercalcaemia*, *hyperchylomicronaemia*, *diabetic ketoacidosis*, *uraemia*, *hypothermia*, *pregnancy (third trimester)*
Trauma *Postoperative trauma*, *blunt abdominal trauma*, *postrenal or cardiac transplant*, *ERCP*
Penetrating duodenal ulcer
Methyl alcohol
Organophosphate poisoning
Scorpion venom
Ischaemia *Polyarteritis nodosa*, *systemic lupus erythematosus*, *thrombotic thrombocytopaenic purpura*, *cardiopulmonary bypass*
Drugs *Thiazides*, *furosemide*, *azathioprine*, *mercaptopurine*, *oestrogens (oral contraceptives)*, *procainamide*, *sulphonamides*, *erythromycin*, *tetracycline*, *pentamidine*, *metronidazole*, *L-asparaginase*, *phenformin*, *valproic acid*, *paracetamol*, *salicylates*, *ACE inhibitors*, *losartan*, *propofol*, *nucleoside-analogue reverse transcriptase inhibitors*

Table 27.2 Revised Atlanta criteria 2013

Mild acute pancreatitis
Absence of organ failure
Absence of local complications
Moderately severe acute pancreatitis
Local complications and/or
Transient organ failure (<48 h)
Severe acute pancreatitis
Persistent organ failure (>48 h)

Clinical Features

- Mostly patient present with dull, constant, acute onset abdominal pain usually in the epigastric region, sometimes radiating to the back.
- Other symptoms include nausea, vomiting, anorexia and diarrhoea.
- Patient may have tachycardia, fever and/or hypotension.
- A few patients exhibit jaundice.
- On per abdomen examination, abdominal tenderness, guarding and distension may be present.
- Some patients may have dyspnoea, pleural effusion or acute respiratory distress syndrome (ARDS).

Table 27.3 Modified Marshall scoring system for organ dysfunction

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal[a]					
(Serum creatinine, μmol/l)	≤134	134–169	170–310	311–439	>439
(Serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)[b]	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental oxygen (l/min)	**FiO_2 (%)**				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

A score of 2 or more in any system defines the presence of organ failure
[a]A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl
[b]Off inotropic support

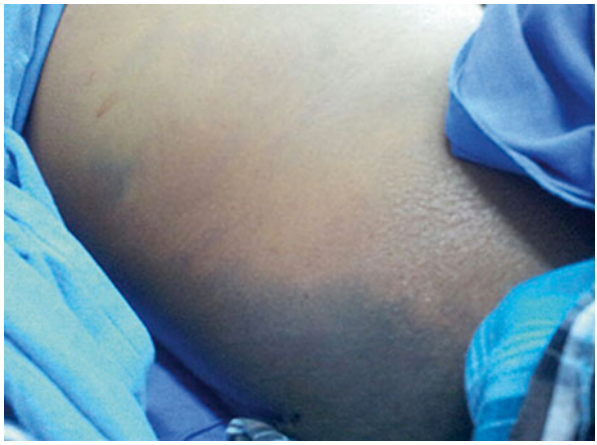

Fig. 27.2 Grey Turner's sign – contributed by Dr. Sandeep David, CMC Vellore, India

- Patients with severe acute pancreatitis may present with haematemesis or melaena and may be haemodynamically unstable.
- Patients with severe necrotising pancreatitis may have the following findings:
  - Cullen sign – bluish discolouration around the umbilicus due to haemoperitoneum
  - Grey Turner's sign – reddish-brown discolouration along the flanks resulting from retroperitoneal haemorrhage (Fig. 27.2)

Differential Diagnosis

Any acute abdomen or sometimes cardiac as well as pulmonary conditions can mimic AP. Some of the common differentials are enlisted in the box below.

- Acute mesenteric ischaemia
- Perforated gastric or duodenal ulcer
- Dissecting aortic aneurysm
- Biliary colic
- Acute myocardial ischaemia
- Ectopic pregnancy
- Intestinal obstruction
- ARDS

Diagnosis

- The diagnosis of AP should be considered in presence of two of the following three criteria:
  I. Typical abdominal pain suggestive of AP
  II. Serum amylase and/or serum lipase more than three times the upper limit of normal value
  III. Characteristic feature of AP in abdominal imaging
- Detailed history should be taken to find out the cause of AP, including history of alcohol consumption, hyperlipidaemia, similar episodes in the past, abdominal trauma and past history of gallstones or ERCP. Medication history should be asked to rule out drug induced AP.
- Apart from serum amylase and lipase, complete blood count including haematocrit, liver function test, serum triglyceride levels, serum calcium, blood urea nitrogen (BUN) and serum electrolytes should be checked to look for aetiology as well as to assess severity of AP.
- Serum triglyceride level of >1000 mg/dl is considered significant as a cause of AP in absence of gallstones and history of alcohol abuse.
- ECG – to rule out acute coronary syndrome.
- Chest x-ray erect view to look for air under diaphragm in case of intestinal perforation and also to aid to diagnosis of any pulmonary pathology, e.g. ARDS.
- In female patients under reproductive age group, bedside urine pregnancy card test should be done to rule out ectopic pregnancy.
- Transabdominal ultrasound should be done in all patients of AP to look for possible causes [17].
- In patients >40 years of age without any identifiable cause of AP, pancreatic tumours should be suspected as a probable cause [18, 19].

- Contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) of the abdomen should be done only in patients in whom diagnosis is not certain or in those patients who do not show any signs of improvement within 48–72 h of hospital admission [20].

Management

- Assess and stabilise airway, breathing and circulation.
- Early aggressive intravenous hydration [21] with isotonic crystalloids to be started for all patients to correct hypovolaemia due to third spacing of fluids, vomiting, reduced oral intake, increased respiratory loses and/or diaphoresis. Special precaution to be taken in patients with renal and/or cardiac disease.
- Lactated Ringer's solution is the preferred crystalloid over 0.9 % normal saline for fluid replacement [22].
- Adequate analgesia should be given at the earliest. Inj. morphine at a loading dose of 0.1 mg/kg body wt. followed by 0.05 mg/kg body wt. every 5 min can be administered until the pain is relieved [23].
- Nasogastric (NG) tube to be inserted and patient to be kept nil per orally (NPO) to give rest to the inflamed pancreas; however prolonged fasting should be avoided. Early oral feeding in acute pancreatitis is beneficial in terms of shorter hospital stay, decreased infectious complications and decreased morbidity and mortality [24].
- Prophylactic antibiotics should not be given for severe AP and sterile necrosis [25]. Antibiotics should be given only if there is evidence of infected necrosis, extrapancreatic infection, cholangitis, bacteraemia, catheter-acquired infections, urinary tract infection and/or pneumonia.
- ERCP should be done within 24 h of admission in patients with concurrent acute pancreatitis and acute cholangitis [26].
- Patients with moderately severe or severe acute pancreatitis should be admitted to an intensive care unit.

Summary and Algorithm (Fig. 27.3)

Acute pancreatitis is associated with emotional, physical, as well as financial burden on the society [3] with significant morbidity and mortality. Early diagnosis and early aggressive intravenous hydration can reduce morbidity and mortality as well as prevent complications. Contrast-enhanced computed tomography (CECT) and/or magnetic resonance imaging (MRI) should be reserved for patients who fail to improve clinically or in whom diagnosis is not confirmed. Patients with moderately severe or severe acute pancreatitis should be admitted to intensive care unit whenever possible. It is important to rule out other life-threatening differential diagnosis of acute pancreatitis before shifting the patients from the emergency department.

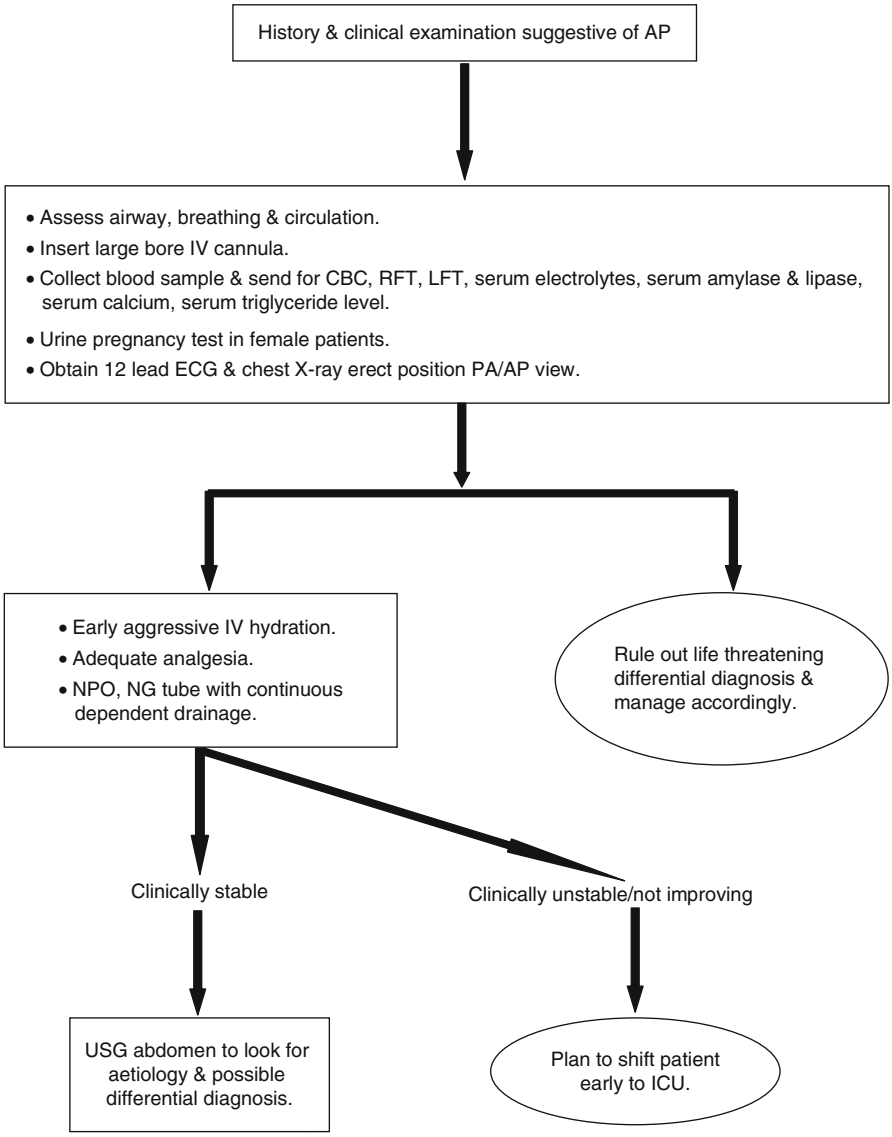

Fig. 27.3 Approach algorithm for acute pancreatitis in ED

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Chapter 28
Gastrointestinal Bleeding

Sridhakshini Sathasivam

Upper Gastrointestinal Bleed

Acute upper gastrointestinal bleeding (UGI bleed) is a common life-threatening emergency with a 10 % mortality rate [1]. Traditionally it is described as bleeding occurring from the GI tract proximal to the ligament of Treitz.

Presentations

Patients commonly present with melaena or haematemesis.

- In about 15 % of patients with haematochezia, the cause could be a large UGI bleed [2].
- Presyncope, collapse, dyspeptic symptoms and diffuse abdominal pain are some of the other presenting symptoms in patients with UGI bleed.

Aetiology

The commonest causes of GI bleed include peptic ulcer bleed and gastro oesophageal varices [3].

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DOI 10.1007/978-81-322-2710-6_28

Other important causes include:

- Gastroduodenal erosions
- Oesophagitis
- Mallory-Weiss tear
- Upper GI malignancy
- Angiodysplasia
- Miscellaneous (Crohn's disease, Meckel's diverticula)

History and Physical Examination

- History of alcohol intake, presence of dyspeptic symptoms, ingestion of NSAIDs, aspirin, other antiplatelet agents and anticoagulants.
- Prior history of UGI bleed – a significant proportion of patients tend to re-bleed from the same lesion.
- History of co-morbid conditions like coronary artery disease, congestive heart failure, renal disease, hypertension and COPD would influence the management and have prognostic implications.
- Risk assessment using validated tools such as Blatchford score or Rockall score is widely advocated by several guidelines, to provide appropriate level of care [4].

Management

The objectives of initial management include:

(a) Appropriate resuscitation.
(b) Rectify clotting abnormalities.
(c) Facilitate definitive management.

- Patients should be assessed for potential airway threats especially in those with ongoing massive haematemesis or altered mental status to facilitate a safe endoscopy reducing the risk of aspiration.
- Appropriate fluid resuscitation should be carried out initially with crystalloids using wide bore cannulae.
- In patients with massive bleed, blood products including packed cells, fresh frozen plasma and platelets where appropriate should be utilised. Fresh frozen plasma should be transfused in patients with international normalised ratio or activated partial thromboplastin time 1.5 times greater than normal [5].
- *Caveat*: *Blood should be used cautiously*, *avoiding overtransfusion particularly in patients with variceal bleeding*.
- Patients with variceal bleeding are at risk of renal failure. They also develop infections due to transmigration of organisms to the peritoneum which may

induce hepatorenal failure. Prophylactic antibiotics have been proven to reduce the incidence of hepatorenal failure and hence reduced mortality by several trials [6]. Inj. Ceftriaxone 1 g intravenously is the preferred antibiotic.

- The use of terlipressin and somatostatin as adjunct therapies prior to endoscopy is recommended in suspected variceal bleeding to reduce portal pressure [7]. Terlipressin is administered as an IV bolus in a dose of 2 mg in the emergency department.
- Proton pump inhibitors although widely used in non-variceal bleeding are only proven to help in post endoscopy patients to prevent rebleeding [8]. It is to be continued for a period of 72 h.
- Balloon tamponade using a Sengstaken-Blakemore tube could be used in those with massive bleeding from oesophageal varices as a temporary measure.

Endoscopy

Endoscopy is the key investigation which provides a diagnosis and enables effective treatment to stop the bleeding to be carried out in cases of both variceal and non-variceal bleeding. It should be offered to all patients presenting with a significant UGI bleed [9].

- Patients with signs of haemodynamic instability need to undergo UGI endoscopy immediately post resuscitation and the rest of the patients ideally within 24 h of arrival.
- Endoscopic treatment of a bleeding ulcer would entail using a mechanical device like a clip or thermos-coagulation or injecting thrombin. These treatments are often used in conjunction with local injection of adrenaline. Patients continuing to bleed post endoscopy may be referred for interventional radiology or surgical treatment.
- In a patient with variceal bleeding, endoscopic band ligation is preferred to sclerotherapy for obvious mortality benefits [10]. If endoscopic methods fail to stop the bleeding from the varices, the patient could be referred for transjugular intrahepatic portosystemic shunts (TIPS).

Patients presenting with a massive bleed or haemodynamic instability should be managed in the high dependency care areas post endoscopy.

Lower Gastrointestinal Bleed

Lower gastrointestinal bleeding (LGIB) is a frequent cause of hospital admission amounting to 10–20 % mortality of the hospital admissions [1]. LGIB is distinct from upper GI bleeding in its causes and management.

Acute lower gastrointestinal bleeding (LGIB) is defined as bleeding that is of recent duration, originating beyond the ligament of Treitz.

Its presentation can vary with the source of bleeding, such as:

- Bloody diarrhoea might be suggestive of inflammatory or infective colitis.
- Maroon stools, with LGIB from the right side of the colon.
- Bright red blood per rectum with LGIB from the left side of the colon.
- Melaena with caecal bleeding.

Aetiology

The most common causes of LGIB are [11]:

- Diverticular disease
- Benign anorectal diseases – haemorrhoids, anal fissure and fistula-in-ano
- Inflammatory bowel disease
  - Crohn's disease of small bowel, colon or both
  - Ulcerative colitis
  - Non-infectious gastroenteritis and colitis
- Neoplasia

Presentation

History and physical examination are essential parts of an initial evaluation of lower gastrointestinal bleeding. They can give clues into the aetiology and anatomical source of bleeding.

History should include:

- The nature and duration of bleeding, including stool colour and frequency.
- Associated symptoms, including abdominal pain, recent change in bowel habits and fever.
- Weight loss.
- Whether this is a first or recurrent episode of gastrointestinal bleeding.
- Significant past medical history (including peptic ulcer disease, liver disease, cirrhosis, coagulopathy, inflammatory bowel disease).
- Previous medication use (NSAIDs and/or warfarin).
- In patients with cancer, the history of radiation, chemotherapy or both should be considered.
- Presence or absence of chest pain/palpitations, dyspnoea or postural symptoms.

The physical examination should be thorough and include the skin, oropharynx, nasopharynx, abdomen, perineum and anorectum to evaluate for sources of bleeding.

A nasogastric (NG) tube may be necessary to confirm the presence or absence of blood in the stomach, because brisk UGIB can present as LGIB in 15 % of the patients [3]. In case of high suspicion obtain an oesophago-gastro-duodenoscopy.

Treatment

- Initial resuscitation involves establishing large-bore IV access and administration of normal saline.
- Bloods should be sent for full blood count (FBC), electrolyte levels, urea and creatinine and coagulation studies including type and cross-match. The patient's blood loss and haemodynamic status should be ascertained, and in cases of severe bleeding, the patient may require invasive haemodynamic monitoring to direct therapy.
- Red cell transfusion should be considered after loss of 30 % of the circulating volume.
- Colonoscopy – In haemodynamically stable patients with mild to moderate bleeding or in patients who have had a massive bleed that has stabilised, colonoscopy should be performed initially.
- Angiography – In patients in whom the bleeding site cannot be determined on colonoscopy and in those with active brisk LGIB, angiography scan should be performed to locate the bleeding site as well as to intervene therapeutically.
- Emergency surgery – The indications for surgery include the following:

  (a) Persistent haemodynamic instability with active bleeding
  (b) Persistent, recurrent bleeding
  (c) Transfusion of more than four units packed red bloods cells in a 24-h period

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Chapter 29
Intestinal Emergencies

Dhavapalani Alagappan and Sathya Kaliannan

Introduction

Intestinal emergencies constitute a significant proportion of the Emergency Department attendances worldwide in all ages. Acute appendicitis, bowel obstruction, intestinal perforation and acute mesenteric ischaemia are amongst the commonest presentations encountered which are dealt with in this chapter.

Appendicitis

Introduction

Acute appendicitis, the commonest surgical emergency, is known to present in a variety of ways [1]. Abdominal pain is often the primary complaint, but the site of pain could vary depending on the position of this mobile vestigial organ. In the very young children and the elderly patients, the signs are often subtle and there could be a delay in presentation.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_29

Pathophysiology

Appendicitis is typically known to be caused by obstruction of the lumen by faecolith. The obstruction leads to increase in intraluminal pressure and inflammation. Appendicular perforation ensues if this inflammation progresses untreated.

Clinical Features

- The diagnostic sequence of colicky central abdominal pain followed by vomiting with migration of the pain to the right iliac fossa (McBurney's point, which lies two thirds of the way along a line drawn from the umbilicus to the anterior superior iliac spine) is only present in 50 % of patients [2]. The initial pain represents a referred pain resulting from the visceral innervation of the midgut, and the localised pain is caused by involvement of the parietal peritoneum.
- Abdominal symptoms may include loss of appetite, nausea and vomiting.
- Fever.
- The various positions of the inflamed appendix in the right iliac fossa lead to subtle differences in the presenting signs and symptoms:
  - Retrocaecal/retrocolic (75 %) [1]—Pain in the right loin and tenderness is commonly seen. The caecum overlying the appendix often precludes deep tenderness and muscle rigidity. Irritation of the psoas muscle may result in hip flexion and worsening of the pain on hip extension (psoas stretch sign).
  - Subcaecal and pelvic (20 %)—Suprapubic pain and urinary frequency are common. Irritation of the rectum may lead to diarrhoea. Microscopic haematuria may be present on urine analysis leading to diagnostic difficulties.
  - Pre-ileal and post-ileal (5 %)—Vomiting and diarrhoea may result from irritation of the distal ileum.

Diagnosis

- In spite of several advances in diagnostic modalities, appendicitis is still considered to be a clinical diagnosis.
- Leucocytosis and inflammatory markers like ESR and CRP are nonspecific. Leucocytosis in combination with ESR and CRP often improves sensitivity.
- Urinalysis to look for other causes of lower abdominal pain.
- Women in child-bearing age need urine pregnancy test.
- In managing appendicitis, the decision to remove an uninflamed appendix will have to be weighed up against the consequences of a perforation.
- Imaging: Ultrasonography (sensitivity of 86 %; specificity of 81 %) is less sensitive and specific in comparison to a CT scan (sensitivity of 94 % and specificity of 95 %).

- The Alvarado scoring system is a very useful tool in diagnosing appendicitis [3]. It is known by the mnemonic 'MANTRELS', and it is scored as follows (total 10 points):

Migration of pain to right iliac fossa	1 point
Anorexia	1 point
Nausea or vomiting	1 point
Tenderness in right lower quadrant	2 point
Rebound tenderness	1 point
Elevation in temperature ≥37.3 °C	1 point
Leucocytosis ≥10,000	2 points
Shift of neutrophils to the left—neutrophilia >75 %	1 point

Interpretation of total Alvarado score [4]

Total score ≥7	High probability of appendicitis
Total score 4–6	Doubtful
Total score ≤3	Low probability of appendicitis

Treatment

- NPO.
- IV access with fluid resuscitation.
- Analgesics—IV opioids titrated to pain relief.
- Anti-emetics if vomiting.
- Patients who are presenting to ED with septicaemia from appendicitis will need intravenous antibiotics. IV antibiotic is also advocated for those who undergo laparotomy.
- Acute appendicitis risks the complication of a perforation if untreated and hence often surgery is preferred.
- However, a meta-analysis done comparing surgery versus primary antibiotic therapy has concluded that antibiotics merit consideration as primary treatment in patients presenting with uncomplicated acute appendicitis [5].

Bowel Obstruction

Introduction

Bowel obstruction can largely be divided into small bowel obstruction (80 %) or large bowel obstruction (20 %). It could be functional or due to a mechanical cause. Nonmechanical obstruction could be due to ileus (involving both small

and large bowel) or pseudo-obstruction (limited to large bowel). The commonest causes of mechanical bowel obstruction are due to post-operative adhesions and hernias [6].

Pathophysiology

With advanced intestinal obstruction, progressive dilatation of intestine causes raised intraluminal pressure which impedes venous drainage, leading to oedema and hyperaemia of the affected segment. Subsequently, reduced arterial flow results in necrosis and perforation of the bowel. The above sequence of events happens much more rapidly in a closed loop obstruction where a segment of bowel is obstructed proximally as well as distally. An intestinal volvulus is a typical example of closed loop obstruction.

Causes of Intestinal Obstruction

Some common causes of small bowel obstruction are adhesions, hernia, intussusceptions, lymphomas, intestinal tuberculosis and stricture.

Large bowel obstructions may be caused by carcinoma, faecal impaction, volvulus (Fig. 29.1), ulcerative colitis, diverticulitis and intussusceptions.

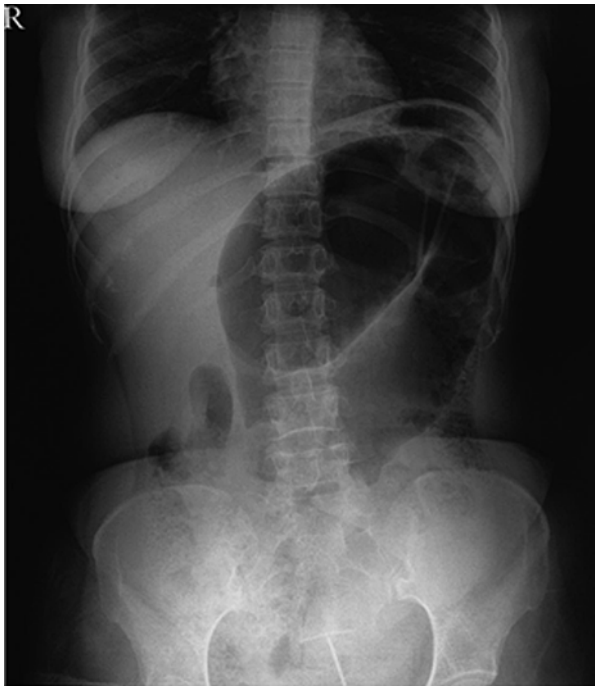

Fig. 29.1 X-ray of the abdomen showing caecal volvulus which presented as bowel obstruction

While adhesive obstructions occur often in those with prior history of abdominal and pelvic surgeries, they could occasionally occur without previous surgeries in patients with intra-abdominal inflammations like diverticulitis, Crohn's disease, etc. [7, 8].

Clinical Features

Abdominal pain, distension, vomiting and obstipation (inability to pass flatus or faeces) are the four commonest symptoms associated with bowel obstruction [9]. Abdominal pain is often crampy in nature, and it is likely to be less intense in adynamic ileus. If the pain is severe and associated with signs of peritonism, bowel ischaemia or impending perforations are likely.

The severity of the symptoms depends on the site of obstruction (proximal versus distal) and completeness of obstruction.

The history should help the clinician to consider other differential diagnoses and also ascertain the cause of obstruction.

Examination should include looking for signs of dehydration and shock as fluid is lost by vomiting and into the intraperitoneal space through the transmural route as well. Abdominal examination should include assessing for scars, masses, hernia and a rectal examination seeking faecal impaction, rectal growths, etc.

Investigations

Laboratory investigations:

- Haematocrit and serum urea—elevated in individuals suffering from dehydration.
- Electrolytes: metabolic alkalosis with hypokalaemia and hypochloraemia.
- Metabolic acidosis, elevated serum lactate level and high white cell count may suggest bowel ischaemia.

Radiology:

- Plain film radiography and CT are the imaging modalities commonly employed in suspected intestinal obstruction.
- The plain film should be the initial imaging method of choice as it is quick, widely available and inexpensive (Fig. 29.2). The findings in a supine film would include fluid-filled distended bowel loops. A cut off of 3 cm for small bowel and 6 cm for large bowel film is widely accepted to signify obstruction. The risk of perforation increases with progressive distension. Multiple air fluid levels would signify obstruction in an erect or lateral film.
- The CT scan is, however, a much more sensitive and specific tool and is more likely to point towards the site of obstruction, determine if it is partial or

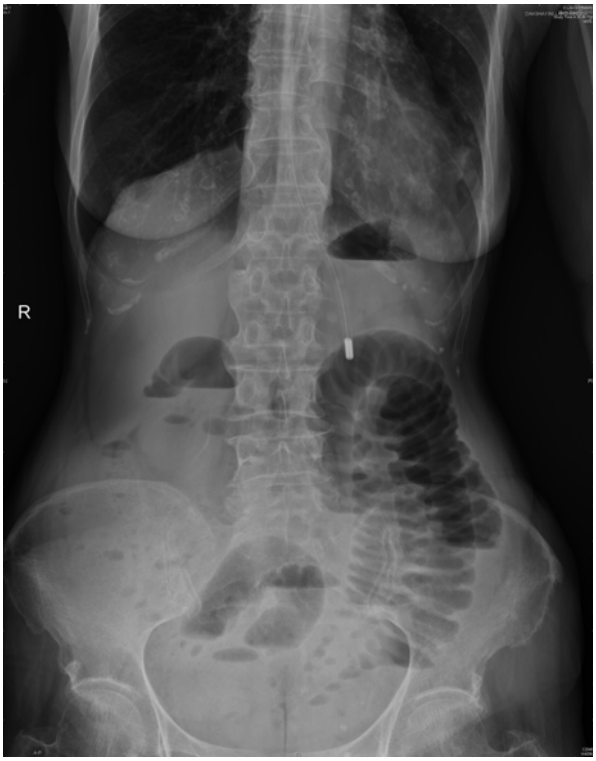

Fig. 29.2 X-ray of the abdomen showing dilated small bowel loops with valvulae conniventes and multiple air fluid levels suggestive of small bowel obstruction

complete obstruction [10], help identify the cause of obstruction (inflammatory, adhesions, hernias, etc.) [11, 12] and pick out complications (ischaemia, necrosis and perforation) [13].

Treatment

- Nil by mouth.
- IV cannula with fluid resuscitation (0.9 % saline) and monitor the response with heart rate, blood pressure and hourly urine output. CVP monitoring may be needed in elderly patients requiring larger volume of resuscitation.
- Correction of electrolyte abnormality (e.g. hypokalaemia) with renal function monitoring.
- Analgesia—IV opioids (morphine) titrated to pain relief.
- Anti-emetics.
- NG tube to be placed if distension/vomiting is significant.

- Surgical team referral.
- Broad-spectrum antibiotics are commonly administered because of concerns that bacterial translocation may occur in the setting of SBO; however, there are no controlled data to support or refute this approach [14].

Intestinal Perforation

Introduction

Gastrointestinal perforations in India are caused by a significantly different aetiological spectrum compared to the western world. The prognosis in patients presenting with perforation depends on several factors including time of presentation to the hospital since onset of symptoms, the underlying cause, if the perforation was a contained one or a free perforation contaminating the peritoneal cavity and the comorbid conditions of the individual.

In free perforations particularly involving the colon, the overall mortality rate is relatively high (approximately 20–40 %), due to complications such as septic shock.

Aetiology and Pathophysiology

The commonest causes in India causing intestinal perforations excluding penetrating trauma include [15]:

- Acid peptic disease (45 %)
- Appendicitis (19 %)
- Typhoid (12 %)
- Tuberculosis (10 %)

The other causes include ingestion of NSAIDs, diverticulitis, inflammatory bowel disease and colonic cancer related perforations.

Once perforation occurs, extrusion of the bowel contents leads to a stage of chemical peritonitis. Subsequently bacterial peritonitis sets in, and this stage happens earlier in distal small bowel and colonic perforations. Untreated bacterial peritonitis leads to sepsis and multi-organ failure [16].

Clinical Features

- Sudden-onset abdominal pain is the commonest presenting symptom. The location of pain varies depending on the site of perforation (RUQ/epigastric in duodenal perforation, right lower quadrant in appendicular perforation, etc.).

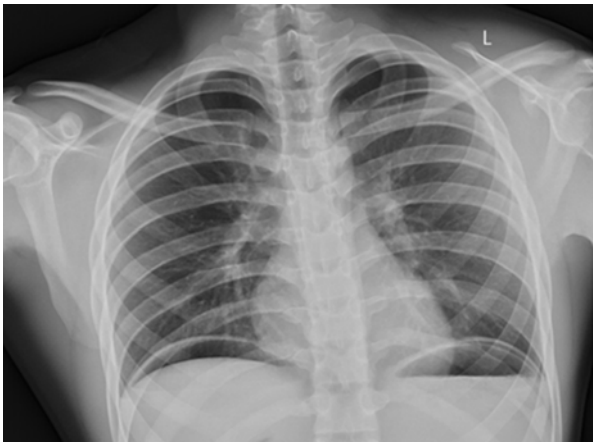

Fig. 29.3 An erect chest X-ray demonstrating free intra peritoneal air

- Vomiting is frequently present.
- History of NSAID ingestion is to be sought.
- On examination, the patient often lies still. Tenderness initially is localised to the region of perforation. Generalised tenderness, fever, tachycardia and hypotension are present in delayed presentations where peritonitis has set in.

Investigations

- Laboratory investigations are often unhelpful.
- An erect chest X-ray has a sensitivity of approximately 70 % in identifying free intraperitoneal air [17] (Fig. 29.3)
- CT scans of the abdomen are very useful in identifying the perforation and localising it pointing to the possible diagnosis.

Treatment

Surgery is the mainstay of treatment for intestinal perforation. In the emergency department, the following measures are to be instituted:

- IV fluid therapy with crystalloids, aggressive resuscitation in those with septic shock.
- Patients to be kept nil by mouth.
- IV antibiotics to patients with signs of septicaemia. Antibiotics should cover aerobic and anaerobic organisms [18].

In the absence of symptoms and signs of generalised peritonitis, a nonoperative policy may be used with antibiotic therapy directed against Gram-negative and anaerobic bacteria.

Acute Mesenteric Ischaemia

Introduction

Acute mesenteric ischaemia is a life-threatening vascular emergency with a high mortality [19]. It has remained a diagnostic challenge despite advances in the diagnostic methods. The prognosis depends on prompt diagnosis and early institution of treatment to restore blood flow which helps prevent bowel necrosis and thus reduce mortality.

Pathophysiology and Causes

Acute mesenteric ischaemia is classified into non-occlusive mesenteric ischaemia and occlusive mesenteric ischaemia. The occlusive mesenteric ischaemia is further classified into acute mesenteric arterial embolism and acute mesenteric arterial thrombosis. Mesenteric venous thrombosis is another entity apart from the above. The superior mesenteric artery is the vessel most commonly affected due to its angle with the aorta.

- Nearly 50 % of the cases of acute mesenteric ischaemia are caused by arterial embolism mostly from a cardio-embolic source like atrial fibrillation, myocardial infarction, endocarditis, valvular heart disease, etc. [20].
- The arterial thrombosis contributed to by atherosclerosis and hypercoagulable states accounts for close to 25 % of the cases of acute mesenteric ischaemia. In a mesenteric vessel which is affected by atherosclerosis, a low flow state leads to the formation of a thrombus. There is initially shedding of the mucosa with bloody stools and subsequently necrosis ensues.
- Non-occlusive ischaemia occurs with low output states like cardiogenic shock, hypovolaemia, inotrope infusions, etc. [21].
- Venous thrombosis is more often associated with conditions like clotting disorders, pancreatitis, hepatitis, recent abdominal surgeries and abdominal infections.

Clinical Features

The symptoms are often acute in onset and associated with a rapid deterioration in clinical course in patients with acute mesenteric arterial embolism or thrombosis, while non-occlusive mesenteric ischaemia or mesenteric venous thrombus has a gradual onset and a protracted clinical course.

- Sudden-onset severe abdominal pain, out of proportion to the physical findings.
- Nausea, vomiting.
- Forceful bowel evacuation with vomiting and diarrhoea.
- GI bleeding may be seen. Gross bleeding which is relatively rare suggests that right colon might be ischaemic.

- With the commencement of bowel infarction, peritoneal signs, haemodynamic instability, and signs of sepsis with multi-organ failure ensue. Distension and severe rebound tenderness with guarding develop as a consequence of bowel infarction.

Diagnosis

Since acute mesenteric ischaemia has an unclear initial presentation with high mortality contributed by delay in diagnosis and initiation of treatment, high index of suspicion and an early CT angiography will aid the diagnosis [22].

Laboratory tests and plain abdominal radiography is done to exclude other diagnoses, such as intestinal obstruction or a perforated viscus.

- Blood tests could be normal in early stages; suggested blood investigations include:
  - FBC might reveal haemoconcentration and significant leucocytosis.
  - Blood gases to look for metabolic acidosis with high anion gap and raised lactates.
  - Urea, electrolytes and glucose.
  - Blood typing and cross-matching.
  - ECG to look for AF, recent MI.
  - Coagulation profile.
- Characteristic radiographic abnormalities, such as thumb printing, are seen in a minority of patients. Air in the portal vein is a late finding and is associated with a poor prognosis.
- Definitive investigations: CT angiography after surgical referral.
- CT angiography is reported to have a high sensitivity and specificity in establishing a diagnosis of acute mesenteric ischaemia. Bowel wall oedema is the commonest finding. However, the specific findings include identifying SMA or SMV thrombosis, non-enhancement of bowel wall, intestinal pneumatosis and portal venous gas [19].
- MRI with MR angiography is as sensitive as CT but less commonly used as it is a less practical tool.

Other differential diagnoses to consider include ovarian torsion, colitis, bowel perforations, volvulus of midgut and splenic vein thrombosis.

Management

- NBM
- IV fluids to correct shock with response monitoring like urine output, HR, BP, CVP.

- Analgesics—morphine titrated to pain.
- Broad-spectrum IV antibiotic.
- Urgent surgical referral.
- The cause of the ischaemia and the experience of the clinician will determine the treatment options. Non-occlusive ischaemia is treated medically, whereas patients with occlusive AMI are likely to need surgery [19].
- If the patient exhibits signs of peritonitis and bowel infarction is suspected, then the patient should be subjected to surgery.

These patients often require a protracted course in the hospital.

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Chapter 30
Jaundice

Praveen Eadala

Key Points
- Jaundice is not a diagnosis but a manifestation of pathology.
- Jaundice requires the evaluating doctor to examine comprehensively, investigate appropriately and commence management diligently.
- The causes of jaundice include life-threatening conditions that require resuscitation and stabilisation.

Introduction

Jaundice is a common clinical presentation to the emergency department that can be caused by a variety of disorders. It is not a diagnosis but a feature of elevated serum bilirubin and a marker of hepatobiliary or haematologic dysfunction. Patients with jaundice could present with symptoms such as abdominal pain, itching or fever. Jaundice means yellowish staining of the skin, sclera and mucous membranes by bilirubin [1]. The normal serum concentration of bilirubin is less than 1 mg/dL [17 μmol/L], and it is not clinically detectable until serum bilirubin reaches 2.5 mg/dL [1]. The total bilirubin can be divided into two fractions: conjugated [direct] bilirubin and unconjugated [indirect] bilirubin. Identification of the type can help to narrow down the cause of jaundice. The key questions to ask when seeing a patient with jaundice in the emergency department are as follows:

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_30

- Type of jaundice and underlying process causing it
- Is it an acute process or acute on a background of chronic liver disease
- Is there liver failure

This chapter provides an overview of the diagnostic approach and early management of jaundice in adults.

Metabolism

Bilirubin is derived predominantly [80 %] from the breakdown of haemoglobin present in the red blood cells and the rest comes from haeme-containing proteins [1, 2]. The reticuloendothelial cells destroy the red blood cells, releasing water-insoluble unconjugated bilirubin into the circulation where it is bound to albumin and enters liver cells. In liver it undergoes glucuronidation by a family of enzymes called uridinediphospho-glucuronosyltransferases [conjugation] [2, 3]. The conjugated bilirubin is actively transported across the canalicular membranes into the biliary system. This is then stored as part of bile in the gallbladder and released into the duodenum [3, 4]. Most of the bile salts are de-conjugated in the terminal ileum and absorbed by the intestinal epithelial cells which then enters the portal circulation and returns to the liver [enterohepatic circulation]. The bile that is not absorbed enters the colon where the colonic bacteria break bilirubin to stercobilin or urobilinogen. The former is excreted in the stool, whilst the latter is reabsorbed into the bloodstream and excreted in the urine [4]. Conjugated bilirubin can also enter the circulation from diffusion out of the hepatocytes. Bilirubin is filtered by the glomerulus and then reabsorbed. Under normal circumstances, no conjugated bilirubin is excreted, but if the filtered load exceeds the absorptive capacity, conjugated bilirubin can be detected in the urine [4].

Clinical Presentation

The cause of jaundice is wide, and they have symptoms of these diseases. The duration of symptoms is also varied. Patients with jaundice may present with the following:

- No symptoms or extrahepatic manifestation of the liver disease
- Change of skin or eye colour or symptoms of acute illness
- Weight loss or pruritus if non-infectious aetiology
- Abdominal pain with bile duct stones and pancreatic or biliary tract cancers
- Can present with life threatening features in patients with massive haemolysis, acute cholangitis, fulminant liver failure and acute fatty liver of pregnancy [5]. These conditions should be treated as a medical emergency when resuscitation, stabilisation and treatment should be started in the emergency department with early involvement of the specialists.

Jaundiced patients with acute liver failure are very ill at presentation and require close monitoring whilst in the emergency department as the mortality approaches 80 % in this situation [5]. The two most common causes of acute liver failure worldwide are paracetamol poisoning and viral hepatitis [5, 6].

Causes of Jaundice

The bilirubin metabolism occurs in three phases: pre-hepatic, hepatic and post-hepatic and any problems at each of these phase deals to development of jaundice. Jaundice is thus classified as pre-hepatic, hepatic and post-hepatic jaundice which is shown in Table 30.1.

The cause of jaundice can also be divided by the type of bilirubin elevated [conjugated or unconjugated]. Some of the disease processes or conditions can cause both types of hyperbilirubinaemia. The causes of *unconjugated [indirect] hyperbilirubinaemia* are tabulated in Table 30.2. *Conjugated [direct] hyperbilirubinaemia* occurs uncommonly due to inherited causes [Dubin-Johnson and Rotor syndrome], but the most common causes are acquired. These are tabulated in Table 30.3.

Diagnostic Approach

Approach to a jaundiced patient begins by taking a detailed history, careful physical examination and initial laboratory results. A possible cause could be obtained in most cases from this, or it will help to direct the relevant investigations needed to identify the cause. The sensitivity of history and examination in identifying intrahepatic vs extra-hepatic disease as a cause for jaundice was 86 % in 220 subjects from a study in Scandinavia [7].

Table 30.1 Causes of jaundice

Pre-hepatic causes	Intrahepatic causes	Post-hepatic causes
Haemolysis	Hepatocellular disease	Gallstones, biliary strictures
Reabsorption of a large haematoma	Viral infections	Infections – [cytomegalovirus [CMV], Epstein-Barr virus [EBV] and HIV]
Drugs	Chronic alcohol use	Malignancy
Haemolytic anaemia	Autoimmune disorders	Pancreatitis
G6PD deficiency	Drugs, pregnancy	
Hereditary spherocytosis	Parenteral nutrition	
Sickle cell disease	Dubin-Johnson syndrome	
	Rotor's syndrome	

Table 30.2 Causes of unconjugated hyperbilirubinaemia

Overproduction of bilirubin	Impaired bilirubin uptake	Impairment of conjugation
Haemolysis, mechanical valves, paroxysmal nocturnal haemoglobinuria, disseminated intravascular coagulation and haemolytic uraemic syndrome	Heart failure, portosystemic shunts and drugs like probenecid and rifampicin	Gilberts, Crigler-Najjar syndrome, Wilson disease and advanced liver cirrhosis

Table 30.3 Causes of conjugated hyperbilirubinaemia

Hepatocellular injury	Cholestasis
Hepatocellular carcinoma, cholangiocarcinoma, metastatic disease, secondary biliary cirrhosis, cryptogenic cirrhosis	Intrahepatic Viral hepatitis, alcoholic hepatitis, non-alcoholic steatohepatitis, primary biliary cirrhosis, drugs and toxins, sepsis/ hypoperfusion, infiltrative diseases, total parenteral nutrition, pregnancy and cirrhosis
Hereditary [Wilson's disease, alpha-1-antitrypsin deficiency, haemochromatosis]	
Viral hepatitis [CMV, HSV], bacterial: [tuberculosis', leptospirosis, syphilis, brucellosis], fungal [candida, histoplasmosis, cryptococcus], parasitic[ascaris, clonorchis, schistosomiasis, echinococcus] protozoa [amoebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis]	Extrahepatic Bile duct stones, tumours, primary sclerosing cholangitis, AIDS cholangiopathy, acute or chronic pancreatitis, strictures and parasitic infections
Toxic medications [alcohol, chlorinated hydrocarbons, Amanita phalloides toxin, aflatoxin]	
Immunologic [autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis] and nonalcoholic steatohepatitis	

History

A detailed history should include the following:

- Duration of onset and associated symptoms, presence or absence of pain, fever, constitutional symptoms and weight [loss/gain].
- History of abdominal operations [gallbladder/liver/pancreatic surgery]
- Medication use [prescribed, over-the-counter drugs, herbal preparations, food supplements and recreational drugs]
- Hepatitis risk factors [travel, intravenous drug use, sexual contacts]
- History of inherited disorders [both liver diseases and haemolytic disorders]
- Alcohol consumption and toxic substance exposure

Clinical Examination

Check for tachycardia [fever, anaemia or distress from pain], tachypnoeic and/or hypoxic [effusions/ascites/sepsis/anaemia/pulmonary oedema] and hypotension [anaemia, sepsis, fluid shifts].

- Signs of chronic liver failure [ascites, splenomegaly, spider naevi, palmar erythema, gynecomastia] or acute liver failure.
- Disease-specific features such as Kayser-Fleischer rings in Wilson disease, xanthomas in primary biliary cirrhosis, hyperpigmentation of haemochromatosis or a Courvoisier sign [malignancy].
- Abdominal examination
  - Assess liver size [enlarged in hepatitis, tumours or shrunken in cirrhosis] and tenderness [cholestasis, heart failure or inflammation].
  - Ascites [chronic liver disease, rapid onset in portal vein thrombosis or tender in spontaneous bacterial peritonitis].
  - A Murphy's sign indicates acute cholecystitis.
  - Charcot's triad [fever, right upper quadrant pain and jaundice] indicates ascending cholangitis.
- Cardiorespiratory examination to look for signs of heart failure, effusions or pulmonary oedema [from heart failure, sepsis or end-stage liver disease].
- Neurological examination to assess the mental status [conscious level, orientation and cognitive function].

Interpretation of Laboratory Tests

The initial laboratory tests should include full liver function tests, full blood count, coagulation screen and albumin. The abnormalities in each of the liver tests help to identify the various causes of jaundice.

Normal alkaline phosphatase [*ALP] and aminotransferases [ATS]*

- Hepatic injury or biliary disease is not the cause of jaundice.
- Jaundice is due to haemolysis or inherited disorders of bilirubin metabolism.

Raised ALP predominantly: suggests biliary obstruction or intrahepatic cholestasis

- Elevated in non-liver causes such as bone diseases and pregnancy.
- Measure GGT if this raised confirms hepatic origin of ALP.

Predominant ATS elevation: suggests cause is by intrinsic hepatocellular disease

- Further tests should be performed to evaluate a cause: viral hepatitis; liver autoantibodies [autoimmune liver disease]; serum levels of iron, transferrin and ferritin for haemochromatosis; serum levels of copper and caeruloplasmin for Wilson disease; and alpha-1-antitrypsin activity for alpha-1-antitrypsin deficiency.

  Prothrombin time and albumin: measures synthetic function of the liver

- If PT does not correct with vitamin K it suggests moderate to severe hepatocellular disease but in cases of obstructive jaundice PT will correct with vitamin K administration.
- Albumin [low albumin] is affected predominantly in chronic disorders.

Radiological Tests

- Ultrasonogram is the first-line test recommended [8] due to its wide availability, low cost and no radiation exposure. This is the most sensitive imaging technique for detecting biliary stones and benign obstruction.
- Computed tomography is the recommended test if malignant process or pancreatic disease is suspected. Scanning can provide more information about liver and pancreatic parenchymal disease [9].
- If parenchymal involvement of the liver is suspected, then magnetic resonance imaging is the test of choice [8].
- Endoscopic retrograde cholangiopancreatography is primarily a therapeutic procedure [10] and is recommended for post-operative biliary leaks or strictures, palliation of malignant biliary obstruction, pancreatic duct stones or leaks and diagnosis of pancreatic malignancies [10–12].

Liver Biopsy

It provides information on liver architecture and is useful when blood/imaging results are not helpful but is rarely required in emergency situation [13–15].

Treatment

The cause of jaundice will direct the treatment i.e. when specific therapy must be initiated otherwise it is largely supportive if no specific cause is identified. Generally patients with fever, coagulopathy, altered mental status or intractable pain should be hospitalised and symptoms treated. Patients with massive haemolysis, acute cholangitis, fulminant liver failure and acute fatty liver of pregnancy [5] present with life-threatening features. These conditions should be treated as a medical emergency when resuscitation, stabilisation and treatment should be started in the emergency department with early involvement of the specialists.

Extrahepatic Obstruction

- Consider biliary drainage.
- Ascending cholangitis: start broad-spectrum antibiotics and obtain surgical review.
- Patients with sepsis – biliary drainage either by ERCP or cholecystostomy should be established [10, 16].
- For bile duct obstructions from gallstones or strictures [benign or malignant] patients will benefit from decompression by ERCP [10, 12, 17].

Hepatocellular Injury

- Exclude acute liver failure [evidence of coagulopathy or altered mental status].
- Hepatic encephalopathy can be treated with lactulose or phosphate enemas. Patients who present with severe encephalopathy [somnolence and coma] may need to be intubated to protect their airways and are at increased risk for developing cerebral oedema and herniation.
- Definitive treatment in some cases for fulminant liver failure is transplantation.

Paracetamol-Induced Liver Injury

- Treatment can prevent the development of acute liver failure and transplantation.
- Give activated charcoal if patients present within an hour of ingestion and if no contraindications [18–20].
- Treatment for paracetamol-induced liver toxicity is N-acetylcysteine [NAC] [19–21]. NAC is administered if serum paracetamol levels are above the treatment line on the Rumack-Matthew nomogram [18–22].
- The dose is 150 mg/kg IV over 60 min, then 50 mg/kg over 4 h and then 100 mg/kg over 16 h [18, 20].
- If given within 8 h of ingestion, NAC is 100 % protective from liver injury but shown to be beneficial if given after that time [18–20].

Other Causes of Hepatocellular Injury

- Corticosteroids for patients with autoimmune hepatitis [23–25].
- Drug-induced liver injury is managed conservatively. Stop the offending drug and wait for bilirubin to normalise [26, 27]. This can take few weeks to months. Trial of short course of steroids or ursodeoxycholic acid can be tried [26, 27].

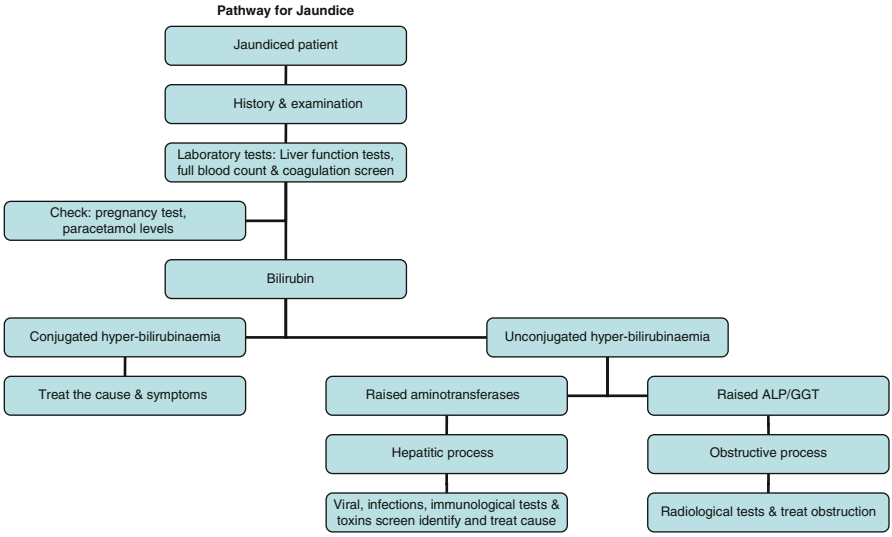
Pregnant Women

- *Hyperemesis gravidarum* generally occurs in the first trimester, characterised by nausea and vomiting. Jaundice is seen in half the women, the cause of which is unknown [28]. Jaundice disappears after resumption of oral intake, and treatment consists of hydration and anti-emetics [28].
- *Intrahepatic cholestasis of pregnancy* is an idiopathic cause of jaundice that occurs in the early third trimester presenting with pruritus followed by jaundice [29, 30]. These patients are at increased risk for preterm delivery and intrauterine foetal demise [29, 30].
- *Acute fatty liver of pregnancy* occurs in the third trimester, and sometimes it presents after delivery. Patients present with nausea, vomiting and right upper quadrant pain. Development of jaundice usually follows these symptoms. If untreated it can progress rapidly to fulminant hepatic failure and death. Prompt delivery is the treatment.

Haemolysis

- Massive haemolysis: Treatment depends on the cause of the haemolysis
- Drug-induced haemolytic anaemia should avoid the offending agent.
- Blood transfusion for those who are symptomatic.
- Discuss with haematologist in cases of disseminated intravascular coagulopathy.

Pathway for Jaundice



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Part VII
General Medicine and Allied Specialties

Chapter 31
Acute Thyroid and Adrenal Disorders

P.E. Rama Subrahmanyam

Part A – Acute Thyroid Disorders

Key Points

- Adequate understanding of the aetiology and pathophysiology is the key for prompt management of thyroid disorder.
- Thyroid crisis is a decompensated state of thyroid hormone-induced hypermetabolism due to:
  - Excess thyroid hormone synthesis and release
  - Peripheral effects of thyroid hormone
  - Underlying precipitating event
- Myxoedema coma is usually in elderly with undiagnosed or undertreated hypothyroidism.
- Hydrocortisone in thyroid crisis decreases peripheral conversion of T4 to T3 and in myxoedema coma helps to tide over the adrenal insufficiency.
- Management of the precipitating cause is the main supportive treatment in thyroid crisis and myxoedema coma.

Introduction

Acute thyroid disorders are infrequently observed in clinical practice with a poorly defined incidence. They represent a long-standing dysregulation of thyroid gland, usually precipitated by an acute illness. They are either caused by overt dysfunction

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_31

resulting in myxoedema coma or hyperfunctioning of the gland giving rise to thyrotoxicosis. Despite utmost care, mortality remains high, 30–50 % in myxoedema coma and 30–40 % in thyroid storm thereby necessitating immediate and aggressive intervention in emergency department.

Thyroid Storm

Thyroid storm is a condition in which multiple organ dysfunction results from failure of the compensatory mechanisms of the body owing to excessive thyroid hormone activity induced by some factors in patients with thyrotoxicosis. Although rare, it is a life-threatening condition requiring emergency treatment [1–3].

Aetiology of Thyroid Storm

The excess thyroid hormone is released from the thyroid gland as a result of excess thyroid hormone production or by processes that disrupt the follicular structure of the gland with subsequent release of stored hormone. Table 31.1 shows the precipitating factors for thyroid storm.

Pathophysiology of Thyroid Storm

Thyroid hormone influences almost every tissue and organ system in the body. It increases tissue thermogenesis and basal metabolic rate (BMR) and reduces serum cholesterol levels and systemic vascular resistance. Some of the most profound effects of increased thyroid hormone levels are on the cardiovascular system [4], but even then the pathophysiology of thyroid storm is unclear; the hypothesis suggested is an increase in free T_3 concentrations and increase in β-adrenergic receptor activation. In presence of both a larger availability of adrenergic receptors and a reduction of thyroid

Table 31.1 Precipitating factors in thyroid storm

Precipitating factors in thyroid storm
General
Infection, non-thyroidal trauma or surgery, N psychosis, parturition, myocardial infarction or other acute medical problems
Thyroid specific
Radioiodine, high doses of iodine-containing compounds (e.g. radiographic contrast media), discontinuation of antithyroid drug treatment, thyroid injury (palpation, infarction of an adenoma), new institution of amiodarone therapy

hormone binding to TBG (thyroid hormone-binding globulin), the leak of catecholamine provoked by an acute event (i.e. triggering factor) finally precipitates TS. There is usually a precipitating event that sets off the thyroid storm. There is no clear cut-off level for free T_4 or free T_3 to predict severe thyrotoxicosis. What is important is to recognise the severity of thyrotoxicosis and treat the patient appropriately.

Clinical Features

Thyroid storm has now become a rare entity owing to early detection and treatment of thyrotoxicosis.

Thyroid storm presents with:

- An exaggeration of the features of uncomplicated thyrotoxicosis
- An alteration in mental status
- Irreversible cardiovascular collapse and death if proper treatment is not initiated in the emergency department

Cardinal features include:

- Cardiovascular: severe tachycardia, atrial fibrillation, systolic hypertension and congestive heart failure may occur, particularly in the elderly, and most patients have systolic hypertension.
- Fever (usually 38.5 °C).
- Gastrointestinal dysfunction (vomiting, diarrhoea and occasional jaundice).
- Agitation, confusion, delirium or coma.
- Biochemical: hyperglycaemia, leucocytosis, hypocalcaemia and abnormal liver function tests.

Diagnosis of Thyroid Storm

The prerequisite for the diagnosis of thyroid storm is a definite biochemical evidence of thyrotoxicosis along with the scoring system based on the clinical criteria as shown in Table 31.2 [5]. A score between 25 and 44 is suggestive of impending thyroid storm, and a score >44 is suggestive of thyroid storm.

Investigation and Treatment of Thyroid Storm

Prompt recognition and aggressive treatment employing a multifaceted approach are generally effective at correcting the homeostatic decompensation. Routine investigations along with thyroid function tests should be carried out. However, treatment

Table 31.2 The clinical scoring system for diagnosis of thyroid storm

Criteria		Score
Thermoregulatory dysfunction		
Temperature	99–99.9 °F (37.2–37.7 °C)	5
	100–100.9 °F(37.8–38.2 °C)	10
	101–101.9 °F(38.3–38.8 °C)	15
	102–102.9 °F(38.9–39.3 °C)	20
	103–103.9 °F(39.4–39.9 °C)	25
	≥104 °F (40 °C) or higher	30
Central nervous system effects		
Absent		0
Mild agitation		10
Delirium, psychosis, lethargy		20
Seizure or coma		30
Gastrointestinal dysfunction		
Absent		0
Diarrhoea, nausea, vomiting or abdominal pain		10
Unexplained jaundice		20
Cardiovascular dysfunction		
Tachycardia	90–109 beats/min	5
	110–119 beats/min	10
	120–129 beats/min	15
	130–139 beats/min	20
	≥140 beats/min	25
Congestive heart failure	Absent	0
	Mild oedema	5
	Moderate bibasilar rales	10
	Severe pulmonary oedema	15
Atrial fibrillation	Absent	0
	Present	10
History of precipitating event (surgery, infection, etc.)		
Absent		0
Present		10

should be initiated without awaiting the results in clinically suspected cases. Adrenal reserve may be impaired. Infective screening, e.g. urine, chest x-ray, blood cultures and sputum, is essential. ECG should be done to check for arrhythmias.

Thyroid studies: Usually, there is elevated triiodothyronine (T3), thyroxine (T4) and free T4 levels; increased T3 resin uptake; suppressed thyroid-stimulating hormone (TSH) levels; and an elevated 24-h iodine uptake. TSH levels are not suppressed in the rare instances of excess TSH secretion.

The initial stabilisation and management of systemic decompensation are as follows:

- Supplemental oxygen.
- Ventilatory support.

- Intravenous fluids: Dextrose solutions are the preferred intravenous fluids to cope with continuously high metabolic demand.
- Correction of electrolyte abnormalities and cardiac arrhythmia.
- Aggressively control hyperthermia by applying ice packs and cooling blankets and by administering acetaminophen.
- Antiadrenergic drugs (e.g. propranolol) to minimise sympathomimetic symptoms. High doses of β-blocker should be given, and propranolol at a dose of 80–120 mg every 6 h is recommended.

Specific therapy of hyperthyroidism follows several strategies, including:

1. Inhibition of hormone synthesis and release
2. Inhibition of peripheral conversion of T4 to T3
3. Blocking of the systemic effects of excess thyroid hormone

1. Inhibition of thyroid hormone synthesis and release: Inhibition of thyroid hormone can be achieved by either PTU or carbimazole (less useful). PTU inhibits iodine and peroxidase from their normal interactions with thyroglobulin to form T4 and T3. This action decreases production of thyroid hormone. Propylthiouracil can be given by the mouth, nasogastric tube or rectally at a rate of 250 mg every 4–6 h or methimazole 20–30 mg PO q6h.

   Inhibition of thyroid hormone release is achieved by iodine given orally or via a nasogastric tube to block the release of THs (at least 1 h after starting antithyroid drug therapy). This delay allows the antithyroid drug to inhibit thyroid hormone synthesis, which otherwise may be enhanced by unopposed iodide.
2. Inhibition of peripheral conversion of T4 to T3 can be achieved by: Administration of hydrocortisone 100 mg IV q8h or dexamethasone 2 mg IV q6h. Glucocorticoids also serve in preventing relative adrenal insufficiency due to hyperthyroidism and provide vasomotor stability.

Alternative therapies:

Lithium 300 mg PO q8h appears to be actively concentrated in the thyroid follicular cells and inhibits thyroid hormone release [6, 7]. Lithium should be monitored regularly to maintain a concentration of 0.6–1.0 mEq/L.

Treat the underlying cause:

- Broad-spectrum antibiotics if an infection is the precipitating factor.
- Any other medical condition precipitating thyroid storm should be addressed like DKA, HONK, myocardial infarction and hypoglycaemia.

(Note: Cholestyramine, 4 g every 6–8 h, binds thyroid hormone in the gut and thus interrupts the modest enterohepatic circulation of thyroid hormone; its use will lead to a more rapid lowering of circulating thyroid hormones. In exceptional cases, peritoneal dialysis or plasmapheresis may be needed.)

Once the patient is stable, the differential diagnosis of thyroid disease underlying thyroid storm should be accurately investigated, with the aim of distinguishing thyroid hyperfunction, destructive thyroiditis or thyrotoxicosis factitia.

The managemnt algorithm for Thyroid storm can be summarised as in Fig. 31.1

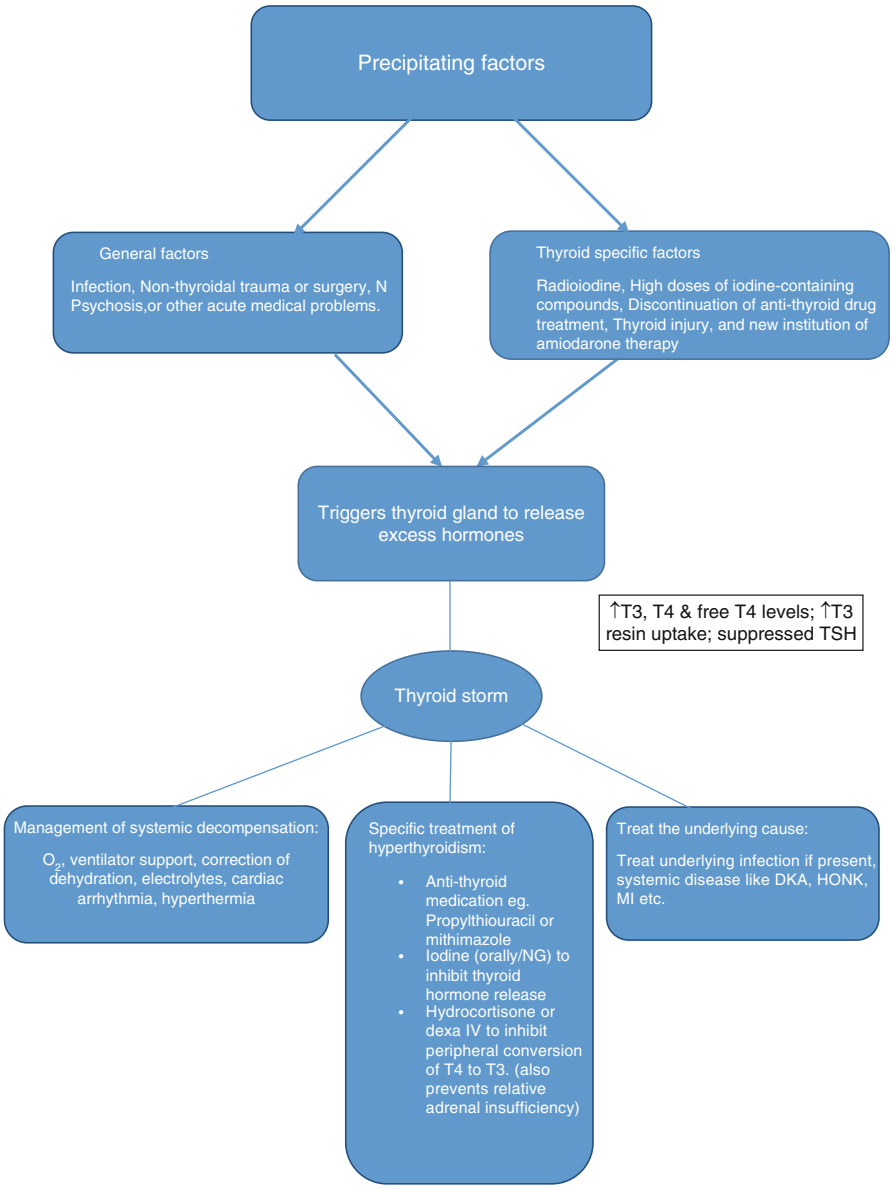

Fig. 31.1 Approach to Thyroid storm (algorithm)

Myxoedema Coma

Myxoedema coma is a rare decompensated state of extreme hypothyroidism with a high mortality rate (25–60 %) [8, 9] even with early diagnosis and appropriate treatment. It is typically found in elderly patients with undiagnosed or undertreated hypothyroidism [10].

Aetiology and Pathophysiology

Myxoedema coma results as a consequence of critical decompensation of a patient due to stress. The stress factors include: infection, hypothermia, intoxication, drugs, cerebrovascular accident, congestive cardiac failure and trauma. More than 95 % of patients have primary thyroid disease like autoimmune thyroid disease or hypothyroidism secondary to ablative procedures on the thyroid.

Thyroid hormone is essential for cellular metabolism, and all organ systems are affected if hypothyroidism is severe and prolonged. Decreased thyroid function results in:

- Depressed basal metabolic rate
- Decreased oxygen consumption
- Impaired energy production

The cardiovascular system is particularly susceptible leading to depressed myocardial contractility and bradycardia resulting in low cardiac output and profound hypotension resulting in decreased cerebral perfusion.

Clinical Features

Patients with myxoedema coma classically demonstrate features of severe hypothyroidism, which includes dry skin, thin hair, periorbital swelling, non-pitting oedema of the hands and feet, hoarse voice, macroglossia and delayed tendon reflexes along with central nervous system features including respiratory depression secondary to a decreased hypoxic ventilatory drive and an impaired response to hypercapnia [11–13]. This will eventually lead to myxoedema coma characterised by altered mental status in the form of confusion, lethargy, obtundation or frank psychosis.

Hypothermia is universal and often the first clinical indication of myxoedema coma. Body temperatures lower than 94 % and a core body temperature lower than

88 % have been reported [14]. The mortality of myxoedema is directly correlated with the degree of hypothermia. The lower the temperature, the worse is the prognosis.

Other features include bradycardia, depressed cardiac contractility, anorexia, nausea, abdominal pain, constipation, respiratory depression, respiratory muscle weakness, respiratory acidosis and hypoxaemia.

Diagnosis and Treatment

The diagnosis of myxoedema coma is based on the presence of clinical characteristics in a known patient of hypothyroidism, and this suspicion should be confirmed by thyroid function tests.

Thyroid function studies demonstrate:

- Low total and free thyroxine (T4)
- Low total and free triiodothyronine (T3)
- TSH: increased in primary hypothyroidism but normal or decreased in central pathology

Other biochemical studies show hyponatraemia, hypoglycaemia, hypoxemia, hypercapnia, elevated lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and cholesterol.

Enlarge cardiac silhouette due to pericardial effusion on chest x-ray.

ECG demonstrates profound bradycardia and low-voltage complexes.

The three principles of management are:

1. Rapid institution of thyroid hormone replacement
2. Treatment of the precipitating cause
3. Supportive treatment providing adequate ventilation and correcting biochemical parameters

Thyroid hormone therapy administers T3, T4 or combination.

- T3 is given as an initial dose of 10 mcg, followed by 10 mcg every 8–12 h until there is clinical improvement and patient is able to take it orally. T4 is given in a loading dose of 200–300 mcg intravenously, followed by 100 mcg 24 h later and then a daily dose of 50 mcg. Thereafter, the daily dosage can be adjusted according to the laboratory results.
- The second most important drug is hydrocortisone because thyroid replacement may unmask coexisting adrenal insufficiency and precipitate adrenal crisis dosage: 100 mg IV q6–8 h given along with thyroid replacement for several days later tapered and stopped after assessment of adrenal function.

Supportive treatment:

IV fluid boluses for hypotension: Pressor agents should be avoided in such patient as they precipitate an arrhythmia, and also response to pressors is poor until thyroid replacement is initiated.

Consider hypertonic saline for severe hyponatraemia.

Hypothermia should be treated with space blankets, since active rewarming leads to circulatory collapse.

Part B – Acute Adrenal Disorders

Key Points

- Sudden withdrawal of steroids and precipitation by intercurrent illness are by far the most common causes of adrenal crisis in ED.
- Patients with adrenal crisis manifest with profound shock, hypoglycaemia, hyperkalaemia and hyponatraemia.
- Hydrocortisone 100 mg IV should be initiated even before awaiting the results of serum cortisol and ACTH.
- Blood pressure control in pheochromocytoma is the mainstay of management, and phenoxybenzamine is the drug of choice.

Introduction

Acute adrenal disorders are rare life-threatening situations, requiring prompt clinical suspicion and immediate replacement of fluids, electrolytes and hormones. The disorders of adrenal cortex result in various manifestations, such as severe deficiency of corticosteroids in adrenal crisis in turn leading to fluid-electrolyte disturbances, whilst excessive unregulated production of steroids results in Cushing's syndrome. Pheochromocytomas on the other hand are functional tumours of adrenal medulla presenting with hyperadrenergic spells.

This section is aimed to channelise the thought process of the emergency physician to recognise the subtle clinical manifestations at tip of the iceberg and dwell deep towards the endocrine abnormalities and deal with the appropriate management of these potentially life-threatening conditions.

Acute Adrenocortical Insufficiency

Adrenal insufficiency results from inadequate adrenocortical function and may be due to Addison's disease, previous bilateral adrenalectomy, pituitary disorders, hypothalamic dysfunction or sudden withdrawal of long-term oral steroids in people with chronic diseases.

Table 31.3 Causes of adrenal insufficiency

Primary adrenocortical insufficiency (Addison's disease)	Secondary adrenocortical insufficiency
Anatomic destruction of adrenal gland	Disease of the hypothalamic-pituitary axis
Idiopathic – probably autoimmune	Tumour
Infective – TB, AIDS, disseminated fungal infection	Apoplexy
Haemorrhage – anticoagulant therapy, Waterhouse	Granulomatous disease
Friderichsen syndrome	Suppression of the hypothalamic-pituitary axis
Infiltration – carcinoma, lymphoma, sarcoidosis, amyloidosis	Exogenous steroids
Metabolic failure of the adrenal gland	
Congenital adrenal hyperplasia	
Drugs, e.g. ketoconazole, etomidate	

Aetiology of Adrenal Insufficiency

The adrenal insufficiency can be divided into two major categories, primary and secondary adrenal insufficiency (Table 31.3).

- Primary adrenal insufficiency: both glucocorticoid and mineralocorticoid functions are lost.
- Secondary adrenocortical insufficiency: only glucocorticoid function is lost due to disease or suppression of the hypothalamic-pituitary axis, but mineralocorticoid function is preserved. The causes of adrenal insufficiency are listed in Table 31.4.

Acute Adrenocortical Insufficiency (Adrenal Crises)

Acute adrenal crisis is a life-threatening state caused by insufficient levels of cortisol from an acute insult in a patient with chronic insufficiency or more commonly from withdrawal of exogenous steroids (Table 31.4).

Clinical Features

The onset is gradual with features including weight loss, lethargy, weakness, vague abdominal pain, nausea, vitiligo, oligomenorrhoea and pigmentation of buccal mucosa, palmar creases, elbow and knees. In adrenal crises, the patient can be profoundly shocked (tachycardia, hypotensive, vasoconstricted, oliguric) and hypoglycaemic.

Table 31.4 Precipitating factors for acute adrenal crises (in alphabetical order)

Alcohol
Asthma
Exogenous steroid withdrawal/reduction
Hypothermia
Infection
Myocardial infraction
Stroke
Trauma

Table 31.5 Emergency approach of adrenal crisis

Clinical features: anorexia, nausea, vomiting, craving for salt, headaches, memory loss, postural hypotension, tachycardia, abdominal pain, shock, unexplained pyrexia
Step 1: Take blood for urea, electrolytes, glucose and cortisol (low serum cortisol <200 nmol/L indicates adrenal insufficiency. If ACTH is raised, it indicates primary and a low ACTH suggests secondary adrenal insufficiency. High serum cortisol>550 nmol/L excludes adrenal insufficiency. Intermediate serum cortisol 200–550 nmol/L requires Synacthen test)
Step 2: Commence an IV infusion of 0.9 % saline (to reverse fluid and sodium deficiency). Correct hypoglycaemia
Step 3: 100 mg IV hydrocortisone bolus should be administered immediately followed by 100 mg of IV hydrocortisone six hourly for 24–48 h or until oral therapy can commence

Investigations

In the early phases of adrenal destruction, the laboratory investigations may not be abnormal but adrenal reserve is decreased; hence, adrenal stimulation with ACTH is necessary to uncover the abnormalities at this stage of the disease.

In advanced stages, there are obvious manifestation of hyponatraemia and hypokalaemia; hence, serum sodium, potassium, chloride and bicarbonate should be checked along with other causes identifying the cause of the acute adrenal insufficiency (e.g. infective screen). In all the suspected cases of adrenal crisis, serum cortisol and ACTH should be sent but should not delay the treatment with hydrocortisone.

Management of Adrenal Crises

Management of suspected case of adrenal crisis should be done in a stepwise manner as shown in the Table 31.5 and the algorithm Fig. 31.2.

- Intravenous fluids should be continued till oral therapy is commenced.
- Patient may require several litres of fluids for resuscitation if the crisis was preceded by severe dehydration secondary to nausea or vomiting, but cardiac status should be the guide for further fluid resuscitation.
- Fludrocortisone is only required in primary adrenocortical insufficiency and is not commonly given in the emergency department.

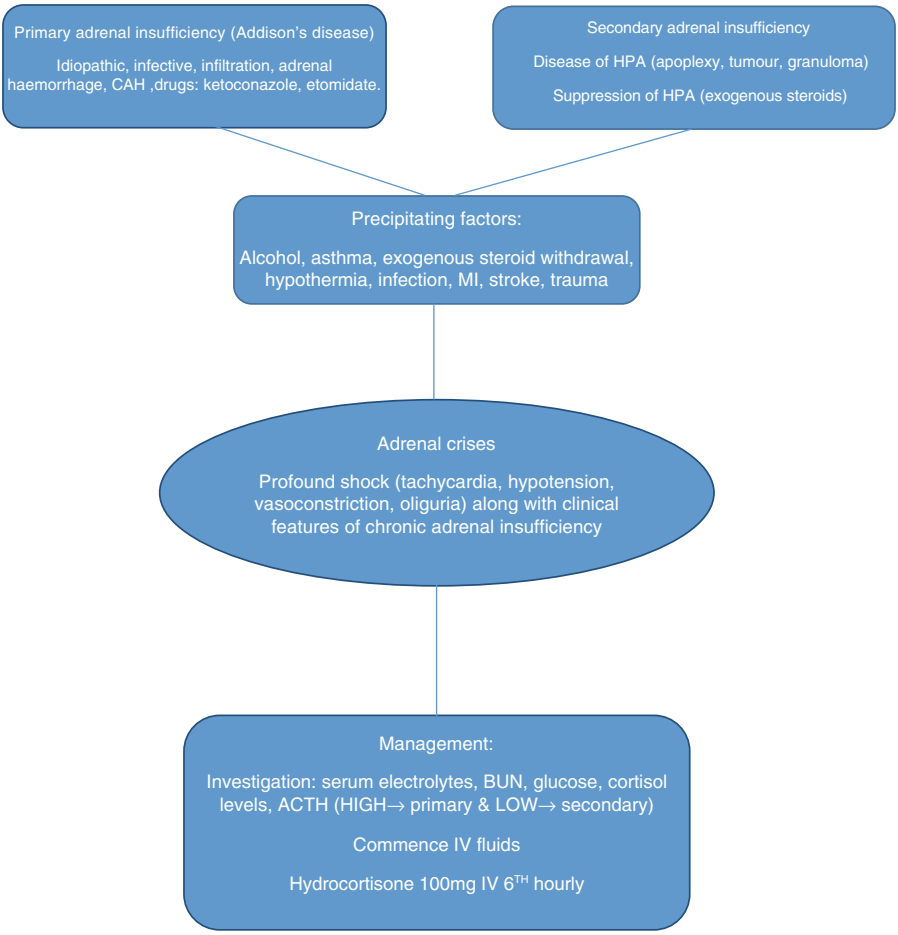

Fig. 31.2 Adrenal insufficiency: algorithm

- Monitor for hypoglycaemia and treat with 10 % glucose IV if necessary.
- Underlying infections should be screened and treated with appropriate antibiotics.

Cushing's Syndrome

Cushing's syndrome and Cushing's disease are the complex metabolic disorders that result in excess glucocorticoids in the body and are associated with impairment of circadian oscillation [15, 17]. This is most commonly caused by patients taking exogenous steroids for other medical conditions. Excluding the exogenous causes, adrenocorticotropic hormone-secreting pituitary adenomas account for nearly 70 % of all cases of Cushing's syndrome [16].

Epidemiology

In general, CS is a rare disease. The reported incidence of endogenous CS worldwide ranges from 0.7 to 2.4 cases per million per year [18]. Commonly affected age group ranges from 20 to 50 years with a marked female preponderance (1:5 ratio of male vs. female).

Causes

CS is a heterogeneous disorder that arises from prolonged exposure to elevated levels of either endogenous or exogenous glucocorticoids resulting in a broad spectrum of eventually fatal comorbidities such as diabetes and hypertension (Table 31.6).

Clinical Features

CS comprises of numerous general and endocrine symptoms and side effects, some of which might be entailed with fatal outcome.

Excess cortisol levels result in:

- Facial plethora
- Hirsutism
- Gonadal dysfunction
- Menstrual irregularities
- Depression
- Infections due to generalised immune suppression
- Striae
- Vascular fragility
- Hypokalaemia, muscle weakness
- Osteoporosis and eventually fractures

The metabolic consequences of cortisol excess include weight gain, central obesity, skin atrophy, glucose intolerance entailed by diabetes and insulin resistance, dyslipidaemia, hypertension and clotting disorders (eventually even hypercoagulability) [19].

Table 31.6 Causes of Cushing's syndrome

Endogenous causes of Cushing's syndrome		Exogenous causes of Cushing's syndrome
ACTH-dependant Cushing's syndrome	ACTH-independent Cushing's syndrome	Intake of steroids in high doses over an extended period of time Iatrogenic administration of ACTH
Pituitary adenoma (Cushing's disease) Ectopic tumours secreting ACTH or corticotropin-releasing hormone (CRH)	Adrenocortical tumours or hyperplasia	

Investigations

Obtain a thorough drug history to exclude exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing. The clinical suspicion should be followed by a step-by-step diagnostic workup. The diagnostic studies involved in the evaluation of patients with suspected Cushing's syndrome fall into two categories:

1. Confirming the presence of true hypercortisolism
2. Establishing the precise aetiology

Diagnosis of hypercortisolism (irrespective of its origin) comprises the following:

- Complete blood count including serum electrolytes and blood sugar
- Urinary free cortisol (UFC) from 24 h urine sampling and circadian profile of plasma cortisol, plasma ACTH, dehydroepiandrosterone, testosterone itself and urine steroid profile, low-dose dexamethasone test and high-dose dexamethasone test, after endocrine diagnostic tests
- Magnetic resonance imaging (MRI), ultrasound, computed tomography (CT) and other localization diagnostics

The laboratory findings suggestive of Cushing's syndrome include: hyperglycaemia, hypokalaemia and hypocalcaemia. Ectopic Cushing's syndrome should always be ruled out in patients with severe hypertension and hypokalaemia [20].

Management of Cushing's Syndrome

Cushing's syndrome may occasionally present as an acute emergency. In suspected cases of Cushing's syndrome caused by exogenous glucocorticoid exposure, the following steps should be carried out:

- A detailed drug history and any relevant drug-drug interactions.
- In an emergency situation, treatment should focus on management of severe metabolic disturbances, followed by rapid resolution of the excess glucocorticoid exposure, and subsequent confirmation of the cause and its treatment.
- If the cause of Cushing's syndrome is exogenous steroids, these may be gradually tapered off and eventually stopped, if possible.
- The definitive treatment for endogenous Cushing's syndrome is selective removal of the tumour from the affected organ.
- Pharmacotherapy is an option in the case of failure of surgery for Cushing disease or in ectopic ACTH secretion where the source cannot be identified.

Medical therapy can be categorised in three different groups:

Inhibition of steroidogenesis: The drugs which inhibit steroidogenesis either by enzyme inhibition or by destroying the adrenal cells include mitotane,

aminoglutethimide, metyrapone, trilostane and ketoconazole. Etomidate is one of the parenteral drugs which can be used in case of emergency situations and is commenced at 2.5 mg/h and titrated subsequently according to cortisol levels [21].

Suppression of adrenocorticotropic hormone: Somatostatin receptor ligands like pasireotide [22] and dopamine agonists like cabergoline can lower ACTH secretion caused by a pituitary adenoma.

Antagonism of the glucocorticoid receptor: Mifepristone binds to the glucocorticoid receptor with a fourfold higher affinity than dexamethasone and an 18-fold higher affinity than cortisol and hence acts as antagonist.

However, the majority of common drugs are not available for parenteral administration, which may evoke a management problem in emergency settings or in patients unable to tolerate oral medication.

Pheochromocytoma

Introduction and Epidemiology

Pheochromocytomas are the catecholamine-secreting functional tumours that arise from the chromaffin cells in the adrenal medulla (80–85 %) or extra-adrenal chromaffin cells (15–20 %) and can originate in either the parasympathetic or sympathetic ganglia [23].

Aetiology and Pathophysiology

Pheochromocytomas were known as the 10 % tumours, meaning that 10 % of cases were familial, 10 % bilateral, 10 % malignant and 10 % extra-adrenal [24]. They may arise sporadically or be inherited as features of multiple endocrine neoplasia type 2 or several other pheochromocytoma-associated syndromes. They account for 0.1–0.2 % of cases of systemic hypertension; 35 % of them are hereditary in adults [25–27] and up to 40 % are hereditary in children [28]. The prevalence is equal in men and women and is reported in people of all races.

Clinical Features of Pheochromocytoma

The clinical presentation of pheochromocytoma is variable (Table 31.7). The clinical suspicion of pheochromocytoma should arise if one or more of the following features are present:

Table 31.7 Signs and symptoms associated with catecholamine-secreting tumour

Spell-related signs and symptoms
Anxiety and fear of impending death, diaphoresis, dyspnoea, epigastric and chest pain, headache, hypertension, nausea and vomiting, pallor, palpitation, tremor
Chronic signs and symptoms
Weight loss, tremor, dyspnoea, cold hands and feet, anxiety, headache, hypertension, orthostatic hypotension, fever, fatigue, nausea, vomiting
General increase in sweating
Nontypical of pheochromocytoma: flushing

- Hyper adrenergic spells (e.g. self-limiting spells of nonexertional palpitations, diaphoresis, headache, tremor, pallor).
- Resistant hypertension.
- A familial tumour that predisposes to catecholamine-secreting tumours (e.g. multiple endocrine neoplasia (MEN) 2).
- Labile hypertension and paroxysms of hypertensions and tachycardia.
- In emergency situations, it should be noted, however, that most patients do not have tachycardia but have bradycardia due to reflex cardiac slowing in response to norepinephrine-mediated vasoconstriction.
- Sustained tachycardia would suggest an epinephrine-secreting tumour.

Diagnosis of Pheochromocytoma

The three key elements for the diagnosis of pheochromocytoma are clinical suspicion, biochemical testing and localization studies.

Biochemical studies: documentation of catecholamine excess can be difficult because hormonal activity of tumours fluctuates, resulting in considerable variation in serial catecholamine measurements. Thus, there is some value in obtaining tests during or soon after a symptomatic crisis. On the other hand, most tumours continuously leak O-methylated metabolites, which are detected by metanephrine measurements. The following biochemical tests can be performed:

- The plasma-free metanephrine levels and normetanephrines
- Twenty-four hours urinary free catecholamine level in the initial screening test
- Plasma catecholamines

Emergency physician should also look for evidence of hypertensive end-organ damage (e.g. renal failure, proteinuria, left ventricular hypertrophy, retinopathy and papilloedema).

Localization studies involve imaging (CT/MRI), radio-labelled catecholamine precursors to localise the tumour and genetic testing.

Treatment

Hypertensive crises (systolic BP >250 mmHg): Blood pressure control is the mainstay of the treatment when the patient arrives to the emergency department. First step is to block the effects of catecholamine excess by controlling HTN and expanding intravascular volume. Establish adequate alpha blockade and subsequently instituting a beta-blocker or a calcium channel blocker if needed to control blood pressure and heart rate. A hypertensive crisis may be precipitated by drugs that inhibit catecholamine uptake, such as tricyclic antidepressants and cocaine, opiates, anaesthesia induction and x-ray contrast media; hence, a thorough history should be retrieved from the patient.

- Intravenous phentolamine (a potent alpha-2 blocker) 1 mg followed by 5 mg bolus infusions.
- IV nitroprusside not more than 3 μg/kg/min can be started as the initial rescue to control hypertension.
- Hydration and a high-salt diet (>5 g/day) are given to offset the effects of catecholamine-induced volume contraction associated with alpha blockage.
- Provide volume expansion with isotonic sodium chloride solution
- Initiate a beta-blocker only after adequate alpha blockade, to avoid precipitating a hypertensive crisis from unopposed alpha stimulation [29].

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Chapter 32
Biomarkers in Emergency Medicine

Anoop T. Chakrapani

Introduction

According to the National Institutes of Health (NIH) Biomarkers Working Group, a biological marker (biomarker) is 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]'. In Emergency Medicine, most of the biomarker research has been concentrated in the field of cardiology, sepsis and renal failure, due to the significance of early detection and interventions.

Biomarkers can be diagnostic as well as prognostic. Diagnostic biomarkers assume greater significance in the ED as they help in clinical decision-making and faster patient disposition. An ideal biomarker should aid in early diagnosis, help in risk stratification, be able to monitor the response to treatment and predict outcomes. Even though biomarkers have been extensively studied by researchers, only a few handfuls have been proven to be useful in a cost-effective manner for clinical decision-making in the ED. *A biomarker should always be evaluated in the clinical context only and should never be depended upon as a standalone method for decision-making*.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_32

Acute Coronary Syndrome

The significance of biomarkers in acute coronary syndrome lies not only in making a diagnosis of acute coronary syndrome (ACS) but also making sure that patients are disposed from the ED in a timely manner after ruling out ACS, without increasing the chances of adverse cardiac events:

Cardiac troponins: The troponin complex is a protein molecule comprised of subunits, viz. troponin I(TnI), troponin T(TnT) and troponin C(TnC). Injury to the cardiac muscle causes leakage of these subunits into the circulation within hours, and the levels remain elevated for up to 2 weeks. Elevated troponin levels indicate myocardial necrosis or injury, but may not be specific to an ischaemic aetiology [2]. Troponin values above the 99th percentile are taken as the cut-off points in assessment of cardiac ischaemia (Fig. 32.1). In order to diagnose acute myocardial

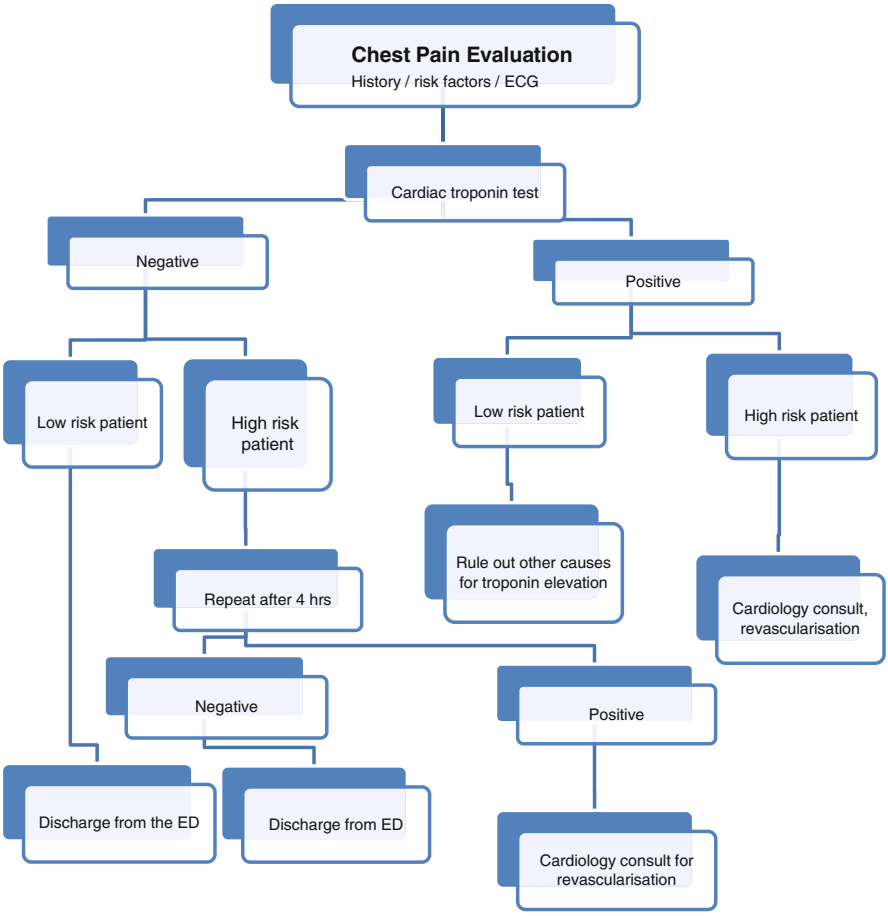

Fig. 32.1 Clinical decision-making pathway for troponin elevation in chest pain evaluation [2]

infarction, there needs to be a 20 % rise/fall from the baseline at 3–6 h [3]. A change in cardiac troponins can be detected in the circulation by 4–6 h by the conventional methods and as early as 2 h by high sensitive assays. In patients with negative troponins within 6 h of onset of symptoms suggestive of ACS, the markers should be remeasured in the timeframe of 8–12 h after symptom onset [4]. Recent studies have looked upon identifying as well as excluding MI by looking at changes in marker levels (delta values) over a shortened time frame like 2 h [5].

Elevated troponins are found in many conditions (Table 32.1), which increase the chances of misinterpretation, if not correlated clinically. A rise/fall in troponin levels can detect acute MI in such patients.

Creatine kinase-MB was the predominant cardiac marker before the advent of troponins. CK-MB rises 4–6 h after the onset of MI and peaks by 12–24 h. The levels come back to baseline by 12–48 h. This shorter time frame of CK-MB helps in detecting re-infarction in a patient with already high troponin levels. CK-MB can also be elevated along with CK, in the setting of trauma, rhabdomyolysis, etc.

Risk factors are recurrent angina, angina at rest, heart failure or LV EF <0.40, haemodynamic instability, sustained ventricular tachycardia, diabetes mellitus, PCI <6 months and post CABG.

Heart Failure

Various biomarkers have been identified for the diagnosis of heart failure. The newer entries into this field include galectin-3, hsCRP, MR-proANP (midregion pro-atrial natriuretic peptide), PAPP-A (pregnancy-associated plasma protein A), etc.

Currently the most prominent marker is B-type natriuretic peptide (BNP), secreted from the ventricles as a result of neurohormonal activation, due to volume overload and resulting myocardial stretch. Troponin I also is a significant marker for cardiac failure.

High plasma *BNP and NT-proBNP* levels are very specific for elevated filling pressures in patients with left ventricular dysfunction. A BNP level <100 pg/ml can essentially rule out acute HF in most cases [6].

Patients presenting with right ventricular failure secondary to pulmonary embolism or pulmonary hypertension, valvular heart disease, atrial fibrillation, renal

Table 32.1 Examples of non ACS and causes of elevated troponin levels

Cardiac	Non-cardiac
Congestive cardiac failure	Pulmonary embolism
Myocarditis	Renal failure
Pericarditis	Sepsis
Infiltrative diseases	Stroke
	Blunt chest trauma

failure and advanced age may also have elevated levels of BNP or NT-proBNP. Obesity will result in lower values of pro-BNP which may mask cardiac failure.

NT-proBNP Interpretation
- *<300 pg/ml* – Unlikely to be heart failure
- *>900 pg/ml* – Highly likely to be heart failure
- *>1,200 pg/ml* – Likely to be heart failure, in severe renal failure

It is recommended that the algorithm for HF diagnosis should include BNP assay as the first step along with ECG and chest X-ray [7] (Fig. 32.2).

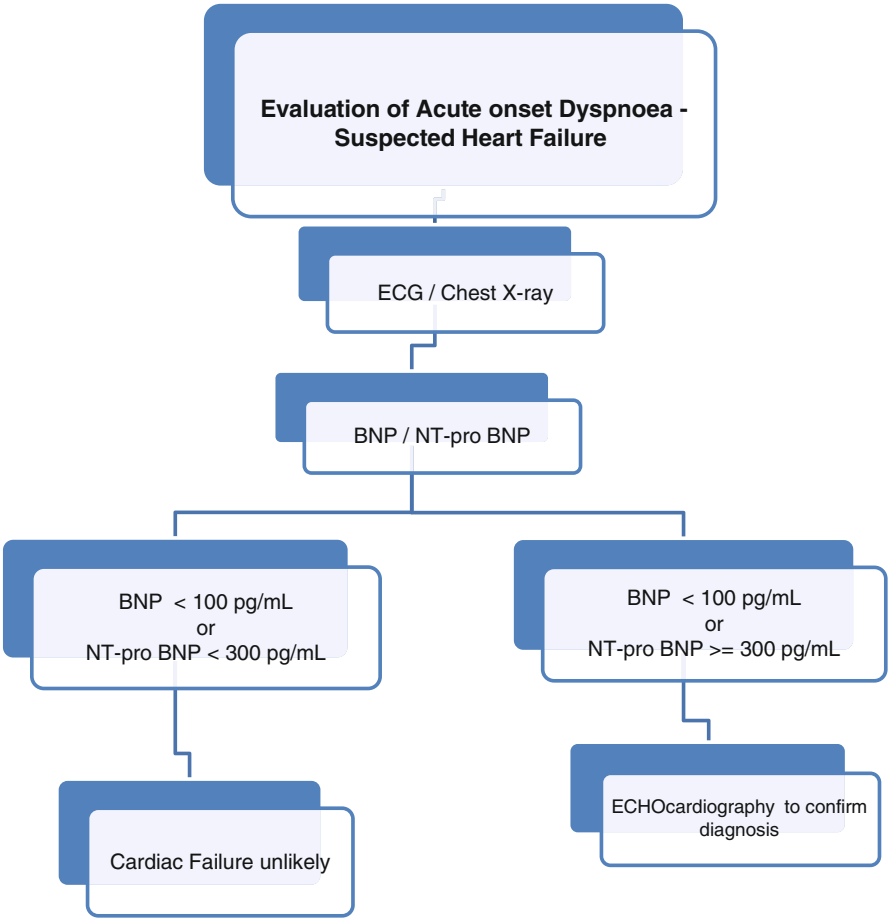

Fig. 32.2 Clinical decision-making pathway for evaluation of cardiac failure [17]

Pulmonary Embolism

Biomarker evaluation in suspected cases of pulmonary embolism is helpful in ruling out the diagnosis in low probability scenarios, rather than confirming a diagnosis (Fig. 32.3). The markers used are d-dimer, troponins, BNP and ischaemia modified albumin (IMA).

D-dimer is a degradation product produced by plasmin during fibrinolysis. It has high sensitivity but very low specificity. In patients with low pretest probability as evidenced by scoring systems by Well's score (Table 32.2) and a negative d-dimer value, the diagnosis of pulmonary embolism can be essentially ruled out without any increase in symptomatic venous thromboembolism on follow-up [8].

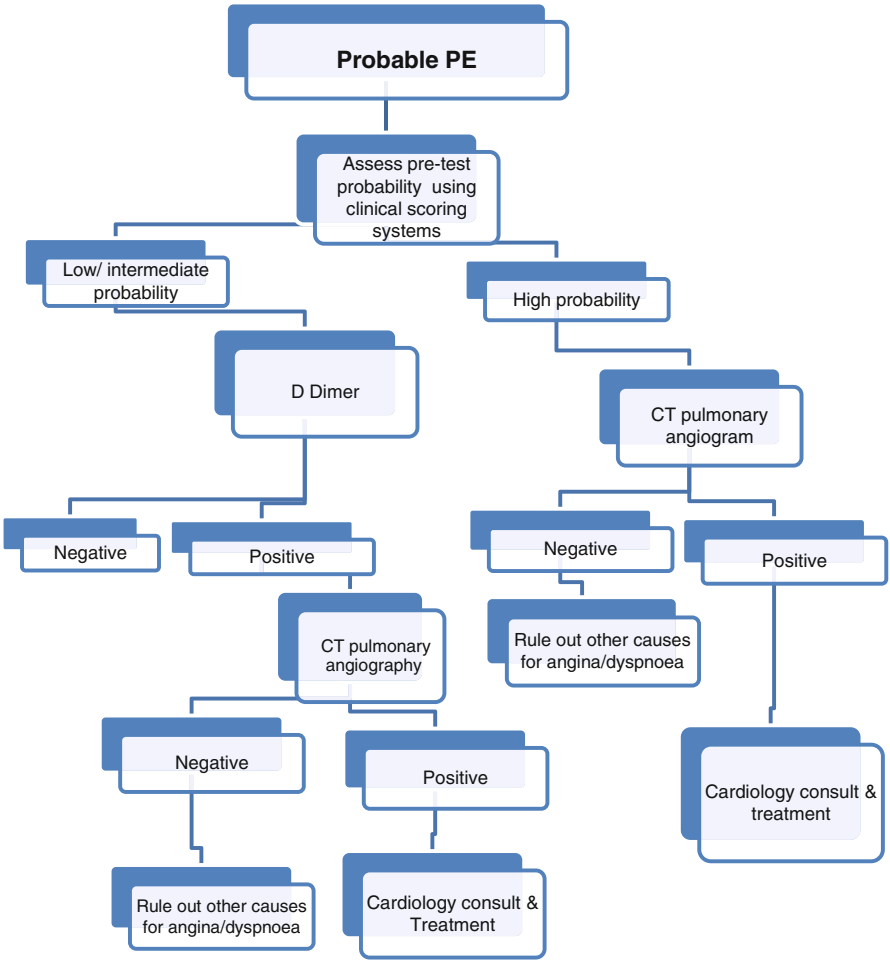

Fig. 32.3 Clinical decision-making pathway for evaluation of suspected pulmonary embolism [11]

Table 32.2 Well's score for pulmonary embolism

Risk factor	Score
Suspected deep venous thromboses	3
Alternative diagnosis less likely than PE	3
Heart rate >100 beats/min	15
Prior venous thromboembolism	15
Immobilisation within prior 4 week	15
Active malignancy	1
Haemoptysis	1

Risk score interpretation (probability of PE): >6 points, high risk (78.4 %); 2–6 points, moderate risk (27.8 %); <2 points, low risk (3.4 %) [9]

Ischaemia modified albumin (IMA) has been found to be better than d-dimer in a few studies due to its better positive predictive value [10]. Cardiac troponins and BNP may be elevated in patients with PE with RV dysfunction. The elevated troponin levels can be confusing to a clinician who has ACS as a potential differential.

Sepsis

More than 170 biomarkers have been identified as useful for evaluating sepsis [12]. The significant ones that are helpful in the evaluation of sepsis are C-reactive protein, procalcitonin and serum lactate (Fig. 32.4).

C-reactive protein is synthesised in the liver as an acute phase reactant. Serum CRP levels increase in response to any inciting stimulus and can even go up to 500 mg/L. There can be mild elevation in elderly, pregnancy and viral infections. But, it lacks specificity as it becomes elevated in a variety of conditions like burns, myocardial infarction, post-operative status, rheumatic diseases, etc. The sensitivity and specificity of CRP as a marker for bacterial infections are 68–92 % and 40–67 %, respectively [13]. Plasma CRP levels correlates with the severity of infection which is useful to assess the response to treatment [14].

Normal value	<10 mg/L
Onset	2 h
Peak time	36–48 h
Plasma $T_{1/2}$	~19 h

Procalcitonin (PCT) is a precursor of calcitonin, which is secreted from thyroid C cells. In infectious conditions, PCT is released from nearly all tissues including the lung, liver, kidney, pancreas, spleen, colon and adipose tissues. In a meta-analysis, serum PCT median value of 1.1 ng/ml was found to be more

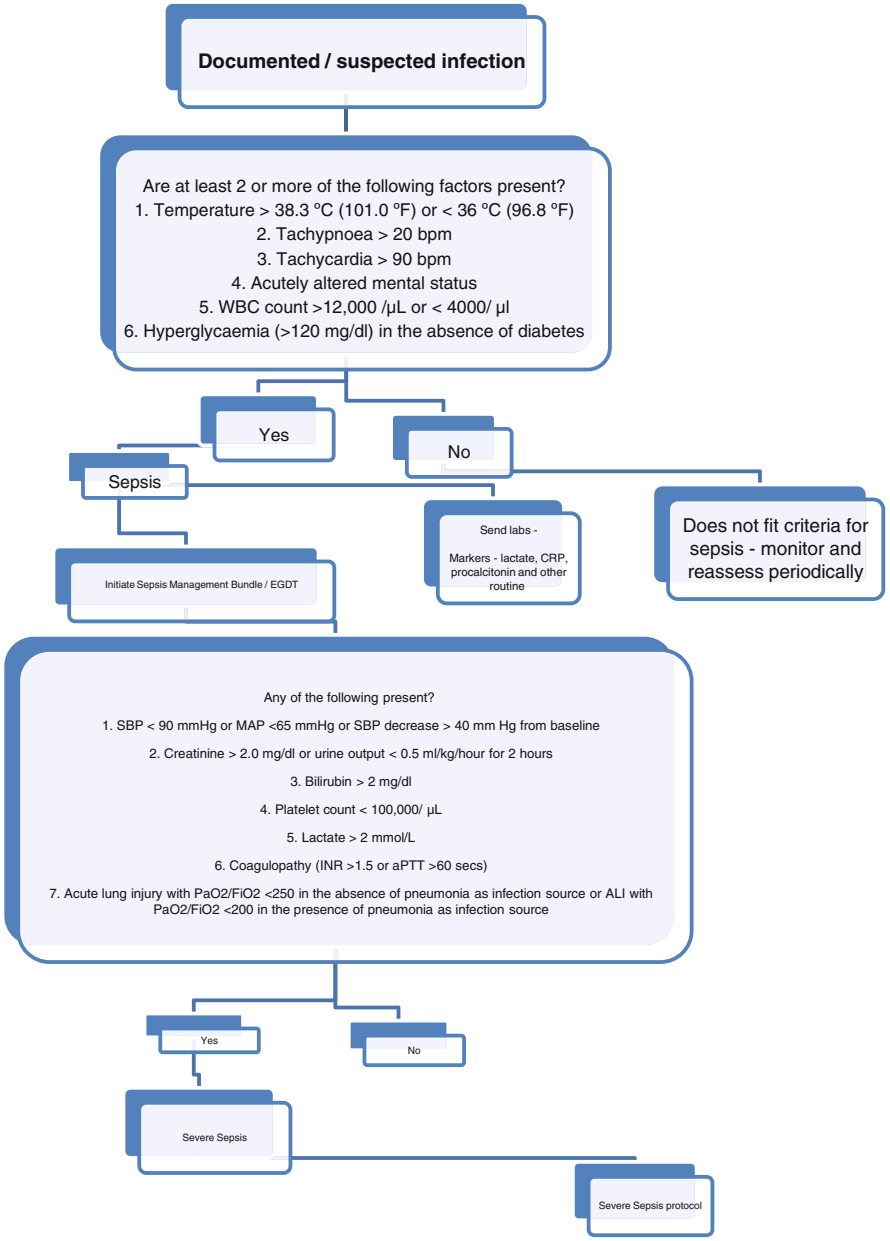

Fig. 32.4 Clinical pathway for suspected sepsis

specific (specificity – 81 %) than CRP (67 %) for differentiating bacterial infection [15]. This makes PCT favourable for guidance of antibiotic stewardship as well [16].

Normal value	<0.1 ng/ml
Onset	4 h
Peak time	24 h
Plasma $T_{1/2}$	24 h

Serum lactate: Lactate levels in the body rise when anaerobic metabolism increases as is the case of sepsis and hypoperfusion. Lactate clearance has a very significant role in the 'early goal-directed therapy' of patients with sepsis. A lactate level of >4 mmol/L indicates higher in-hospital mortality compared to levels <2.5 mmol/L (28.4 % vs. 4.9 %) [17]. Recent studies have shown that patients with serum levels of 2–4 mmol/L were also at an increased risk [18]. The higher the lactate clearance from the body, better the outcome [19].

Acute Kidney Injury

The conventional evaluation of renal function includes assessment of creatinine, urea and GFR. The time lag between the onset of injury and derangement of these values is often high. Serum creatinine values vary widely based on age, gender, muscle mass, etc. Alternatively, the markers that can identify kidney injury earlier are human neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), cystatin C, etc., of which the most promising has been NGAL.

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein that has a role in repair and reepithelialisation in the kidney. Elevated levels of NGAL (>50 μg/L) have been found in the plasma and urine samples of patients with acute kidney injury [20]. Urinary NGAL has been studied more in paediatric population and can detect kidney injury following transplantation, cardiac surgery as well as contrast-induced nephropathy [21] early.

Head Injury

Markers are emerging which may help reduce the radiation exposure to patients with mild head injury. S100 calcium binding protein B (S100B) is a glial-specific protein which is primarily expressed by a subtype of mature astrocytes. It is elevated in neuronal damage which makes it a potential marker for CNS insults. In a recent study, it was found that adult patients with mild head injury, without additional risk factors and with S100B levels of <0.10 mcg/L within 3 h of injury, can safely be discharged from the hospital without neuroimaging [22].

Point of Care Testing (POCT)

POCT refers to diagnostic evaluation at or near the site of patient care and is increasingly becoming the norm at the moment. Many of the EDs in tertiary centres have already started adapting POC testing which makes it the next revolutionary step in faster healthcare delivery. But, the challenge lies in transferring the resultant advantage to improvement in patient care and disposition.

Advantages
- Improved patient turnaround time, faster and improved decision-making capacity and patient disposition
- Better patient management as early intervention possible
- Improved patient workflow in the department
- Improved economic outcomes for the ED/hospital
- Staff upskilling – does not need extensive skills to operate the machine

Disadvantages
- Compromise on quantitative accuracy of the tests
- Needs frequent QC
- High investment and maintenance costs

Conclusion

The sheer volume and variety of biomarkers in the research pipeline points towards the fact that no one marker is an ideal choice. A scoring system based on multiple markers would probably provide more clarity than individual markers. Clinicians should remember that these should always be used as tools that complement the clinical decision-making process, rather than replacing the process itself.

Reference ranges for biomarkers [23]

Biomarker	Reference range
Troponin I	<0.4 μg/L
Troponin T	≤0.13 μg/L
B-type natriuretic peptide	<167 ng/L
D-dimer	<0.5 mg/L
C-reactive protein	<0.08–3.10 mg/L
C-reactive protein, hs	<0.02–8.0 mg/L
Lactate	0.6–1.7 mmol/L

Reference values are affected by many variables, including patient population and laboratory methods used and should not be taken as the sole guide for clinical decision-making.

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Chapter 33
Bleeding and Coagulation Disorders

Rebecca Mathews and Reeba Mary Issac

Key Points
- The main function of the haemostatic system is to prevent blood loss from an intact blood vessel and to minimise blood loss in case of vascular injuries.
- Abnormalities of the components involved in the haemostatic system will lead to excessive bleeding.
- There is no single laboratory test available to fully evaluate bleeding disorders. A battery of screening and specific tests must be employed for accurate diagnosis and appropriate management.

Introduction

Haemostasis is the property of the circulation that maintains blood as a fluid within the blood vessels and the system's ability to prevent excessive blood loss upon injury [1]. Normal haemostasis involves three components: vessel wall (endothelium), platelets and coagulation cascade.

Blood normally flows through a closed circulatory system. The blood vessels and their constituents are critical in controlling the physiologic functions of the circulatory system. A traumatic injury such as a cut to the finger causes vascular injury resulting in bleeding. To minimise blood loss, circulating platelets and clotting factors are mobilised to form a clot which occludes the injured vessel and prevents

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_33

further loss of blood. The formation of clot is limited to the area of injury so that normal circulation is maintained in vessels elsewhere in the body.

Pathophysiology

The following sequence of events takes place at the site of vascular injury (Fig. 33.1):

1. Transient arteriolar vasoconstriction mediated by reflex neurogenic mechanisms and endothelin, a potent vasoconstrictor released by endothelium.
2. Platelet adhesion and activation occurs by binding to exposed subendothelial matrix which is highly thrombogenic. Platelet adhesion is mediated by von Willebrand factor. Platelet activation causes recruitment of additional platelets which aggregate or bind each other through fibrinogen. This results in the formation of a *primary haemostatic plug*.
3. The extrinsic pathway of coagulation cascade is physiologically the most relevant pathway. It is activated by Tissue Factor, exposed at the site of injury. Simultaneously intrinsic pathway is also activated resulting in the formation of thrombin and conversion of fibrinogen to fibrin. Polymerised fibrin and platelet aggregates together form a stable permanent plug to prevent further bleeding. This is known as *secondary haemostasis*.
4. The process of coagulation is controlled and limited to the site of injury by naturally existing inhibitors:
    - Tissue factor pathway inhibitor

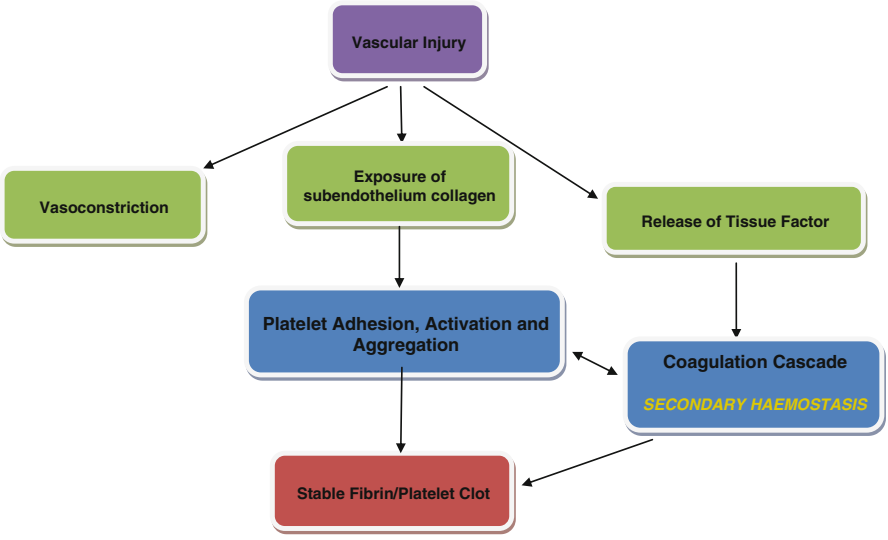


Fig. 33.1 Schematic representation of physiologic haemostasis

- Protein C and S
- Antithrombin III
- Fibrinolytic system – produces plasmin from plasminogen by tissue plasminogen activator. Plasmin rapidly digests fibrin to fibrin degradation product (FDP).

Classification of Bleeding Disorders

Bleeding disorders can be classified into four categories [2].

(A) Vessel wall disorders
(B) Platelet disorders
(C) Coagulation disorders
(D) Fibrinolytic disorders

Vessel Wall Disorders

The diagnosis of blood vessel disorders is most often made by exclusion. Screening tests of haemostasis are often normal. Associated clinical features are usually characteristic. Blood vessel disorders can either be inherited or acquired (Table 33.1).

Platelet Disorders

Platelet disorders may be divided into two categories based on:

(a) Aetiology – Congenital (Table 33.2) and Acquired (Table 33.3)
(b) Type – Thrombocytopaenias and Thrombocytopathies

Table 33.1 Vessel wall disorders

Inherited causes	Acquired causes
Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu disease)	Senile purpura
Ehlers-Danlos syndromes	Cushing Syndrome
Marfan syndrome	Drugs- corticosteroids
Osteogenesis Imperfecta	Allergic purpura, Scurvy
Pseudoxanthoma Elasticum	Infections
	Purpura simplex

Table 33.2 Congenital platelet disorders

Thrombocytopaenic – quantitative platelet deficiency	Thrombocytopathies – qualitative or functional platelet defect
May-Hegglin anomaly	Glanzmann thrombasthaenia
Wiskott-Aldrich syndrome	Platelet-type von Willebrand disease
Neonatal alloimmune thrombocytopaenia	Bernard-Soulier syndrome

Table 33.3 Acquired platelet disorders

Thrombocytopaenic – quantitative platelet deficiency	Thrombocytopathies – qualitative or functional platelet defect
Autoimmune or idiopathic thrombocytopaenic purpura (ITP)	Drug-induced (e.g. aspirin, NSAIDs, penicillin, cephalosporins)
Thrombotic thrombocytopaenia purpura (TTP)	Uraemia
Cytotoxic chemotherapy	Alcohol dependency
Drug-induced (e.g. quinine, quinidine, gold salts, trimethoprim/sulfamethoxazole, rifampin)	Liver disease
Leukaemia	Myeloproliferative disorders,
Aplastic anaemia	Macroglobulinaemia
Myelodysplasia	Acquired platelet-type von Willebrand disease
Systemic lupus erythematosus	
Associated with infections: HIV, malaria, dengue	
Disseminated intravascular coagulation	

Coagulation Disorders

Coagulation disorders can be divided into inherited and acquired causes (Table 33.4).

Fibrinolytic Disorders

Increased fibrinolytic activity is associated with increased risk of bleeding. These disorders are usually caused by a deficiency in *α2-plasmin inhibitor or plasminogen activator inhibitor*. Laboratory coagulation tests are normal with the exception of decreased fibrinogen and increased FDP levels.

Approach to a Patient with Bleeding Disorder

Evaluation of patients with a bleeding disorder is a multistep process that involves a detailed history taking, physical examination and laboratory evaluation [3]. It is important to differentiate between bleeding due to local factors and a generalised bleeding disorders, Inherited or acquired defects and primary or secondary haemostatic defect.

Table 33.4 Coagulation disorders

Inherited	Acquired
Haemophilia A, Haemophilia B, Haemophilia C	Anticoagulant related – Heparin, Coumarin
Factor XI, XII, X, V, XIII, I deficiencies	Disease related- liver disease, vitamin K deficiency, DIC
von Willebrand disease	Acquired inhibitors of coagulation- specific and nonspecific (lupus anticoagulant)

History Taking

1. First and foremost is to rule out local causes for the bleeding.
2. Severity of the bleeding tendency can be assessed by enquiring the following:
   - Frequency of bleeding
   - Bleeding following surgery or any invasive procedure previously. If no treatment needed, it indicates a mild type of bleeding disorder.
   - Spontaneous bleeding – indicates severe bleeders.
   - Hospital visit is required in very severe bleeding disorders.
   - Extent and quantity of bleeding.
   - Nature of arresting the bleed.
3. History of drug intake should also be asked for, as many drugs are known to affect the haemostatic mechanism.
   E.g.: Aspirin, Non-steroidal anti-inflammatory drugs, penicillins, cephalosporins, nitrates, nitroprusside, phenothiazines, tricyclic antidepressants.
4. Once these things are established, one would like to know whether it is inherited or acquired. Inherited bleeding disorders usually present very early in life and give history of similar complaints in the family. A pedigree analysis may determine the type of inheritance. There are three patterns of inheritance of a hereditary disorder:

   X linked disorder- e.g. Haemophilia A, Haemophilia B
   Autosomal recessive – e.g. Afibrinogenaemia, von Willebrand Disease, Deficiency of Factor V or X, Bernard-Soulier syndrome, Glanzmann thrombasthaenia
   Autosomal dominant- e.g. Hereditary haemorrhagic telangiectasia, May-Hegglin anomaly.

Physical Examination

On examination the type and sites of bleeding should be noted.

- Bleeding is from single or multiple sites.
- Bleeding is spontaneous or as a result of trauma.

There are various characteristic clinical features (Table 33.5) that can be used to distinguish a platelet or primary haemostatic disorder from a coagulation or secondary haemostatic defect [4].

Certain symptoms are relatively specific in fibrinogen and Factor XIII deficiency i.e. umbilical stump bleeding, large haematomas inappropriate for trauma and delayed wound healing [5].

Laboratory Evaluation

There is no single laboratory test for the evaluation of a defective haemostasis [6]. Screening tests (Table 33.6) will be done initially to determine if a detectable abnormality exists. If it does exist, confirmatory specific tests will be necessary to define the disorder.

Platelet Count and Peripheral Smear Examination

- Exclude thrombocytopaenia as a primary cause of bleeding by performing a full blood count and a blood-film examination.
- The blood film provides valuable information about platelets including their size, granule content and number.
- Platelet dysfunction should be evaluated in the laboratory to exclude potential coagulation defects that may be the primary or additional cause of bleeding.

Table 33.5 Patterns of bleeding manifestation in haemostatic disorders

Primary haemostatic defect	Secondary haemostatic defect
Immediate bleeding	Delayed bleeding
Mucocutaneous bleeding	Deep tissue bleeding (muscle/joints)
Purpura, Petechiae, epistaxis and menorrhagia	Haemarthroses and intramuscular haematomas

Table 33.6 Screening tests (non-specific)

Tests of primary haemostasis	Platelet count Peripheral smear examination Bleeding time Platelet function analysis
Tests of secondary haemostasis	Prothrombin time Activated partial thromboplastin time

Bleeding Time

Bleeding Time is the traditional initial test for detecting and evaluating primary haemostasis. The bleeding time (BT) was the first in vivo test of platelet function. It is defined as the time taken by a standardised skin wound to stop bleeding. It is used to evaluate the function of platelets and blood vessel integrity. Normal range is 2.5–9.5 min.

Prolonged bleeding time is seen in the following conditions:

- Vascular disorders
- Thrombocytopaenia
- Disorders of platelet function – Glanzmann thrombasthaenia, Bernard-Soulier disease
- von Willebrand disease

Bleeding time, though simple to perform, is poorly reproducible, invasive, insensitive and time consuming.

Platelet Function Analyser

The Platelet Function Assay test is performed with a laboratory analyser termed the PFA-100.

This test has replaced bleeding time test to a large extent. But it is not always sensitive to all platelet function defects and can give false negative results [7].

Prothrombin Time

Normal range is 11–16 s. *It* tests the extrinsic and common pathway. Prolonged PT indicates deficiency of FVII, FX, FV, FII and Fibrinogen. As there is variability among individual laboratory reagents, PT test is reported commonly along with its INR (International Normalised Ratio). A normal coagulation profile is reported as an INR of 1.0.

Prothrombin Time is prolonged in:

1. Inherited deficiency of FVII, FX, FV, FII and Fibrinogen.
2. Vitamin K deficiency
3. Oral anticoagulant therapy: PT is the standard test for monitoring oral anticoagulant therapy.
4. Disseminated intravascular coagulation.

Activated Partial Thromboplastin Time

Normal range is 27–37 s. It tests the intrinsic and common pathway. Those patients with mild bleeding disorders may have normal APTT values because most reagents do not detect mild deficiency states. In such cases, specific factor assays can be done if clinical suspicion is high.

There are disorders which are not associated with bleeding but show prolonged APTT values e.g.: F XII deficiency, prekallikrein and high molecular weight kininogen deficiencies and lupus anticoagulant.

APTT is prolonged in:

1. Inherited deficiency of FXII, FXI, FIX, FVIII, FX, FV, FII and Fibrinogen.
2. Disseminated intravascular coagulation
3. Liver disease
4. Heparin: Heparin therapy is monitored by APTT test. Heparin inhibits thrombin, F Xa, XIa and FIXa.
5. Circulating inhibitors.

Thrombin Time

It is the time taken by plasma to clot when thrombin is added. It is usually done when both Prothrombin Time and Activated Partial Thromboplastin Time are prolonged. Thrombin Time is prolonged in disorders of fibrinogen – afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia.

Normal range is 8–12 s.

Specific Tests for Haemostasis

Platelet Aggregometry

Platelet aggregometry was developed in the early 1960s and is now considered as the ‘gold standard’ of platelet function testing [8].

Mixing/Correction Studies

If a coagulation factor deficiency is suspected and if there is isolated prolongation of PT or APTT, mixing studies should be performed to determine whether factor deficiency or inhibitor is present [9].

Coagulation Factor Assays

Factor assays are based on the ability of dilute patient plasma to correct the clotting time of a specific factor deficient plasma as measured by PT (II, V, VII, X) or APTT (VIII, IX, XI, XII) [10].

Factor Inhibitor Assay: Bethesda Assay

Bethesda Assay will quantify the amount of inhibitors once it is detected on mixing studies in patients with bleeding disorders [11]. One inhibitor unit is defined as the amount of inhibitor that inactivates 50 % of the factor in the normal plasma pool. Factor VIII inhibitors are the most common especially in haemophilia A.

Urea Clot Solubility Test

Urea clot solubility test is a screening test of FXIII function. In FXIII deficiency, all the screening tests of haemostasis are normal [12].

Euglobin Clot Lysis Test

Euglobin clot lysis measures fibrinolytic activity. Time taken for Clot lysis is measured which is usually completed within 2–6 h. Accelerated lysis (<2 h) is indicative of increased fibrinolysis [13].

D-Dimer Assay

D-dimers are fibrin degradation products containing factor XIIIa cross linked fibrin portion. They are present in the blood of most healthy individuals in only negligible amounts (100–200 ng/mL). Elevated levels of D-dimer is seen in Disseminated intravascular coagulation and venous thromboembolism (VTE), which can present as either deep vein thrombosis (DVT) or pulmonary embolism (PE) [14].

Automated Coagulation Methods

Automated methods (coagulometers) are available in detecting tests like Prothrombin time, Activated Partial Thromboplastin Time, Thrombin Time, Fibrinogen assays, D-Dimer and antithrombin assays [15]. This is helpful if large number of tests must be done daily.

Thromboelastography

Thromboelastography is a method of testing efficiency of coagulation in blood. It is a whole blood assay for blood clot analysis and evaluates the elastic properties of whole blood [16].

It is commonly used in assessing haemostasis in liver transplantation, obstetric procedures and cardiac surgery.

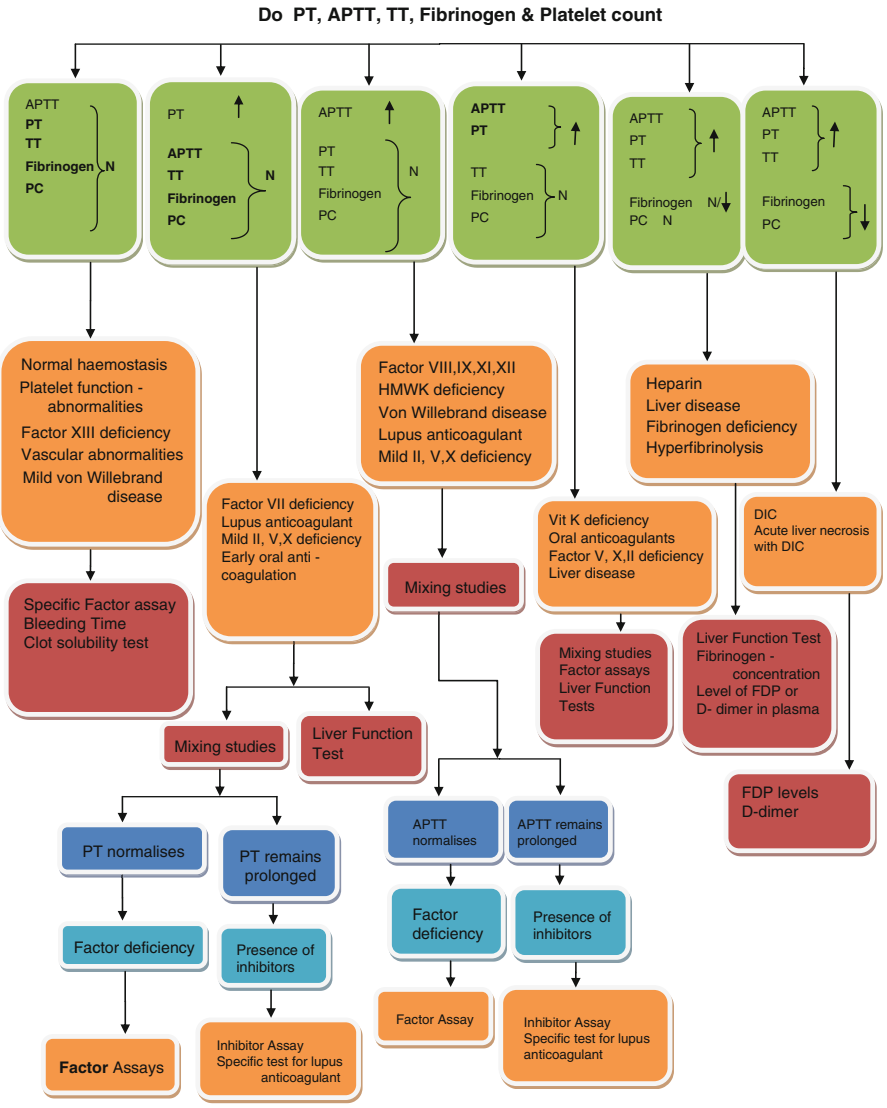
Management of Bleeding Disorders

1. In coagulation factor deficiencies – Fresh frozen plasma/Cryoprecipitate/Factor concentrates can be given.

   Prophylactic or therapeutic replacement may be indicated when PT and APTT values are 1.5 times the upper limit of normal or midpoint of the normal range. FFP infusions that increase factor concentrations by 20 % will have greater impact on greatly prolonged PT or APTT than on a mildly prolonged PT or APTT [17].
2. In quantitative/qualitative platelet disorders, platelet concentrates can be given. One unit of platelet concentrate can increase platelet count by 5000–10,000/μl.
3. Other supportive measures can also be given
   - Antifibrinolytic agents e.g.: Epsilon aminocaproic acid and tranexamic acid.
   - 1-Desamino -8D-arginine vasopressin (DDAVP) [1]
   - Protamine in case of heparin.

These adjuvants are very effective and used to its full potential since Blood and its products are hazardous and should be avoided.

Algorithm for Approach to Bleeding Disorders



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Chapter 34
Blood Transfusion Reactions

Sajit Varghese

Key Points
- It is prudent to anticipate, identify, and intervene with blood transfusion reactions, at the earliest.
- The incidence, presentation, and prognosis of each type of blood transfusion reaction are different.
- Prevention is a wise alternative.

Introduction

Blood transfusion is a lifesaving procedure, especially in the emergency setup. When indicated, a promptly and safely undertaken blood transfusion can help in speedy recovery of the patient. Modern-day medical practices now involve more of transfusing blood components like packed red blood cells, platelets, or frozen plasma, specifically based on indication and need of the patient. With every transfusion, there is attached a risk of developing transfusion-associated reactions, which may be trivial or sometimes life threatening. An emergency physician needs to bear this in mind while embarking on any transfusion procedure.

Today, blood transfusion has developed into a specialty medicine in itself. The challenge is not only to decide when to give and how to give a blood transfusion but also how much to give and when to stop.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_34

Pathophysiology

Blood transfusion-associated complications involve: *transfusion reactions*, *non-immunological complications*, and *transmission of infectious diseases*.

Non-immunological complications include the following:

- Hypothermia (rapid transfusion of cold or frozen blood components)
- Hyperkalaemia (leakage from inside stored red blood cells)
- Hypocalcaemia (citrate used for storing blood products can bind to calcium in plasma)
- Coagulopathy (due to calcium binding with citrate, the coagulation pathway cannot propagate)
- Haemosiderosis (as a result of iron overload from red cells transfused, the excess iron deposits in important organs → frequently seen with repeated blood transfusion receiving patients)

Blood transfusion is an important parenteral route of entry of infectious microorganisms, and such *transmission of infections* is a dreaded complication. The infections at risk of getting transmitted are:

- Malaria
- Chagas' disease
- Babesiosis
- Hepatitis B and C
- Human immunodeficiency virus (HIV) 1,2
- Bacterial infections, mainly due to Gram-negative organisms like *Escherichia*, *Yersinia*, *Pseudomonas*, and others.
- Human T cell lymphotropic virus (HTLV) 1
- Parvovirus B19
- West Nile virus
- Cytomegalovirus

And many other viral, bacterial, and parasitic infections

For an emergency physician, it is a common practice to deal with some or the other complications while transfusing blood to a needy patient in the emergency department.

The different blood products which are now available are designed for specific indications and replacing the particular deficient blood component. These are:

- Packed red blood cells (PRBCs) (about 200 mL)
- Platelet-rich concentrate (about 50 mL)
- Fresh frozen plasma (about 200 mL) – contain plasma proteins and coagulation factors
- Cryoprecipitate (about 15 mL) – contain mainly factor VIII, von Willebrand factor, and fibrinogen

There are also other plasma derivatives like albumin, factor VIII concentrates, and others.

For a blood transfusion reaction to occur, one of the following two mechanisms needs to be operational (Fig. 34.1):

Immune mechanism needs an antigen, an antibody, and their interaction.

Nonimmune mechanism needs a trigger from some physicochemical characteristics in the donor or recipient blood.

The following entities play a role in one or the other type of blood transfusion reactions:

- In donor cell components, for example, in platelet-rich concentrate, the main cell components are platelets.
- Donor plasma components, for example, antigenic lymphocytes in donor plasma, white blood cells with HLA antigens in the donor packed red blood cell plasma, and allergic plasma proteins in donor plasma.
- Recipient plasma components, like preformed antibodies against HLA antigens.
- Most importantly, the ABO antigen-agglutinin system and Rh factor incompatibility, the basis of crossmatching before every blood transfusion, failing which serious haemolytic reactions can occur [2].

Transfusion reactions can broadly be divided into: *haemolytic*, *allergic*, and *others* [1].

The basis of all types of transfusion reactions, whether acute onset or delayed, lies in the immune system responses of donor and recipient. *Haemolytic* reactions can be due to incompatible blood grouping, while pre-sensitisation or atopy defines *allergic* transfusion reactions.

Patients more prone to develop blood transfusion reactions include pregnant women, multiparous women, and patients on regular/repeated blood transfusions like in chronic kidney disease and severe haemolytic anaemias.

Clinical Presentation

- *Haemolytic transfusion reactions* can be *immediate* or *acute* (within 24 h) or *delayed* (after 24 h, usually within 3–10 days). Preexisting antibodies in recipient's blood against donor red cell antigens is the prime cause, mostly due to ABO incompatible blood component or in multiparous women with previous sensitisation. Clinical presentation is dramatic and includes fever with rigours, fainting, chest tightness, chest or abdominal pain, tachycardia, tachypnoea, hypotension, oliguria, and/or haematuria. Fortunately, the incidence of such reactions is rare nowadays [5, 6].

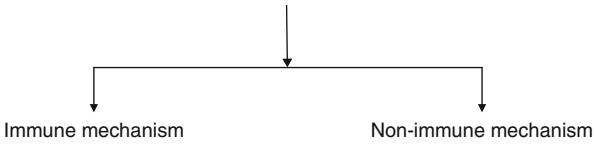


Fig. 34.1 Basic mechanisms for blood transfusion reactions

- *Allergic transfusion reactions* range from mild hives/urticaria to fatal laryngeal oedema or anaphylactic shock. Preformed antibodies in recipient blood to certain plasma proteins in donor blood or presence of anti-IgA in recipient blood may trigger these reactions. Again, the incidence of such reactions is uncommon.
- Among *other types of transfusion reactions*, febrile-type nonhaemolytic reactions (FNHR) occur as a response to donor white blood cell antigens. Such reactions are usually benign. Based on incidence, they are the most common transfusion reactions universally [1].

Special Concerns

There are three other unique conditions associated with blood transfusion reactions, which are worth a mention:

- *Posttransfusion purpura* (*PTP*) is a significant thrombocytopaenia occurring about 7–10 days post-platelet concentrate transfusions. This usually is rare, occurs in multiparous women or patients who have had multiple transfusions earlier, and is due to production of antibodies against platelet surface antigens, notably HPA-1a.
- *Transfusion-related*/*transfusion-associated graft* versus *host disease* (*TAGVHD*) is characterised by fever, rashes, diarrhoea, liver failure, and/or marrow failure, which may occur as a delayed complication and can be fatal. It occurs due to donor lymphocytes battling against the recipient HLA antigens in an immune-deficient host or an immune-suppressed host or an immune-related/immune-shared host [2].
- *Transfusion-related acute lung injury* (*TRALI*) is an immediate/acute onset noncardiogenic pulmonary oedema, due to activated neutrophils trapped in pulmonary circulation, usually on account of multiparous women donors having large quantities of anti-HLA antibodies (immune TRALI). Nonimmune TRALI is when no donor plasma antibodies are found, but there is definite response to certain reactive lipid products found on membranes of donor red cells. Fortunately, incidence is less common, and the condition is self-limiting usually [3].

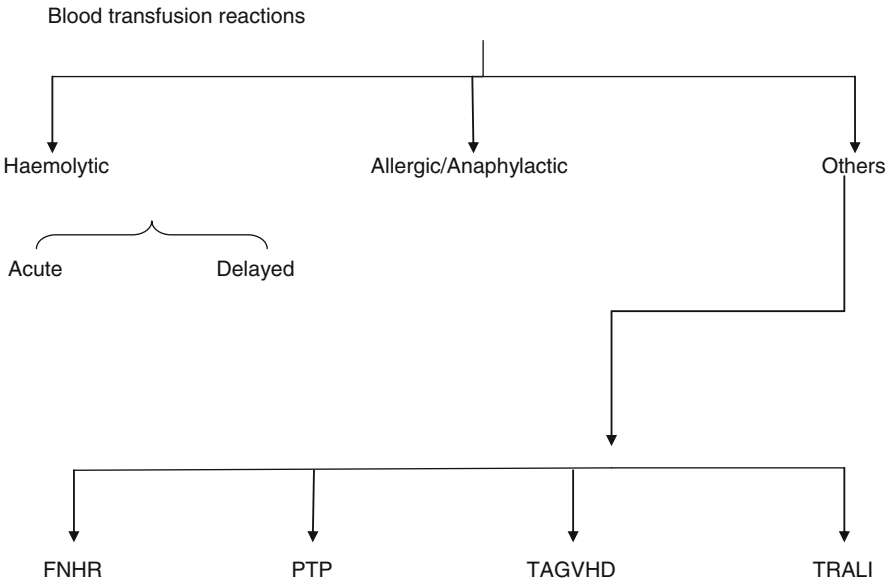
Management and Prevention

- *Haemolytic transfusion reactions* are managed aggressively. The transfusion is immediately stopped, and the blood bank officer on duty is to be informed. A duly filled transfusion reaction form, along with fresh posttransfusion blood samples (for re-crossmatching and tests for haemolysis like serum bilirubin/lactate dehydrogenase/Coombs test), and the donor blood product along with the attached tubing need to be sent to the blood bank. Antipyretics, forced diuresis with intravenous normal saline and loop diuretics, and monitoring of vital parameters are essential. An adequate clear urine output of 80–100 ml/h is a good prognostic

sign. Prevention of these reactions is inevitable, by ensuring proper crossmatching and labelling of blood product at the blood bank as well as correct recipient identification and blood product confirmation by the transfusing physician.

- *Allergic reactions* can be prevented or managed with antihistamines like oral or parenteral diphenhydramine. For serious consequences, subcutaneous adrenaline 0.1–0.5 mg and/or parenteral dexamethasone can be given. Plasma-washed blood products can be encouraged.
- *Febrile type nonhaemolytic reactions* (*FNHR*) can be easily managed with antipyretics. White blood cell – reduced blood products can be encouraged [4].
- *Posttransfusion purpura* (*PTP*) is managed with intravenous immunoglobulin or plasmapheresis. Further platelet transfusions are best avoided in this setting, to prevent clinical worsening.
- *Transfusion-related*/t*ransfusion-associated graft* versus *host disease* (*TAGVHD*) is a complicated and serious condition, may need all possible immune-suppressive measures ranging from glucocorticoids to immunotherapy to bone marrow transplantation, and has poor prognosis. It is best avoided by irradiation of cellular components in blood products before transfusion.
- *Transfusion-related acute lung injury* (*TRALI*) is managed with supportive ventilatory measures depending on respiratory parameters and usually resolves with time [2].

Algorithm for Blood Transfusion Reactions



Inference

Blood transfusion is a procedure which, when properly undertaken, can be utmost rewarding for the emergency physician.

The best way to prevent a blood transfusion reaction is by encouraging autologous transfusion, that is, the recipient's own blood is stored and saved for his/her future needs.

The emergency physician should comply with the following:

1. Must ensure that the donor blood product is properly cross-checked with the recipient's blood sample by the blood bank personnel and also properly labelled thereafter.
2. Must personally check for the viability of the blood product as well as ensure that the product has been adequately screened for transmittable diseases like HIV (human immunodeficiency virus), syphilis, and hepatitis B and C.
3. Must be adequately knowledgeable of the comparative risk and incidence of any type of transfusion reaction, associated with transfusion of specific blood products, for example, platelet products and cryoprecipitate.
4. Must know when to temporarily stop the transfusion in the presence of a minor reaction, like mild itching/fever, and when to disconnect the transfusion permanently and initiate the transfusion reaction management protocol in the presence of a major adverse event.
5. Must understand that a major blood transfusion reaction is a notifiable event; it must be immediately reported to the blood bank personnel and the concerned blood bank duty doctor.
6. Must promptly fill the transfusion reaction form and dispatch to the blood bank, on realising the occurrence of a haemolytic transfusion reaction.
7. Must ensure that the donor blood unit and its attached intravenous tubing set must immediately reach the blood bank, along with fresh blood samples of the recipient, on the stroke of a haemolytic transfusion reaction.
8. Must act quickly to take adequate measures to save the recipient from fatal reaction complications like hypotension, anaphylaxis, or acute kidney injury.
9. Must realise the importance of proper documentation of the full procedure of blood transfusion in detail, whether eventful or uneventful and include the time of starting and stopping the transfusion with reason and also the pre- and post-transfusion vital data like temperature, pulse, and blood pressure.
10. Must keep in mind the fact that large blood transfusions can be adventurous but may compromise the health of the sick patient further, by causing electrochemical, thermal, or coagulation profile alterations.
11. Must know that taking proper measures can decrease the mortality associated with blood transfusions, which nowadays, is more due to transfusion-related acute lung injury and transfusion-associated sepsis, than due to haemolytic complications.

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Chapter 35
Dermatological Emergencies

S. Senthilkumaran

Key Points
- No two skin diseases look alike.
- Primary skin lesions may be obliterated by secondary lesions.
- Fever with a rash is key to recognise more of dangerous conditions.
- Travel history and occupational history provide key information to make accurate diagnoses.
- Vigilant care should be taken in immunocompromised patients.

Introduction

A wide variety of dermatological complaints, varying from benign to life-threatening skin disorders, may be encountered in the emergency department (ED), either as the chief complaint or discovered incidentally in the ED visits. Nevertheless, rashes are common reason for a visit to the emergency department. Exhaustive review of all dermatological conditions is beyond the scope of this chapter. The clinical pathways presented here will prepare the emergency physician to quickly identify the most common rashes and practically to consider the worst possible aetiology of the constellation of symptoms [1].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_35

Diagnostic Approach

The first priority is to assess whether the patient is seriously ill and needs immediate management or is less acutely sick giving time to obtain history. A history of the presenting complaint is an important starting point. A rational structure is required, although this may become curtailed with practice.

History

Gathering information about the character and progression of the rash, along with other key elements, is essential to detect lethal rashes. A focused history includes the elements enumerated in Box 35.1.

Box 35.1: Focussed History for Acute Dermatological Emergencies

- Onset and spread of rash
- Site of onset
- History of spreading
- Contact with ill persons
- Recent travel
- Animal exposure
- Medication use
- Occupation
- Vaccinations
- Immunological status
- Sexual exposure
- Any aggravating or relieving factors
- Associated symptoms – itching, fever or pain

Physical Examination

- Physical examination to ascertain haemodynamic stability and to identify life-threatening events such as sepsis or anaphylaxis.
- Examination should be performed from head to toe on the undressed patient with a sufficient source of lighting to appreciate subtle colour changes.
- Remove any creams, make-up or anything else that may obscure the true nature of the lesions.
- Examination of mucous membranes, hair, nails and scalp should be part of the examination.
- Particular attention should be given to the following conditions:
  - New-onset murmur
  - Generalised lymphadenopathy

- Oral, conjunctival or genital lesions
- Hepatosplenomegaly
- Arthritis
- Meningismus or neurologic dysfunction

Dermatological Examination

- Obtain an overall view of the rash, because visual inspection is the vital tool of assessment. Most skin diseases are diagnosed by their characteristic appearance or morphology of the lesions [2].
- A magnifying glass may be used when looking at a single lesion.
- The entire lesion should be palpated with a gloved finger to assess its texture and to see whether firm pressure leads to blanching, is friable or bleeds easily.
- Primary lesions are basic physical changes in the skin which are caused directly by the disease process that makes up a rash (Table 35.1). These can change over time into a secondary lesion as the disease process matures or due to physical changes (Table 35.2) (e.g. a blister developing into erosion and becoming encrusted in herpes infections).
- In skin examination, pattern recognition and analysis are critical. It includes the morphology, colour, distribution, pattern, arrangement, extent and evolutionary changes of the lesions. A basic understanding of the various types of rashes is essential in making an accurate assessment and in the determination of the severity and acuteness of the patient's illness [3].

Table 35.1 Primary skin lesions

Term of description	Characteristics
Macule	Change in the colour or texture of the skin. Since it is flat, it cannot be detected by running one's fingers over the lesion while keeping the eyes closed
Papule	Solid, raised lesion that has distinct borders and is less than 1 cm in diameter. Papules may have a variety of shapes in profile (domed, flat-topped, umbilicated) and may be associated with secondary features such as crusts or scales
Plaque	Solid, raised, flat-topped lesion, greater than 1 cm in diameter
Nodule	Raised solid lesion more than 1 cm in size and may lie in the epidermis, dermis or subcutaneous tissue
Vesicle	Raised lesions less than 1 cm in diameter that are filled with clear fluid
Bullae	Circumscribed, fluid-filled lesions that are greater than 1 cm in diameter
Pustule	Circumscribed, elevated lesions that contain pus. They are most commonly infected (as in folliculitis) but may be sterile (as in pustular psoriasis)
Wheal	Area of oedema in the upper dermis
Cyst	Sac-containing fluid or semisolid material, i.e. cells or cell products

Table 35.2 Secondary skin lesions

Term of description	Characteristics
Erosion	Total or partial loss of epidermis. It does not leave a scar on healing
Ulcer	Complete loss of epidermis and partial loss of dermis. It scars on healing
Excoriation	Caused by scratching. It can result in erosions or ulcers
Fissures	Slits in skin which can extend into dermis
Scale	Flakes of skin on the primary lesion
Atrophy	Loss or thinning of epidermis, dermis or subcutaneous tissues. The skin appears white, papery and translucent with loss of surface markings
Striae	Linear lesions that can appear atrophic, deep purple or pink as the result of changes in connective tissue. They commonly occur due to misuse of topical steroid therapy
Pigmentation	Hypo- or hyperpigmentation can occur after healing of primary or secondary lesion

Diagnostic Testing

- Investigations may be helpful when a definite diagnosis cannot be arrived at, with a reasonable degree of confidence.
- Swabs can be taken for bacteriology and virology examination.
- Skin scrapings for microscopy can be useful to diagnose ectoparasitic infections such as scabies.
- Fungus can be confirmed by *potassium hydroxide exam* (*KOH test*).
- The presence of herpesvirus can be rapidly confirmed by *Tzanck preparation*.
- *Wood's lamp* is a long ultraviolet lamp (wavelength 360–365 nm). It has a number of uses and is a helpful clinical screening tool.
- *Grams staining* are vital in order to identify the presence of and the type of bacteria in the lesion.
- *VDRL/RPR* is a serologic test performed in any case of suspected syphilis or in patients who have a generalised, maculopapular rash.
- Serological tests can be used to support the diagnosis of conditions such as systemic lupus erythematosus, syphilis and human immunodeficiency virus infection.

Diagnostic Dermatological Procedures

Few simple bedside diagnostic procedures can readily provide confirmation of a first impression and are the definitive method of differentiating between skin problems [4].

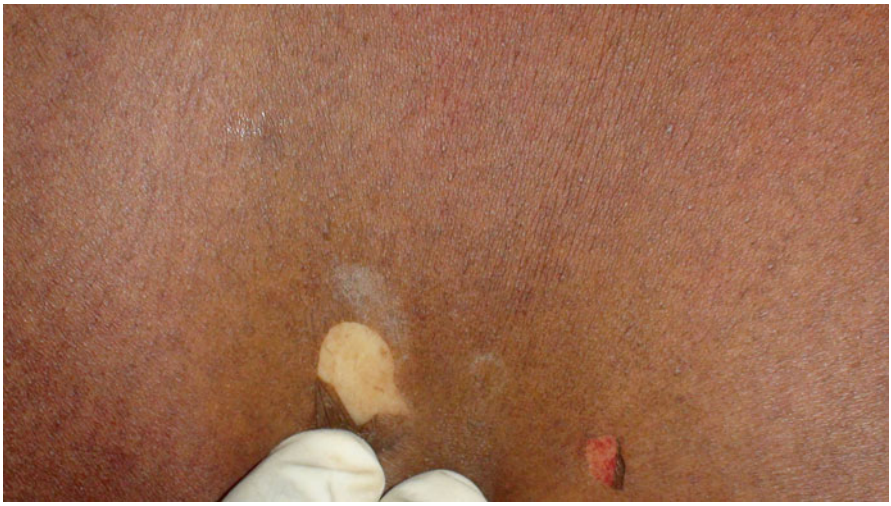


Fig. 35.1 Nikolsky sign

- *Diascopy* is a technique in which a piece of clear glass is pressed against the skin while the observer looks directly at the lesion under pressure. It is used to distinguish between haemorrhagic and inflammatory lesions. If the lesion blanches with pressure, it is an inflammatory lesion (e.g. wheals of urticaria), and if it is non-blanchable, then it is haemorrhagic lesions (petechiae or purpura).
- *Dermatographism* is an exaggeration of the physiologic triple response of Lewis (whealing tendency) when the skin is stroked. It is the commonest form of physical urticaria.
- *Nikolsky sign* (Fig. 35.1) is a sloughing of full skin with lateral pressure. Diagnostic possibilities include pemphigus and toxic epidermal necrolysis due to staphylococcal scalded skin syndrome. It may be seen in severe cases of erythema multiforme, epidermolysis bullosa, pemphigoid and variegate porphyria also.
- *Asboe–Hansen sign* (Fig. 35.2) is a blister that spreads into clinically normal skin with light lateral pressure.

Differential Diagnosis

The differential diagnosis for a rash is enormous and is a challenge for the emergency physician to differentiate benign skin disorders from the more serious, fatal conditions that require immediate intervention [5] (Box 35.2).

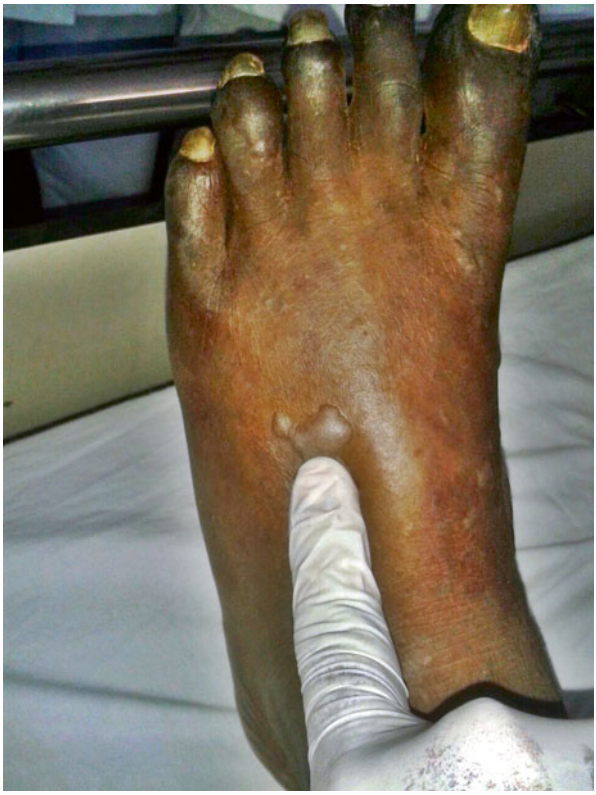


Fig. 35.2 Asboe-Hansen sign

Box 35.2: Deadly Rashes

- Toxic epidermal necrolysis (Fig. 35.3)
- Stevens–Johnson syndrome (Fig. 35.4)
- Toxic shock syndromes (Fig. 35.5)
- EM major
- Disseminated herpes zoster
- Urticaria with anaphylaxis (Fig. 35.6)
- Pemphigus vulgaris (Fig. 35.7)
- Rocky Mountain spotted fever
- Meningococcaemia
- Disseminated gonococcaemia

Fig. 35.3 Toxic epidermal necrolysis

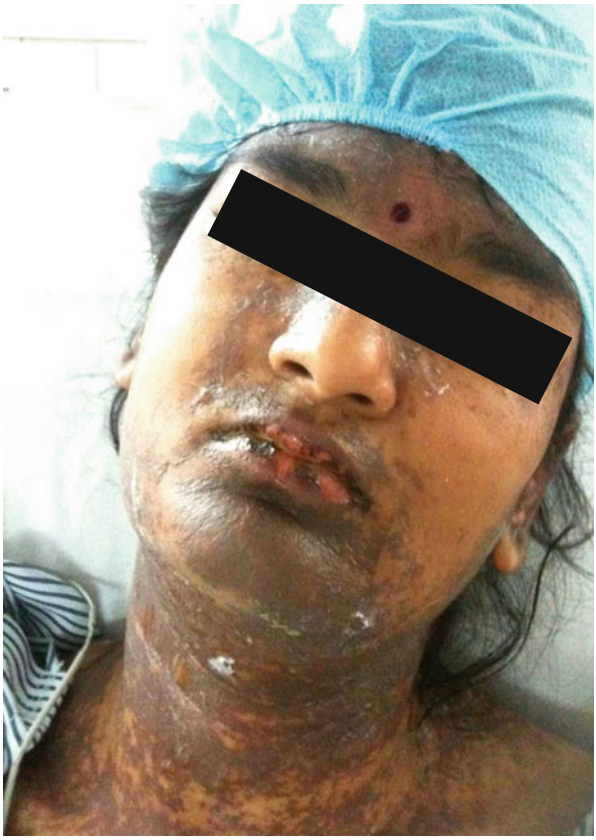


Fig. 35.4 Stevens–Johnson syndrome

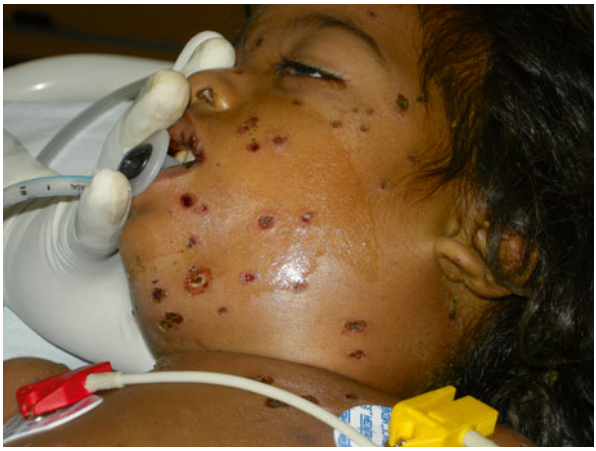


Fig. 35.5 Toxic shock syndrome

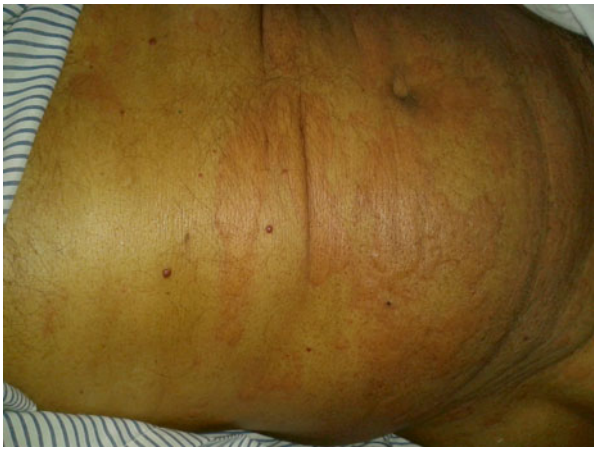


Fig. 35.6 Urticaria with anaphylaxis

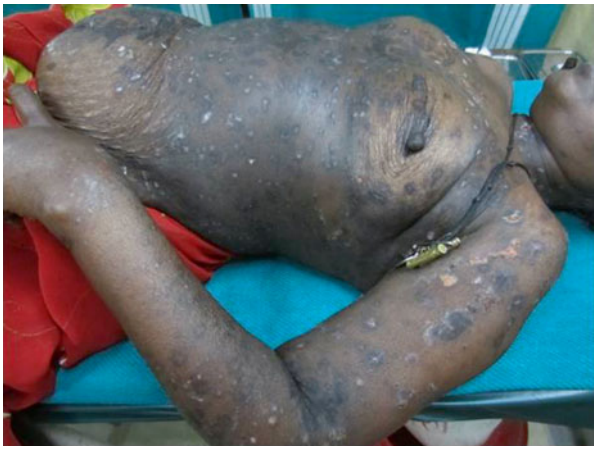
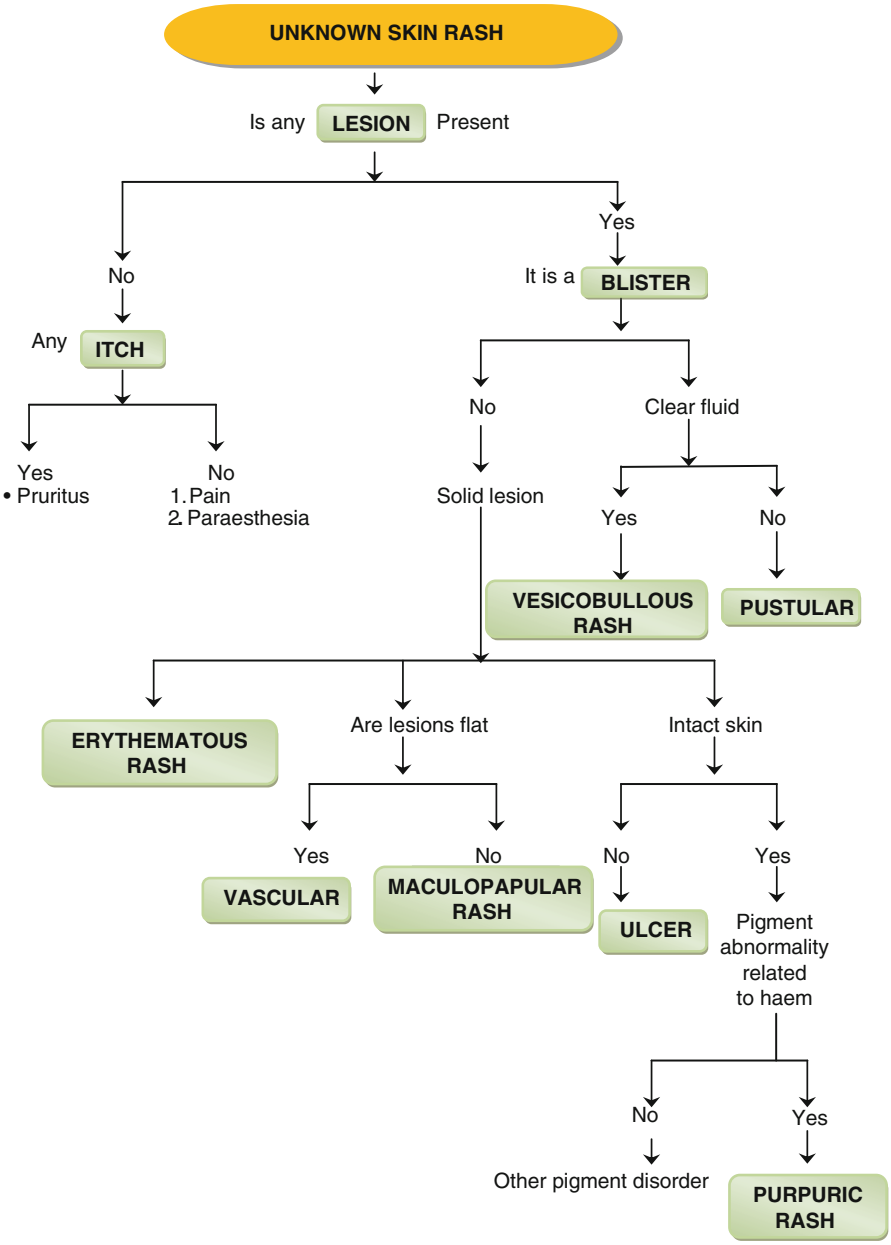


Fig. 35.7 Pemphigus vulgaris

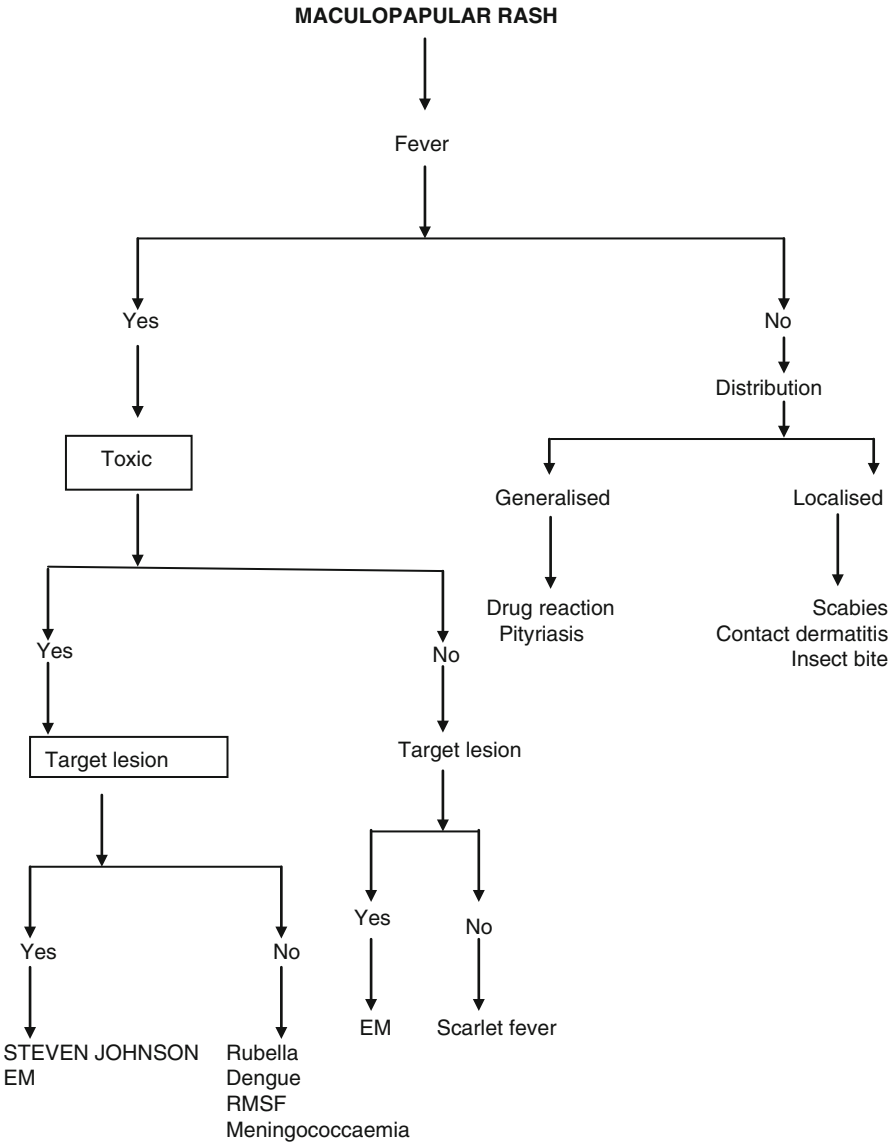
Diagnostic Decision-Making

This clinical pathway will categorise the potentially lethal rash into six major categories based on morphology: (1) Maculopapular, (2) Erythematous, (3) Non-erythematous, (4) Petechial/Purpuric, (5) Pustular, (6) Vesiculobullous. Once this is achieved (Section "Clinical pathway 1"), it can then further narrow down the differentials, based on the pattern/distribution.

Clinical Pathway 1



Clinical Pathway 2



- EM - Erythema multiforme
- RMSF - Rocky mountain spotted fever
- HSP - Henoch–Schonlein purpura

Maculopapular Rashes: (Clinical Pathway 2)

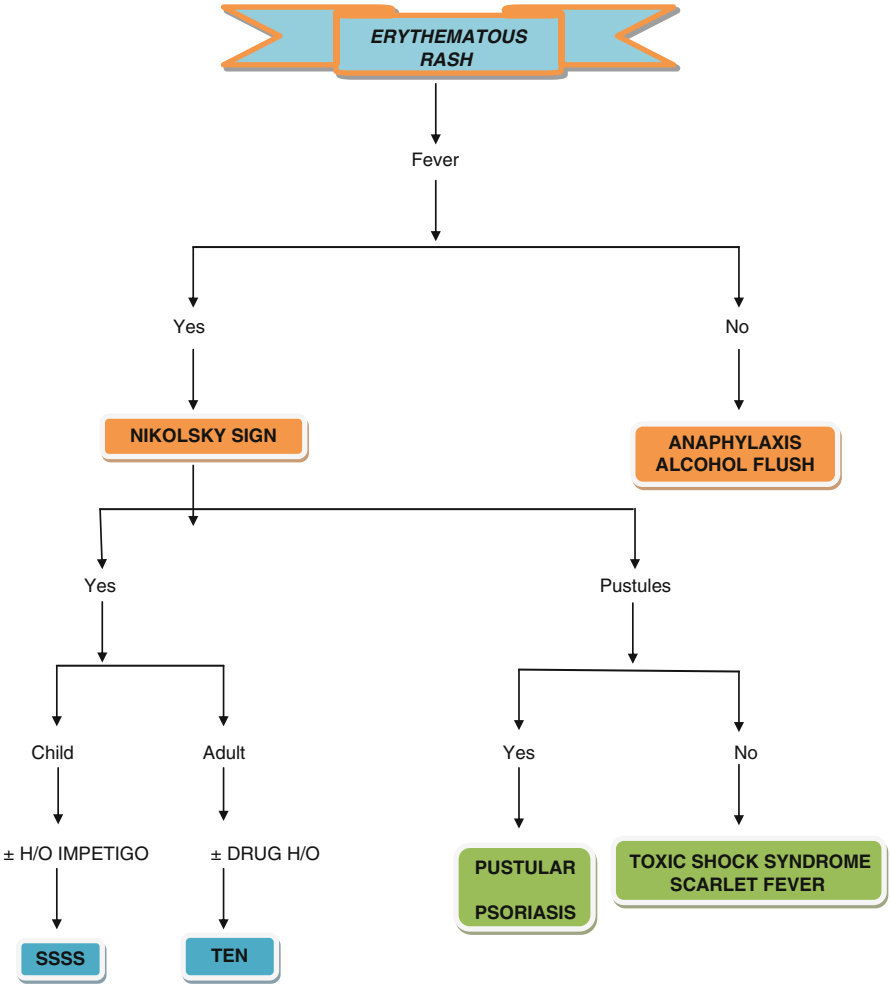
Maculopapular rashes are the most common types of rash and are differentiated based on the distribution of the rash and systemic toxicity (Table 35.3).

Table 35.3 Differential diagnosis of maculopapular rashes

Distribution	Disease
Centrally distributed rash with systemic toxicity	Viral exanthema
	Lyme disease
	Typhus fever
Centrally distributed rash without systemic toxicity	Pityriasis rosea
	Cutaneous drug allergy eruptions (Fig. 35.8)
Peripherally distributed rash with systemic toxicity	Rocky mountain spotted fever
	Secondary syphilis
	Meningococcaemia
	Cutaneous anthrax
	Erythema multiforme
	Stevens–Johnson syndrome
Peripherally distributed rash without systemic toxicity	Scabies
	Eczema
	Psoriasis

Fig. 35.8 Cutaneous drug allergy eruptions

Clinical Pathway 3



Erythematous Rashes: (Clinical Pathway 3)

It is described as diffuse redness of the skin due to capillary congestion and is differentiated from other rashes based on the presence or absence of fever and the Nikolsky sign. The differential diagnosis is extensive. Some of these diagnoses are not immediately life-threatening, such as a viral exanthema [6], staphylococcal scalded skin syndrome (Fig. 35.9) and Kawasaki disease. Others are rapidly lethal, such as the toxic shock syndrome (TSS), toxic epidermal necrolysis (TEN) and necrotising fasciitis.

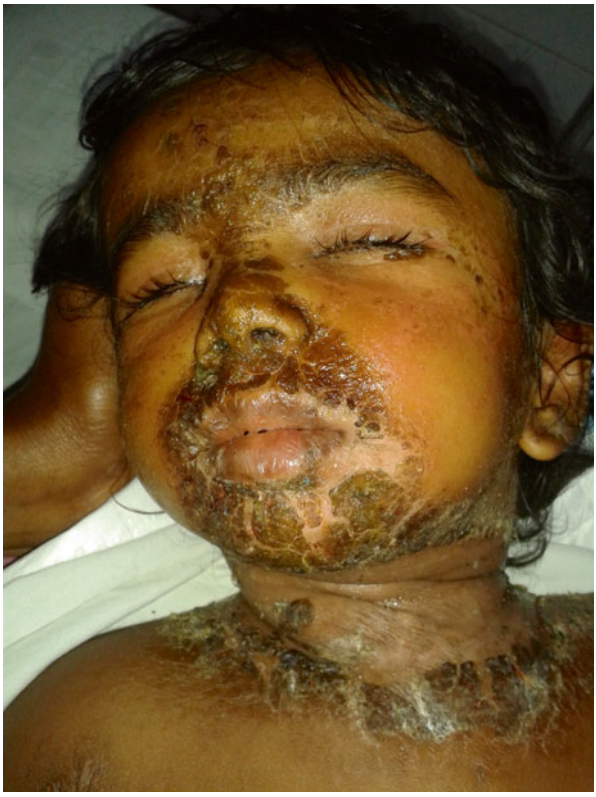
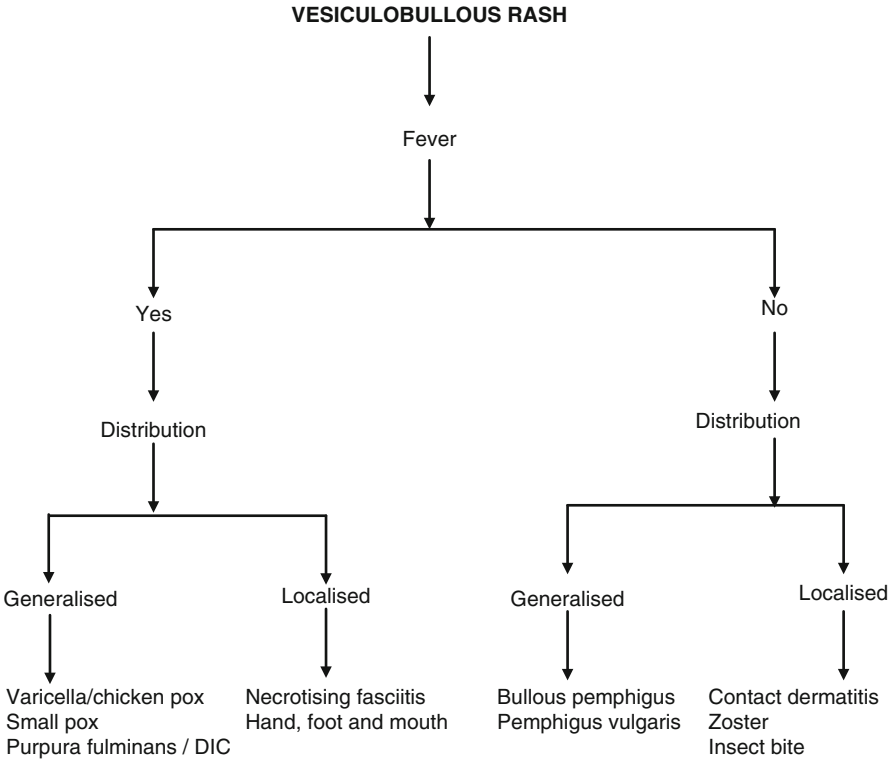


Fig. 35.9 Staphylococcal scalded skin syndrome

Clinical Pathway 4



Vesiculobullous Rash: (Clinical Pathway 4)

Vesiculobullous rashes incite significant anxiety in both patients and in physicians. Nevertheless, the differential diagnosis can be simplified by classifying patients based on presence of fever and rash distribution such as chickenpox (Fig. 35.10), purpura fulminans (Fig. 35.11) or bullous pemphigus (Fig. 35.12).

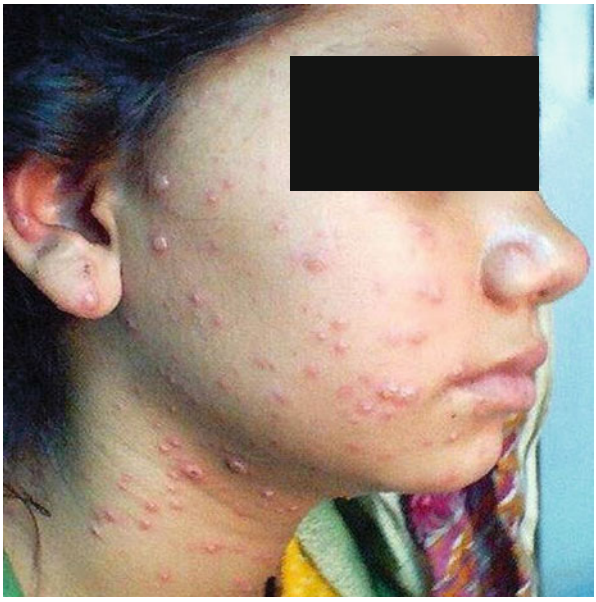


Fig. 35.10 Chickenpox

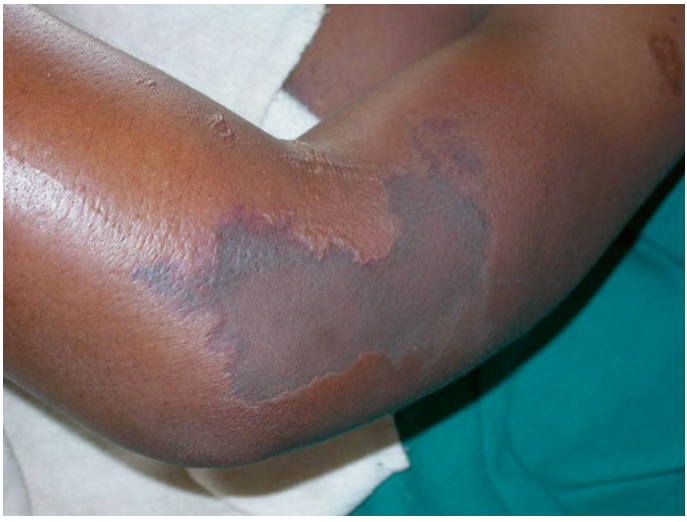


Fig. 35.11 Purpura fulminans

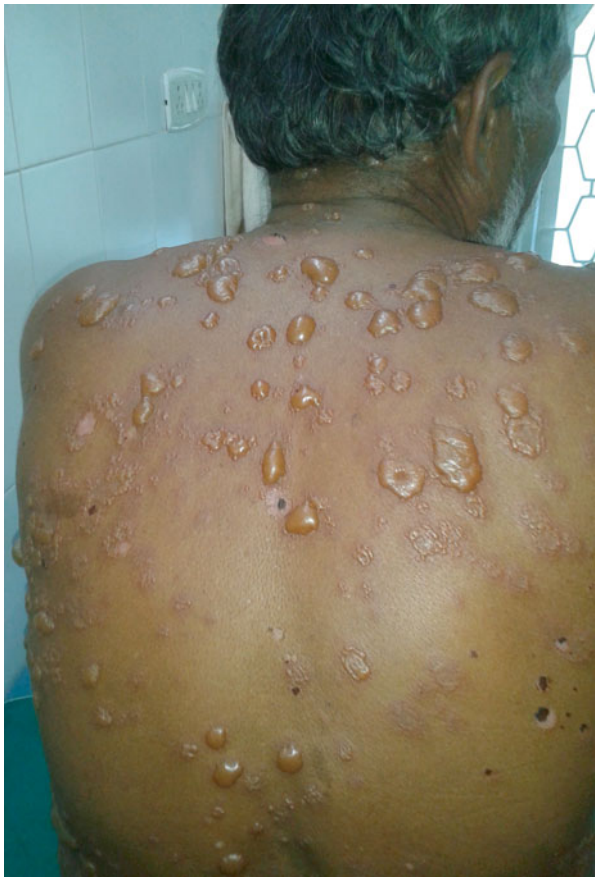
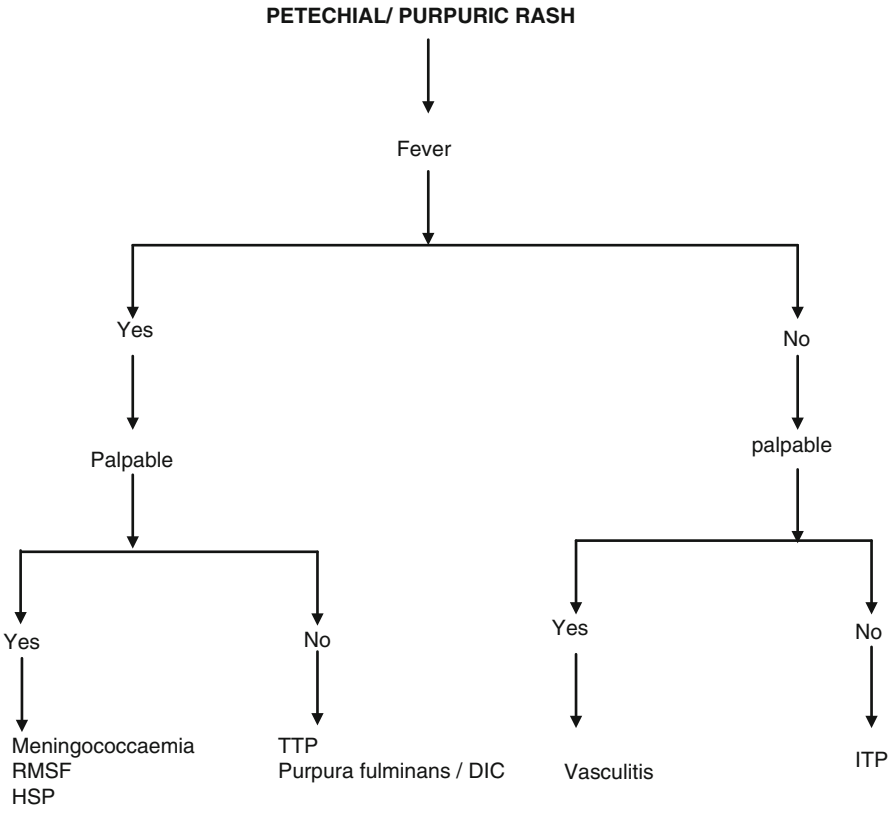


Fig. 35.12 Bullous pemphigus

Clinical Pathway 5



Petechial/Purpuric Rashes: (Clinical Pathway 5)

Purpura results from the extravasation of blood from the vasculature into the skin or mucous membranes. Therefore, purpuric lesions do not blanch with pressure. It may represent a relatively benign condition or herald the presence of a serious underlying disorder. Purpura may be palpable or non-palpable. The presence of palpable lesions will aid in differentiating between petechial and purpuric rashes. Palpable purpura arises in vasculitic diseases secondary to inflammation or infection (e.g. *Henoch–Schonlein purpura*) (Fig. 35.13). Non-palpable purpura presents in thrombocytopenic conditions (flat, subcutaneous haemorrhages) (e.g. *Thrombotic thrombocytopenic purpura*) (Fig. 35.14). Petechiae do not blanch with pressure. Patients with petechiae/purpura with fever or toxicity require emergent evaluation.

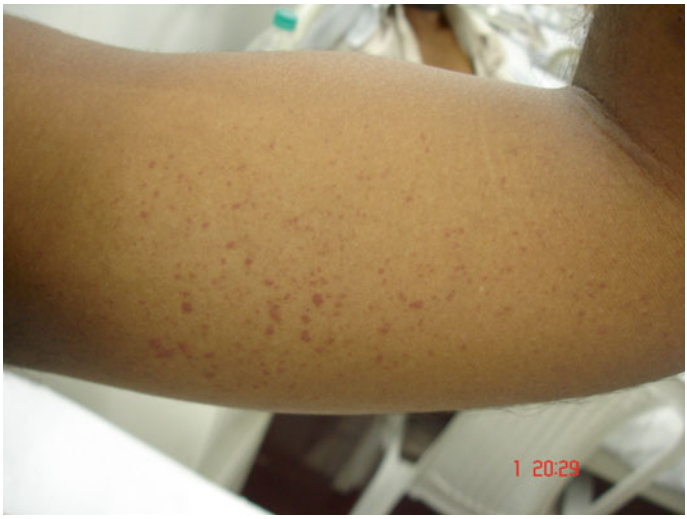


Fig. 35.13 Thrombotic thrombocytopenic purpura

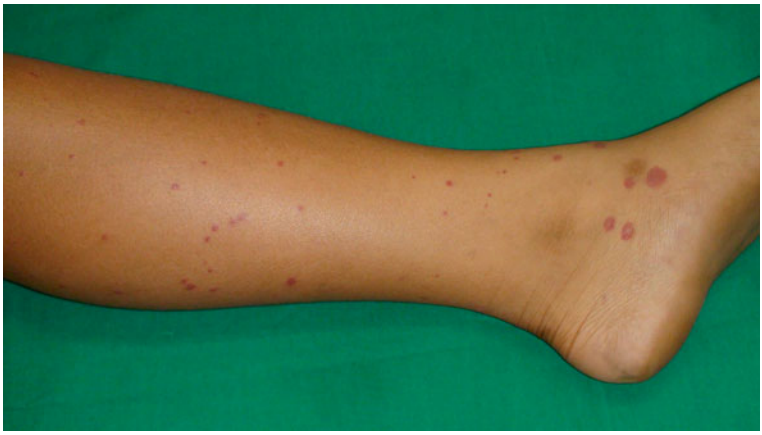


Fig. 35.14 Henoch–Schonlein purpura

Disposition

Depending on the working diagnosis and clinical condition of the patient, management plan can be abridged with any one choice [7].

1. *Admission in the ICU and treated immediately as an emergency*
   - Patients who need aggressive resuscitation will require admission to the ICU.
2. *Admission for further assessment and treatment*
   - When the patient is 'ill but not toxic', necessitate in-patient care.
3. *Observation in the ED*
   - Patients with anaphylaxis and responding promptly to therapy, angioneurotic oedema and urticaria need close observation for at least 24 h in the ED because recurrences are common.
4. *Advisable to seek a dermatologist's opinion*
   - Patients should be referred to a dermatologist where the diagnosis is unknown or unclear.
5. *Can be treated at home, assuming no features of concern are present*
   - After a thorough evaluation in the ED, several patients can be discharged and sent home with instructions as most of the cutaneous disorders take at least a week or longer to resolve.

Pearls and Pitfalls

- Always look for mucosal involvement, in patients suggestive of erythema multiforme.
- Do not forget to obtain ophthalmologic opinion in patients with Stevens–Johnson syndrome.
- Treat patients with urticaria who have features of anaphylaxis with epinephrine and haemodynamic support.
- Purpura with fever is always life-threatening.
- Thrombotic thrombocytopenic purpura should be suspected in patients with thrombocytopenia, neurologic symptoms and renal dysfunction.
- Patients with extensive desquamation and blistering should be admitted in a burns unit.

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Chapter 36
Diabetic Emergencies

Sandeep Balanrao Gore

Introduction

Diabetic Emergencies are common presentations to the Emergency Department, which, if not managed appropriately, has the potential of grave significance. So it is very much essential for an emergency physician to possess adequate knowledge, skill and competence to manage patients with diabetic emergencies.

In this chapter, the following presentations are discussed in detail: hypoglycaemia, diabetic ketoacidosis and hyperosmolar hyperglycaemic state.

Section A: Hypoglycaemia

Key Points

1. Always check the blood sugar level and exclude hypoglycaemia in any patient presenting to the emergency department with altered sensorium/ any neurological deficit/isolated hemiparesis/coma.
2. Correct hypoglycaemia quickly and effectively.
3. Attempt to identify the aetiology of the hypoglycaemic event.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_36

Definition and Introduction

Hypoglycaemia is defined as the serum glucose level below 50 mg/dl [1].

Prompt diagnosis and treatment is required to prevent disastrous aftereffects since the brain utilises glucose as its primary energy source. Therefore, delayed treatment results in neuronal damage.

Profound untreated hypoglycaemia may result in coma, dysrhythmia and even death.

Pathophysiology

Hypoglycaemia attacks mainly two organ systems:

1. The autonomic nervous system
   Autonomic response to hypoglycaemia results in adrenergic symptoms such as sweating, tachycardia, restlessness, anxiety, tremors and palpitations.
2. The central nervous system
   Decreased glucose supply to neurons results in generalised weakness, inability to concentrate, fatigue, blurring of vision, confusion, somnolence and altered mental status.

Causes

1. Oral hypoglycaemic agents and insulin:
   (a) Change in medications
   (b) Change in dosing pattern of insulin
   (c) Overdose of these medications
   (d) Skipping meals after taking medications
2. Drugs:
   Salicylates, haloperidol, ethanol, quinine, thiazides, pentamidine and didanosine are drugs capable of inducing hypoglycaemia.
3. Hormonal disorders
4. Infection
5. Insulin-secreting tumours
6. Starvation
7. GI (gastrointestinal) surgery

8. Malaria
9. Deliberate self-harm or homicide by a large dose of insulin or oral hypoglycaemic agents

Diagnosis

Diagnosis should be done by checking the blood sugar level. Point of care testing of blood sugar level is recommended for quick diagnosis. A serum glucose level less than 50 mg/dl in adults and below 40 mg/dl in infants and children is diagnostic.

Investigations

1. Blood sugar level
2. Complete blood count to rule out infection
3. Serum electrolytes to screen for associated electrolyte imbalance
4. Creatinine to check the presence of diabetes-related parenchymal renal damage
5. Urinalysis to rule out urinary tract infection
6. Chest X-ray to screen for lung infection in elderly patients
7. Electrocardiogram to screen for associated acute coronary event

Treatment

1. If the patient is conscious and cooperative, administer 15–20 g of fast-acting oral carbohydrates, i.e. sugar lumps/glucose powder followed by glucose biscuits and milk with sugar [2].
2. If the patient is drowsy/unconscious, then first secure airway, breathing and circulation.
3. Connect the patient to a cardiac monitor and pulse oximeter.
4. Administer oxygen by a mask if SpO2 is less than 94 %.
5. Obtain a large-bore intravenous access, and collect blood samples for complete blood count, electrolytes and creatinine.
6. Administer 50 ml of 50 % dextrose intravenously as a bolus followed by saline flush. Fifty per cent dextrose is hypertonic. If it is not followed by saline flush, it may cause thrombophlebitis.

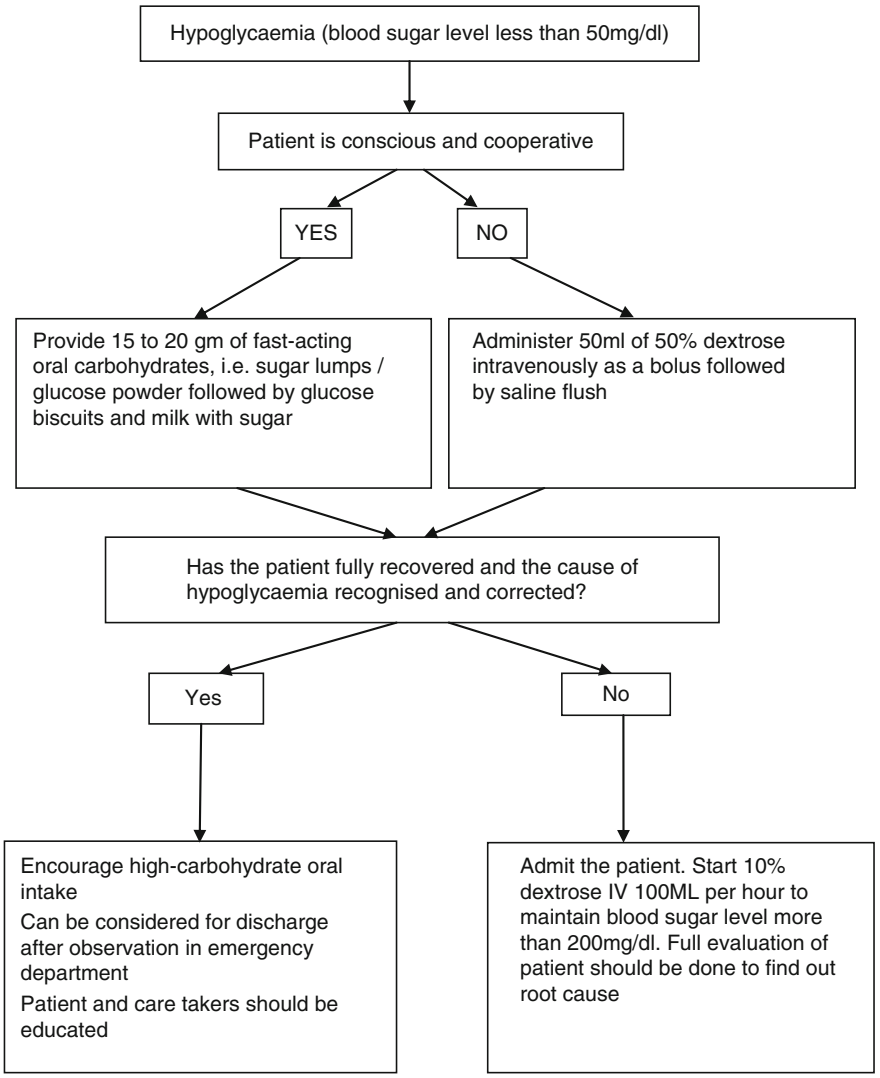
Administration of 100 ml of 25 % dextrose as a bolus is also equally effective, and it carries less risk of thrombophlebitis.

7. If the patient is taking a long-acting oral hypoglycaemic agent or long-acting insulin, then start 10 % dextrose infusion 100 ml per hour to maintain the blood sugar level more than 200 mg/dl. The blood sugar level should be monitored frequently.
8. Patients should be encouraged to take high-carbohydrate food after regaining consciousness.
9. If the patient does not respond to intravenous dextrose, then administer glucagon 1 mg intramuscularly.
10. Inj. Octreotide could be considered in hypoglycemia associated with sulphonylurea overdose [3].
11. Hypoglycemia in the pediatric age group should be treated with Inj. 10 % dextrose. The recommended dose is 2.5 ml ml/kg and it should be administered intravenously. The dose of glucagon in pediatric age group is 10–20 mcg/kg and it should be administered intramuscularly.
12. Patients in whom no obvious cause is found for hypoglycaemia or who are on long-acting oral hypoglycaemic agents/long-acting insulin or those who are exhibiting neurological deficits despite correction of hypoglycaemia should be advised for admission.
13. Those patients who get fully recovered after an initial bolus of dextrose and in whom the cause of their current episode is recognised and corrected can be considered for discharge after observation in the emergency department.

Prevention

1. The patient and his caretakers must be made aware about the different causes of hypoglycaemia and their preventive measures.
2. They should be educated to recognise early signs and symptoms of hypoglycaemia.

Algorithm: Hypoglycaemia



Section B: Diabetic Ketoacidosis

Key Points

- Fluid replacement is a key component in the management of diabetic ketoacidosis.
- The use of the sliding scale is recommended in deciding the dose of intravenous infusion of insulin.
- Serum potassium monitoring and its judicious replacement are vital. The clinical presentation of diabetic ketoacidosis may mimic as acute surgical abdomen. Every patient presenting to the emergency department with abdominal pain, vomiting and dehydration should be tested for blood sugar and ketone levels.

Introduction

Diabetic ketoacidosis (DKA) is a true medical emergency. It is one of the most dangerous acute life threatening complications of diabetes mellitus.

Mortality in DKA is <1 % in adults and more than 5 % in the elderly and patient with comorbid life-threatening illnesses [4].

Pathophysiology

The following three steps describe the pathophysiology of DKA [5]:

1. *Insulin deficiency or resistance* causes decreased utilisation of glucose, increased gluconeogenesis and increased glycogenolysis which result in hyperglycaemia, leading to osmotic diuresis, electrolyte imbalance, cellular dehydration and shock.
2. Reduced insulin secretion in addition to increased insulin resistance, result in activation of counter regulatory hormones (Glucagon, Catacholamines, cortisone, and growth hormone), which leads to lipolysis and generation of free fatty acids. These acids undergo beta oxidation in hepatic mitochondria and consequently, the production of keto acids. These keto acids result in ketonaemia, ketonuria, vomiting, dehydration, electrolyte imbalance and high anion gap metabolic acidosis and shock.
3. The counter-regulatory hormones also are responsible for gluconeogenesis from the *breakdown of protein* which results in muscle wasting. This protein breakdown leads to decreased immunity and more susceptibility to infection.

Precipitating Factors

1	Infection
2	Acute myocardial infarction
3	Inadequate insulin doses
4	Cerebrovascular accident
5	Major trauma
6	Surgery
7	Pregnancy
8	Discontinuation of insulin
9	Drugs affecting the metabolism of carbohydrates, viz. corticosteroids, sympathomimetic drugs, antipsychotic drugs, etc. [5]

Presenting Features

Symptoms	Signs
Nausea	Hypotension
Vomiting	Tachycardia
Abdominal pain	Loss of skin turgor
Polyuria	Kussmaul respiration
Polydipsia	Smell of acetone in breath
Altered sensorium	

Diagnostic Criteria for DKA

For the diagnosis of diabetic ketoacidosis, the following criteria should be met:

- Blood glucose level >250 mg/dl
- Anion gap >10
- Bicarbonate level <15 mEq/l
- pH <7.3 with moderate ketonaemia [5]

Urine test strips and some assays for serum ketones may underestimate the degree of ketosis because they detect acetoacetic acid and not the beta hydroxybutyric acid, which is usually the predominant keto acid. So anion gap measurement is vital in making the diagnosis of diabetic ketoacidosis.

Patients with a hyperosmolar, nonketotic condition have prominent mental status changes. Serum glucose levels generally are much higher (>600 mg/dl), and there is no anion gap metabolic acidosis.

Investigations

1. Blood gas analysis: This is needed to check the metabolic state of the patient.
2. Complete blood count: This is needed to screen underlying bacterial infection. Increased leucocyte count with left shift suggests underlying bacterial infection.
3. Electrolytes: This is required to screen associated electrolyte imbalance and also needed to guide fluid and insulin therapy.
4. Blood urea nitrogen: This is needed to calculate osmolality.
5. Phosphate, magnesium and calcium levels. These tests are essential, since osmotic diuresis leads to hypomagnesaemia. Hypomagnesaemia may inhibit parathyroid hormone secretion, causing hypocalcaemia and hyperphosphataemia. The initiation of insulin therapy may lead to Hypophosphatemia, which if not diagnosed promptly (phosphate <0.1 mg/dl) may lead to hypoxia, rhabdomyolysis, hemolysis, respiratory failure, and cardiac dysfunction [6].
6. Blood glucose and ketone levels.
7. Urinalysis: It is helpful to determine the level of ketosis, hyperglycaemias and possible source of infection.
8. Blood and urine culture: This is needed for rational antibiotic use.
9. Chest X-ray: This is needed to screen lung infection.
10. ECG: This is required to rule out acute coronary event as a precipitant. It is also helpful to pick up deranged potassium levels.

Principles of Management

- Aggressive fluid resuscitation
- Normalising metabolic status
- Correction of electrolyte imbalance and acidosis
- Diagnosis and treatment of precipitating factors
- Prevention of complications

Management

1. Secure the airway and breathing. Give oxygen if SpO2 is less than 94 %.
2. Put the patient on continuous cardiac and pulse oximetry monitoring.
3. Obtain two large bore intravenous accesses. Collect blood samples for blood gas analysis, complete blood count, electrolytes, BUN, Serum Creatinine, phosphate, magnesium and calcium levels, blood glucose level, blood ketone level. Collect sample for urinalysis. Obtain blood for culture and sensitivity if infection is suspected as a precipitating factor.

Table 36.1 Sliding scale for insulin IVI [5, 9]

Blood glucose level	Dose of IVI (unit/h)
130–160 mg/dl	1
161–200 mg/dl	2
201–270 mg/dl	4
More than 270	6

Tip: If the plasma glucose level does not fall by 50–75 mg/dl in the first hour, the insulin dose should be doubled

IVI intravenous infusion

Table 36.2 Guidelines for potassium repletion [5, 9]

Serum potassium level	Supplementation of potassium through fluid
<3 mmol/l	40 mEq KCL/l of fluid
<4 mmol/l	30 mEq KCL/l of fluid
<5 mmol/l	20 mEq KCL/l of fluid
More than 5 mmol/l	No potassium supplementation is required

Tip: When KCL is added to normal saline, rate of fluid administration should be adjusted in such a way that potassium should be administered more rapidly than the rate of 10–20 mEq/h

4. Give 1 l of normal saline over 20–30 min.
5. Give an initial bolus of insulin at 0.1 unit/kg, and then start insulin IVI according to the sliding scale (refer to Table 36.1).
6. Start empiric antibiotics on suspicion of infection until culture results.
7. Consider administering sodium bicarbonate in patients (particularly patients with circulatory failure) with pH below 6.9. Give 100 mEq of sodium bicarbonate in 400 ml of sterile water with 20 mEq of KCL at over 2 h at constant rate.

   The routine use of supplemental bicarbonate in the treatment of DKA is not recommended [7] as fluid and insulin therapy decreases lipolysis and resolves ketoacidosis in most of the cases.
8. Obtain 12 lead ECG and chest X ray.
9. Insert a Foley catheter and monitor urine output.
10. Check out electrolyte levels and give another 1 l of normal saline or half normal saline with or without potassium (depending upon electrolytes) over another 1 h.
11. Consider supplementation of potassium according to Table 36.2.
12. The goal is to give 4 l of fluid over the first 4 h.
13. Magnesium replacement should be carried out, by administrating 2 gm of magnesium sulfate in 100 ml of normal saline over 20 min at constant rate.
14. Continue insulin IVI until anion gap resolves.
15. Give prophylactic low-molecular-weight heparin injection: enoxaparin at 30 mg SC BD.

16. Monitor and record vital signs, mental status, electrolytes, blood sugar level, anion gap and input-output balance every 2 h.
17. Consider central venous catheterisation and central venous pressure monitoring during fluid replacement.
18. Treatment should be continued until blood sugar level is <250 mg/dl and ketoacidosis corrected (pH >7.3, bicarbonate >18 mmol/l). Hyperglycaemia and ketoacidosis correction should happen with a mean duration of 6 h and 12 h, respectively [8].

Complications

1. Hypoglycaemia and hypokalaemia

   Frequent blood sugar level and potassium monitoring is recommended to avoid this complication.
2. Cerebral oedema

   This is more common in children. It is associated with a mortality rate of 20–40 %. So prevention of cerebral oedema in paediatric patients is crucial.

   It can be prevented by avoiding excessive hydration and rapid reduction of plasma osmolality.

   In children, IV fluids should be commenced with a bolus of 10 ml/h. It can be repeated as required in up to 30 ml/h. *It is advisable not to start insulin in paediatric patients until intravenous fluids have been administered for at least 1 h.*

   Mannitol injection/infusion and invasive ventilation can be considered in the management of cerebral oedema.
3. Vascular thrombosis

   It can be prevented by using prophylactic low-molecular-weight heparin.
4. Pulmonary oedema

   It may be potentially related to excessive fluid correction. It can be avoided by protocol-based fluid resuscitation and central venous pressure monitoring.

Prevention

1. Rendering optimal health education to the patient and patient's family is important. The importance of regular and adequate insulin therapy should be emphasised to the patient and the patient's relatives.
2. The patient should contact a healthcare provider early if any infection is suspected.
3. Set blood sugar goals for the patient, and regularly review it.
4. Educate the patient regarding blood sugar level monitoring at home using a glucometer.

Section C: Hyperosmolar Hyperglycaemic State (HHS)

Key Points

- Acute coronary syndrome can be a precipitating factor of HHS or it may be precipitated by HHS. Procure an ECG in all adult patients with HHS.
- A flow sheet of clinical and laboratory parameters must be maintained as it will determine the efficacy of medical treatment as well as reduce the complications.
- Steady, gradual correction of blood sugar level and serum osmolality is of paramount importance.

Introduction

Hyperosmolar hyperglycaemic state commonly occurs in elderly patients with type 2 diabetes mellitus. Vulnerable patients include the following:

(a) Those who take inadequate medication
(b) Those who are noncompliant with treatment
(c) Those who have inadequate fluid intake
(d) Those who have acquired concomitant infection

HHS has an insidious onset and coma is a common occurrence, in comparison with diabetic ketoacidosis.

Pathophysiology

HHS lowers the level of free fatty acids, and therefore, there are less free fatty acids available for ketogenesis. The availability of insulin is sufficient to prevent ketogenesis, but it is not sufficient to prevent hyperglycaemia. Hence, progressive hyperglycaemia and hyperosmolality and absence of significant ketogenesis are observed in HHS.

Clinical Features

Symptoms	Signs
Generalised weakness	Loss of skin turgor
Anorexia	Dry tongue and oral mucosa
Fatigue	Sunken eyes
Drowsiness	Hypotension
Polyuria	Tachycardia
Focal/generalised seizures	Hypothermia
Coma	Stupor

Lethargy and reduced consciousness are directly proportional to serum osmolality [10].

Diagnostic Criteria for HHS

Blood sugar level is more than 600 mg/dl, serum osmolality is more than 330 mOsm/kg and severe ketoacidosis is absent.

Blood pH usually remains more than 7.3 and bicarbonate more than 18 mEq/l.

Precipitating factors (in alphabetical order)

- Acute coronary syndrome
- Cerebrovascular accident
- Certain drugs, i.e. diuretics, beta-blockers, phenytoin, lithium, steroids, calcium channel blockers, etc.
- Heat-related illness
- Inadequate intake of water
- Inadequate oral intake
- Infection
- Irregularity or inadequate antidiabetic medications
- Renal insufficiency
- Upper gastrointestinal bleeding

Investigations

1. Blood sugar level.
2. Serum electrolytes: This is required to screen associated electrolyte imbalance and also needed to guide fluid and insulin therapy.
3. Magnesium, phosphate and calcium levels

   Hypomagnesaemia is a common finding in type 2 diabetes. Serum magnesium levels should be monitored and replaced accordingly [11].

   Osmotic diuresis leads to hypomagnesaemia. Hypomagnesaemia may inhibit parathyroid hormone secretion, causing hypocalcaemia and hyperphosphataemia.

   Hypophosphataemia can also occur after the start of insulin therapy. If not diagnosed promptly, it may lead to hypoxia, rhabdomyolysis, haemolysis, respiratory failure and cardiac dysfunction.
4. Serum creatinine: This is needed to screen and monitor renal function.
5. Blood urea nitrogen: This is needed to calculate osmolality.
6. Blood gas analysis: This is needed to screen and monitor the metabolic state of the patient.
7. Complete blood count: Increased leucocyte count with left shift suggests underlying bacterial infection.
8. Blood culture and sensitivity: This is needed for rational antibiotic use.
9. Urinalysis: It is helpful to determine the level of ketosis, hyperglycaemias and possible source of infection.
10. Osmolality. Patients who are in coma have osmolality more than 330 mOsm/l. If osmolality is less than this and patient is comatose, then look for another cause of reduced conscious level.

$$\text{Osmolality} = 2 \times (\text{Na} + \text{K}) + \text{Glucose} / 18 + \text{Blood Urea Nitrogen} / 2.8$$

11. ECG: This is required to rule out acute coronary event as a precipitant. It is also helpful to pick up deranged potassium levels.
12. Chest X-ray: It is helpful to rule out chest infection.

Basic Principles of Management

- Correcting fluid deficit
- Correcting electrolyte abnormalities (especially potassium and sodium)
- Correcting hyperglycemia and serum osmolality
- Recognising the precipitating factors and close monitoring of the patient

Management

1. Secure the airway and breathing.
   Administer oxygen by mask 4 L/min if SpO2 is less than 94 %.
2. Obtain two large-bore intravenous accesses, and collect blood samples for investigations.
3. Connect the patient to a cardiac monitor.
4. Fluid therapy:
   - Give 1 l of IV fluids over the first 20–30 min as a bolus.
   - Administer another 1 l over 1 h.
   - Administer another 1 l over the next 2 h.
   - Administer 1 l over 4 h in lesser time, depending upon central venous pressure.

   The chosen fluid should be either normal saline (0.9 % NaCl) or half normal saline (0.45 NaCl), depending upon initial serum sodium value.
   The total fluid deficit in HHS is 20–25 % of total body weight. Fluid deficit should be calculated individually in litres. It ranges from 8 to 10 l.
   Fifty per cent of calculated fluid deficit should be corrected in the first 12 h, and the remaining deficit should be corrected over the next 24 h.
5. Insulin therapy:
   - Give an initial bolus of insulin of 0.1 U/kg intravenously, and then start insulin intravenous infusion (IVI) at the rate of 0.1 U/kg/h.
   - If the initial blood sugar level does not fall by at least 50 mg/dl after the first hour of infusion, double the dose of insulin infusion.
   - The rate of intravenous infusion of insulin should be adjusted in such a way that there will be a steady fall in the blood glucose level by 50–60 mg/dl per hour [12].
   - Once the blood sugar level falls below 300 mg/dl, reduce insulin IVI to 0.05 U/kg/h and replace IV fluid with dextrose normal saline.
   - The blood sugar level should be maintained between 250 and 350 mg/l until plasma osmolality falls below 315 mOsm/l [12].

6. Potassium monitoring and correction if needed.
   Use the following table for making a decision for potassium correction:

Serum potassium level	Supplementation of potassium through fluid
<3 mmol/l	40 mEq KCL/l of fluid
<4 mmol/l	30 mEq KCL/l of fluid
<5 mmol/l	20 mEq KCL/l of fluid
More than 5 mmol/l	No potassium supplementation is required

Tip: When KCL is added to normal saline, the rate of fluid administration should be adjusted in such a way that potassium replacement should not happen more rapidly than the rate of 10–20 mEq/h.

7. Obtain an ECG.
8. Insert a Foley catheter and monitor urine output. Send urine for analysis and culture sensitivity.
9. Check electrolytes, glucose level, BUN, mental status, central venous pressure, urine output, input-output balance and vital parameters of the patient every 2 hours. Maintain a flow sheet of the same.
10. Give prophylactic low-molecular-weight heparin as HHS is a hypercoagulant state and patients are prone to deep vein thrombosis.
11. After resolution of HHS, i.e. when serum osmolality falls below 315 mOsm/l, the blood sugar level is between 250 and 300 mg/dl, and the patient becomes fully conscious, one should encourage the patient to eat and gradually switch over to subcutaneous insulin.
12. One should find out precipitating factor and treat it accordingly.

Complications

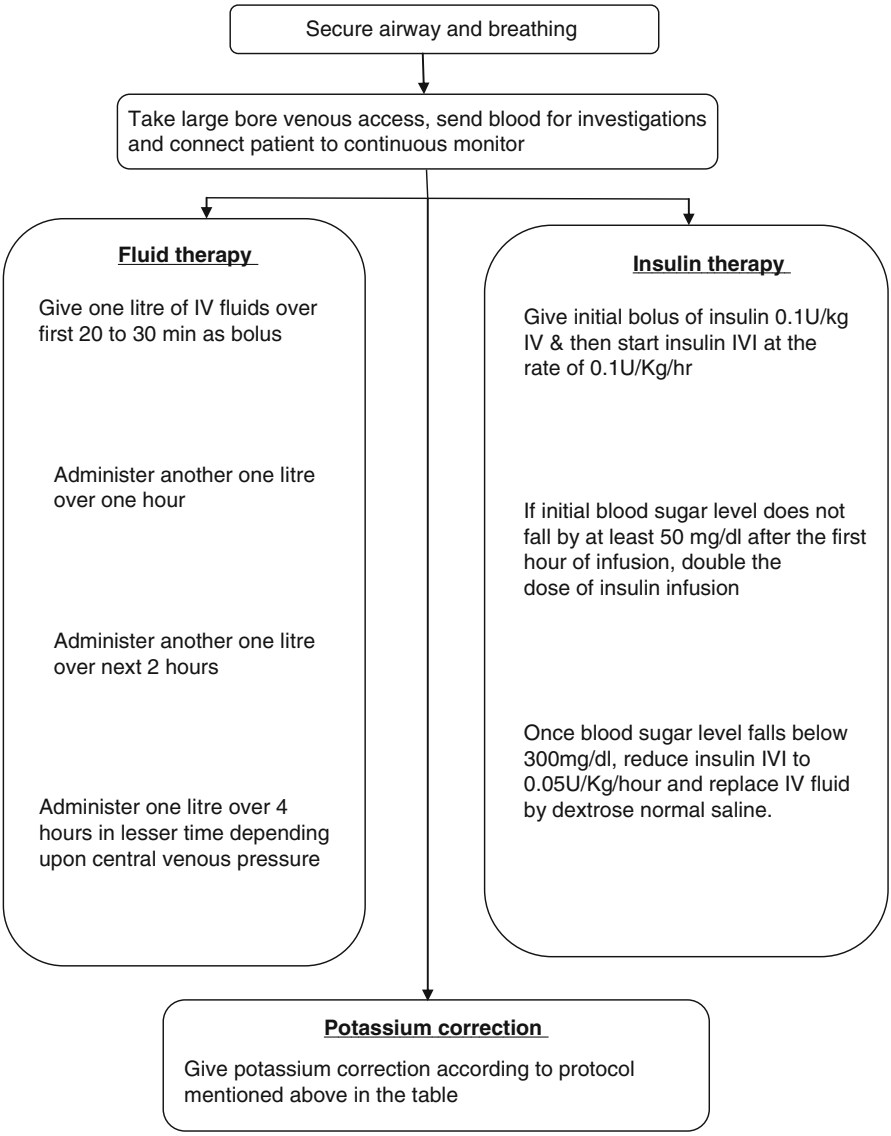
Most of the complications are similar to DKA. Cerebral oedema is rarely observed in adults.

Pulmonary oedema, hypo- or hyperkalaemia and hypoglycaemia can be prevented by close clinical and laboratory parameter monitoring of the patient on data sheets.

Prevention

1. Patient and patient caretaker education regarding the disease and the precipitating factors.
2. A caretaker or family member should be there with the elderly diabetes mellitus patient.
3. Drinking water should be readily available for patient.
4. Early contact with the healthcare system is recommended.
5. The importance of regular antidiabetic medications and adequate water intake should be emphasised.

Algorithm: Management of Hyperosmolar Hyperglycemic State



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Chapter 37
Febrile Neutropaenia

N.V. Maheshwari

Key Points

- Febrile neutropaenia (FN) should be suspected in all immune-compromised patients who present to the emergency department (ED) with fever and neutropaenia.
- FN is a time-dependent life-threatening condition.
- The following features clearly have an impact on the high morbidity and mortality:
  - Prompt recognition in patients who have recently received chemotherapy
  - Investigation for a potential infective source
  - Initiation of empirical broad-spectrum antimicrobial based on local microbial aetiology

Introduction

Febrile neutropaenia (FN) is an inevitable side effect following chemotherapy due to myelosuppression. Bodey et al. in 1960 were the first to record that fever complicated neutropaenia [1]. Despite the advances in diagnostic armamentarium, aggressive chemotherapy and usage of broad-spectrum antimicrobial treatment, infection in the neutropaenic patients is still a major cause of morbidity and mortality and thus recognised as a medical emergency [2].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_37

With increase in the life expectancy due to disease-free states and usage of permanent intravascular access for outpatient antimicrobial treatment (OPAT), febrile neutropaenia (FN) could be the prime reason of acute attendance to the ED [2]. It is important for the healthcare staff to be conversant with its atypical presentations, evolving microbial aetiology leading to appropriate triage and immediate commencement of broad-spectrum antimicrobial treatment, for FN is a time-dependent life-threatening condition. This chapter will briefly outline the definition, epidemiology, pathophysiology, infective aetiology, risk factors, triage and management of FN relevant to the emergency department.

Definition

Febrile neutropaenia is generally defined as an oral temperature of >38.3 °C (or 38 °C on two occasions) with absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L OR $\leq 1.0 \times 10^9$/L with a projected nadir of $\leq 0.5 \times 10^9$/L [3].

Epidemiology

- In the United States, the annual incidence of FN accounts to 7–43 cases per 1,000 cancer patients, including haematological malignancies [4].
- FN-associated mortality varies from % 50 to 70 %, if not treated appropriately within 48 h of presentation. Prompt initiation of empirical broad-spectrum antibiotics has demonstrated a decline in mortality to 10 % and improvement in the response rate up to 70 %.

Pathophysiology

Host defence is divided into three main categories:

1. Barriers: Skin, normal flora, mucous, pH, gut motility and cilia
2. Non-specific immune response: Neutrophils, inflammation
3. Specific immune system: Cell-mediated and humoral immunity

Neutrophils are the most numerous blood white cells that constitute the primary defence against a pathogen (total white blood cells: $4.0–11.0 \times 10^9$ cells/L, absolute neutrophil count: $3.0–7.0 \times 10^9$ cells/L). They phagocytise the microbe, kill it and die releasing cytokines. These chemical mediators attract the tissue macrophages which process the foreign antigen and present to the T lymphocytes, thus linking the non-specific to specific immunity. This constitutes the process of inflammation which clinically manifests as fever.

Neutropaenia occurs due to three main reasons:

1. Decreased production/suppression of bone marrow precursor cells: Drug, infections, radiation, nutritional deficiency and bone marrow failure
2. Rapid turnover: SIRS, severe sepsis, immune mediated and endocrinal
3. Shift in neutrophils homing: Splenic sequestration and hypersplenism

Bone marrow suppression following chemotherapy results in neutropaenia, compromising their first line of cellular defence mechanism against pathogens. Infection should be on the top of all differentials while clerking an ill patient who has received chemotherapy in the last 6 weeks and presents to the ED, with or without fever.

Aetiology

When a neutropaenic patient presents with fever, always suspect an infection, unless proved otherwise. Pathogen detection rates by blood culture vary from 7 % to 31 % depending on the malignancy type (solid organ tumours, haematological malignancies), use of prophylactic antibiotics and presence of central venous catheter (CVC). Host endogenous flora is the major cause of infection. Causative pathogens vary between healthcare centres depending on their level of care (secondary/tertiary/referral), speciality units (haemato-oncology, bone marrow and organ transplant, burns, vascular, paediatric facilities), antimicrobial usage as well as infection control policies. Over the last two decades, a shift in pathogens causing blood stream infections (BSI) has been noted [5] (Table 37.1).

This shift in microbial aetiology could be attributed to the increased usage of empirical broad spectrum β-lactams and glycopeptides, usage of antifungal prophylaxis in neutropaenic patients along with restricted use of quinolones in many healthcare institutions [6]. An increase in antibiotic-resistant strains like m*ethicillin-resistant S. aureus* (*MRSA*), *vancomycin-resistant enterococci* (*VRE*), extended spectrum β-lactamase (ESBL) gram negatives and fluconazole-resistant *Candida non-albicans* spp. has been a growing microbial challenge.

Table 37.1 Predominant microbes causing bloodstream infections in febrile neutropaenia

Pathogens	BSI (%)
Gram-positive cocci: *S. aureus*, *Coagulase-negative staphylococci*, *Viridans streptococci* and *Corynebacterium* spp.	60–65 %
Gram-negative bacilli: *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*	20–24 %
Polymicrobial	10–12 %
Fungi *Candida albicans and non-albicans* spp. (*C. glabrata*, *C. krusei*)	2–5 %
Anaerobes	2 %

Risk Factors

Several risk factors [7, 8] have been identified that can predispose a neutropaenic patient towards developing an infection (Fig. 37.1). A clear knowledge of them will help physicians to triage and initiate goal-directed therapy. Risk of FN is highest after the first cycle of chemotherapy, with a peak incidence between day 7–14 post chemotherapy. The risk varies from 5 % to 50 %, depending upon the tumour type and chemotherapy regime. The longer the duration and degree of neutropaenia, the higher is the risk. However, the risk profile will change with the advent of new anti-neoplastic agents and with the prophylactic use of growth factors like granulocyte colony-stimulating growth factors (G-CSF) in patients with ≥20 % risk of developing FN, as recommended by international cancer organisations.

Clinical Presentation

Due to immunosuppression, neutropaenic patients may not mount the classical symptoms and signs of inflammation. It is essential to take a detailed history including exploration of atypical presentations, nature of recent chemotherapy, usage of prophylactic antibiotics or steroids, recent surgery and drug allergy. An initial assessment of airway and circulatory system, with prompt resuscitation if necessary, followed by a thorough physical and systemic examination (Table 37.2) should be undertaken.

Depending on the sepsis severity, clinical syndromes could manifest as localised infection, bacteraemia, systemic involvement or pyrexia of unknown origin (PUO).

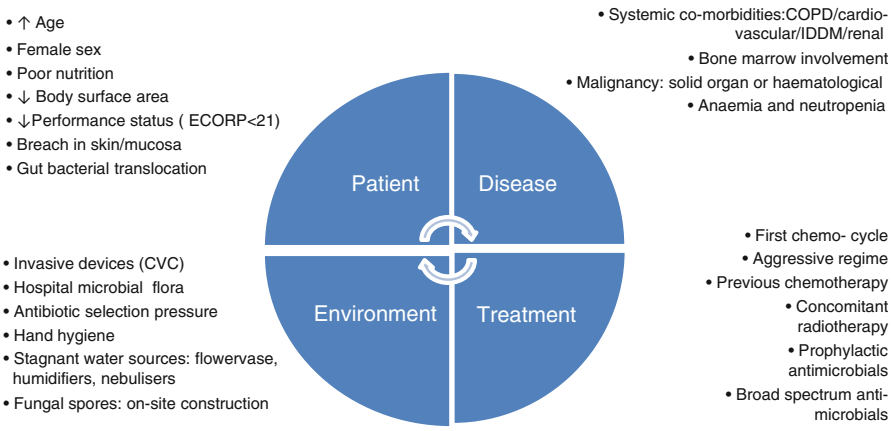


Fig. 37.1 Risk factors for developing febrile neutropaenia

Table 37.2 Initial assessment in a suspected case of febrile neutropaenia

1. Assess *indwelling venous catheters* for redness, discharge, swelling, tenderness, rigors while using the IV line
2. *Symptoms and signs of infective foci*
Respiratory system: shortness of breath, productive cough, pneumonia, pleural effusion
Gastrointestinal tract: mucositis, oral thrush, odynophagia (candidal oesophagitis), unexplained diarrhoea, generalised abdominal tenderness (typhlitis, CMV colitis), peritonitis, tenesmus (perirectal abscess)
Oropharyngeal: thrush, odynophagia (candidal oesophagitis)
Sinus tenderness: bacterial or fungal sinusitis
Skin: rash or thrush in moist areas like axillae, groin, perineum
Genitourinary infections, genital discharge
CNS: meningitis, encephalitis, brain abscess
Deep seated abscess in liver, lungs, kidneys, perirectal, bones and para-vertebral
Deep seated infections such as infective endocarditis (IE) or spinal discitis
Eyes: visual impairment (herpetic, candidal ophthalmitis or CMV chorioretinitis)
3. Knowledge of any *prior positive microbiology* will help guide empirical antibiotics

History and Examination

Key Factors

- Recent chemotherapy (within 6 weeks and the regime type)
- Fever >38 °C for 1 h
- Neutropaenia: ANC of $\leq 1.0 \times 10^9$/L

Systemic Features

The common features include rigors, lassitude, loss of appetite, nausea and vomiting. Patient may not feel his own self.

Hypothermia (<35 °C), tachycardia and hypotension are signs of impending sepsis and shock.

Patients can present anywhere in the continuum of sepsis cascade ranging from SIRS, early sepsis, severe sepsis and septic shock with multi-organ failure leading to death.

Diagnostic Tests

1. Attempt to take laboratory samples before initiating empirical antimicrobial therapy, without delaying the initiation of treatment.

2. Although pathogen is identified in 33 % of cases only, this should not discourage clinician to take clinical samples.
3. Communicate with the laboratory staff and consult the pathology manual, when in dilemma about test choices and interpretation.

Primary Investigations

- Urgent complete blood count and differential white cell count (ANC) to assess bone marrow activity.
- Blood cultures: At least two sets, both from the CVC and the peripheral vein should be taken concomitantly. A difference in the time to positivity between peripheral and central line cultures of >2 h is indicative of indwelling line infection.
- Blood glucose – usually low in sepsis.
- Renal function test and liver function test.
- Urinalysis and culture.
- Coagulation profile.
- C-reactive protein.
- Serum lactate as predictor of tissue hypoperfusion [9].
- Sputum microscopy and culture.
- Stool microscopy and culture.
- Chest X-ray.

Secondary Tests

Based on localising symptoms and signs, further additional tests should be considered:

- Pus swab, infected line site swabs and IV line tips for culture sensitivity.
- Screening for resistant organisms: Nasal and throat swabs for *Methicillin-resistant Staphylococcus aureus* (MRSA), rectal swabs for vancomycin-resistant enterococci and carbapenemase resistant organisms in centres where it is prevalent.
- Respiratory secretions: Nondirected bronchial lavage (NBL) or bronchoscopic lavage for respiratory virus PCR. Many centres do twice weekly respiratory surveillance cultures to know their local microbial flora.
- Rapid urinary antigen test: *S. pneumoniae* and *L. pneumophila* infections.
- Lumbar puncture: CSF (gram staining, culture and sensitivity).
- Echocardiogram for suspected infective endocarditis.

- High-resolution CT scan of the chest, abdomen and pelvis, if the patient continues to have fever despite 72 h of appropriate antibiotics.
- Serum ß-D-glucan and galactomannan levels for suspected invasive fungal infections.
- Cultures for acid fast bacilli.

Management

The success of management lies in early recognition of impending sepsis, vigorous resuscitation of respiratory and circulatory functions and prompt initiation of broad-spectrum empirical antimicrobial treatment, especially within the first 60 min of hospital presentation, 'the golden hour rule'. The 2014 revised 'international guidelines for management of severe sepsis and septic shock' by the Surviving Sepsis Campaign echoes this as the 'goal of the therapy' (Grade 1B recommendation) [9].

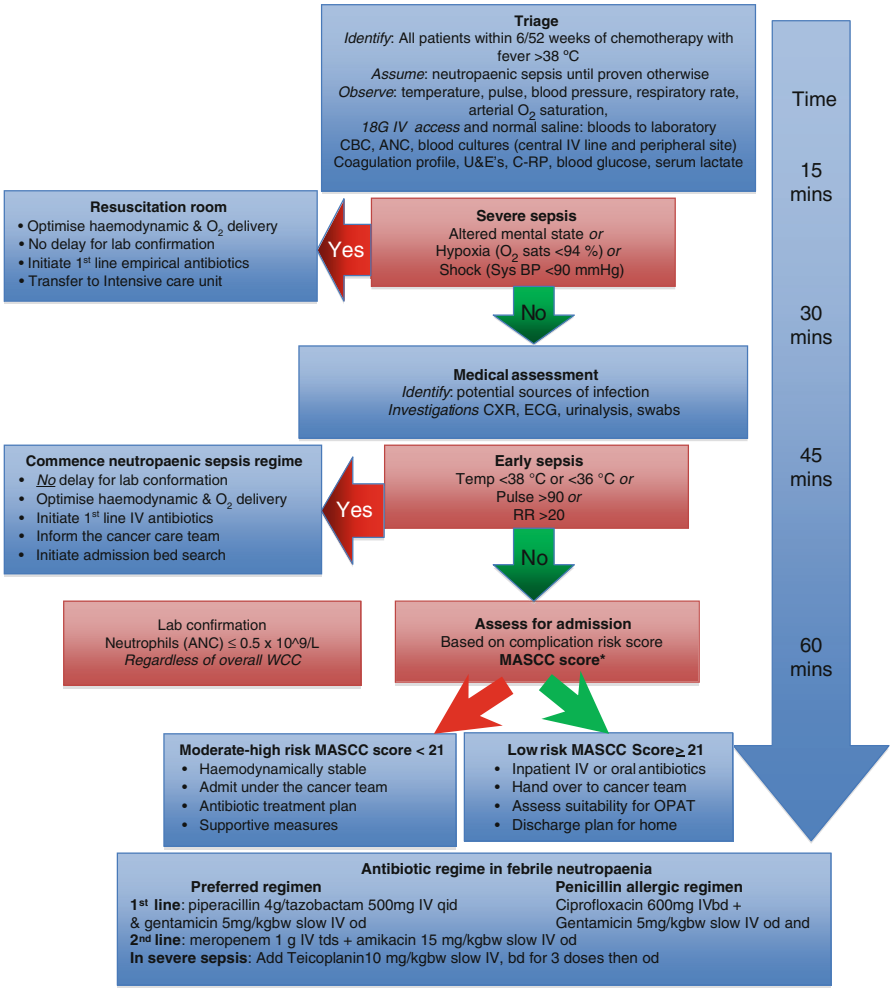
Triage assessment by the skilled front-line ED staff is the key. Laboratory confirmation of an underlying aetiology may not be available at the time of initial assessment; hence, early management should be based on the clinical judgement and vital organ functions. Early sepsis should be differentiated from severe sepsis with signs of multi-organ dysfunction (altered mental state, hypoxia and shock).

Clinical Pathways

The 60-min 'door-to-needle time' target should be one of the primary goals [9]. A retrospective cohort study of 2,731 patients with septic shock, of which 7 % had neutropaenic sepsis, reported 8 % fall in survival with every hour delay in commencing appropriate antimicrobials. The in-hospital mortality decreased from 33 % to 20 % (odds ratio 0.30, 95 % CI 0.11–0.83) if they received effective antimicrobials within 1 h of assessment in ED [10, 11].

A median time varying from 15 min to 9 h has been reported between the initial assessment in ED and administration of the first dose of empirical broad-spectrum antibiotics [10]. The most common reasons for delay were prolonged ED waiting times, delay in recognition of FN, appropriate antibiotic not in stock in ED and non-availability of FN clinical protocol. Hence, we envisage the front-line healthcare workers need a simple clinical pathway to understand what needs to be achieved in the 'golden hour'. This clinical pathway can be used as a concise tool for the prompt recognition and management of potential neutropaenic sepsis alongside other differentials as myocardial infarction, acute stroke.

First 60 min 'Golden Hour': Neutropaenic Sepsis Clinical Pathway [10]



MASCC (Multinational Association for Supportive Cancer Care) score index [3]					
Burden of illness		No hypotension (systolic BP >90 mmHg)	5	No dehydration	3
None/mild	5	Solid tumour or lymphomas with no	4	Outpatient status (at onset of fever)	3
Moderate	3	previous fungal infection		Age>60 years	2
Severe	0	No COPD	4		
Nine parameters, Scores ≥ 21 are at low risk of complications					

Next 48 h

Once the patient is stable and the need for hospital admission is decided, the ongoing management should be in a cancer unit, under the care of the haemato-oncologist team. A good liaison and well-documented ED case notes should expedite the transfer between the ED and the cancer unit. For optimal outcome, the patients should be constantly observed in the five main areas: monitoring of vital organs, ANC, antimicrobials, fluid and electrolyte balance and chemotherapy drugs. A clear plan of action should be documented between the treating clinicians, haemato-oncologist, pharmacist and microbiology/infectious disease team.

Treatment

In FN it is safer to commence empirical broad-spectrum antibiotics assuming infection, pending culture results. Based on local microbial flora, antimicrobial resistance patterns and the hospital antimicrobial policy, choose the first-line empirical antibiotics:

1. Potent new-generation ß-lactams (cefepime, carbapenems) are used either as single empirical agent or in combination with an aminoglycoside.
2. Piperacillin-tazobactam is used in combination with an aminoglycoside to avoid emergence of resistance in *Pseudomonas spp*.
3. Synergetic combinations like aminoglycosides or a quinolone with ß-lactams tend to be more effective in severe sepsis.
4. Add IV glycopeptides (vancomycin or teicoplanin) if severely unwell and IV line infection or higher risk of MRSA is suspected.
5. The median time to clinical response is around 5–7 days. In low-risk cases, antimicrobials should be continued for at least 2–5 days once the patient is afebrile, culture negative and non-neutropaenic.
6. De-escalation to narrow spectrum antimicrobials should be done based on the patient's condition and culture sensitivity results. Bactericidal agents should be chosen to prevent breakthrough bacteraemia.
7. Therapeutic drug monitoring (serum levels) of aminoglycosides and glycopeptides and antimicrobials should be done to avoid organ toxicity.
8. If fever does not respond or patient deteriorates at 48 h, consider changing to second-line antibiotics IV meropenem and IV amikacin with or without IV teicoplanin. Thorough investigation for occult infective foci for atypical bacteria, *Mycoplasma* and *Legionella*, or fungal, viral and multiresistant organism

should be considered followed by addition of empirical antifungal agent and/or antiviral according to hospital antimicrobial policy.
9. Infected CVC should be removed with suspected tunnel or Portacath™ pocket infection and persistent or gram-negative bacteraemia and candidaemia. In stable patients IV glycopeptides or line locks could be used to salvage line infections with coagulase-negative *Staphylococcus* spp.
10. In high-risk, culture negative patients who are still neutropaenic, antibiotics need to be continued for at least 2 weeks despite being afebrile [4].

Differential Diagnosis

While clerking a patient with FN, the following differentials should be considered and investigated:

- Chemotherapy infusion-related fever with chills, nausea and vomiting.
- Release of cytokines due to chemotherapy-induced tumour cell degradation.
- Drug-related fever: Look for relative eosinophilia.
- Non-infective causes of inflammation: Myocardial infarction, acute stroke, pulmonary embolism and thromboembolism.
- Autoimmune diseases: Vasculitis and paraneoplastic syndromes.

Complications

Low-risk patients with MASCC score ≥21 tend to get serious medical complications at 6 % with an estimated mortality of 1 %. High-risk patients pose a higher tendency towards complications as follows:

- Treatment failure: Suspect fungal, viral, atypical respiratory pathogens and *M. tuberculosis* complex. Antimicrobial resistance is also an emerging cause of static response or treatment failure.
- Antibiotic-associated diarrhoea (*Clostridium difficile*) or toxin-induced diarrhoea by *Staphylococcus aureus*.
- Distant infective emboli and abscess formation.
- Recurrence of cancer.
- SIRS, severe sepsis, septic shock and death.

Prognosis

Mortality: If not treated appropriately within the first 48 h, associated mortality is 50 %. Hospital stay averages between 5 and 14 days (median 11.2 days) for approx. 80 % of the medium to high-risk patients.

Follow-Up

Upon discharge, patient and their carers should be educated about warning signs of FN, given instructions on IV line care and good infection control practises. They should have a list of emergency contact numbers, in the event of need.

Prevention

Time lag between the onset of symptoms and reaching hospital (door to needle time) can have a major impact on the outcome, especially in patients from remote areas or in countries with limited resources [11].

- Prophylactic use of antibiotics and myeloid growth factors and G-CSF is under investigation.
- Infection prevention and control measures [3].
  - Reverse barrier nursing in an isolation room can be considered in vulnerable immunocompromised patients.
  - Strict hand washing by healthcare staff, patients and visitors should be encouraged.
  - Restricted visiting hours can be implemented.
- Promote deep breathing exercises, early mobility and maintain skin integrity.
- Promote good oral hygiene and low-fibre diet to avoid bacterial translocation.

Conclusion

Febrile neutropaenia is a life-threatening emergency and needs urgent attention. It is an inevitable complication following myelosuppressive chemotherapy leading to hospitalisation and the need of broad-spectrum intravenous antibiotics. Prompt recognition, prudent antimicrobial treatment within the golden hour in ED followed by a multidisciplinary management can impact upon the patient outcome.

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Chapter 38
Geriatric Emergencies

Sethu Babu

Key Points

- The clinical characteristics and needs of elderly in the emergency department are quite different than the younger patient.
- Life-endangering diseases can present with atypical features or with subtle symptoms and signs in elderly often leading to a delayed or missed diagnosis.
- Presence of multiple comorbid conditions and cognitive impairment usually complicates the clinical presentations as well as treatment decisions.
- A comprehensive workup including detailed history, physical examination, and liberal investigations and imaging is recommended than a brief goal-directed or symptom-based workup.
- Altered mental status, falls, functional decline, acute coronary syndromes, stroke, infections with or without sepsis, acute abdominal pain and trauma are the common geriatric syndromes in the emergency department.
- Psychosocial and environmental issues are important and necessitate multidisciplinary input to ensure safe and effective disposition of these patients from the emergency department.

Introduction

Chronological age of 65 years or above is accepted as the defining criteria for geriatric patients in most developed countries [1]. This large heterogeneous group is further classified into three subpopulations commonly referred as "young-old"

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_38

[65–74 years], "old" [75–84 years], and "old-old" [85 years and older]. Worldwide, the number of elderly persons is expected to more than double from 841 million people in 2013 to more than 2 billion in 2050 [2]. In United States, patients over the age of 64 years account for 15–18 % of ED visits [3]. Of these, about 35 % requires admission as inpatient, and a significant proportion of this gets admitted to intensive care units [3]. The common geriatric syndromes encountered in the emergency department include altered mental status, functional decline, fall, trauma, acute abdominal pain, infections, acute coronary syndromes, cerbrovascular accidents and exacerbations of chronic respiratory disorders.

There are unique characteristics and special needs which have to be kept in mind while addressing elderly patients in the emergency department. The clinical presentation of geriatric patients is usually complex with more of atypical manifestations: confounding effects of comorbid diseases, super added cognitive dysfunction, polypharmacy and associated adverse drug reactions, psychosocial issues and lack of adequate social support, etc. [4]. Assessment of these issues usually demands a comprehensive approach with detailed clinical and liberal laboratory and imaging evaluations. This is justified in the context that a brief focused evaluation can overlook many life-threatening conditions in these patient group. Moreover, the attending physician should also try to understand the baseline functional status of the patient prior to the presentation as it has got important prognostic implications. Thus, it requires great skill, knowledge, and patience from the part of the attending physician and the health-care team as such to effectively and safely manage this vulnerable patient population.

Approach to Unstable Elderly Patient in Emergency Department

In general, the principles of resuscitation in elderly patients are same as the standard guidelines followed for adult patients. But it is desirable for the emergency physician to speak to the immediate relatives or to the patient himself if possible to see whether there is any advance directive or patient's wishes for end of life care decisions. If present, it has to be respected before taking treatment decisions.

The special characteristics in elderly while assessing airway, breathing, and circulation are summarized in clinical pathway 1.

- Nasal airway or nasogastric tube has to be inserted gently with care as the nasal mucosa is very friable and has a tendency to bleed in elderly patients.
- Always examine the oral cavity in unconscious patients for loose fitting dentures or partly chewed food as they can cause potential airway obstruction and if present has to be removed.
- Bag mask ventilation may be difficult to perform or ineffective in edentulous elderly patients. Hence it is prudent to keep well fitting dentures in situ while bag mask ventilation. But artificial dentures always have to be removed before attempts of intubation.
- Difficulty in extending neck or in opening mouth has to be anticipated while attempting intubation due to degenerative diseases of spine and temporomandibular joints.

- Arterial blood gases are an important adjunct to the clinician as the clinical response to hypoxia, hypercapnia, and acidosis can be blunted in elderly.
- Arterial hypotension (systolic BP <90 mmHg) when present is an ominous sign.
- Apparently "normal" pressures do not rule out shock in elderly as these patients are "notorious" to show features of hypoperfusion even at normal blood pressures. Reduced chronotropic response to hypovolemia in elderly due to comorbid conditions or due to drugs like beta-blockers can also result in underestimation of the serious nature of the illness [5].
- Serial assessment of blood pressures and arterial blood gas examination to see trends in lactate, base excess, and acidosis can identify such potential high-risk candidates early [6].
- Fluid resuscitation should follow in the standard fashion with fluids or blood in an elderly patient who is hemodynamically unstable in the emergency department. But it should be careful with constant monitoring to avoid pulmonary oedema.
- Early blood transfusion should be considered in elderly unstable trauma patient.

Clinical Pathway 1: Approach to an unstable elderly in the emergency department

1. Assessment of airway

- Examine the oral cavity for ill fitting dentures or food particles. Remove them if present.
- Edentulous airway can result in ineffective bag-mask ventilation.
- Well fitting dentures can be kept in place while bag-mask ventilation but has to be removed prior to intubation attempts.
- Anticipate difficulty in extending neck or in opening mouth.

2. Assessing breathing

- Elderly patients are prone to airway obstruction secondary to risk factors like food or ill fitting dentures.
- Arterial blood gas is an important adjunct to clinical examination.

3. Assessing circulation

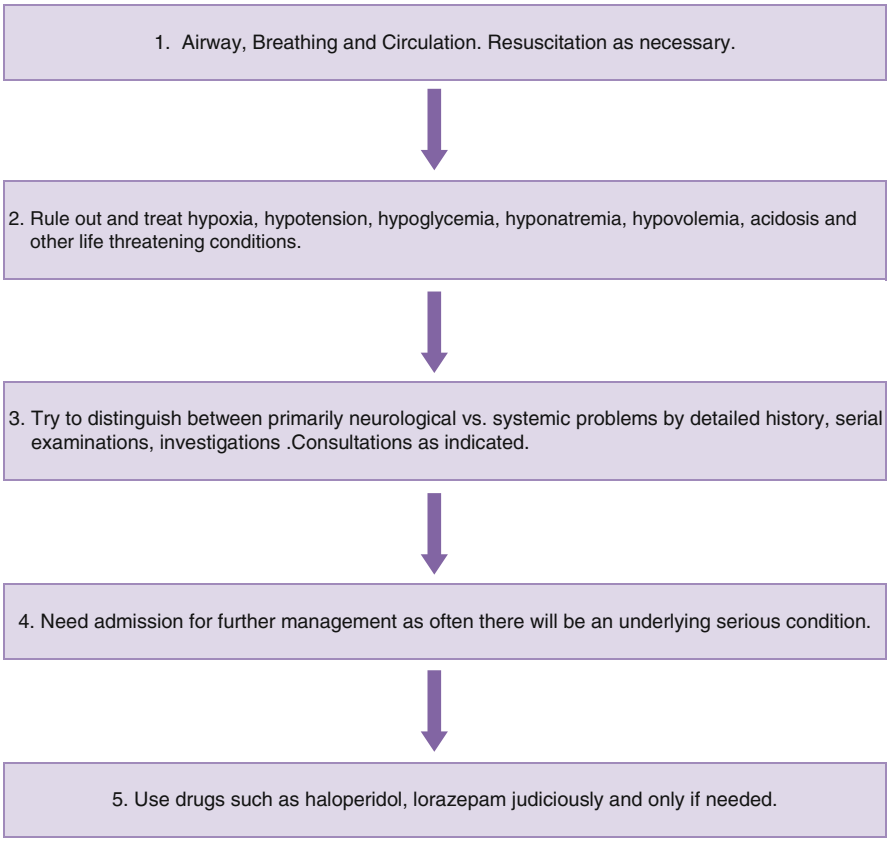
- Arterial hypotension when present is an ominous sign.
- Older patients may show features of hypo-perfusion at 'normal' pressure.
- Keep high index of suspicion for serious conditions even if symptoms are vague or minimal.
- Serial examination of vital parameters is very important to identify high risk candidates.

Common Geriatric Syndromes in Emergency Department

Altered Mental Status

- At least 25 % of elderly patients in the ED have altered mental status [7, 8].
- Delirium is an acute confusional state, and dementia is a chronic confusional state.
- Etiology of delirium is often mutltifactorial but often represents an underlying medical emergency.
- Diagnosis of delirium is clinical and is based on assessment of the level of consciousness and cognition. The confusion assessment method (CAM) is a useful tool for diagnosing delirium at ED [9].
- The important management steps in the emergency department are illustrated in clinical pathway 2.
- The first priority is to address predisposing and precipitating factors like hypovolemia, hypotension, hypoxia, hypoglycemia, hyponatremia, acidosis, etc.
- Often inpatient admission is needed for the management of the underlying illness.
- Drugs like haloperidol or lorazepam may be used in cases of extreme agitation but with caution and at titrating doses.

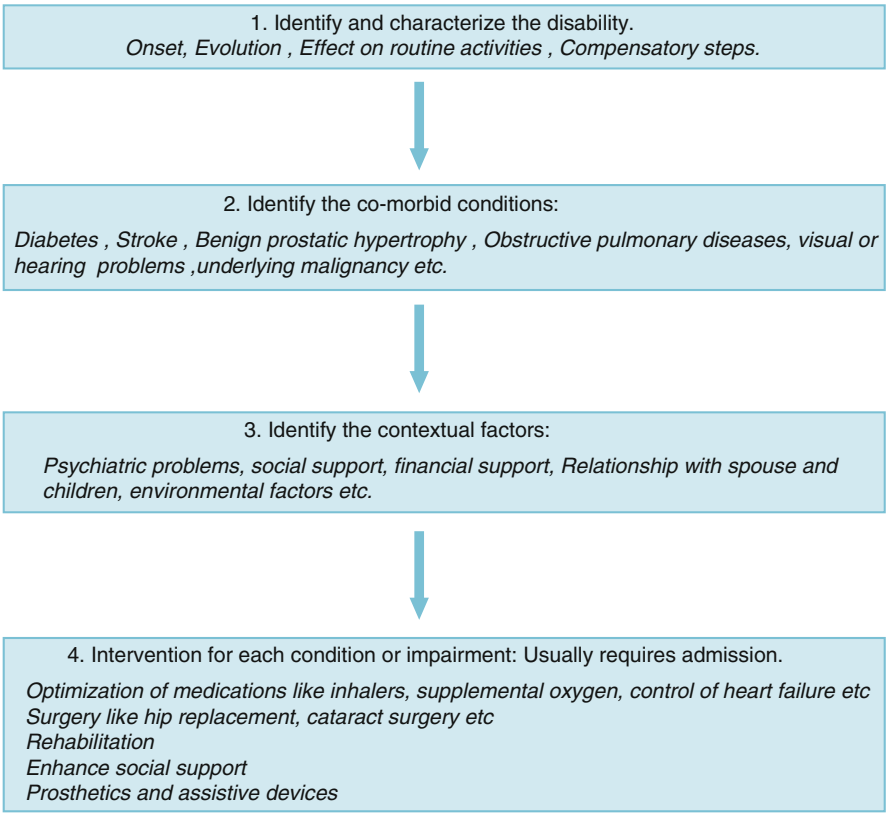
Clinical Pathway 2: Approach to an elderly with altered mental status



Decline in Functional Status

- Functional status reflects how well a person is able to meet his or her own daily needs like feeding oneself, dressing up, getting out of bed, bathing, toileting, etc.
- The attending physician should not misinterpret a decline in functional status as a part of normal aging process.
- Functional status of an elderly patient can be formally assessed with the use of standard scales for basic activities of daily living. Activity of daily living (ADL) is one such tool and is shown in Fig. 38.1.
- New onset functional decline is often precipitated by medical, psychological, or social reasons.
- Patients with unexplained functional decline need admission for evaluation and management.
- Functional decline is an important predictor of further functional decline, repeat ED visits, hospitalization, need for home care or institutionalization, and death [10, 11].
- The general approach to a patient with decline in functional status is illustrated in clinical pathway 3.

Clinical Pathway 3: Approach to an elderly with decline in functional status



1. Feeding oneself	4. Toileting
2. Dressing oneself	5. Getting in and out of bed/chair
3. Bathing	6. Continence

Fig. 38.1 ADL scale

Falls

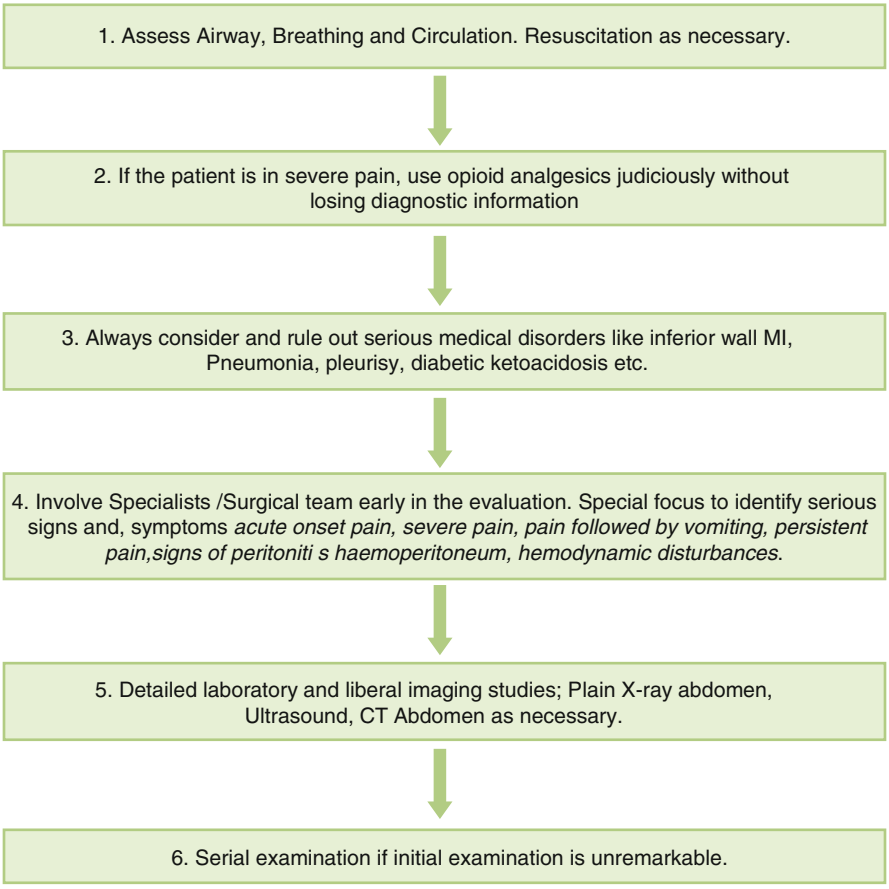
- Falls account for approximately 10 % of emergency visits in elderly [12, 13].
- Falls are the most common cause of fatal as well as nonfatal injuries in geriatric population.
- A fall should be treated as a symptom, and the physician should evaluate the causes and consequences of fall.
- The most common reasons for injurious fall-related ED visits among the elderly were fractures (41.0 %), followed by superficial/contusion injuries (22.6 %) and open wounds (21.4 %) [13].
- Serious injuries associated with fall include hip fracture, rib fracture, subdural hematoma, other serious soft tissue injuries, or head trauma.
- It is important to remember that a fall can signal a sentinel event in an elder person's life triggering a downward spiral of complicating events, finally leading to death.

Acute Abdominal Pain in Elderly

- Acute abdominal pain in elderly usually poses a challenge to the clinician as the symptoms are often nonspecific, abdominal findings are often subtle, and the presence of comorbid conditions can complicate the definitive surgical procedures.
- Common causes of acute abdominal pain in elderly include acute cholecystitis, acute appendicitis, peptic ulcer perforation, mesenteric ischemia, acute pancreatitis, ruptured abdominal aortic aneurysm, bowel obstruction, and diverticular diseases.
- Elderly usually presents with atypical symptoms, often significantly late in the course of the illness.
- It is essential to consider serious medical conditions like inferior myocardial infarction, pneumonia, pleurisy, diabetic ketoacidosis, and pulmonary embolism in all cases of suspected acute abdomen.
- Abdominal tenderness may not be present or poorly localized. Guarding or rebound tenderness might be difficult to appreciate.
- Serial abdominal examination is important as new signs tend to appear with time.

- High-risk features include acute onset of pain, severe pain, pain followed by vomiting, worsening or persistent pain, signs of peritonitis, hemoperitoneum, and hemodynamic disturbances.
- Liberal imaging is the usual protocol with plain x-ray abdomen, abdominal ultrasound, and CT abdomen as necessary.
- Patients with continuing symptoms but with unremarkable laboratory and imaging studies should be observed and serially evaluated as necessary.
- Approach to elderly with abdominal pain is illustrated in clinical pathway 4.

Clinical Pathway 4: Approach to an elderly patient with acute abdominal pain



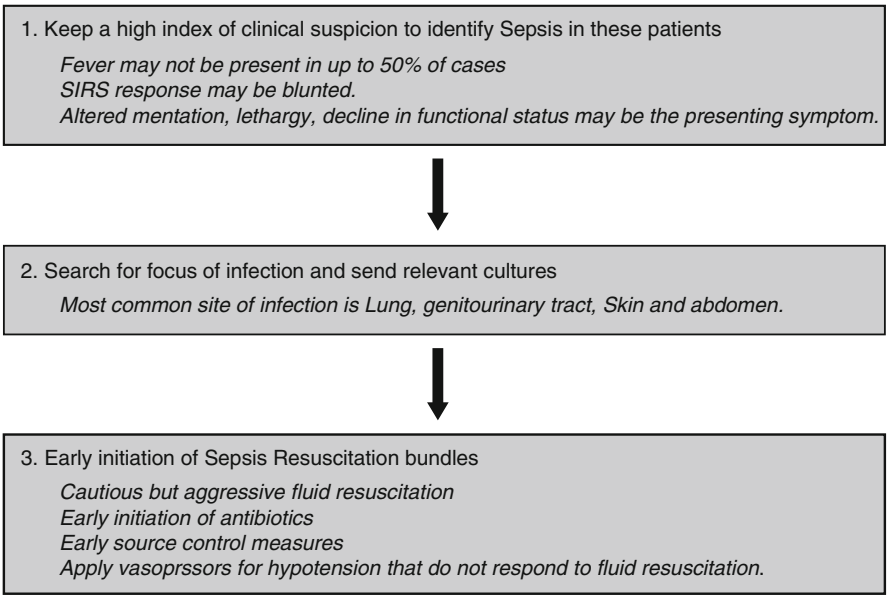
Medication-Related Problems

- Adverse events related to drugs are common in elderly population and are a common cause for ED visits.
- Elderly are more susceptible to serious and fatal adverse drug effects due to polypharmacy, lack of monitoring, nonadherence, use of multiple medications, use of over-the-counter medications, wrong dosage, altered drug metabolism, and propensity for drug interactions.
- The risk factors for serious adverse drug reaction in elderly include "old-old" patient, lean body mass, more than 6 chronic medical illnesses, 9 or more drugs, more than 12 doses per day, and a previous history of adverse drug reaction [18].
- Most commonly encountered problematic drugs include diuretics, NSAIDs, warfarin, digoxin, antidiabetic agents, antiepileptic agents, chemotherapeutic agents, antibiotics, and psychotropic drugs [19].
- Detailed drug history, reviewing prescriptions, and direct verification of current medications may prove to be very helpful strategies while evaluating geriatric patients in the ED.

Infections in Elderly

- Elderly are significantly more prone to infections and its life-threatening complications.
- Presentation of infection can be atypical with lack of fever or localizing features. Sepsis can present with subtle clinical features like lethargy, decline in functional status, or confusion.
- Usual site of infections include the lung, urinary tract, skin, and abdomen.
- High index of suspicion is necessary to early identify the patients with sepsis.
- Management of severe sepsis and septic shock in elderly should follow the standard guidelines used for adults like international surviving sepsis guidelines [14].
- Early initiation of antibiotics and other sepsis resuscitation bundles is found to improve mortality and functional recovery [15–17].
- The salient points in the clinical approach to an elderly with suspected sepsis are summarized in clinical pathway 5.

Clinical Pathway 5: Approach to an elderly with suspected sepsis in the ED



Elder Abuse and Neglect

- Elder abuse is defined a single or repeated act or lack of appropriate action, occurring within any relationship where there is an expectation of trust which causes harm or distress to an older person [20].
- It can result either from an act of commission or of omission and may present as physical abuse, psychological abuse, sexual abuse, care giver neglect, self-neglect, and financial exploitation.
- It should be suspected in patients who present with unexplained or multiple injuries in various stages of evolution.

Trauma in Elderly

- Trauma in elderly is associated with increased mortality and complications compared to younger population.
- Elderly are prone to significant trauma injury following a relatively trivial mechanism.
- Physiological response to trauma in elderly is different from that of younger population and is often subtle or atypical, leading to delayed recognition of shock or serious injuries.

- Under triage is associated with increased mortality rate in elderly trauma patient.
- The primary survey in elderly trauma patient is same as for any other trauma patient.
- The secondary survey in elderly trauma patient should emphasize on specific issues as described below:
  - The current medications which can influence evaluation and treatment like antiplatelets, beta-blockers, anticoagulants, etc.
  - Consider and rule out common acute nontraumatic conditions that can complicate the patient's presentation like acute coronary syndrome, dehydration, hypovolemia, hyper- or hypoglycemia, acute renal failure, dyselectrolytemia, etc.
  - Laboratory assessment should particularly focus to detect tissue hypoperfusion [blood gas, serum lactate, and base deficit], associated organ dysfunction [blood urea, serum creatinine], and coagulation status [platelet count, PT/APTT/INR, etc.].
  - Initial imaging should include liberal use of computed tomography (CT) scanning for blunt injury. The liberal use of CT scan imaging has become controversial because of concerns of radiation exposure and cost. But considering the benefits, imaging should include all CT scans needed to rule out injury in appropriate areas at risk.
- Details regarding specific patterns of injury are beyond the scope of this chapter, and readers are instructed to read the session on trauma.

Disposition

Large majority of elderly presents to emergency department with Non specific complaints. More than 60 % of them will be having an underlying serious medical illness. It may be difficult to diagnose it at the initial assessment despite a detailed attempt. Reassessing the patient after a period of observation is an important and useful step that enhances patient safety and outcome. Developing an appropriate disposition plan which incorporates a multidisciplinary input and strategic steps like observation periods is essential for safe disposition of elderly patients in the emergency department.

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Chapter 39
Near Hanging

T.V. Ramakrishnan

Key Points
- All patients presenting with near hanging, irrespective of their initial presentation such as severe respiratory distress and/or severe neurological deficits, require aggressive resuscitation and management, as they usually recover completely.
- C-spine stabilization and airway management are of utmost importance.
- Evaluate for associated injuries.
- All survivors require psychiatric support and aftercare.

Introduction

External pressure exerted by a ligature to the neck in a person who is partially or wholly suspended causing death is defined as hanging. A situation in which an individual survives hanging long enough to reach the medical center is referred to as near hanging [1, 2].

The body is suspended by its neck that causes strangulation. A complete hanging is described as one in which the body does not touch the ground, and the whole weight of the victim is suspended at the neck. If some part of the victim's body is in contact with the ground, it is described as incomplete hanging.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_39

In India, hanging is the most common method chosen to attempt suicide among adults. In the United States, hanging is the second most common form of suicide, accounting for 23 % of suicides in the year 2007, with more than half between the age group of 15 and 44 years [3], and majority of the victims are males. Among hanging victims, history of drug or alcohol abuse is frequent, as is psychiatric illness [4]. Even though hanging is the primary cause of suicidal deaths, especially among young male adults, there are very few studies on the injury patterns and outcomes of near-hanging victims and hardly any statistics available on its epidemiology. Assessment of the airway with C-spine immobilization is a crucial component of prehospital care.

Pathophysiology

- The jugular veins in the neck are relatively superficial and unprotected, thus rendering them vulnerable to compression by external forces.
- The ligature causes venous outflow obstruction in the brain causing stagnant hypoxia and loss of consciousness within 15 s.
- This results in decreased muscle tone which allows compression by external force to become more tightened, leading to brain injury, due to complete arterial occlusion resulting in death.
- Significant amount of energy is required externally to compress the airway structures than the vascular structures.
- Vagal reflexes like severe bradycardia and cardiac arrest are caused by external pressure on the carotid body.
- Pulmonary sequelae like aspiration pneumonitis, pulmonary oedema, and adult respiratory distress syndrome (ARDS) are commonly seen in near-hanging survivors.

Clinical Features

- Depending on the mechanism of hanging, the presenting signs and symptoms vary. Clinical features include evidence of ligature around the neck as hyperemia, abrasion, or ecchymosis (Fig. 39.1).
- Patients are usually agitated due to cerebral anoxia, resulting in cerebral oedema. They require restraint which is achieved with muscle relaxant and intubation, thus preventing further hypoxic insult to the brain.
- Tardieu's spots may be seen. Described by Ambroise Tardieu – a French forensic physician – these are petechial hemorrhages on mucous membranes, conjunctiva, and over the skin, cephalad to the obstruction. When the ligature tightens, it causes a rise in venous pressure and results in congestion and capillary rupture. The same mechanism leads to subconjunctival hemorrhages [5] (Fig. 39.2).

- Fractures of the cartilaginous and bony structures in the neck may lead to airway obstruction. Fractures of the cricoid and hyoid may present with subcutaneous air and/or bony crepitus over the larynx. This injury leads to oedema of the neck, which predisposes the patient to airway obstruction. Therefore, it is prudent to plan for early elective intubation, if indicated.
- Patients can present with dyspnea, stridor, dysphonia, dysphagia, hemoptysis, and odynophagia.
- Pulmonary oedema can be due to two reasons – (a) massive discharge of catecholamines from the brain can produce pulmonary oedema due to intense vasoconstriction of the vasculature causing fluid to be shifted to the lungs and (b) negative intrathoracic pressure produced when the patient tries to inspire forcefully through a closed glottis when the airway is obstructed, with the same resultant effect [5].
- Blunt vascular injury occurs due to compression of the common carotid artery against the transverse process of the fourth to sixth cervical vertebrae. This could

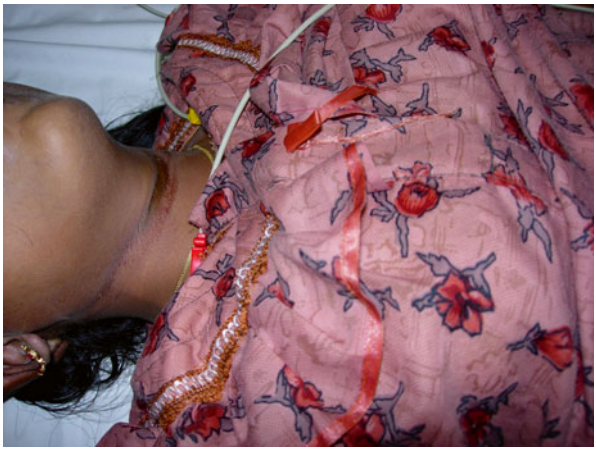

Fig. 39.1 Ligature mark

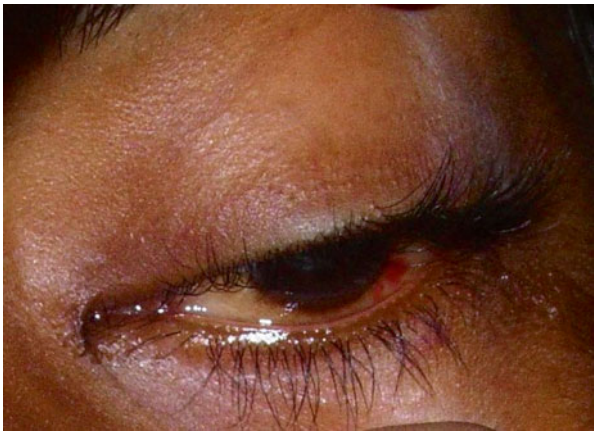

Fig. 39.2 Subconjunctival hemorrhage

cause disruption of the tunica intima or media, resulting in hemorrhage. This complication is usually delayed and remains undiagnosed in the early phases of assessment.

Investigations: Laboratory

- Arterial blood gas (ABG) analysis should be preferably obtained before intubation, if possible. This would serve as a baseline during future ventilator management.

Imaging

- Plain soft-tissue radiographs of the neck are indicated to identify laryngotracheal injuries through findings such as tracheal deviation (either from oedema or hemorrhage), subcutaneous emphysema, or fracture of hyoid bone.
- Chest X-ray is done after intubation to check the position of the tube and to identify evidence of aspiration.
- CT brain is indicated, if the patient presents with altered sensorium.
- CT scan of the neck helps to detect fractures and soft-tissue abnormalities which are not detected in an X-ray.

Treatment of Near Hanging

- Even though C-spine injuries are not commonly encountered in suicidal near hanging, all precautions to protect the C-spine prior to intubation must be undertaken.
- Intubation is indicated in patients with stridor, low GCS, and respiratory distress.
- In any patient with airway deterioration and unsuccessful endotracheal intubation, cricothyroidotomy should be performed. If cricothyroidotomy is rendered difficult due to associated neck injuries, percutaneous translaryngeal ventilation is used to oxygenate the patient temporarily until definitive airway is obtained.
- Intravenous (IV) access is obtained. Fluid resuscitation performed judiciously [6].
- Patients are prone for aspiration when they present with low GCS.
- Near-hanging patient must be monitored for cardiac arrhythmias.
- In patients with laryngeal oedema, consider administration of steroids [7].
- Administer antibiotics when there is evidence of neck injury with subcutaneous emphysema because the deeper tissues of the neck can get infected [7].

- In patients with raised intracranial pressure or cerebral oedema, supportive care is provided by elevating the head end of the bed, ensuring adequate oxygenation and cerebral perfusion, and preventing secondary neurologic injury [7].
- In order to prevent further insult from cerebral ischemia and also to treat from hanging-induced seizures, phenytoin should be administered [7].
- Mannitol can precipitate pulmonary oedema [8] and its role is unclear. It will be prudent to rule out pulmonary oedema before considering mannitol for the treatment of raised intracranial pressure.
- If the intent of near hanging is suicidal, consider evaluating the patient for ingestions.

Near-hanging survivors are prone to depression and violent behavior and usually manifest personality disorders. Psychiatric consultation and follow-up are mandatory.

Complications

- Respiratory complications: In near-hanging patients, ARDS and aspiration pneumonia may develop, complicate the clinical course, and are the primary cause of delayed mortality.
- Stenosis of the trachea and scarring of neck tissue.
- Neurologic sequelae: In near-hanging patients, a wide array of complications such as transient hemiplegia, seizures, muscle spasms, and central cord syndrome are observed [6]. Short-term autonomic dysfunction, long-term paraplegia, and quadriplegia are the complications noted due to spinal cord injuries.
- Psychiatric disturbances

Prognosis

- The prognosis is poor in patients who are in cardiac arrest on arrival to the ED.
- However, GCS on arrival is not a reliable of poor prognosis, since there can be dramatic improvement in altered mental status, with the commencement of oxygen therapy and assisted ventilation.

Summary

- Patients who arrive at the ED with signs of life must be treated aggressively.
- Always protect the C-spine.

- Intubate and ventilate patients with GCS <8.
- Complications such as pulmonary oedema and aspiration pneumonia need to be identified and treated.
- CT scan is mandatory in patients with altered sensorium.
- Psychiatric assessment and review are mandatory.

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Chapter 40
Oncological Emergencies

Sameer Rathi

Key Points

- Oncotherapy patients who present to the emergency department are experiencing significant disease conditions; however, frivolous they may appear to be, unless proven otherwise.
- Early fluid resuscitation, rapid empirical diagnosis, blood and urine cultures and early commencement of broad-spectrum antibiotics are primary interventions required in the emergency department.
- Spinal cord compression should be ruled out in chemotherapy patients with back pain.
- Superior vena cava syndrome is rarely life threatening and requires tissue diagnosis of malignancy, prior to treatment initiation.
- Neoplastic pericardial effusion can arise insidiously, and bedside echocardiography is the modality of choice for establishing the diagnosis.
- Hypercalcaemia due to malignancy is associated with a poor prognosis.

Introduction

Patients with malignancy on various modality of treatment – post surgery, chemotherapy and radiotherapy – may present to the emergency department (ED) for various reasons related to their disease condition. These malignancy-related

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_40

emergencies can be collectively called as oncological emergencies [1–3]. This chapter focuses on few of the common oncological emergencies, excluding febrile neutropenia, which is featured as a separate chapter in this book.

Tumour Lysis Syndrome

Introduction

- Tumour lysis syndrome is a metabolic disturbance caused by rapid destruction of tumour cells and release of intracellular ions (potassium, phosphate, calcium), metabolic by-products (uric acid from nucleic acid metabolism) and intracellular proteins into the systemic circulation [1–3].
- It is most commonly seen with treatment-responsive haematological malignancy.
- With advances in chemotherapy, it is also occasionally seen with treatment of solid tumours [4].

Clinical Presentation

Clinical presentation is the result of biochemical abnormalities like hyperuricaemia, hyperkalemia, hyperphosphataemia and hypocalcaemia (secondary to hyperphosphataemia), affecting renal, cardiac and nervous systems.

- Acute renal failure secondary to deposition of urate crystals in the renal tubules.
- Intracellular protein breakdown releases phosphate in the systemic circulation and lowers serum calcium levels by formation of a calcium phosphate precipitate, which deposits in renal glomeruli and tubules, further contributing to renal impairment [5].
- Hypocalcaemia will clinically manifest as muscle spasms, tetany, seizures and rarely cardiac arrhythmias [5].
- Hypovolaemia and pre-existing renal impairment further worsen the clinical syndrome.
- Hyperkalemia along with hypocalcaemia may result in life-threatening ventricular dysrhythmias [4].

Management

As for any illness, in tumour lysis syndrome, prevention is better than cure.

- Aggressive hydration and allopurinol (xanthine oxidase inhibitor) 300–600 mg/day prophylaxis should be started in high-risk patients before treatment initiation [6].

- Rapid hydration will improve glomerular filtration and prevent precipitation of urate and calcium phosphate crystals in renal tubules and also correct electrolyte disturbances [7].
- Hyperuricaemia should be treated with allopurinol 600–900 mg/day and rasburicase (recombinant urate oxidase) 0.2 mg/kg/day [6].
- Alkalization of urine (pH >7) enhances excretion of uric acid [7].
- Hyperkalemia is a life-threatening emergency and should be treated with beta-adrenergic agonist nebulisation, sodium bicarbonate, glucose insulin drip and sodium-potassium exchange resin. Intravenous calcium is advocated only in case of cardiac dysrhythmias and seizures.
- Hemodialysis is advised if medical measures fail or patient is unstable and needs rapid correction of electrolyte disturbance. Repeat dialysis may be required in many cases.
- Prognosis is poor with renal failure.

Hypercalcaemia

Introduction

- Incidence of hypercalcaemia in cancer patients is 10–20 %.
- Severe hypercalcaemia requiring treatment is 1–3 %.
- Often seen in advanced stage of disease and has poor prognosis.
- Hypercalcaemia can be defined as corrected serum calcium >2.60 mmol/L [8].
- The most common mechanism is production of parathyroid hormone-related protein (PTH-RP) that binds to parathyroid hormone receptors, thereby mobilizing calcium from bones and increasing renal reabsorption of calcium (80 %).
- Hypercalcaemia resulting from increased osteoclastic activity is seen with bone metastases from lung and breast cancer and multiple myelomas (20 %).
- Rarely tumour production of parathyroid hormone (PTH) or vitamin D can cause hypercalcaemia (<1 %) [8, 9].

Clinical Presentation

- Clinical symptoms depend on the rate of development of hypercalcaemia rather than actual serum calcium levels.
- Majority of patients with moderate hypercalcaemia are asymptomatic but are dehydrated.
- CNS symptoms range from fatigue, lethargy, somnolence, and psychosis to coma [10].
- GI symptoms like nausea, vomiting, constipation, ileus, weight loss, anorexia, gastroduodenal ulcer and rarely pancreatitis may be seen.

- Polydipsia, polyuria, dehydration, nephrocalcinosis, and nephrolithiasis may be seen.
- Cardiovascular involvement causes bradycardia and atrial and ventricular arrhythmias [8–10].

Management

- Routine blood investigations should include serum calcium, phosphate, urea, creatinine and other electrolytes.
- ECG may show prolonged PR, short QT interval, bradycardia, and widened T wave.
- Hydration with isotonic saline is mainstay of initial management as most of patients are dehydrated and have a negative fluid balance of at least 4 L. Rehydration is needed in mild asymptomatic cases (Ca^{++} <3 mmol/L) [8].
- Furosemide 40–60 mg may be useful if diuresis is inadequate.
- Pharmacological treatment of hypercalcaemia includes bisphosphonates, corticosteroids and calcitonin.
  - Bisphosphonates inhibit osteoclast activity and should not be given till patient is adequately hydrated and has a good urine output.

    Pamidronate (90 mg over 4–24 h) slow IV infusion
    Zoledronic acid (1 mg/min) slow IV infusion
    Etidronate by slow IV infusion
  - Gallium nitrate, mithramycin, and plicamycin are replaced by bisphosphonates due to their toxicity [9, 10].
  - Corticosteroids, e.g. prednisolone 40–100 mg IV or PO, decrease cytokine release and intestinal calcium absorption especially in lymphomas and myelomas.
  - Calcitonin 4–6 U/kg s.c. will reduce serum calcium by inhibiting osteoclast and calciuric effect.
- Denosumab, an anti-RANKL monoclonal antibody, is used to treat bone metastases [8].
- Haemodialysis is indicated for those who present with severe neurological symptoms and renal failure or cannot tolerate hydration.

Superior Vena Cava Syndrome (SVC Syndrome)

Introduction

- Clinical syndrome secondary to the effects of elevated venous pressure in the upper body resulting from obstruction of blood flow through SVC, caused by compression, infiltration or thrombosis [11, 12].
- Malignant mass causing external compression is the most common cause, accounting 60–80 % of cases.

- Lung cancer (esp. non-small cell carcinoma) and lymphoma (esp. high-grade NHL) are the most common causes along with metastatic lesions.
- SVC syndrome as the initial presenting sign of cancer is suggestive of poor prognosis [1–3].
- Benign causes contributing one third of cases may be due to intravascular thrombosis secondary to the frequent use of intravascular devices and catheters.

Clinical Presentation

- Symptoms are secondary to venous obstruction, and severity of symptoms depends on the rate and degree of obstruction.
- SVC syndrome is rarely an emergency (except when neurological symptoms develop or are associated with respiratory compromise), as symptoms develop over a period of time, giving enough time for collateral vessel formation.
- Facial swelling, periorbital oedema, dyspnoea and arm swelling are usually seen.
- Thoracic and neck vein distention (Fig. 40.1), facial oedema (Fig. 40.2), tachypnoea, dysphagia, cough, hoarseness of voice, plethora of the face, oedema of the upper extremities and cyanosis are seen in extreme cases.

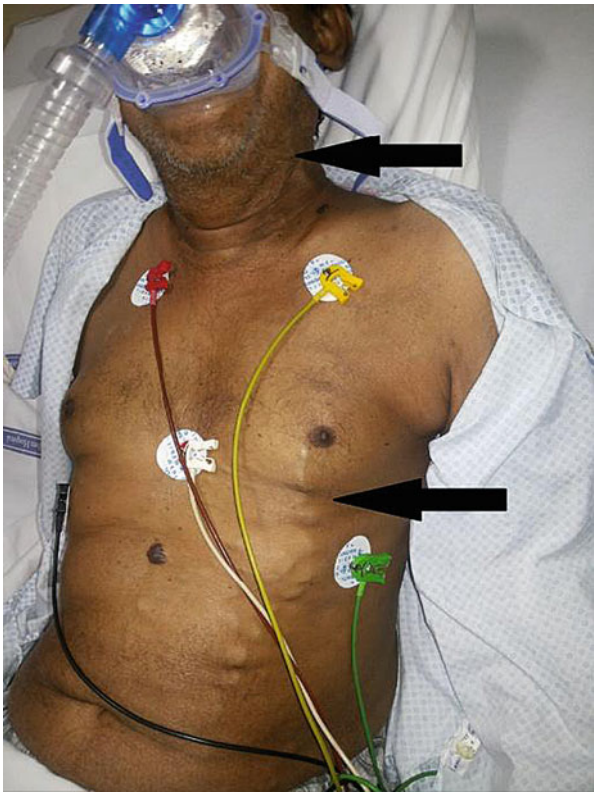

Fig. 40.1 Distended neck and anterior abdominal wall veins

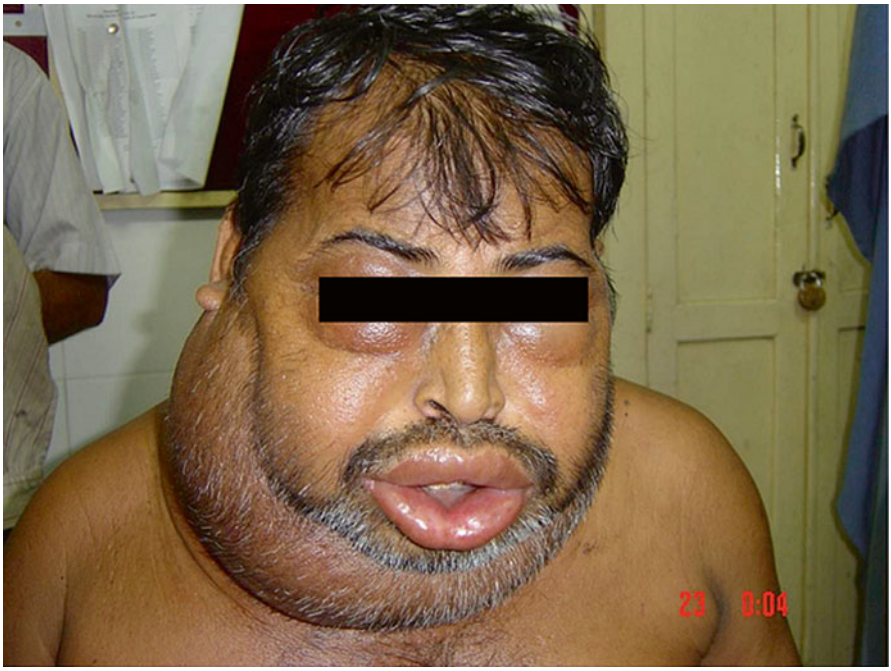

Fig. 40.2 Facial oedema (Courtesy: Prof. Suresh S. David, Pushpagiri Medical College, Tiruvalla 689101 India)

- CNS symptoms, visual changes, dizziness, confusion, seizures and coma are secondary to increased intracranial pressure and cerebral oedema.
- SVC syndrome may present along with spinal cord compression and is called Rubin's syndrome.

Management

- Pericardial tamponade and heart failure should be ruled out.
- Chest radiograph may show mediastinal mass and pleural effusion.
- CT chest with intravascular contrast is the investigation of choice and will help in assessing patency of SVC [12].
- Venography is not indicated routinely.
- Biopsy for confirmation of a malignant cause is indicated before initiating radiotherapy and chemotherapy [11, 12].

Supportive Treatment

- Head elevation to decrease venous pressure.
- Supplemental oxygen, as indicated.
- Corticosteroids and loop diuretics are commonly used, but there is no proven evidence of their benefit.

Definitive Treatment

- Planned as per histological diagnosis.
- Radiation therapy and stent placement in SVC are options available in case of life-threatening emergency [11].
- Chemotherapy produces complete relief of symptoms in 80 % of patients with non-Hodgkin's lymphoma and small cell lung cancer and 40 % in those with non-small cell lung cancer [11, 12].
- Surgical bypass grafting is an alternative for stenting in chemoresistant and radioresistant cancers.
- Removal of an inciting intravascular object has to be considered, and prophylactic anticoagulation in these cases may have some role.
- Prognosis of patient with SVC syndrome depends on underlying tumour type.
- Patients of lymphoma have better survival rates as compared to bronchogenic carcinoma.
- Median life expectancy is 6–12 months.

Malignant Spinal Cord Compression Syndrome (MSCC)

Introduction

- MSCC is compression of the spinal cord, or cauda equina, by direct pressure and/or vertebral collapse, secondary to metastatic spread of disease, leading to neurological deficit and paralysis.
- With early and prompt management, the patient can retain good quality of life independently or with minimum debility.
- The most common cause of MSCC is metastasis to vertebrae from solid organ tumours.
- Patients are pre-diagnosed with malignancy; rarely, it can be the first presentation of cancer.

- Thoracic vertebrae (68 %) are most commonly involved. Cervical and lumbosacral presentations are seen in 15 % and 19 % of cases, respectively.

Clinical Presentation

- The most common complaint is progressive back pain – radicular – usually in the dorsal spine, worse in supine position, and aggravated by straining (e.g. coughing, sneezing or at defecation).
- Muscle weakness in proximal group of limbs, sensory loss.
- Bladder, bowel and/or erectile dysfunction may be present.
- Localised spinal tenderness on palpation.

Management

- MRI of the whole spine is the diagnostic modality of choice.
- CT with or without myelography, if MRI is contraindicated or inaccessible.
- Plain radiograph can locate a tumour in 70–90 % cases but is less useful.
- Routine labs, blood counts and biochemistry.
- Manual spine stabilization to prevent further injury.
- Early involvement of specialists in oncology, radiotherapy and spinal surgery.
- Appropriate analgesia, if needed, opioids.
- Corticosteroids to be considered in ED; dexamethasone 16 mg PO or intravenous (IV) stat followed by 8 mg BD (IV or PO) with proton pump inhibitor cover [8].
- Radiotherapy is beneficial in radiosensitive tumours. MSCC is a radiotherapy emergency.
- Prognosis depends upon pretreatment neurological status of the patient.
- Surgery indicated only if diagnosis is doubtful; tissue diagnosis is required or spine stabilization is essential.
- Patients' functional status and likely prognosis should be considered before surgery.

Malignant Pericardial Tamponade

Introduction

- Malignant pericardial effusions occur in up to 20 % of cancer patients but are frequently asymptomatic.
- Most commonly, it is seen in lymphoma and lung, breast and oesophageal cancers.

- It can also develop as a complication of radiotherapy or chemotherapy.
- Pericardial tamponade is a result of increasing fluid accumulation in the pericardium, leading to rise of intracardiac pressure – interfering with ventricular expansion and filling, reduced stroke volume and cardiac output – and shock, resulting in death if not treated.

Clinical Presentation

- Dyspnoea, orthopnoea, chest pain, dysphagia, hoarseness of voice and hiccups are presenting symptoms.
- The severity of symptoms depends on the rate and volume of fluid accumulation.
- Generally, cardiovascular collapse occurs when the normal amount of pericardial fluid (15–50 ml) increases rapidly to >200 ml or more and then slowly accumulates further.
- Large effusions developing gradually are well tolerated and are asymptomatic.
- Muffled heart sounds, raised jugular venous pressure and hypotension (Beck's triad).
- Pulsus paradoxus and Kussmaul's sign along with tachycardia and reduced pulse pressure may be seen [13].

Management

- ECG – low-voltage pattern and occasionally electrical alternans.
- Enlarged cardiac silhouette with clear lung fields ("water bottle" appearance of the heart) may be seen on chest radiography.
- Echocardiography is the gold standard and can give information regarding fluid quantity and cardiac function.
- CT thorax may be considered.
- Asymptomatic patients do not require specific treatment.
- Symptomatic patients must undergo pericardiocentesis ideally under ultrasonography guidance. Emergency percutaneous pericardiocentesis in ED should only be considered for patients with haemodynamic compromise [14].
- Elective treatment options include percutaneous pericardiocentesis by a cardiologist, pericardial sclerosis, subxiphoid pericardial window, pericardiectomy or pericardiotomy by thoracotomy or video-assisted thoracoscopy.
- Catheter drainage is recommended for large effusion and to prevent reaccumulation of fluid [14].
- Prognosis of patients with malignant pericardial tamponade depends on the underlying type and extent of disease.

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Chapter 41
Pituitary and Parathyroid Disorders

Anoop James George and Suresh S. David

Pituitary Disorders

Keynotes
- Pituitary failure occurs due to multiple reasons including genetic abnormalities, trauma, infections, empty sella syndrome, Sheehan's syndrome, etc.
- The functioning of the hormones depends on the integrity of hypothalamo-pituitary axis.
- Management of pituitary failure is by replacement therapy of the deficient hormones.

Introduction

- The pituitary gland derives its name from the Greek word *ptuo* and Latin word *pituita*, meaning phlegm which reflects its nasopharyngeal origin.
- It is situated in the sella turcica of the middle cranial fossa. The pituitary gland is formed by the anterior lobe, the posterior lobe and a vestigial intermediate lobe [1].
- The intermediate lobe synthesises and secretes melanocyte-stimulating hormone.
- Pituitary gland, along with hypothalamus, orchestrates the functions of endocrine glands like thyroid, adrenal, gonads and breast [2].
- Preservation of the hypothalamo-pituitary unit is critical for integrating the functions of pituitary gland which include fertility and sexual development, lin-

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_41

ear and organ growth, lactation, stress responses, thermal regulation and carbohydrate and mineral metabolism.
- Disorders of pituitary gland arises from either hyperfunctioning or hypofunctioning of the gland, either due to a mass or other structural abnormalities (Table 41.1).

Pituitary Mass

- They often present insidiously, progressing over years or decades.
- An expanding pituitary mass causes erosion of the bony confinements and invades the surrounding soft tissues, causing both suprasellar and parasellar compression leading to local and general manifestations.
- The most common manifestation of a pituitary mass, including an adenoma, is headache. This can result either from the stretching of the dural plates in case of intrasellar tumours or compression of the surrounding structures in case of suprasellar tumours [3].
- Severity of headache does not correlate with the size of the adenoma or the presence of suprasellar extension.
- Pituitary masses can manifest with haemorrhage and infarction in conditions like [4]:
  - Pregnancy.
  - Pituitary tumours.
  - Hypotensive episode in elderly patients with unsuspected pituitary tumours.
- Rarely, they manifest with CSF leak, which can predispose to meningitis.
- Pituitary masses, including adenomas, are often associated with compression of surrounding healthy tissue and resultant hypopituitarism. It can also occur due to compression of the hypothalamo-pituitary stalk.

Table 41.1 Hormones released from anterior pituitary gland and their actions

Cells	Hormone produced	Target	Actions	Disorders
Corticotroph	ACTH	Adrenal cortex	Glucocorticoid synthesis Cell homeostasis	Cushing's disease
Somatotroph	GH	Bone and muscles	Linear and organ growth and development	Acromegaly/gigantism Dwarfism
Lactotroph	Prolactin	Mammary glands	Lactation	Amenorrhoea Galactorrhoea Sexual dysfunction
Thyrotroph	TSH	Thyroid gland	Thyroid hormones secretion, thermogenesis, protein metabolism	Hypo-/hyperthyroidism
Gonadotroph	LH, FSH	Gonads	Regulates ovulation and spermatogenesis	Hypogonadism Infertility

- Pituitary masses may undergo silent infarction, leading to development of a partial or totally empty pituitary sella. The pituitary reserve may however be normal, as the surrounding rim of pituitary tissue is fully functional.
- Pituitary tumour transforming gene (PTTG) has shown to be highly abundant in all pituitary tumour types, especially prolactinomas [5].

Pituitary Adenomas

- Account for 15 % of all intracranial neoplasms and 90 % of all sellar masses [6].
- They are usually benign, monoclonal and autonomous tumours, leading to increased expression of a single pituitary hormone. They usually have a slow doubling time and rarely resolve spontaneously [7].
- They also occur with certain genetic syndromes like Carney's syndrome, McCune-Albright syndrome, MEN 1 syndrome and familial acromegaly.
- The diagnostic challenge is to effectively distinguish a pituitary adenoma from other parasellar masses, as the management and prognosis of pituitary adenomas differ markedly from other non-pituitary masses (Table 41.2).
- Microadenomas are generally less than 10 mm in diameter. They are often confined to the sella (intrasellar).
- Macroadenomas are greater than 10 mm in diameter. They usually extend beyond the confinements of the sella and impinge upon adjacent sellar structures (suprasellar).

Box 41.1: Aetiology for Pituitary Disorders
- Hereditary conditions
- Infections
- Inflammations
- Tumours
- Trauma
- Structural anomalies
- Drugs
- Nutrition and chronic illness

Table 41.2 Effects of an expanding pituitary mass [8, 9]

Local effects	General effects
Bitemporal hemianopsia; scotoma	Growth failure
Diplopia; ophthalmoplegia; ptosis	Headache; seizures
Anosmia	Reduced or altered appetite, thirst and sleep
Loss of visual acuity	Obesity: diabetes insipidus
Optic atrophy; pupillary abnormality	Thermal dysregulation; ANS dysfunctions
Visual hallucinations	Dementia; personality disorders

Table 41.3 Pituitary disorders and their relevant screening tests

Disorder	Screening test
Prolactinoma	Serum prolactin levels
Acromegaly	IGF-I (age- and gender-matched controls)
	OGTT with serial GH measurements obtained at 0, 30 and 60 min
Cushing's disease	24-h urinary free cortisol levels Dexamethasone suppression test ACTH assay

Evaluation of a Pituitary Mass

- The initial evaluation should be done to rule out a functional pituitary mass as 90 % of pituitary tumours are adenomas. The screening for functional pituitary adenoma includes the investigations listed (Table 41.3).
- Magnetic resonance imaging (MRI) is the investigation of choice to study pituitary tumours. Microadenomas appear as hypodense areas as compared to the normal gland after enhancement with Gadolinium [10].
- Mass effects of an expanding pituitary mass on the adjacent structures can also be visualised on an MRI.
- The posterior pituitary lobe exhibits a discrete bright spot of high signal intensity on T1-weighted images, which may be absent in posterior pituitary lesions [11].
- A CT scan may help in visualising the bony structures including the sellar floor and its erosion by an expanding mass. Pituitary CT scan mainly aids in the identification of haemorrhagic lesions, metastatic deposits and evidence of calcification.
- Receptor imaging techniques like single-photon emission CT (SPECT) can be helpful in identifying tumours, but its use is limited as normal tissues are also identified.
- I-iodobenzamide single-photon emission scanning uses radiolabelled D2 receptor antagonist which helps in imaging prolactinomas [12].
- Neuro-ophthalmic evaluation is also often required as most persons present with visual abnormalities. They also help in pretreatment assessment of visual status and also in identifying recurrence of mass.

Management

- No interventions are required in asymptomatic cases unless a possible expansion and compression of the adjacent structures is anticipated. The main goals of treating a pituitary tumour are:
  - Relieve local effects of compression.
  - Correct hormone hypo-/hypersecretion.
  - Maintain pituitary trophic function.
- The management of symptomatic pituitary tumours includes surgical, medical or radiotherapeutic interventions.

- Surgical approach is often performed in cases of pituitary tumours causing central compressive mass effects or for removal of a hypersecreting functional tumour. Transsphenoidal resection is the most preferred technique in resecting anterior pituitary tumours.
- Medical approach mainly aims at antagonising the receptors expressed by the tumour cells using targeted ligands, thus suppressing the hypersecretion of hormones.
- Radiation is commonly indicated after resection of a potentially recurring or inadequately resected pituitary mass, such as nonfunctioning pituitary adenoma, craniopharyngioma or chordoma.

Pituitary Failure

- Failure or impaired synthesis of one or more of anterior pituitary hormones can result due to multiple conditions (Box 41.1).
- The order of diminished trophic hormone reserve function by pituitary compression usually follows the order GH > FSH > LH > TSH > ACTH. The corticotroph cell is usually the last cell to lose function (Table 41.4).
- Prolactin deficiency is very rare, except in cases of complete pituitary destruction or genetic syndromes.
- The clinical manifestations depend on which hormones are deficient.

Table 41.4 Evaluation of anterior pituitary function

Hormone deficiency	Test to assess function	Normal outcome
Adrenocorticotrophic hormone(ACTH)	ACTH stimulation test	Peak cortisol ≥20 μg/dL
	Insulin tolerance test	Peak cortisol response >18 μg/dL
	CRH stimulation test	Peak ACTH ≥2–4-fold
Thyroid-stimulating hormone (TSH)	TRH stimulation test	Peak TSH ≥2.5-fold or Total T3 increases ≥5–6 mU/L
Prolactin (PRL)	Serum prolactin levels	PRL ≥2.5-fold
Growth hormone (GH)	Insulin tolerance test	GH peak >3 μg/L
Luteinising hormone (LH) and follicular cell-stimulating hormone (FSH)	GnRH stimulation test	FSH 1.5–2-fold, or by 2 IU/L
	Serum testosterone	LH ≥2–3-fold, or by 10 IU/L

Adapted from Williams Textbook of Endocrinology 11th edition, Tables 8-35

Table 41.5 Hormone replacement therapy for adult hypopituitarism

Hormone deficient	Replacement therapy	
Adrenocorticotropic hormone	Hydrocortisone 10–20 mg daily in divided doses	
Growth hormone	Somatotropin 0.2–1.0 mg SC daily	
Thyroid-stimulating hormone	l-Thyroxine 0.05–0.2 mg daily according to T4 levels	
Vasopressin	Intranasal desmopressin 5–20 μg twice daily	
	Oral DDAVP 300–600 μg daily, usually in divided doses	
Follicle-stimulating hormone/ luteinising hormone	Males	Females
	Testosterone enanthate 200 mg IM every 2–3 weeks	Conjugated oestrogen 0.65 mg/day
	Testosterone gel 3–6 g daily	Ethinyl estradiol 0.02–0.05 mg/day
	Testosterone skin patch 2.5–5.0 mg/day	Estradiol skin patch 4–8 mg twice weekly

Adapted from William's Textbook of Endocrinology 11th edition, Tables 8-36

- Deficiency of vasopressin, released from the posterior pituitary, is more common following pituitary surgeries. It commonly manifests as central diabetes insipidus or hyponatraemia. Diabetes insipidus is corrected with adequate hydration and drugs like chlorpropamide, carbamazepine, amiloride, thiazide diuretics, etc.
- The management of hypopituitarism is by replacement of the deficient hormones (Table 41.5)

Parathyroid Disorders

Key Points
- The most common cause of primary hyperparathyroidism is adenoma of the gland, whereas the most common cause of hypoparathyroidism is sequel to neck surgery.
- Immediate correction of parathyroid crisis (calcium levels >14 mg) is with IV fluids and bisphosphonate.
- Immediate correction of hypocalcaemia is with 10 % calcium gluconate.

Introduction

- Parathyroid glands are concerned mainly with regulation of calcium homeostasis in the body, the action being mediated by parathyroid hormone (PTH).
- Parathyroid hormone is released in response to low serum calcium levels. It helps in raising serum calcium levels by:

  - Stimulating osteoclasts which cause bone resorption and mobilising calcium into circulation.
  - Acts on kidneys to decrease calcium clearance and enhances synthesis of 1,25-dihydroxyvitamin D which in turn causes increased calcium absorption from the gastrointestinal tract [13].

- High serum levels of calcium and 1,25-dihydroxyvitamin D normally inhibits the release of PTH from the parathyroid glands by providing a negative feedback.
- Disorders of parathyroid glands commonly present as abnormalities in serum calcium levels – either hypercalcaemia or hypocalcaemia.

Hyperparathyroidism

- Primary hyperparathyroidism is the most common cause of hypercalcaemia.
- Most common cause of primary hyperparathyroidism is parathyroid adenoma (85 %).
- Most patients are usually asymptomatic and the diagnosis is often incidental during evaluation of serum electrolytes.
- Common risk factors include prior neck radiations, age more than 50 and female sex; women have a twofold increased risk of developing primary hyperparathyroidism than men [14, 15].
- Secondary hyperparathyroidism is usually associated with chronic kidney disease due to decreased levels of 1,25-dihydroxyvitamin D and resulting hypocalcaemia. Other causes include vitamin D deficiency secondary to low dietary intake, lack of sun exposure, malabsorption, liver disease and chronic illness [16].
- Tertiary hyperparathyroidism is usually seen in advanced renal failure due to autonomous overproduction of PTH from a hyperplastic parathyroid gland [16, 17].

Symptoms

- Cardiovascular symptoms include palpitation, dyspnoea, angina and syncope, hypertension, valvular calcifications and left ventricular hypertrophy [18].
- Common renal symptoms include polydipsia, polyuria and renal colic [19].
- Skeletal abnormalities include arthralgia, bone pain and pathological fractures, gout and pseudogout [17].
- Neuromuscular symptoms include anxiety, confusion, fatigue, lethargy, depression, insomnia and impaired vision [19].
- Gastrointestinal symptoms include nausea, vomiting, epigastric pain, constipation and anorexia [17].

Clinical Findings

- Abdominal findings include tenderness along the flanks and epigastrium due to nephrolithiasis and pancreatitis, respectively [14].
- Common cardiovascular findings include hypertension, arrhythmias and oedema due to congestive heart failure
- Neuromuscular signs include depression, emotional instability, lethargy, muscle weakness, delirium and coma [14].
- Other findings may include neck mass, lymphadenopathy and band keratopathy [18].

Causes of Hypercalcaemia

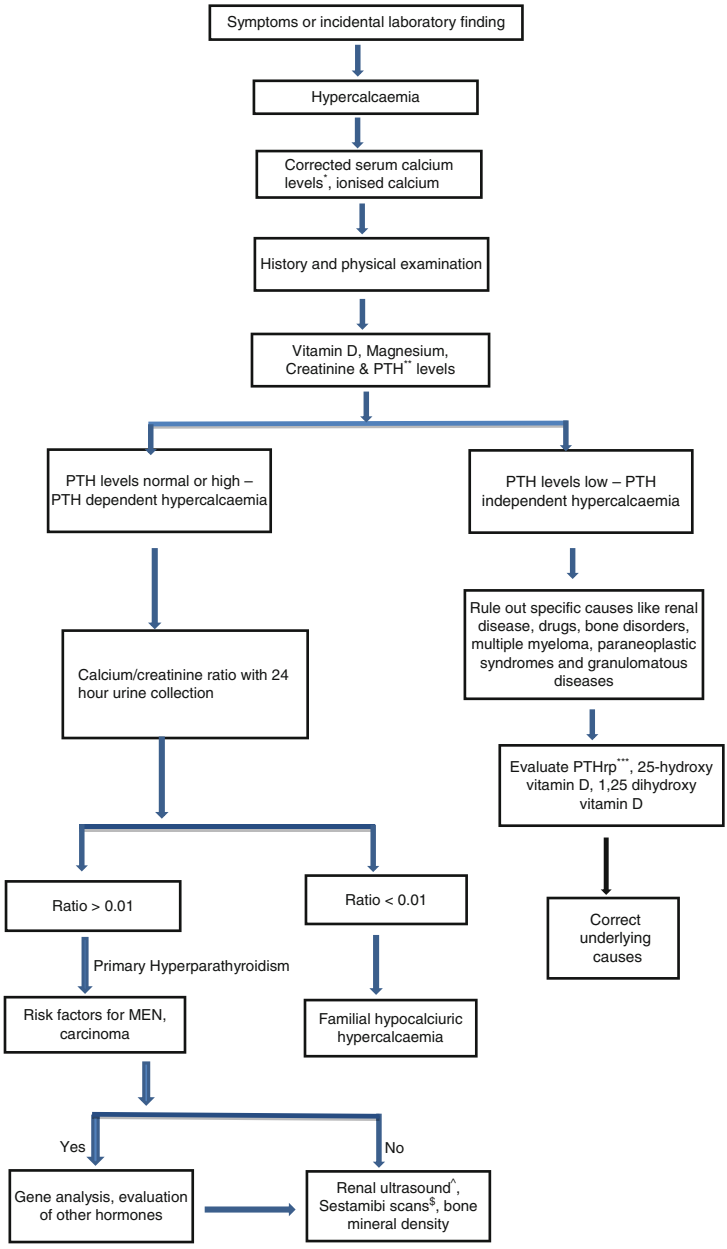
Parathyroid hormone dependent [14, 20, 21]

- Parathyroid adenoma causing primary hyperparathyroidism
- Familial hypocalciuric hypercalcaemia
- Lithium associated
- Genetic disorders like MEN-1 and 2, familial hyperparathyroidism
- Tertiary hyperparathyroidism

Parathyroid hormone independent [14, 20, 21]

- Acute or chronic renal failure
- Excess vitamin D
- Paraneoplastic syndromes
- Osteolytic metastasis and multiple myeloma
- Drugs like thiazide diuretics, theophylline, milk-alkali syndrome, vitamin A intoxication
- Endocrine disorders like thyrotoxicosis and adrenal insufficiency

Evaluation of Hypercalcaemia



* - Corrected serum calcium = measured serum calcium + 0.8 (4 – measured serum albumin)
** - PTH – parathyroid hormone
*** - PTHrp – parathyroid related peptide
$ - Sestamibi scan – choice of localisation study in primary hyperparathyroidism
^ - renal ultrasound to rule out nephrolithiasis

References [14, 18, 22, 23].

Management of Hyperparathyroidism

- Surgical removal of parathyroid glands is the treatment of choice in patients with symptomatic primary hyperparathyroidism. The role of surgery in asymptomatic cases is yet unclear [21, 24].
- Indications for performing parathyroidectomy in asymptomatic cases with primary hyperparathyroidism include [25]:
  - Age less than 50 years
  - Serum calcium level more than 1.0 mg/dL above the upper limit of normal
  - Bone mineral density T-score of less than 2.5 at any one of three sites (i.e. hip, spine or wrist) and/or any previous fragility fracture (z scores should be used in premenopausal women and in men younger than 50 years).
  - Creatinine clearance less than 60 mL/min/1.73 m^2 (1 ml/s/m^2).
- Calcimimetic agents like cinacalcet can be used in cases where surgical removal is not possible or contraindicated. They help in effectively lowering the serum calcium levels without affecting bone density [26].
- Bisphosphonate therapy and hormone therapy can be tried in asymptomatic patients with primary hyperparathyroidism. They help to improve the bone density. Alendronate is the preferred drug for long-term management with bisphosphonates [27].
- Secondary hyperparathyroidism is usually managed by treating the underlying causes. Other measures include calcium and vitamin D supplementation and calcimimetic agents.
- Parathyroid crisis or severe hypercalcaemia (calcium levels >14 mg/dL) is managed by volume repletion with normal saline (2–4 L/day) and bisphosphonates (intravenous pamidronate). Calcitonin can be used as a second-line agent.

Hypoparathyroidism

- Hypoparathyroidism most commonly occurs as a result of inadvertent damage of parathyroid glands during neck surgery [13].
- Autoimmune destruction of the gland is another major cause of hypoparathyroidism. It can occur either isolated or as part of a multiple endocrine deficiency syndrome.
- Pseudohypoparathyroidism is a genetically determined condition characterised by resistance of body tissues to actions of PTH. The clinical picture is usually hypoparathyroidism with elevated serum PTH levels [13, 20].
- Hypoparathyroidism most commonly presents with hypocalcaemia, the symptoms depending on duration, severity and rate of development.

Symptoms

- Cardiovascular symptoms include palpitations, dyspnoea, syncope and oedema.
- Neurologic symptoms include headache, impaired vision, circumoral numbness, paraesthesia, muscle twitches and seizures [20].

Clinical Findings

- Cardiovascular findings include hypotension, dysrhythmia and features of congestive heart failure.
- Neuromuscular findings include anxiety, depression, cognitive impairment and dementia. Others signs include Chvostek sign and Trousseau sign, movement disorders and Parkinsonism [13]
- Other common findings include dry skin, brittle hair and cataract formation [20].

Causes of Hypoparathyroidism

Irreversible causes (parathyroid destruction)

- Postsurgical
- Post radiation
- Autoimmune destruction of gland
- Metastatic infiltration
- Deposition of heavy metals like iron[1]

Reversible causes (defective secretion or action)

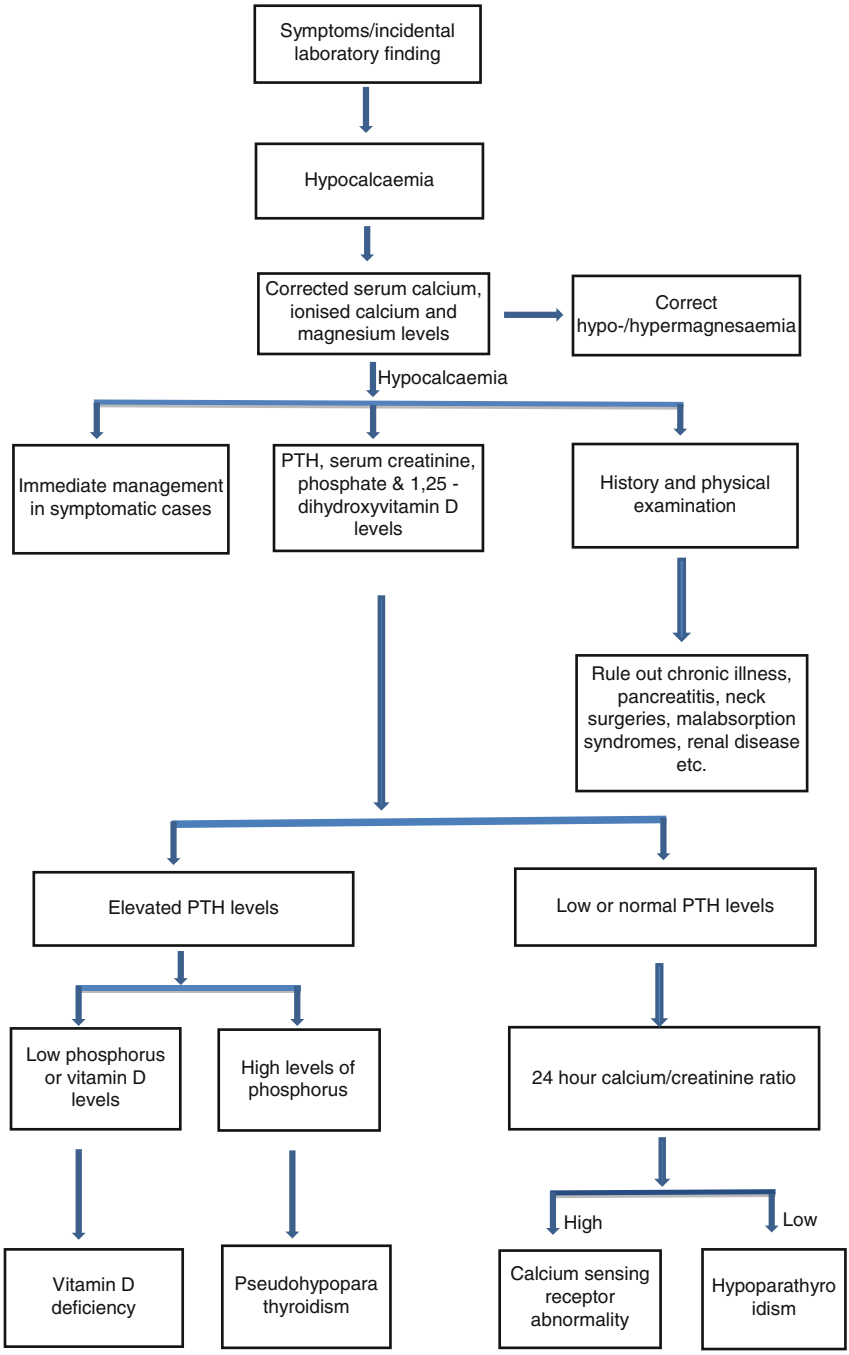
- Drugs
- Metabolic disorders
- Chronic illness
- Hypo-/hypermagnesaemia

Other causes

- Pseudohypoparathyroidism
- Genetic disorders of PTH synthesis

[1] Iron deposition is common in thalassaemia patients with frequent blood transfusions.

Evaluation of Hypocalcaemia



Evaluation Using Laboratory Values

Diagnosis	PTH	Phosphorus	25-hydroxy vitamin D	1,25-dihyroxy vitamin D
Chronic kidney disease	Elevated	Elevated	Normal	Low
Hypoparathyroidism	Low	Elevated	Normal	Normal/low
Pseudohypoparathyroidism	Normal/ low	Elevated	Normal	Normal
Vitamin D deficiency	Elevated	Normal/ low	Low	Normal/elevated

References [13, 18, 28, 29]

Management of Hypoparathyroidism

- Immediate management of symptomatic hypocalcaemia is with calcium gluconate, 1–2 g intravenously, given slowly over 10 min. Clinical and electrocardiographic monitoring is required during correction of hypocalcaemia. This is followed by slow infusion of 10 g of calcium gluconate in 1 L of 5 % dextrose at 1–3 mg per kg per hour [20].
- Other treatment modalities in cases of long-standing hypoparathyroidism include vitamin D supplementation, thiazide diuretics and dietary modifications which help to raise serum calcium levels.
- The role of PTH therapy in the treatment of hypoparathyroidism is being studied, but data is limited in this regard [13].

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Part VIII
Infectious Diseases

Chapter 42
Acute Fever of Indeterminate Cause

Shashiraj Eswarappa and Babu Urumese Palatty

Key Points

- Fever may be an indicator of illness that requires hospitalisation. It is essential for ER physicians to triage febrile patients in the ER as critically ill, high risk or stable with known or unknown source, so that appropriate measures can be taken.
- Common causes of fever include self-limited illnesses, occult infections and non-infectious illnesses. But the cause of fever may remain obscure in majority of cases.
- A protocol-based approach to fever in the emergency room saves time and resources.
- Antipyretic therapy is helpful in relieving discomfort in febrile patients, but may not influence the outcome, except in neurologically compromised febrile patients.

Introduction

- Fever is defined as a temperature of >37.2 °C (>98.9 °F) in the morning or >37.7 °C (>99.9 °F) in the evening [1].
- A temperature of ≥38.3 °C (≥101 °F) is generally used to define fever in sick patients [2], and temperature between 37.5 and 38.3 °C can be termed as low-grade fever [3].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_42

- A fever of less than 3 weeks' duration with no localising symptoms or signs to indicate a cause or source of fever is labelled as 'acute fever of indeterminate cause' (AFIC) [4]. It should not be confused with 'fever (pyrexia) of unknown origin', a term used for prolonged fever of more than 3 weeks duration with no cause identified despite investigation up to a week as inpatient.

Epidemiology

- Fever is one of the common symptoms among patients attending the emergency department.
- In 2005, fever was the third most common complaint among patients attending an emergency department (ED) in the USA, accounting for 4.4–7.5 % of all ED consultations and was a prominent complaint (about 30 % of consultations) among non-surgical patients [5].
- Fever is also an important predictor of illness that may require admission, particularly among elderly patients [6, 7].
- Fever in patients with AFIC could be due to self-limited illnesses, occult infections or non-infectious illnesses or processes. According to studies, cause of fever could not be established in 8–80 % of febrile cases [8].
- AFIC poses a formidable challenge to emergency physicians especially in resource-limited settings. A systematic, protocol-based approach taking into consideration the local infectious fever epidemiology saves time as well as resources.

Pathophysiology

- Fever is an adaptive response to exogenous pyrogens from various infectious and non-infectious pathologies.
- Fever is produced as result of release of pro-inflammatory cytokines (also called as endogenous pyrogens) such as interleukins (IL-1, IL-6), tumour necrosis factor and interferons into the circulation on exposure to exogenous pyrogens like bacterial toxins and products.
- These cytokines in the circulation act at the level of central nervous system, especially in the organum vasculosum of the lamina terminalis in the anteroventral third ventricle region of the brain. This results in the release of prostaglandins, mainly PGE2, which induce fever by raising the temperature set point [9].
- In contrast to fever in which rise in temperature is attributed to resetting of the hypothalamic thermoregulatory point, hyperthermic conditions are

known to raise body temperature by various mechanisms including unrestrained heat production, insufficient heat dissipation and impaired thermoregulation [10].

Clinical Features and Physical Examination

- All febrile patients with no known source should undergo a quick clinical evaluation to assess their clinical stability.
- Detailed history is essential to ascertain the chronology of events, pattern of fever, details of medications received or receiving, details of travel in the recent past, co-morbidities, previous surgeries or infections and any clinical symptoms or signs that may help in identifying the possible cause of fever.
- When there are multiple potential causes of fever, syndromic approach will be helpful to narrow-down the possible causes. It will be useful to know whether patient has skin rashes, thrombocytopenia, respiratory distress, encephalopathy, travelled to endemic areas, immunocompromised condition and any foreign body such as ventriculoperitoneal shunt, metallic prosthetic valve, indwelling urinary catheter, etc. [11]. The common conditions associated with different clinical syndromes are listed in Table 42.1.

Table 42.1 Syndromic approach to patients with acute fever of indeterminate origin

Clinical features	Likely diseases
Skin rashes	Viral exanthema, rickettsial infections, meningococcal infections
Thrombocytopenia	Dengue fever, malaria
Respiratory distress	Falciparum malaria, severe bacterial or viral pneumonias, collagen vascular diseases
Encephalopathy	Cerebral malaria, typhoid fever, bacterial or viral meningitis or encephalitis, septic encephalopathy
Travel to endemic areas	Malaria, dengue fever, chikungunya,
Immunocompromised condition	*Pneumocystis jiroveci* infection, tuberculosis
Recent hospital admission	Nosocomial infections (pneumonia, urinary tract infection)
Presence of foreign body such as ventriculoperitoneal shunt, metallic prosthetic valve or indwelling urinary catheter	Meningitis, endocarditis, urinary tract infection

Differential Diagnosis

- Infections are the common causes of fever and account for nearly two-thirds of patients with fever in the ED [7].
- Local fever epidemiology with knowledge about regional distribution and seasonality of infectious diseases is useful in evaluation and planning diagnostic studies.
- Infections that are commonly encountered in tropical countries include dengue fever, chikungunya, rickettsial infections, malaria, typhoid fever, leptospirosis and viral infections such as influenza and hanta virus [11].
- Immunocompromised individuals such as those with HIV infection or AIDS, cancers, post solid organ and stem cell transplants and chemotherapy-induced neutropaenia are susceptible for variety of bacterial, fungal and viral infections.
- Fever can also be caused by non-infectious illnesses such as malignancies and autoimmune disorders in small proportion of patients [8].
- Various studies have reported that the cause of acute undifferentiated fever could not be established in 8–80 % of febrile cases [8].
- Hyperthermic conditions such as heat stroke, drug-induced hyperthermia, neuroleptic malignant syndrome, malignant hyperthermia, thyroid storm and damage to central nervous system caused by intracerebral bleeding can present with high fever, i.e. temperature of >41.5 °C (>106.7 °F). Elucidation of history is often difficult in these cases due to associated impaired consciousness [12].

Investigations

Preliminary Investigations

- Complete blood count is useful, but it is neither specific nor sensitive and cannot discriminate between serious bacterial infection and nonbacterial infection.
- Normal leucocyte counts do not rule out infection.
- Presence of leucocytosis, shift to left or toxic granules may suggest the possibility of bacterial infections.
- High eosinophil counts may indicate parasitic infections or a drug-induced fever.
- Erythrocyte sedimentation rate and C-reactive protein are nonspecific markers of infection or inflammation.
- Urine analysis may be helpful in febrile patients who have clinical features suggestive of urinary tract infection or bacteraemia and in those with indwelling urinary catheter. Urine culture should be sent if patient has or suspected to have urinary tract infection.
- Chest x-ray is useful in patients with unexplained fever to rule out respiratory infections or illnesses. In selected cases, other radiological investigations such as x-rays of paranasal sinuses, ultrasound scan of abdomen and CT scan of abdomen with contrast are helpful in identifying the cause of fever.

Table 42.2 Predictor of bacteraemia – systemic inflammatory response syndrome (SIRS) [13]

SIRS is diagnosed if 2 of the following are present:
• Temperature <36 °C or >38 °C
• Heart rate >90/min
• Respiratory rate >22/min OR partial pressure of CO_2 >32 mmHg
• White blood cell count <4,000/μL OR >12,000/μL OR >10 % immature neutrophils or band forms
Blood culture is indicated if SIRS is present

- Blood cultures are reported to have low yield when routinely ordered in all febrile patients. Hence, it is prudent to use them in patients suspected to have bacteraemia. There are many methods available to predict occult bacteraemia, and detecting presence of systemic inflammatory response syndrome (SIRS) is one way to decide about blood culture (Table 42.2) [13].
- Procalcitonin is another useful test for emergency physicians for early detection of bacterial/parasitic infection as well as critical illness in patients with AFIC. Studies have indicated that procalcitonin at levels above 0.2 μg/l is associated with bacterial infections, and levels above 2 μg/l are associated with critical bacterial/parasitic infections. At procalcitonin levels below 0.2 μg/l, bacteraemic infections are unlikely, and at levels above 5 μg/l, risk of severe sepsis/septic shock is high [14].
- After clinical assessment and review of preliminary reports, further evaluation can be planned.
- It includes sputum analysis, thyroid function tests, liver function tests, body fluid (pleural, synovial, ascitic) analysis, stool analysis, etc.
- Peripheral blood smear is another useful test to look for bands or toxic granules that may suggest bacterial infection and also to look for undiagnosed haematological disorders.

Point of Care Tests

- Rapid diagnostic tests (RDTs) are helpful in the evaluation of patients with AFIC in the emergency departments, especially in resource-limited settings, as these tests provide results immediately and may reduce the need of x-rays, blood and urine tests and empirical use of antimicrobials.
- RDTs that rely on detection of antigen are relatively more sensitive and have been used to diagnose HIV, malaria and dengue successfully [15].
- Many RDTs that rely on detection of antibodies are available for other common tropical infections such as enteric fever, brucellosis, leptospirosis, African trypanosomiasis and visceral leishmaniasis. As antibodies appear late in the blood and sometimes remain in the circulation for a longer duration, antibody-based RDTs are less efficient to identify the pathogen in the initial few days of acute febrile illness, to assess response to treatment and to diagnose relapse of infection.

- RDTs for viral illnesses such as influenza A and B and respiratory syncytial virus have been found to reduce use of other laboratory and imaging tests and overuse of antimicrobials [16].

Management (Refer to Fig. 42.1)

As the diagnosis is uncertain initially, the role of emergency physician is to triage all febrile patients as follows:

- *Critically ill patients*: Patients with compromised airway, breathing or circulation require urgent attention and resuscitation. Severe sepsis and septic shock should be treated according to local sepsis protocols like early goal-directed therapy [17].
- *High-risk patients*: Patients who are considered to be high risk include elderly patients, immunocompromised patients, patients with co-morbidities and those who present with impaired consciousness, breathlessness, severe headache, seizure and inability to stand or walk. Such patients usually require further evaluation and hospitalisation [18].
- *Stable febrile patients with known source*: Patients who are otherwise stable with a known source/cause of fever should be subjected to appropriate investigations to confirm the diagnosis, and specific treatment should be offered.
- *Stable patients with acute fever of indeterminate cause* (*AFIC*): These patients should be evaluated further to identify the cause of fever and are managed as follows [19]:
  - *Patients with fever of 1–3 days duration*. Consider dengue fever, malaria, leptospirosis, chikungunya, etc. Withhold investigations and antimicrobials unless the condition of the patient is worsening.
  - *Patients with fever of 3–4 days duration*. Basic work-up includes complete blood count, urine analysis, malaria parasite and chest x-ray depending on the symptoms. Consider appropriate antimicrobials according to locally published guidelines based on clinical assessment and investigations.
- *Patients with fever of five or more days duration*. Consider blood culture in addition to above-mentioned measures

General Measures

- Pharmacological and non-pharmacological methods to lower temperature in patients with fever are useful to relieve discomfort and constitutional symptoms. They are not useful in influencing the outcome except in neurologically compromised febrile patients [20].

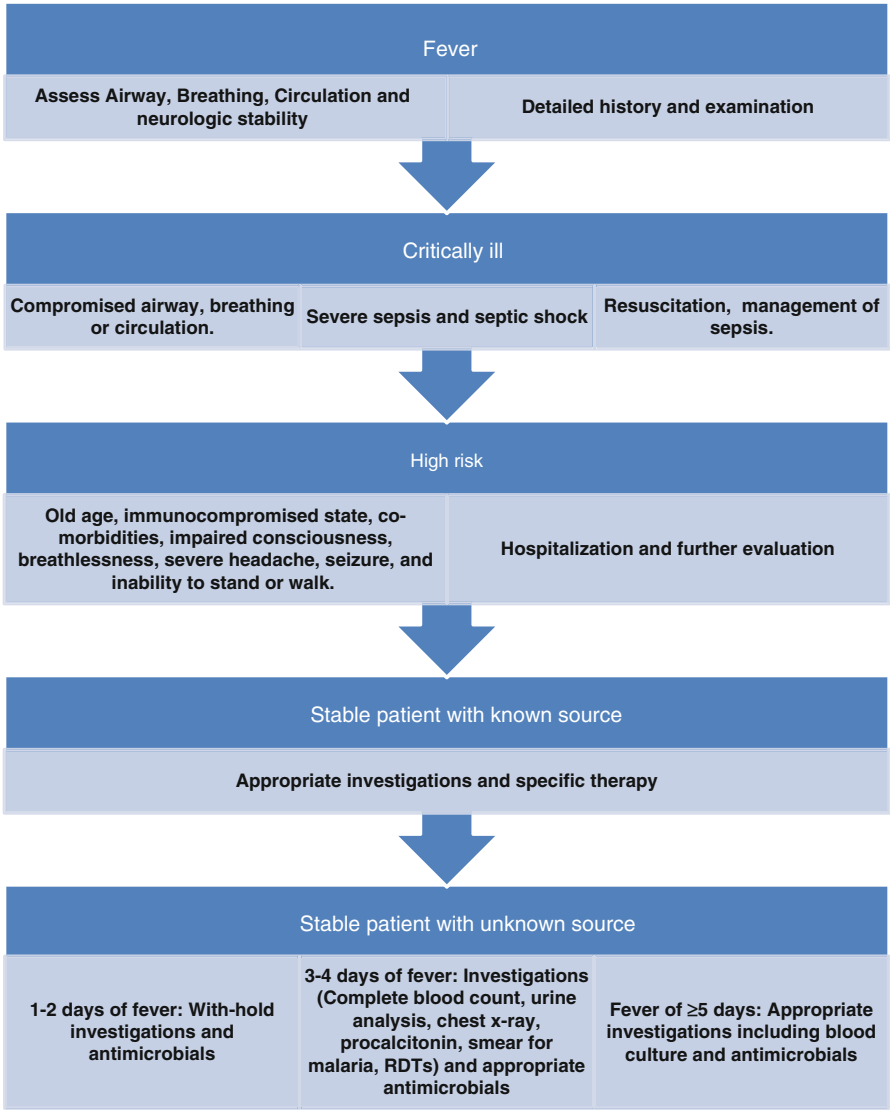

Fig 42.1 Treatment algorithm for acute fever of indeterminate cause

- Non-pharmacological methods include treating patient in a cool environment, removing excessive clothing and sponging with tepid (lukewarm) water. The use of cold water should be avoided as it may increase body temperature by causing vasoconstriction and rigors.
- Paracetamol (acetaminophen), aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used antipyretic drugs and are available as tablets and

rectal suppositories. Patients may require parenteral antipyretics if they are unable to comply with oral medications.

- Hyperthermic disorders require appropriate treatment, antipyretic drugs such aspirin and paracetamol are ineffective, and whole-body cooling is the only effective treatment.
- Dehydration is common among patients with febrile illness. Oral fluids are the safest. Patients need to be encouraged to drink fluids in small quantities more frequently. Intravenous access is essential for high-risk patients as it is useful for drawing blood samples and for administering fluids and drugs in the presence of persistent vomiting or shock.
- Pending investigation reports all high-risk patients including those with sepsis or bacteraemia should receive a broad-spectrum antibiotic depending on local antibiotic sensitivity pattern and antimalarial agents in areas where malaria is likely [18].
- Frequent monitoring of temperature and blood pressure is essential.

Prognosis

- Presence of co-morbidities, high C-reactive protein and suspicion of infection other than upper respiratory infection indicate severe disease in adult patients with fever in the emergency department [21]. Elderly patients with these features require hospitalisation as they are at high risk of revisit after discharge from the emergency department [22].
- Fever in elderly patients indicates a serious illness, more so in the presence of high-grade fever (≥39.4 °C), tachypnoea (respiratory rate ≥30/min), tachycardia (pulse rate ≥120/min), leucocytosis and an infiltrate in the chest x-ray. Hence, such elderly patients should be considered for admission [23].

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Chapter 43
Dengue

Parvinder K. Chawla

Key Points
- Dengue is a dynamic disease with the clinical spectrum ranging from asymptomatic infection to severe dengue which may even be fatal.
- Shock in severe dengue is pathophysiologically different from septic shock and so is its management.
- The clinical course of dengue is not usually predictable at the onset of illness.
- Management should be guided by sequential haematocrit measurement and the phase of the illness.

Introduction

Dengue is an acute illness caused by mosquito-borne *Flavivirus*. Its incidence has increased almost 30-fold in the last 50 years. Seventy-five percent of the current global disease burden due to this disease is borne by Southeast Asia and the Western Pacific regions [1]. In the rest of the world, it is the commonest cause of fever in the recently returned traveller [2]. This disease is unique in many ways and has a very dynamic course. It also has a very high likelihood of being misdiagnosed and inappropriately managed. Emergency physicians, therefore, play a very crucial role in timely identification and appropriate management of infected patients.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_43

Pathophysiology

- Infection with any one of the four serotypes of dengue virus (DENV 1–DENV 4) can result in either asymptomatic infection or symptomatic disease.
- Symptomatic disease may present as just any other viral febrile illness or evolve into the clinical syndrome identified as 'severe dengue'. It remains unclear why this viral infection takes one of these three routes in different patients.
- Both humoral and cell-mediated immunity have been implicated in the pathogenesis.
- *Immune enhancement*, increased selective vascular permeability and *coagulopathy* are the three hallmarks of the pathophysiology of this disease.
- *Immune enhancement*: Primary infection with one of the dengue serotypes is more likely to result in asymptomatic infection or 'benign' self-limiting acute febrile illness whereas subsequent infection with a different serotype is more likely to result in 'severe dengue' with its life-threatening features of *increased vascular permeability*, *coagulopathy* and shock. The root cause behind this phenomenon of '*immune enhancement*' is still being elucidated [3].
- *Increased vascular permeability* is the second hallmark of the disease. This is seen primarily in the critical phase of severe dengue. This phenomenon is typically localised to the pleural and peritoneal beds and is transient, lasting for 24–48 h and is responsible for the shock in severe dengue. Sequential haematocrit measurement and crystalloid and/or colloid infusion just sufficient to maintain the circulating plasma volume is therefore the cornerstone of treatment in the critical phase of severe dengue.
- The third hallmark of dengue is *coagulopathy*. Though thrombocytopenia is seen as a prominent feature of this infection, rapid decline in platelet count during the course of illness is more often a marker of the onset of the critical phase of dengue rather than the primary cause of bleeding associated with this disease. The pathophysiology of bleeding in dengue is multifactorial with thrombocytopenia, platelet function defect, cytokine 'storm' and complement activation all playing a role in its genesis.

Clinical Features

- A large majority of the dengue virus infections are asymptomatic.
- Symptomatic patients can be categorised into *dengue fever*, *dengue fever with warning signs* or *severe dengue*. Incubation period of the disease is 3–7 days.

Dengue Fever

- *Dengue fever* usually presents as just another acute viral febrile illness.
- Fever is usually moderate to high grade, abrupt in onset with or without upper respiratory symptoms.

- Headache, body aches, transient macular rash and mild haemorrhagic manifestations are commonly present.
- Laboratory investigations may show leucopoenia, thrombocytopenia and elevated liver enzymes.
- Most patients recover spontaneously after 3–7 days without any complications.

Dengue Fever with Warning Signs

- Significant plasma leakage presents clinically in the form of warning signs like persistent vomiting, severe abdominal pain, headache, severe lethargy, spontaneous mucosal bleeding or bleeding at previous venipuncture sites.
- Laboratory evaluation may show a rapid decline in the platelet count and rise in haematocrit above the baseline.
- These patients are very likely to go into the critical phase of the disease at the time of defervescence. They should therefore be admitted to the hospital and monitored and managed closely to prevent the development of *severe dengue* [4].

Severe Dengue

- Patient is said to be having *severe dengue* if any one or more of the following features are present in a patient with suspected dengue:

  (a) Severe plasma leakage leading to shock and/or respiratory distress
  (b) Severe bleeding
  (c) Severe organ impairment

- Dengue is therefore a very dynamic disease entity with many of those exposed to the virus going through asymptomatic seroconversion while some going on to develop severe dengue with high fatality rate.
- It is often not possible to predict the full course of the disease at the onset of the febrile illness.
- It is only at the time of defervescence that some patients develop the features of significant plasma leakage thus heralding the onset of the *critical phase* of the disease. Majority recover at this time just like in the other commonly encountered viral febrile illnesses. These patients therefore go directly from the *febrile phase* to the *recovery phase* without going through the intervening critical phase.
- During the *febrile phase*, fever and dehydration need to be managed and patients need to be made aware of the warning signs that herald the onset of significant plasma leakage.
- The phase of significant plasma leakage is the *critical phase* of the disease. It usually lasts 24–48 h. It initially presents as compensated shock and is very likely to be missed by inexperienced physicians, thus leading to the development of ‘severe dengue’. If managed appropriately, patients may recover from

compensated shock without developing hypotensive shock, significant haemorrhage or organ dysfunction.
- In the *recovery phase*, fluid is gradually reabsorbed back from the third spaces. Patients are therefore likely to develop fluid overload and pulmonary oedema if the fluid resuscitation during the critical phase has been excessive or has been extended into the recovery phase of the disease.

Differential Diagnosis

- The differential diagnoses depend upon the local infectious disease epidemiology and the phase of the illness that the patient presents in.
- At the onset of the febrile phase, Dengue presents like any other acute febrile illness. Many of these may be benign self-limiting viral fevers. In India, the differential diagnoses would therefore include tropical infections like Malaria, Enteric fever, Leptospirosis, Scrub typhus apart from other viral febrile illnesses like Influenza etc. In Dengue, patients typically develop high grade fever suddenly.
- During the critical phase, severe sepsis and meningococcal disease would be included in the differential diagnoses. Defervescence or subnormal body temperature at the onset of shock would go in favour of dengue, while persisting fever would go in favour of severe bacterial sepsis. Some patients with Dengue can progress to the critical phase of plasma leakage without defervescence though. Severe Malaria and untreated Leptospirosis and Scrub typhus should be kept as differentials in the critical phase too.
- An astute ED physician should be able to think outside the box and keep non-infectious causes of fever, leucopoenia and thrombocytopenia like SLE and acute leukaemia in mind. Lastly, surgical causes of acute abdomen like acute appendicitis and acalculous cholecystitis also need to be considered in appropriate clinical settings.

Investigations

Investigations are required in a patient with suspected dengue to confirm the diagnosis, to gauge the level of organ involvement and to optimise the management (Tables 43.1 and 43.2).

Tests to Confirm the Diagnosis

- NS1 antigen and anti-dengue IgG and IgM antibodies should be tested in patients with suspected dengue.
- NS1 antigen can be detected by ELISA or rapid antigen detection test.

Table 43.1 Recommended investigations in a patient with suspected dengue

Purpose of the investigation	Ideally recommended	Optional
Tests to confirm the diagnosis	NS1 antigen	Specific investigations for malaria, typhoid, leptospirosis and scrub typhus[c]
	Anti-dengue IgG and IgM antibodies[a]	
	Complete blood count[b]	
Tests to gauge the level of organ involvement[d]	Complete blood count	Liver function tests
		Renal function tests
		Blood group
		Chest X-ray
		Ultrasound abdomen
Tests to optimise the management	Complete blood count, especially sequential haematocrit monitoring[e]	Sequential liver and renal function tests

[a]Rapid detection method or ELISA may be used for antibody detection. The former have a faster turnaround time while ELISA is more sensitive
[b]A falling WBC and platelet count in the appropriate clinical setting makes the diagnosis of dengue likely
[c]Resource availability and local prevalence of these infections should be used as a guide to decide upon these investigations
[d]Clinical judgement and presence of warning signs should be used as a guide to decide upon these investigations
[e]Sequential haematocrit monitoring should be used as the guide to optimal crystalloid/colloid and/or blood transfusion

Table 43.2 'Rule of three' in dengue

Three hallmarks of dengue pathogenesis [3]
Immune enhancement
Increased selective vascular permeability
Coagulopathy
Three presentations of symptomatic dengue [4]
Dengue fever
Dengue fever with warning signs
Severe dengue
Three phases of symptomatic dengue [4]
Febrile phase
Critical phase
Recovery phase
Three WHO treatment groups [4]
Group A
Group B
Group C
Three common pitfalls in the management of dengue [4]
Overhydration in the febrile/critical phase
Delay in identification of the critical phase
Failure to consider colloid/blood transfusion for a patient in the critical phase not responding to crystalloids

- Anti-dengue IgM is the best marker of recent dengue infection. IgM antibodies may persist for almost 3 months after fever onset. IgM/IgG optical density ratio [5] may also be determined, with higher ratios going in favour of primary infections.
- Viraemia can also be detected by viral isolation and viral genome detection methods. Though these can help in the detection of the viral serotype too, they are not available for routine commercial purposes.
- Tests for the other locally prevalent tropical diseases will also need to be carried out to narrow down the differentials arrived at on clinical assessment.

Tests to Gauge the Level of Organ Involvement

- Liver and renal function tests along with the complete blood counts should be done in every patient of suspected dengue coming with warning signs. Baseline haematocrit value is of immense importance.
- Coagulation profile and blood grouping would be required in those with any evidence of bleeding or those with severe dengue.
- Chest X-ray and abdominal sonography should be done if clinically indicated.

Tests to Optimise the Management

- The optimal treatment of dengue depends upon sequential haematocrit measurement. A rising haematocrit especially around the period of defervescence is an indicator of clinically significant plasma leakage. A falling haematocrit in a clinically improving patient signifies optimal resuscitation, while a falling haematocrit in a clinically worsening patient signifies significant occult bleed necessitating fresh whole blood transfusion. A baseline haematocrit value is therefore of immense importance and should be obtained at the first patient visit [4].
- White cell count and platelet count may be normal early in the course of the illness. Falling white cell and platelet counts in an acutely febrile patient make the diagnosis of dengue likely, with a more rapid fall having been associated with more severe disease. A rapid fall in the platelet count accompanied with rising haematocrit at the time of defervescence is a strong predictor of the patient going into the critical phase of dengue. Leucopenia and thrombocytopenia in dengue are only markers of the presence and severity of dengue and do not need to be treated.
- Whenever feasible, a complete blood count should be done in a patient with suspected dengue on the first visit and daily till the critical phase is over. In resource-limited settings, it may be done on alternate days at the time of fever onset, but frequency should be increased to daily at the time of defervescence till the critical phase is over.

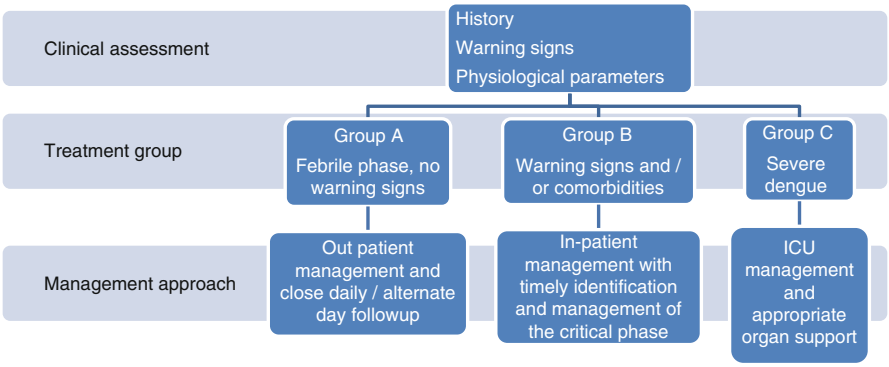

Fig. 43.1 Treatment algorithm for dengue

Treatment

There is no definitive antiviral treatment available for dengue. It is a self-limiting acute febrile illness in most cases. The key to treating the remaining ones correctly lies in timely identification of the warning signs of significant plasma leakage and optimal fluid resuscitation during the critical phase (Fig. 43.1). For the purpose of optimal management, WHO has categorised patients with dengue into three groups: Groups A, B and C.

WHO Group A: Patients Presenting in Early Febrile Phase

- Ensure physiological stability and optimal oral intake.
- Baseline complete blood counts should be obtained.
- Adequate oral fluid intake and paracetamol for fever are the only treatment required at this stage.
- Patients and their caregivers need to be made aware of the warning signs and clearly instructed to report immediately in case the patient develops any one of them. These include severe abdominal pain, persistent vomiting, lethargy, breathlessness, bleeding, decreased urine output or any deterioration around the time of defervescence.
- Patients should be asked to come for daily follow-up in the outpatient clinic after the third day of fever till the patient remains clinically stable 24–48 h post defervescence.
- Complete blood counts should be monitored on a daily basis during this period.

WHO Group B: Dengue with Warning Signs/Pre-existing Co-morbid Conditions

- These should be admitted for close observation and management till they are into the recovery phase of the disease. This category would include pregnant females and patients with renal failure, heart failure, haemolytic anaemia, etc.
- They should be continued on oral fluids and given judicious volume replacement if signs of plasma leakage develop.
- Isotonic crystalloids like 0.9 % NS or Ringer's lactate should be the initial replacement fluid.
- Minimum amount of fluid required to maintain adequate perfusion and urine output of ~0.5 ml/kg/h should be given. Fluid replacement is rarely required beyond 48 h.
- Paracetamol should be continued till defervescence. NSAIDS should be avoided.

WHO Group C: Patients Presenting in Critical Phase

- These patients should be hospitalised or urgently referred to a centre capable of managing them. These centres should have good ICU backup and blood transfusion facilities.
- Timely identification and judicious intravenous fluid resuscitation is the essential and usually the only intervention required for their optimal management.
- The amount of fluid transfused should be carefully titrated with the pre- and post-transfusion haematocrit values. The goals of fluid resuscitation are improving central and peripheral circulation and end organ perfusion.
- Urine output of ~0.5 ml/kg/h is optimal in these patients. Any attempt to increase it beyond this by giving more intravenous fluids is likely to result in the state of fluid overload and its attendant complications as the phase of plasma leakage ends after 24–48 h and fluid is reabsorbed back from the third spaces.
- Switch to colloids if crystalloid transfusion is not resulting in stabilisation of haemodynamics and improvement in the haematocrit values.
- Blood transfusion should be initiated at the earliest if haematocrit falls in a clinically deteriorating patient. This indicates occult haemorrhage. This should be managed with transfusion of fresh whole blood or fresh packed cell transfusion. This holds true even if the haematocrit value is above 30 %. Even though these patients have some degree of thrombocytopenia, platelet transfusion has not been seen to be beneficial in these patients.
- WHO strongly recommends transfusion of fresh whole blood or fresh packed red cells to patients with severe dengue requiring blood transfusion. The rationale behind this recommendation is that fresh blood contains high levels of 2, 3diphosphoglycerate (2, 3 DPG) which results in optimal oxygen delivery to the tissues. Stored erythrocytes have low levels of 2, 3 DPG and thus decreased oxygen-releasing capacity of haemoglobin and functional tissue hypoxia.

Prognosis

Most patients recover fully from the illness. Patients presenting even with severe dengue recover well if managed correctly, taking care to avoid secondary infections and complications resulting from volume overload or prolonged shock leading to irreversible organ impairment.

Prevention

Aedes aegypti, the mosquito responsible for transmitting dengue virus, usually breeds in artificial containers closely associated with human dwellings. This is primarily a day-biting mosquito. Preventive measures are therefore primarily related to eradication of the mosquito breeding sites on the community level and proper clothing to avoid the mosquito bites on a personal level. Because of its day-biting behaviour, use of mosquito bed nets has not been shown to be of help in preventing dengue transmission. No vaccine for dengue prevention is available so far.

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Chapter 44
Dog Bite

Suresh S. David

Key Points
- Appropriate wound management, tetanus prophylaxis and antibiotics are crucial in the management of dog bites.
- Rabies is an incurable disease, once manifestations have occurred. Therefore, appropriate treatment is mandatory in endemic regions of the world.
- Pre- and post-exposure prophylaxis, per recommended guidelines, should form standard protocols for rabies immunisation.

Introduction

About 4.5 million people are bitten by dogs each year and children are more likely to be bitten than adults [1]. Rabies deserves special emphasis in dog bite treatment in rabies-prone countries. This zoonotic viral disease is probably derived from the Sanskrit word '*rabhas*', meaning 'to do violence' [2]. Dog bites are the main transmission agent for humans, through bite or scratch. Bats, monkeys, foxes, cattle, mongoose and cats can also transmit the disease to humans.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_44

Wound Management of Dog Bite

- Assess the bite area for disruption in the skin and underlying structures.
- Wash the wound with soap and water immediately.
- Flush exposed mucous membranes such as eyes, nose or mouth with water. Irrigation with dilute povidone-iodine solution in 250 ml saline, using a 19 or 20 gauge plastic intravenous catheter on a 20 ml syringe, is recommended [3].
- Primary closure of the wound increases risk of infection. However, bites to the face could be sutured, due to cosmesis. Ensure careful monitoring.
- Tetanus prophylaxis is mandatory.
- Antibiotics is recommended, especially to bite injuries of the hand [4]. The current recommendation of antibiotic prophylaxis is a combination of amoxicillin and clavulanic acid for 3–5 days [5]. Infected wounds are usually due to *Pasteurella* spp. Erythromycin and flucloxacillin are to be avoided, due to resistance to these antimicrobials.

Rabies: Pathogenesis

Rabies has the highest case fatality rate of any currently recognised infectious disease. It is caused by a fragile RNA-based virus, which is inactivated by heat and desiccation and is not viable outside the host [6, 7]. The virus enters the body through wounds or by direct contact with mucosal surfaces. It replicates in the tissue and reaches the central nervous system through motor axons [8]. The incubation period varies from 5 days to several years. During this phase, the virus is not easily detected and vaccination may still confer cell-mediated immunity.

Rabies is potentially curable, when the virus exists in cells other than neurons. However, once it gains entry into a neuron, it is sequestered from the immune system and no longer amenable to curative therapy. By the time of clinical onset, the virus is widely disseminated throughout the central nervous system and death usually occurs within 2 weeks [9].

Clinical Features

- The first specific clinical symptom of rabies is neuropathic pain at the site of the bite and this is due to viral replication.
- There are three classical stages of the disease:
  - *Prodromal stage*: the period between exposure and the first ‘flu-like symptoms’ that normally occurs from 2 to 12 weeks.
  - *Excitative stage:* Lasts for 3–4 days and manifests a hyperreactive state to external stimuli, with cerebral dysfunction, insomnia, anxiety and agitation, progressing to delirium. Typical signs include spasms in response to tactile,

auditory, visual or olfactory stimuli (e.g. aerophobia and hydrophobia) alternating with periods of lucidity, agitation, confusion and signs of autonomic dysfunction [10].

– *Paralytic stage:* Due to neuronal damage, resulting in drooling and difficulty in swallowing. The hallmark symptom of rabies is hydrophobia, whereby the patient demonstrates panic when presented with liquids to drink and cannot quench his or her thirst.

Diagnosis

- According to the WHO, a clinical case of rabies is defined as an acute neurological syndrome (i.e. encephalitis) dominated by forms of hyperactivity (i.e. furious rabies) or paralytic syndromes (i.e. dumb rabies) progressing toward coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the onset of symptoms [6].
- Typically, there is history of animal bite or scratch. However, rabies should never be ruled out in the absence of a definite exposure history.
- The differential diagnosis includes encephalitis, particularly infection with herpesvirus, enterovirus or arbovirus.

Laboratory Investigations

- Secretions, biological fluids such as saliva, spinal fluid as well as tissue skin biopsy samples and hair follicles at the nape of the neck can be used to diagnose rabies.
- Brain tissue is the preferred specimen for postmortem diagnosis. Ideally, all samples should be stored at −20 °C or less and should be shipped frozen or refrigerated. If they are shipped at ambient temperature, they should be preserved in 50 % glycerine-saline solution.
- The gold standard investigation for diagnosing rabies is direct fluorescent antibody technique [11].
- Inclusion bodies known as Negri bodies are 100 % diagnostic for rabies infection, but are only present in 71 % of cases [12].

Management of Rabies

Treatment for established rabies is supportive, although there are anecdotal reports of few patients who have survived, after the onset of symptomatic rabies [13, 14]. Patients with rabies are extremely agitated, remain conscious and are often aware of impending death.

- Provide care in a private room, with suitable emotional and physical support.
- Administer intravenous morphine or benzodiazepines for relieving the severe agitation, anxiety and phobic spasms.
- In view of the inevitability of death in most cases, treatment should focus on comfort and avoidance of intubation or life-support measures.
- Immunise the partners of patients, as sexual contact in the early stages of the disease carries risk for transmission.

Human Anti-rabies Vaccine

Cell culture and embryonated egg-based rabies vaccines have proved to be safe and effective in preventing rabies and are used for both pre- and post-exposure prophylaxis.

Anti-rabies Immunoglobulin (ARIG)

- Human rabies immunoglobulin and equine rabies immunoglobulin are the two common types of ARIG available. Human immunoglobulin should be given at 20 IU/kg body weight, while for equine immunoglobulin, a dose of 40 IU/kg is required [15]. Equine immunoglobulin is considerably less expensive and is potent, highly purified and safe, with few adverse events.
- ARIG may be administered up to and including day 7 post-exposure [16].
- Skin tests are not recommended.
- ARIG should preferably be administered into and around the wound site to neutralise the rabies virus still present. Any remaining volume should be injected IM at a site distant from vaccine administration.
- Rabies vaccine should be preferably administered into the deltoid muscle in adults and children aged ≥2 years; in children aged <2 years, the anterolateral thigh is recommended.

Vaccination Schedule

- This consists of pre-exposure prophylaxis and post-exposure prophylaxis.
- As rabies is fatal, there are no contraindications to post-exposure prophylaxis.
- Preferably, the same brand of vaccine should be used for the entire immunisation series. However, switching to another product between doses is reasonable, if sensitivity to a particular vaccine develops [6].
- Prophylaxis should not be discontinued due to development of local or mild systemic signs.

Pre-exposure Rabies Prophylaxis

- Pre-exposure prophylaxis is recommended prior to a bite incident, for those with frequent exposure to animals such as veterinary surgeons, pet handlers, wildlife researchers, travellers and hikers.
- One intramuscular dose is given on each of 3 days 0, 7 and 21 [17]. Day 0 is the date of administration of the first dose of vaccine.
- It is presumed that ARV confers lifelong immunity. Nevertheless, all vaccinated individuals subsequent to rabies exposure should receive an abbreviated course of post-exposure prophylaxis – one dose of ARV is to be administered on days 0 and 3.
- In the event of a subsequent exposure to animal bite, ARIG is not required.
- Post-exposure prophylaxis for previously vaccinated individuals can be deferred in people who have received complete pre- or post-exposure prophylaxis within a maximum delay of 3 months.

Post-exposure Rabies Prophylaxis

Administration of rabies post-exposure prophylaxis is a medical urgency and should start at the earliest opportunity.

- The recommended Essen's regimen consists of one dose of ARV, administered on days 0, 3, 7, 14 and 28. Day 0 is the date of administration of the first dose of vaccine. It is important to complete the initial three doses within 1 week.
- If possible, the suspect animal should be identified and quarantined for observation.
- Prophylaxis should be completed if the suspected animal is not available for testing or observation.
- Prophylaxis should be continued while awaiting laboratory results and during the observation period.

Category of Exposure

ARV and the addition of ARIG are based on the category of exposure: [6].

- *Category I*: Touching or feeding animals, licks on intact skin, contact of intact skin with secretions or excretions of a rabid animal or human. These are not regarded as exposures, and no post-exposure prophylaxis is required.
- *Category II*: Nibbling of uncovered skin, minor scratches or abrasions without bleeding. Vaccine should be injected as soon as possible.
- *Category III*: Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure to bats. Vaccine and rabies immunoglobulin should be administered at distant sites as soon as possible.

Schedule Delays

Deviations of a few days in immunisation schedule are unimportant and do not require complete re-initiation of vaccination. For example, if a patient who has begun post-exposure prophylaxis misses the dose scheduled for day 14 and attends a clinic on day 21, vaccination may be continued with administration of doses at the same intervals as if the patient had been on schedule [18].

Summary and Algorithm

Management of dog bite consists of:

1. Wound management
2. Anti-rabies vaccine schedule
3. Administration of rabies immunoglobulin, if indicated (Fig. 44.1)

Preventive Aspects of the Disease

- Health-care personnel handling rabies patients should adopt standard precautions, which includes personal protective equipment (e.g. clothing, gloves, eye protection) and vaccination.

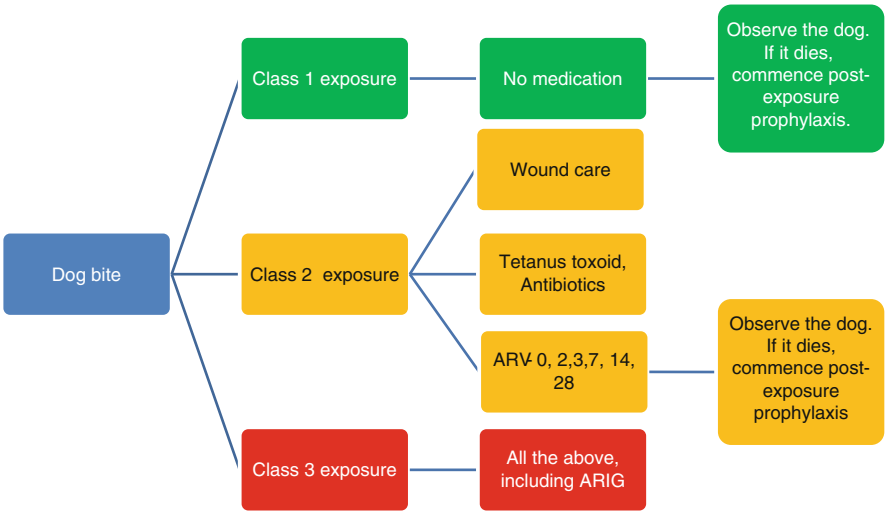

Fig. 44.1 Treatment algorithm for dog bite

- Administration of post-exposure prophylaxis to people exposed to the patient's infectious secretions is recommended.
- Hospitals that are likely to receive rabies patients may consider pre-exposure vaccination for health-care staff.
- Vaccination of domestic animals has led to reduced disease in several low-income countries and is a realistic and achievable goal.
- Health teaching in particular for children about behaviour with strange dogs has shown to reducing the incidence of dog bite [19].

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Chapter 45
Emerging Respiratory Pandemics

Seema Oommen

Key Points
- Since the identity of the respiratory pathogen is not known at the time of admission, emergency department personnel and intensive care staff are at the highest risk of exposure while handling such patients.
- Physical signs in respiratory pandemics are minimal in contrast to the radiological signs.
- Rapid respiratory deterioration necessitating intensive care is a common feature early in the disease.
- Contact, droplet and airborne barrier precautions are necessary to prevent the spread of infection within the hospital.

Introduction

Over the last two decades, there has been an increase in the incidence of emerging and remerging respiratory viruses, primarily of zoonotic origin, capable of causing respiratory infections of pandemic proportions.

The leading pandemic of the new millennium was that of a novel coronavirus called severe acute respiratory syndrome coronavirus (SARS-CoV). It originated in the live game markets in the Guangdong province of southern China in the late 2002 and affected about 8,096 people in over 30 countries, of which 774 died till early 2004 [1]. Palm civets sold in these markets are considered as the source of this infection.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_45

Swine flu is the popular name of the relatively new strain of influenza A/2009/H1N1 that caused a pandemic which began in Mexico and spread rapidly from there across the world in 2009–2010. More than 600,000 laboratory-confirmed cases were reported from more than 200 countries worldwide as of March 2010 with a total of 18,449 deaths as reported by the World Health Organization (WHO) in August 2010 [2]. This is considered an under-representation of the actual numbers as many deaths were never tested or recognized as influenza related [2]. Meanwhile new cases of H1N1 are being diagnosed worldwide including India in 2014.

The WHO estimates a total of 676 laboratory-confirmed human cases of avian flu (H5N1) infection and 398 related deaths in 16 countries from 2003 to 2014 [3]. Avian influenza viruses are divided into the high pathogenicity H5N1 virus with 100 % mortality in the poultry and low pathogenicity H7N9 viruses not associated with severe disease in poultry. Cases of H7N9 are reported mainly from the People's Republic of China.

The most recent respiratory illness was first reported in Saudi Arabia in 2012 and is of a new strain of coronavirus called the Middle East respiratory syndrome coronavirus (MERS-CoV) that shares a genetic relatedness to a similar virus found in camels. By June 2014 there were around 699 laboratory-confirmed infections with 209 deaths [4]. The majority of these cases were from the Middle East countries with few cases in the USA, Europe, Malaysia and the Philippines in Asia.

Thus the crude case fatality rate of H5N1 is highest at 60 %, followed by MERS-CoV (30 %), SARS-CoV (10 %) and the least H1N1 (0.5 %), the latter being most likely under-represented [1–4].

Pathophysiology

Adaptation of the viruses by mutation or reassortment leading to an ability to cross the species barrier into humans, the capability to become established in humans and a sustained ability to pass from one human to the other are the three features needed to cause an infectious disease of epidemic proportions. Combine this with the increased mobility of individuals across the world; transfer of these infections from one part of the globe to the other can take place in a relatively short period of time.

Direct lysis of the host cells is one of the mechanisms of host tissue damage. More important are the indirect consequences of the host immune response which get disrupted, tipping the balance from being favourable to an exaggerated and destructive host immune response leading to an outpouring of pro-inflammatory chemokines and cytokines termed as 'the cytokine storm' [5].

Cytokines like tumour necrosis factor alpha (TNF α), interleukin 6 (IL-6), IL-1β and IL-8 play a major role in tissue damage [5]. Of this IL-1β has been found to be the main cytokine in the broncho-alveolar lavage (BAL) fluids of patient with lung injury [5].

The net result is local diffuse damage to the alveoli (acute lung injury – ALI) due to increased arrival of leucocytes, dilatation of blood vessels and tissue oedema and can swiftly progress to the more severe acute respiratory distress syndrome (ARDS). Spillover of these cytokines into the systemic circulation leads to multisystem organ failure and finally death.

Clinical Features

There is a considerable overlap in the clinical presentation by the common respiratory viruses and other atypical causes of community-acquired pneumonia making arousal of suspicion in the treating physician of an emerging epidemic virus unlikely. Hence suitable samples may not be collected at the appropriate time leading to misdiagnosis and a delay initiation of therapy.

- The common clinical presentation [1, 6, 7] of most respiratory pandemic viruses is that of an 'influenza-like illness (ILI)': an acute respiratory infection with sudden onset of fever (temperature of >38 °C or >100.4 °F), chills, myalgia and a non-productive cough. Sore throat and rhinorrhoea may also be present. Many cases are associated with gastrointestinal symptoms like abdominal pain and diarrhoea.
- A history of contact, in the preceding 10 days of symptom onset with poultry or with a known case in the countries detected to have human avian influenza cases, has to be elicited. Likewise, history of travel to the Middle East countries should arouse suspicion of a MERS-CoV infection.
- Cases may range from a mild ILI to a fulminant viral pneumonia. Rapid clinical deterioration may occur with diffuse viral pneumonitis with hypoxaemia, acute respiratory distress syndrome (ARDS), septic shock, multisystem organ failure and death occurring within a week of onset of illness [7].
- Secondary bacterial pneumonia especially due to *Staphylococcus aureus, S. pyogenes and S. pneumoniae* is a common complication with influenza [7].
- Extremes of age; pregnancy; obesity; presence of pulmonary, cardiac, hepatic, renal or metabolic co-morbidities; and underlying neurological conditions are the common risk factors for severe disease [1, 6].
- Case fatality of H5N1 is much higher than seasonal influenza viruses with rapid clinical deterioration mainly due to early involvement of the lower respiratory tract.

Investigations

Considering the rapid spread of virus in the past within hospitals and community, methods to rapidly identify infected cases are of utmost importance.

Molecular Diagnostic Methods

- The real-time-based polymerase chain reaction (RT-PCR)-based assay is one such means which has proven its worth both during the SARS-CoV and the H1N1 outbreak. The only caveat is that appropriate clinical samples need to be collected at the appropriate time during the disease and should be transported to the laboratory in cold chain in a viral transport medium so as to maintain the viability of the nucleic acid.
- Multiplex PCR can detect simultaneously other viruses causing a similar clinical picture like the seasonal influenza A and B, respiratory syncytial virus (RSV) and human metapneumovirus.
- The most preferred specimen is a nasopharyngeal aspirate or a swab preferably within 1–2 days of onset of disease [6]. Cotton swabs are not recommended due to presence of inhibitors; rayon- or nylon-flocked swabs are used instead. Broncho-alveolar lavage, tracheal aspirates and sputum which contains the highest viral loads are the ideal specimens especially later in the course of illness [6].
- RT-PCR tests may be carried out on serum specimens.
- In case of suspicion of MERS-CoV or SARS-CoV, stool specimens may also be sent to the laboratory.
- Many a times these newer molecular assays may not be available even in established diagnostic molecular laboratories and the specimen may have to be shipped under strict biohazard protocols to the national or a regional reference centre for testing.

Other Diagnostic Tests

- Rapid diagnostic tests available for the diagnosis of influenza have high specificity but low sensitivity and hence a negative result should be interpreted with care [7].
- Though viral cultures don't play a significant role in rapidly diagnosing cases, it is important in confirmation of emerging and re-emerging cases of viral infection, epidemiological typing of isolates and research into vaccines and newer drugs.
- Clinical signs on examination are minimal when compared to the radiological findings of the chest. Chest X-rays typically show diffuse interstitial infiltrates, unilateral or more commonly bilateral ground-glass opacities to focal consolidation that is seen early in the disease [1, 6, 7]. These opacities are usually seen in the lower lungs first and may become widespread affecting larger areas as the disease progresses. High-resolution computed tomography may be required in ambiguous cases.

- Tests done to rule out other infectious aetiology include blood cultures, Gram's stain and culture of the sputum and urinary antigen detection for legionella and pneumococci. Acute and convalescent serum samples may be collected for antibody detection of various pathogens.

Healthcare personnel should be on high alert in the present global climate for any clustering of similar cases. Picking up a probable epidemic early in its course may limit the spread of the infection within the hospital and the community.

Treatment

Treatment is largely supportive for uncomplicated cases, also bed rest and maintenance of hydration, in addition to analgesics and antipyretics. Severe cases require supportive measures including ventilation and antibiotics for secondary bacterial infections.

Antivirals

- Oseltamivir and zanamivir [6, 8] are neuraminidase inhibitors that decrease the release of influenza viruses from infected cells, thus limiting its spread. It has been used extensively in the 2009 H1N1 pandemic. Resistance to oseltamivir has been documented [8]. Best results were obtained when treatment was started within 48 h of symptom onset even before the availability of laboratory results.
- The dosage of oseltamivir for persons above 13 years of age and >40 kg weight is 75 mg twice daily for duration of 5 days.
- For children <15 kg, the dose of oseltamivir is 30 mg twice a day, 15–23 kg is 45 mg twice a day and >23–40 kg is 60 mg twice daily.
- Zanamivir is advised for persons above 5 years of age at a dose of 10 mg (two inhalations) twice a day. Oseltamivir is the drug of choice to treat human cases of avian influenza.
- Unlike influenza there is no specific antiviral or vaccine available for the coronaviruses. A combination of ribavarin and interferon 1α shows synergistic action in vivo and has been used to treat MERS-CoV and SARS-CoV infections but limited data is available on their effectiveness to combat the disease and clinical trials are needed to demonstrate their effectiveness [1].
- Steroids were used during the SARS outbreak to limit the cytokine-mediated lung injury in conjunction with ribavirin but the actual role of steroids has to be elucidated with further studies. Steroids are contraindicated in cases of influenza pneumonia as it may further predispose to secondary bacterial infection.

Prevention

- The incubation period for most influenza viruses including H1N1 is 1–4 days [7], whereas the incubation period for H5N1 is slightly longer ranging from 2 to 8 days.
- Patients with influenza are most infectious in the first 2 days of the onset of illness averaging from a day before the onset of symptoms to 5–7 days after the onset of illness.
- The incubation period of coronaviruses like SARS-CoV and MERS-CoV is around 2–14 days. In contrast to influenza cases, they transmit the virus usually after the fifth day of the onset of disease when viral load maximizes in the nasopharyngeal secretions [1].

Prophylaxis

1. *Immunoprophylaxis* [9]: Exists currently only for influenza. It is advised by the Advisory Committee on Immunization Practices (ACIP) that all persons over 6 months of age be vaccinated annually against the predicted influenza strains which are most likely to cause infections in the next influenza season based on surveillance data. It is available as an annual influenza vaccine incorporating three or four live attenuated or inactivated influenza strains. It is available for administration as nasal sprays (live attenuated vaccine) and the intramuscular or intradermal route (killed vaccine).
2. *Chemoprophylaxis* [7]:
    - Oseltamivir and Zanamivir (neuraminidase inhibitors) are active against both influenza A and B viruses. It is indicated in exposed unvaccinated immunocompromised persons or people with co-morbid conditions who are at a high risk of developing influenza.
    - Oseltamivir should be given within 1 day after exposure at a dose of 75 mg once daily for persons 13 years and above of age for a minimum of 10 days after exposure to a recent contact with a known case of influenza.

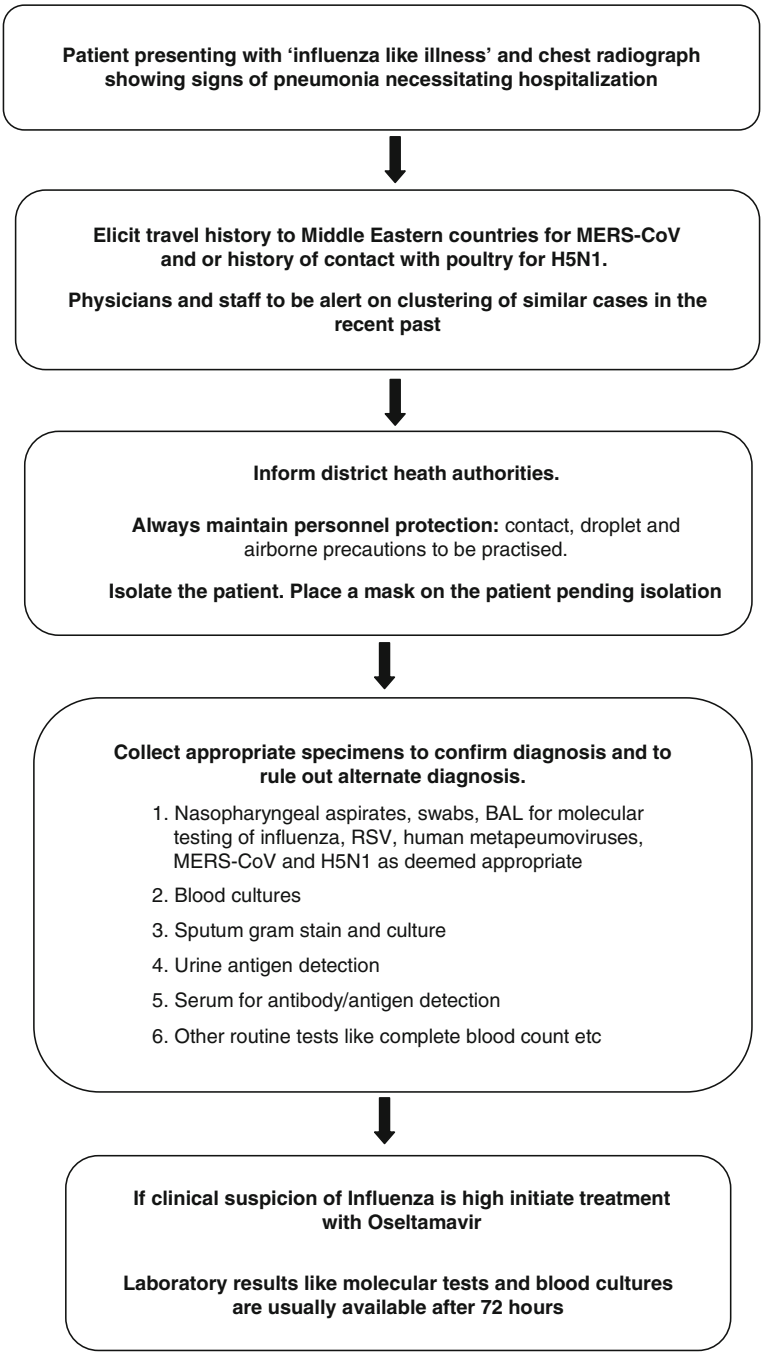
- Zanamivir is prescribed at two inhalations once daily for people above 5 years of age. If the exposed person develops respiratory symptoms, he should be given treatment doses of the drug.
- In case of H5N1, close contacts of strongly suspected cases of human avian influenza and personnel handling infected poultry are advised oseltamivir as chemoprophylaxis [10].

3. *Standard contact*, *droplet and airborne precautions* [11]:

Oftentimes, emergence of an infection of pandemic potential is not routinely expected by physicians and staff in their regular days' work. But going by the past experience especially in case of SARS-CoV, healthcare personnel were the ones at high risk of infection given the close proximity to the patient. Hence it is important that all staff follow the standard contact and droplet precautions for any case suspected to have a respiratory infection.

- Contact and droplet precautions include wearing of personnel protective equipment (PPE) such as gloves, gowns, eye and face shields.
- There is special emphasis on hand hygiene which must be diligently performed before and after contact with the patient, the potentially infectious material generated by him, before wearing and after removing PPE.
- Airborne precautions include placement of patients in an airborne infection isolation room (AIIR) and wearing of N95 or greater respirators and masks. Airborne transmission is especially possible while suctioning a ventilated patient, bronchoscopy, sputum induction, intubation and extubation and cardiopulmonary resuscitation.
- Pending placement of patient in the AIIR a face mask must be placed on the patient and the patient isolated in a single room to prevent spread of infection.
- Environment infection control must be followed per hospital infection control policy using a suitable disinfectant for disinfection and collection, transport and treatment of all infectious waste generated.

Summary and Algorithm



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Chapter 46
Food Poisoning

P.C. Rajeev and Jerry Johny

Key Points

- Food poisoning (FP) or food-borne disease (FBD) often manifests with gastrointestinal symptoms, although other organ involvement is possible.
- Most cases of FBD are self-limited and require only hydration and supportive care.
- Outbreaks of food-borne illnesses can become public health hazards. The emergency physician has a role in verifying the potential for a public health emergency.
- A toxicological emergency can present as FP. Early identification of the same needs a high index of suspicion.

Introduction

- The term FP or FBD covers illnesses acquired through consumption of contaminated food, and the outbreaks are defined as the occurrence of two or more cases of a similar illness resulting from ingestion of a common contaminated food [1].
- Contamination can occur from pathogens, like bacteria, viruses and protozoa, and toxic compounds like pesticides, heavy metals, etc.
- In the past, FBD often caused local or regional outbreaks. However, changes in environment, large-scale production and transport of food, changes in lifestyle, microbial adaptations, migration and travel have resulted in outbreaks that are varied and widespread. Contamination of food can occur during production, storage or transportation.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_46

- There is a major role for the emergency physician in the management of FBD. In addition to managing the individual patient, the ED physician has an added responsibility to check for the potential for a public health emergency. The ED physician has to coordinate with key personnel and help in implementing control and preventive measures.

Epidemiology

- FP remains a major health problem and accounts for 4 % of all death each year. A large proportion of these deaths occur in small children in developing countries [2].
- It is the second leading cause of death among children under the age of five. The global burden of infectious diarrhoea involves three to five billion cases, and nearly 1.8 million deaths annually are caused by contaminated food and water [3].
- A causative agent is never identified in majority of cases.
- FBD can be grouped under infections or intoxications. Infectious causes represent about 85 % of cases and may be divided as denoted (Table 46.1) [4].
- Food-borne infections are likely to become an increasing public health risk as the population ages and the number of immunocompromised patients with diseases, such as human immunodeficiency virus (HIV), diabetes and cancers, lives longer [5].
- Worldwide, most illnesses, hospitalizations and deaths caused by food-borne illnesses are not reported [6].

Pathophysiology

- More than 200 known diseases are caused by food-borne pathogens, and they produce illnesses through a variety of mechanisms.
- These pathogens cause illness either by the presence of preformed toxins that are present in the food before ingestion, by toxins that are produced after ingestion or by penetrating the intestinal epithelial barrier (Table 46.2) [4].
- The normal human intestinal tract has a number of physiologic mechanisms which protect against FBD. The acidic pH of the stomach, normal flora of the intestinal tract, normal intestinal motility and the immunologic tissues that are present in the GI tract help in defence against the invading pathogens. There is increase in susceptibility to FBD due to alteration of these protective mechanisms by medications, chronic systemic diseases, surgery, age or the pathogen itself [7].
- Food-borne pathogens have a number of adaptations that enhance their virulence. Toxins produced by the pathogens alter fluid and electrolyte movement

Table 46.1 Some important food-borne pathogens, toxins and chemicals [4]

Viruses	**Protozoa**	**Toxins**
Rotavirus	*Cryptosporidium* spp.	Tetrodotoxin (pufferfish)
Norwalk virus	*Cytomegalovirus*	Ciguatera poisoning
Hepatitis A virus	*Entamoeba histolytica*	Mushroom toxins
Hepatitis E virus	*Toxoplasma gondii*	Shellfish toxins
	Giardia lamblia	Mycotoxins (e.g. aflatoxins)
		Scombroid poisoning
Bacteria	**Helminths**	**Chemicals**
Bacillus cereus	*Ancylostoma* spp.	Pesticides (organophosphates, antimony)
Escherichia coli spp.	*Strongyloides*	Toxic metals (cadmium, copper, lead, mercury, tin)
Staphylococcus aureus	*Ascaris lumbricoides*	Nitrites (food preservatives)
Campylobacter spp.	*Trichinella spiralis*	Monosodium glutamate
Vibrio cholerae O1 or O139	*Trichuris trichiura*	
Clostridium botulinum	*Taenia solium/saginata*	
Listeria monocytogenes	*Diphyllobothrium* spp.	
Clostridium perfringens		
Salmonella typhi		
S. paratyphi		
Shigella spp.		
Yersinia enterocolitica		

across intestinal mucosal surfaces and cause cell membrane disruption or cell death leading to profuse diarrhoea and dehydration. Enteric viruses produce systemic toxicity by replicating themselves after entering cellular nuclei and causing cell lysis. These viruses require ingestion of only a few viral particles to cause disease.

Clinical Features: (Table 46.3) [8]

- FBD is suspected when two or more people in a household or a close community present simultaneously with GI symptoms. The most common symptoms are nausea, vomiting, diarrhoea and abdominal cramping.
- Severe food-borne infections present most commonly with systemic symptoms of fever, dehydration and malaise.
- The time of onset (incubation period), duration of illness, clinical symptoms, history of recent travel or antibiotic use, as well as the presence of blood or mucus in the stool, recent meals (including type of food, especially raw or uncooked food, unpasteurized or food products), cooking and refrigeration as well as details of others affected by similar symptoms can provide valuable clues to the aetiology.

Table 46.2 Types of FP [4]

Mechanism	Location	Illness	Stool M/E	Examples
Noninflammatory (enterotoxin)	Proximal small intestine	Watery diarrhoea	No faecal leucocytes	*Vibrio cholerae*, ETEC, *Cl. perfringens*, *Bacillus cereus*, *Staph aureus*, rotavirus, *Norwalk virus*, enteric adenoviruses, *Giardia lamblia*, *Cryptosporidium*
Inflammatory (invasion/ cytotoxin)	Colon/distal small intestine	Dysentery/inflammatory diarrhoea	PMN faecal leucocytes	*Shigella*, *Salmonella*, *C. jejuni*, EHEC, *Vibrio parahaemolyticus*, *Cl. difficile*, *E. histolytica*
Penetrating	Distal small intestine	Enteric fever	Mononuclear faecal leucocytes	*Salmonella typhi*, *Y. enterocolitica*, *Campylobacter*

Table 46.3 Major food-borne hazards: clinical features and samples [8]

Time to onset of symptoms	Predominant symptoms	Associated organism or toxin	Samples from cases/food handlers
(a) *Upper gastrointestinal (GI) tract symptoms (nausea, vomiting) occur first or predominate*			
<1 h	Nausea, vomiting, unusual taste, burning of mouth	Metallic salts	Vomit, urine, blood, stool
1–6 (mean 2–4) hours	Nausea, vomiting, retching, diarrhoea, abdominal pain, prostration	Staphylococcus aureus and its enterotoxins	Stool, vomit (swabs from nostril, skin lesions)
8–16 h (2–4 h) if emesis predominant	Vomiting, abdominal cramps, diarrhoea, nausea	Bacillus cereus	Rectal swab, stool
12–48 hours (mean 36 h)	Nausea, vomiting, watery non-bloody diarrhoea, dehydration	Norovirus	Stool
(b) *Lower GI symptoms (abdominal cramps, diarrhoea) occur first or predominate*			
6–96 h (usually 1–3 days)	Fever, abdominal cramps, diarrhoea, vomiting, headache	*Salmonella* spp., *Shigella*, enteropathogenic *E. coli*	Rectal swabs, stool
6 h to 5 days	Abdominal cramps, diarrhoea, vomiting, fever, malaise, nausea, headache, dehydration	*Vibrio cholerae*, *V. vulnificus*, *V. parahaemolyticus*	Stool
3–5 days	Fever, vomiting, watery noninflammatory diarrhoea	Rotavirus, astrovirus, enteric adenoviruses	Stool, vomit
3–7 days	Fever, diarrhoea, abdominal pain (can mimic acute appendicitis)	*Yersinia enterocolitica*	Stool
1 to several weeks	Abdominal pain, diarrhoea, constipation, headache, drowsiness, ulcers, variable often asymptomatic	*Entamoeba histolytica*	Stool
3–6 months	Nervousness, insomnia, hunger pains, anorexia, weight, loss, abdominal pain, sometimes gastroenteritis	*Taenia saginata*, *T. solium*	Stool, rectal swab
(c) *Neurological symptoms (visual disturbances, vertigo, tingling and paralysis)*			
Less than 1 h	Neurological and/or gastrointestinal symptoms	Shellfish toxin	Gastric washing
	Gastroenteritis, nervousness, blurred vision, chest pain, cyanosis, twitching, convulsions	Organic phosphate	Blood, urine
	Excessive salivation, perspiration, gastroenteritis, irregular pulse, pupils constricted, asthmatic breathing	Muscaria-type mushrooms	Vomit

(continued)

Table 46.3 (continued)

Time to onset of symptoms	Predominant symptoms	Associated organism or toxin	Samples from cases/food handlers
1–6 h	Tingling, numbness, gastroenteritis, temperature reversal, dizziness, dry mouth, muscular aches, dilated pupils, blurred vision, paralysis	Ciguatera fish toxin	
2 h to 6 days, usually 12–36 h	Vertigo, double/blurred vision, loss of light reflex, difficulty in swallowing, speaking and breathing, dry mouth, weakness descending, bilateral flaccid paralysis with preserved sensorium	*Clostridium botulinum* and its neurotoxins	Blood, stool, gastric washing
(d) *Generalised infection symptoms (fever, chills, malaise, prostration, aches, swollen lymph nodes)*			
7–28 (mean 14) days	Malaise, headache, fever, cough, nausea, vomiting, constipation, abdominal pain, chills, rose spots, bloody stools	*Salmonella* typhi	Rectal swab, stool
Varying periods (depends on specific illness)	Fever, chills, headache, arthralgia, prostration, malaise, swollen lymph nodes, etc.	*C. jejuni*, *B. anthracis*, *Brucells* sp., *C. burnetii*, *Fr. tularensis*, *L. monocytogenes*, *P. multocida*	

- Comorbidities, including any potential cause of immunodeficiency or use of immunosuppressive drugs, should also be enquired.
- During the clinical examination, special attention should be focused on vital signs, degree of dehydration and abdominal examination. The presence of fever, systemic symptoms and bloody diarrhoea suggests invasive diarrhoeal illness.
- Physical examination should exclude other causes of gastrointestinal emergencies such as appendicitis, perforation and mesenteric ischaemia.

Investigations

- Most patients with FP do not require diagnostic testing as the disease is self-limiting and resolves before the results of stool studies are available.
- Laboratory tests are indicated in toxic patients, patients with suspected invasive pathogens or during outbreaks.
- Stool cultures are required if the patient is febrile, has bloody diarrhoea and has severe abdominal pain or the illness is severe or protracted [9]. Multiple stool specimens are likely to yield better results, and the initial sets should be performed in the ED [9].

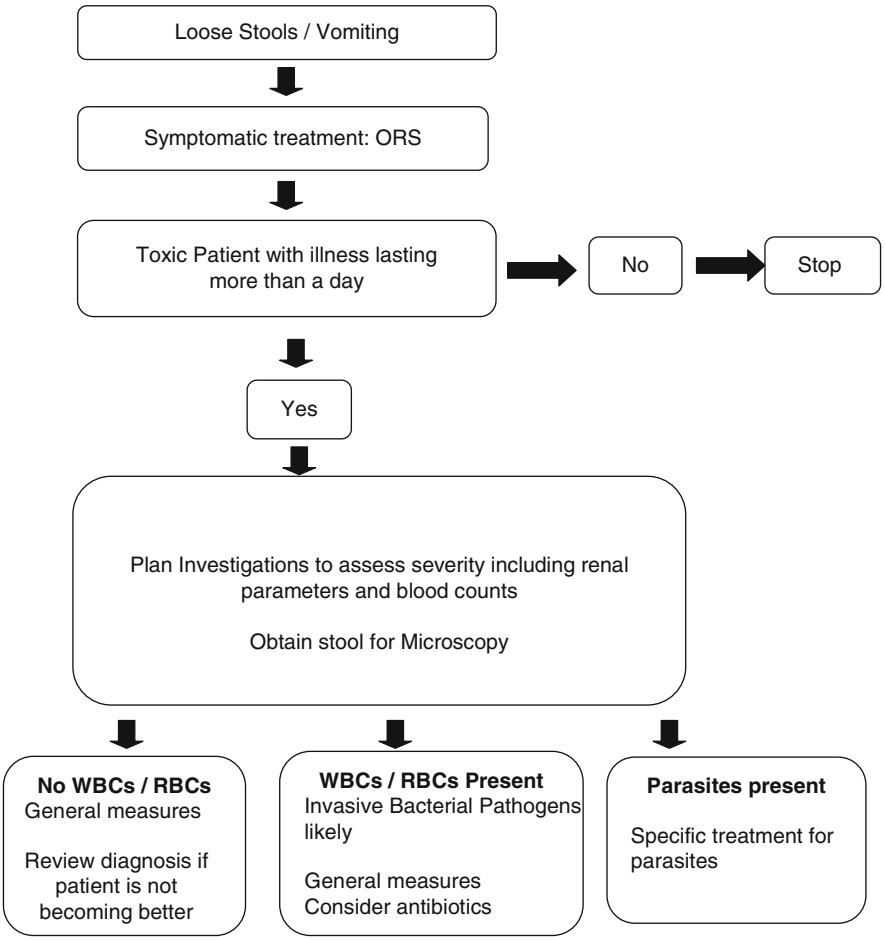
- In patients with chronic symptoms and in immunocompromised, stool examination for ova and parasites should be done.
- Renal function tests, electrolytes and a complete blood count should be obtained in toxic patients.
- Other laboratory tests include faecal leucocytes, lactoferrin, faecal occult blood, *C. difficile* antigen and Gram stain. The presence of leucocytes in stool suggests an invasive pathogen, and stool culture yields are greatly increased [10, 11].
- The investigation and control of FBD outbreaks require multidisciplinary skills in the areas of clinical medicine, epidemiology, laboratory medicine, food microbiology and chemistry, food safety and food control, besides risk communication and management.

Treatment

- Most episodes of acute gastroenteritis due to FBD are self-limited and require only adequate hydration and supportive care.
- Initial treatment of patients with FP should focus on assessment and reversal of dehydration, either through oral rehydration solution (ORS) especially in children or through IV fluids in seriously dehydrated cases (Table 46.4).
- The World Health Organization recommends initial therapy with a glucose-containing fluid for oral rehydration [12]. ORS can be made by dissolving 3.5 g of sodium chloride, 2.9 g of trisodium citrate or 2.5 g of sodium bicarbonate, 1.5 g of potassium chloride and 20 g of glucose or 40 g of sucrose in 1 l of clean water.
- In patients with evidence of more severe dehydration, intravenous fluid resuscitation with normal saline or lactated Ringer's solution is the preferred treatment.
- Antimotility and antisecretory agents are generally avoided in patients with dysentery due to concerns of prolonging the illness.
- Probiotic like lactobacillus has been proven to be effective in restoring the normal gastrointestinal flora that has been disrupted by the diarrhoeal illness. It is more effective with traveller's diarrhoea as well as in non-specific diarrhoea among children.
- The decision to initiate antibiotic therapy for FBD should be based on severity and duration of clinical signs and symptoms (Table 46.5) [13].

Disposition and Follow-Up

- Most patients with uncomplicated FP can be discharged home following initial assessment and symptomatic relief.



Always review the diagnosis and consid er toxicological, metabolic and surgical etiologies in atypical investigations and non-resolving illnesses.

Table 46.4 An approach to FP cases

- Patients who have severe dehydration, systemic symptoms, significant comorbidities or toxic appearance should be admitted for continuous monitoring and definitive management when initial evaluation and stabilisation are complete.
- Discharged patients should receive instructions on proper hygiene, such as frequent hand washing, to protect non-ill family members and contacts.
- Patients discharged with pending stool culture results or other pending stool studies should have follow-up arranged before discharge.

Table 46.5 Treatment of common diarrhoeal diseases

Species	Specific treatment
Bacterial agents	
Enterotoxigenic *Escherichia coli*	Ciprofloxacin 500 mg twice daily for 3 days or co-trimoxazole 960 mg twice daily for 3 days
Campylobacter jejuni	Azithromycin 500 mg once daily for 3 days or erythromycin 500 mg twice daily for 5 days
Salmonella	Ciprofloxacin 500 mg twice daily for 7 days or Azithromycin 1 g once daily for 1 day followed by 500 mg once daily for next 6 days
Shigella	Co-trimoxazole 960 mg twice daily for 3 days, if resistant use ciprofloxacin 500 mg twice daily for 3 days
Vibrio cholerae	Ciprofloxacin 1 g single dose or doxycycline 100–300 mg single dose or co-trimoxazole 960 mg twice daily for 3 days with IV fluids
Yersinia enterocolitica	Ciprofloxacin 500 mg twice daily or co-trimoxazole 960 mg twice daily for 3 days
Clostridium difficile	Metronidazole 400 mg thrice daily or vancomycin 125 mg four times daily for 10–14 days
Viruses	
Rotavirus	Supportive care/rehydration
Norwalk virus	Supportive care/rehydration
Parasites	
Entamoeba histolytica	Metronidazole 800 mg three times daily for 10 days followed by diloxanide furoate 500 mg thrice daily for 10 days
Giardia duodenalis	Metronidazole 400 mg thrice daily for 5 days or tinidazole 2 g single dose
Round worms	Mebendazole 100 mg twice daily for 3 days
Tape worms	Praziquantel 20 mg/kg or niclosamide 2 g single dose
Schistosomiasis	Praziquantel 40–60 mg/kg in 2 or 3 divided doses depending on fluke type

Special Populations

- Elderly patients, young children and the immunocompromised are at increased risk for food-borne diseases. They are more likely to have a severe illness, atypical presentations and long-term sequelae. Patients with HIV or other immunocompromised states can rapidly develop life-threatening symptoms.
- The threshold for diagnostic testing should be much lower than in the general population. Strongly consider admission in this group of patients if dehydration or systemic symptoms are present [14].

Chronic Sequelae of Food-Borne Illnesses

Apart from the immediate effects, several food-borne pathogens are capable of triggering chronic disease, probably via immune mechanisms. Arthritis, septic and reactive, inflammatory bowel disease, haemolytic uraemic syndrome, Guillain-Barré syndrome [15] and several autoimmune disorders can be triggered by food-borne pathogens or their toxins.

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Chapter 47
HIV-Related Emergencies

Menon Sachin Venugopal and Vivek Gopinath

Key Points

1. In all cases with a background history of HIV, assess the risk for opportunistic infections, through physical signs such as oral candidiasis, weight loss, and skin manifestations as well as CD4 counts.
2. Consider TB and PCP in all patients admitted with respiratory symptoms.
3. For patients with HIV with unknown fever, the most probable site of infection is usually the respiratory system or central nervous system.
4. Always obtain a CT brain scan before considering lumbar puncture in HIV patients presenting with headache and altered sensorium.
5. For patients with HIV with unknown fever, the most probable site of infection is usually the respiratory system or central nervous system.
6. Be alert to the possibility of drug toxicity as a potential cause for the symptoms.

Introduction

- HIV-associated diseases and their related emergencies are becoming more common in the emergency department (Figs. 47.1, 47.2, 47.3, and 47.4).
- Many of such patients are unaware of their HIV status or their drug regimen.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_47

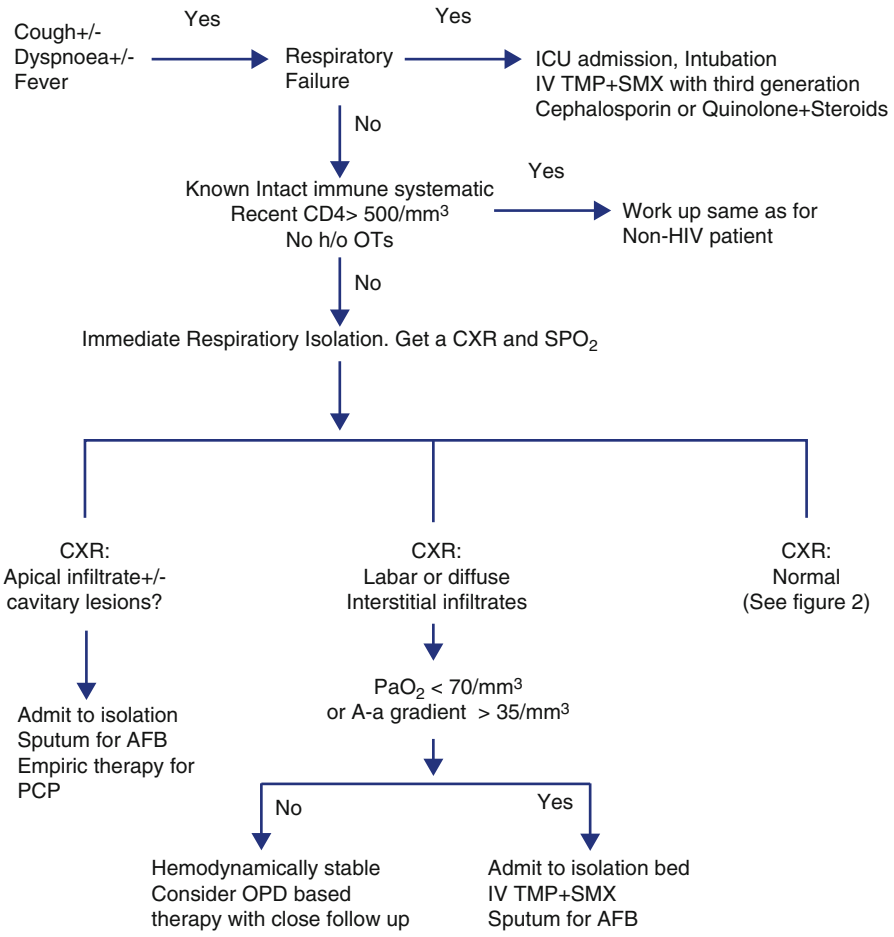
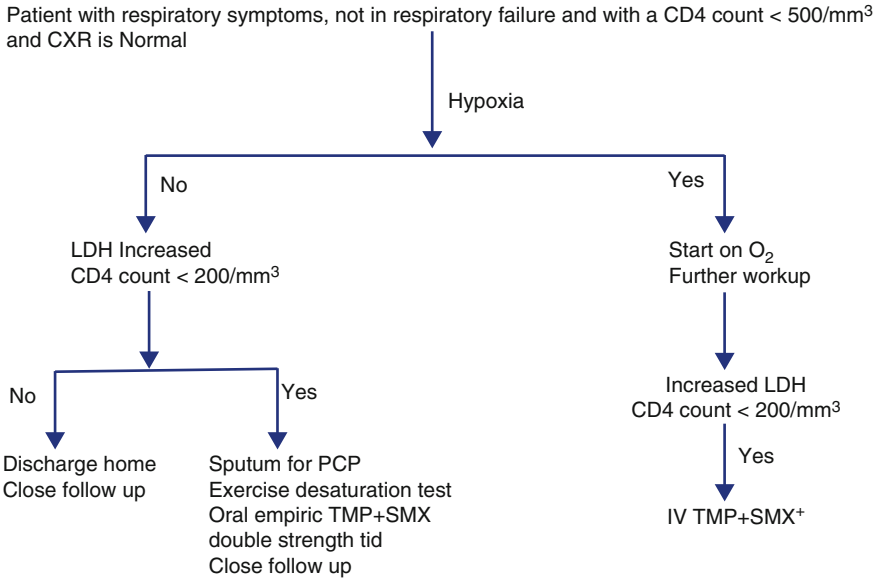


Fig. 47.1 Approach to HIV patient with respiratory symptoms

- Highly active antiretroviral therapy (HAART)-related complications also are becoming common.
- Although AIDS itself is incurable, many AIDS-related complications can be treated, and this can augment the long-term control achieved by HAART.

History

- Enquire patients with constitutional symptoms or chronic cough with fever about their HIV status.
- About 30 % of HIV patients may not voluntarily disclose their HIV status when they present to the ED [1].



*Trimethoprim - sulfamethoxazole: 15 mg/kg of trimathoprim in four divided doses, if sulfa allargy: Use IV paritamidine puls third-ganeration oaphaloeporlin or qulnolone.

OI: Opportunistic infections
TMP + SMX: Trimethoprim + sulfamethoxazole
PCP: Pneumocystis carinii pneumonia

Fig. 47.2 Approach to an HIV patient with respiratory symptoms and a normal chest X-ray. *Trimethoprim-sulfamethoxazole: 15 mg/kg of trimethoprim in four divided doses. If sulfa allergy: use IV pentamidine plus third-generation cephalosporin or quinolone. *OI o*pportunistic infections, *TMP+SMX* trimethoprim+sulfamethoxazole, *PCP p*neumocystis carinii pneumonia

- Increased risk of HIV infection is seen in male homosexuals, bisexuals, intravenous drug users, commercial sex workers, HIV sexual contacts, and hemophiliacs who had blood transfusions before proper HIV screening tests were available and mandatory [2].
- History should focus on the complaints suggestive of infectious etiology such as fever, rash, diarrhea, headache, and respiratory symptoms. Although patients may not be forthcoming with their sexual and drug history, most will confide if the questions are asked in a frank, yet nonjudgmental manner.
- In a suspected HIV patient, the stage of the disease has to be determined. Depending on the stage of the disease, the manifestations of HIV and its complications varies.
- Previous history of hospitalization and serious illnesses should be taken. The history of an opportunistic infection in the past is likely if that patient had a CD4 count less than 200/mm^3 [3].

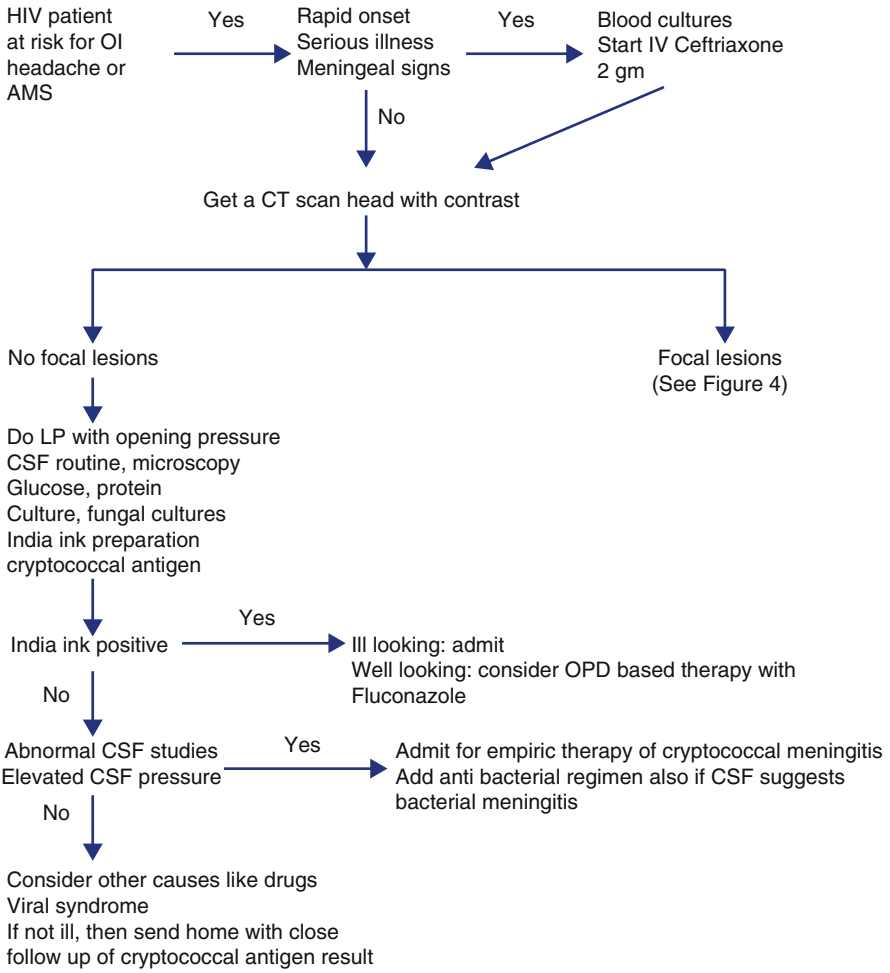


Fig. 47.3 Approach to HIV patient with CNS symptoms

Respiratory Emergencies

- Respiratory complaints constitute the most common symptoms of patients coming to the ER.
- Respiratory symptoms may not always be secondary to infectious diseases, as conditions such as lymphomas or Kaposi's sarcoma, which are common in HIV patients.
- The recommended clinical approach in the ED would be a detailed history, thorough clinical examination, chest X-ray, oxygen saturation, serum LDH, blood cultures, sputum microscopy, and culture for bacteria and fungi.

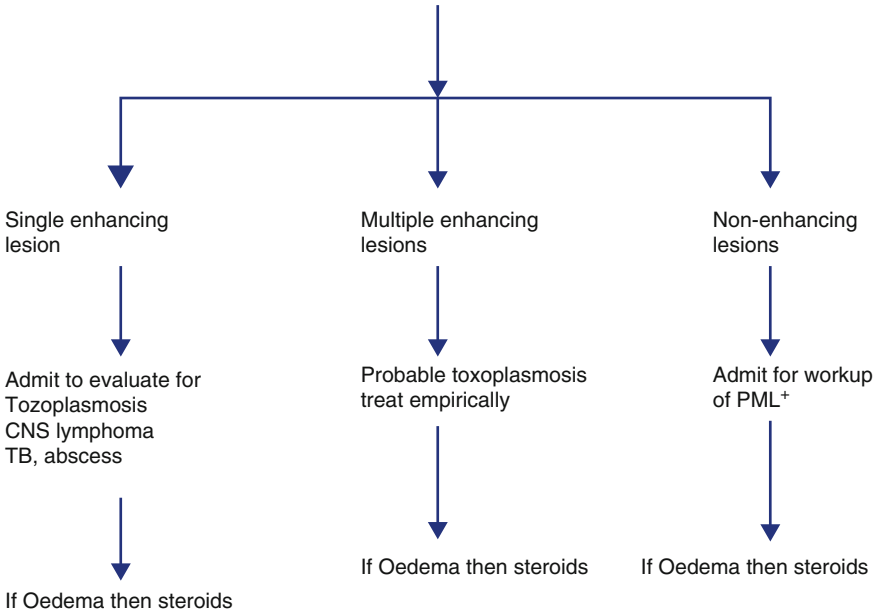


Fig. 47.4 Approach to an HIV patient with CNS symptoms and focal lesions on CT. * progressive multi-focal leukoenchephalopathy

- CD4 count of the patient can give a fairly good idea of the likely pathogens in a patient with HIV. A patient with a low CD4 count and respiratory symptoms should be hospitalized and empirically started on treatment for bacterial pneumonia as it is the most common cause of respiratory symptoms.
- Look for a definitive diagnosis. Patients with low oxygen saturation, severe respiratory symptoms, and diffuse crackles on admission should be suspected to be having *Pneumocystis jiroveci* pneumonia.
- Examination of the oral cavity is essential in all patients presenting with cough, as the presence of oral candidiasis in any patient with dyspnea is suggestive of PCP.

Bacterial Infections

- Patients with HIV are at increased risk of developing infections which are common in immunocompetent individuals.
- Recurrent severe bacterial pneumonia, defined as two episodes in a year, is considered to be a WHO clinical stage 4 diagnosis [4]. Refer to Table 47.1.

- The most common cause of community-acquired pneumonia in adults is *Streptococcus pneumoniae*, especially in patients who have not been vaccinated for it.
- In patients with severe pneumonia, having newer urinary antigen testing can result in a rapid diagnosis of *Streptococcus pneumoniae*.
- Other gram-negative organisms such as *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Escherichia coli*; atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydophila* (*Chlamydia*) *pneumoniae*, and *Legionella pneumophila*; and community-acquired *Staphylococcus aureus* are responsible for the remaining cases of bacterial pneumonia in HIV-infected patients [5].
- Patients with low CD4 counts are at higher risk of developing pneumonia secondary to typical organisms such as *P. jiroveci*, *Cryptococcus neoformans*, *Pseudomonas aeruginosa*, *Toxoplasma gondii*, *Histoplasma capsulatum*,

Table 47.1 WHO clinical staging of HIV infection

Primary HIV infection	Asymptomatic
	Acute retroviral syndrome
Clinical stage 1	Asymptomatic
	Persistent generalized lymphadenopathy
Clinical stage 2	Moderate unexplained weight loss (<10 % of presumed or measured body weight)
	Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
	Herpes zoster
	Angular cheilitis
	Recurrent oral ulceration
	Papular pruritic eruptions
	Seborrheic dermatitis
	Fungal nail infections
Clinical stage 3	Unexplained severe weight loss (>10 % of presumed or measured body weight)
	Unexplained chronic diarrhea for >1 month
	Unexplained persistent fever for >1 month (>37.6 °C, intermittent or constant)
	Persistent oral candidiasis (thrush)
	Oral hairy leukoplakia
	Pulmonary tuberculosis (current)
	Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
	Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
	Unexplained anemia (hemoglobin <8 g/dL)
	Neutropenia (neutrophils <500 cells/μL)
	Chronic thrombocytopenia (platelets <50,000 cells/μL)

Table 47.1 (continued)

Clinical stage 4	HIV wasting syndrome, as defined by the CDC (see Table 47.2)
	Pneumocystis pneumonia
	Recurrent severe bacterial pneumonia
	Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
	Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
	Extrapulmonary tuberculosis
	Kaposi's sarcoma
	Cytomegalovirus infection (retinitis or infection of other organs)
	HIV encephalopathy
	Cryptococcosis, extrapulmonary (including meningitis)
	Disseminated nontuberculous *Mycobacteria* infection
	Progressive multifocal leukoencephalopathy
	Candida of the trachea, bronchi, or lungs
	Chronic cryptosporidiosis (with diarrhea)
	Chronic isosporiasis
	Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
	Recurrent nontyphoidal *Salmonella* bacteremia
	Lymphoma (cerebral or B-cell non-Hodgkin)
	Invasive cervical carcinoma
	Atypical disseminated leishmaniasis
	Symptomatic HIV-associated nephropathy
	Symptomatic HIV-associated cardiomyopathy
	Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis), central nervous system toxoplasmosis

Chlamydia immitis, *Cytomegalovirus*, *Mycobacterium avium* complex, and *Aspergillus* species [6].

- Tuberculosis is a definite possibility in patients with HIV, and the presentation is usually atypical with lower lobe involvement.
- HIV-infected patients may have multi-organism infections. Hence, adequate and appropriate empirical treatment should be considered initially which can be narrowed down to more specific treatment once more data becomes available regarding the patient.
- The best antibiotic for empirical treatment would be a second- or third-generation cephalosporin or cloxacillin, if *Staphylococcus aureus* is suspected.
- It would be prudent to add a macrolide or doxycycline for covering the atypical organisms.
- In places with a high prevalence of tuberculosis, such as India, it is advisable to avoid fluoroquinolones, because of the concern of inducing resistance and also of masking tuberculous infection.
- In HIV-infected patients, who have been recently discharged from a hospital and who are known to have low CD4 counts, broad-spectrum antibiotics should be

considered because of the increased frequency of nosocomial bacterial pneumonias [7]. The antibiotic of choice in such patients would be vancomycin if MRSA or resistant *S. pneumoniae* is suspected or carbepenems (meropenem or imipenem) if ESBL organisms are suspected.

Formerly Pneumocystis Carinii Pneumonia (PCP)

- PCP is the second most common cause of respiratory infections in HIV-infected individuals and can also occur together with bacterial pneumonias or tuberculosis.
- PCP presents classically with a nonproductive cough, worsening dyspnea especially on exertion, and fever.
- On examination the lungs may be clear to auscultation or may have signs out of proportion to the chest X-ray.
- The chest X-ray usually shows bilateral ground-glass opacities but without a lobar pattern of opacities.
- Patients usually have a serum LDH >500 mg/dL. The elevated serum LDH is of supportive benefit in suspecting PCP in patients who have severe respiratory distress especially when chest X-ray or oxygen saturations are unavailable [8].
- The first-line treatment for patients with PCP is intravenous trimethoprim/sulfamethoxazole, although co-trimoxazole tablets can also be used PO if IV preparation is not available.
- Hypoxia shown by significant resting or ambulatory oxygen desaturation or PaO_2 of <70 mmHg on an ABG warrants the use of steroids [8].
- 5–9 % of patients with PCP will develop pneumothorax due to rupture of pneumatoceles. Hence, physicians should be on the guard for signs of the same [9].

Pulmonary Tuberculosis (PTB)

- Mycobacterium tuberculosis is the leading cause of death in HIV patients.
- It is seen that at least a third of HIV patients are infected with TB [10].
- Respiratory complaints especially with recent weight loss, night sweats, evening rise of temperature, and history of contact with TB should be suspected to have PTB.
- Due to the higher risk of developing multidrug-resistant (MDR) TB, patients with past history of TB should be screened for MDR TB. Recent initiation of HAART with development of symptoms should induce suspicion of immune reconstitution inflammatory syndrome (IRIS), which occurs due to reactivation of dormant immunity to the TB bacillus.

- Bedside diagnosis of TB may be possible in the near future as new urinary tests are in the pipeline. This is particularly useful in patients with CD4 <100 cells/mm3 [11].

Asthma and COPD

- HIV patients have a high incidence of bronchial hypersensitivity and high IgElevels. This correlates with the increased prevalence of asthma and COPD in these patients [12].
- Patients with history of TB have irreversible lung damage, leading to chronic lung disease.
- Noninfective causes should also be considered in patients with HIV who present with respiratory symptoms, and a beta agonist can be tried if possible.

Mechanical Ventilation

- Before the advent of HAART, mechanical ventilation of HIV patients was generally not encouraged as the survival was poor. But the introduction of HAART and better understanding of the pathologies of respiratory distress in HIV patients have led to an improved survival of critically ill HIV patients, up to 61–80 % in high-resource settings [13].

Cardiovascular Emergencies

There has been an increased risk of cardiovascular disease in HIV patients. This could be because of the increased survival of patients with the advent of HAART.

Coronary Artery Disease (CAD)

- In HIV infection, there are an increased inflammatory state, endothelial dysfunction, hyperlipidemia, and thrombosis. All these are the right mix to develop CAD [14].
- Treatment with protease inhibitors (PIs) also increases the above responses especially on prolonged treatment [14].
- There is an increased incidence of acute MI after the introduction of PIs and HAART.
- All patients with HIV, with suggestive symptoms, should be evaluated for acute coronary syndrome (ACS). All the revascularization procedures – thrombolysis, percutaneous coronary intervention, and coronary artery bypass grafting – should be considered in patients regardless of HIV infection [15].

Pericardial Disease

- There is a rise in the incidence of pericarditis in patients with HIV and the usual etiology is TB [16].
- The remaining is caused by congestive cardiac failure, Kaposi's sarcoma, and bacterial infections [15].
- The clinical presentation is usually with dyspnea, oedema, and ECG changes of myopericarditis.
- The addition of steroids to the treatment regimen in HIV patients with tuberculous pericardial effusion is still controversial.

Neurologic Emergencies in HIV

- An HIV-infected patient can present with varied neurological manifestations ranging from opportunistic infections to neurocognitive diseases.
- HIV-associated neurocognitive disorders (HAND) include a clinical spectrum ranging from asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [16].
- HAD represents overt dementia and impaired day-to-day functioning, and milder forms exist which could be diagnostic dilemmas.
- Patients with HAND may present with delirium when they have a systemic disease. Seventy-five to 90 % of AIDS patients have neurological manifestations [17].
- Symptoms such as headache, altered sensorium, seizures, or new focal neurological deficit (FND) in an HIV patient should prompt the emergency physician to work up for an opportunistic infection.
- The presence of FND warrants a neuroimaging, at least a CT scan, to rule out focal lesions [17].

Cryptococcal Meningitis

- Cryptococcal meningitis is an opportunistic infection, which if untreated has a mortality rate that can approach 100 %. *C. neoformans*, a fungus, is the causative organism of meningoencephalitis [17].
- It presents with fever, subacute headache, cranial nerve palsies, or altered sensorium.
- Meningeal signs are seen only in a third of the patients, and hence the absence of the same should not preclude the diagnosis of meningitis [18].
- Cryptococcal meningitis usually presents at a CD4 count <100. Emergency physicians should have a high index of suspicion for the same as the CD4 count may not always be readily available to them. An LP should not be delayed and usually shows a lymphocytic predominance.

- The CSF opening pressure (OP) which is normally between 90 and 180 mm H_2O is usually increased to more than 200 mm H_2O in about 75 % of the patients. This elevated CSF OP with the presence to focal neurological deficits warrants the use of serial LPs or measures for continuous drainage of CSF to maintain the OP around 10 mm H_2O.
- Goal of opening pressure reduction is by about 50 % and can usually be obtained by removal of up to 20 cm of CSF. Daily LPs or in severe cases even placement of ventriculoperitoneal shunt may be required.
- The presence of cryptococcal antigen in the serum or CSF has a sensitivity >95 % for confirming a case of cryptococcal meningitis. India ink staining is positive in 80 % of cases of patients with AIDS [22].
- A point-of-care lateral flow cryptococcal assay has been developed which may reduce the delay of diagnosis in resource-limited situations [19].
- The treatment of cryptococcal meningitis consists of three phases:

  1. Induction phase: Amphotericin B combined with 5-flucytosine
  2. Consolidation phase: High-dose fluconazole
  3. Maintenance phase: Low-dose fluconazole

- In resource-limited areas, in the paucity of 5-flucytosine, high-dose fluconazole may be combined with amphotericin B for the induction phase.

Toxoplasmosis

- *T. gondii*, a protozoan, is the most common cause of focal lesions in the brain in HIV patients. It typically is seen in patients with CD4 counts <200 [17].
- Toxoplasmosis typically presents with fever, headache, altered sensorium, FNDs, and seizures. CT scan usually shows focal multiple ring-enhancing lesions. Though serum studies for toxoplasma antibody can be done, a positive serology could be seen in both active disease and previous exposure.
- The initial treatment is with a combination of pyrimethamine and sulfadiazine with folic acid. Co-trimoxazole is an alternative. Majority of the patients will respond to the treatment within 5 days. By 2 weeks 90 % of the patients will have responded to the treatment.
- Patients who do not respond to treatment are required to be evaluated for primary CNS lymphoma (PCNSL).

TB Meningitis

- Meningitis is a manifestation of extra-pulmonary tuberculosis, especially in patients with late stages of immunosuppression. It is associated with high mortality and morbidity. The symptoms are usually nonspecific with headache, fever, multiple cranial nerve palsies, seizures, and altered sensorium. On examination

signs of meningeal irritation may be present. The symptoms are usually present for more than 2 weeks. Acute presentation is also known [20].
- In countries with a high prevalence of tuberculosis like India, it should be high on the differential diagnosis of space occupying lesions.
- The paucity of a rapid and effective point-of-care test for TB meningitis makes the diagnosis difficult in the ED. A CSF examination showing a lymphocytic pleocytosis with low glucose is diagnostic. AFB staining and culture of CSF are less sensitive but have better sensitivity with large-volume LP.
- About 30–50 % of patients with TBM have active pulmonary TB. Hence, chest X-ray and sputum AFB may help in diagnosis. ATT along with steroids should be initiated immediately on diagnosis of TBM [20].

Therapy-Related Emergencies

- HAART is usually initiated in an HIV patient on the basis of the CD4 count and the presence of AIDS-defining conditions (Table 47.2).
- Hepatotoxicity can occur with any of the class of drugs used in HAART. It can range from an asymptomatic increase in transaminases to fulminant hepatic failure. Nevirapine, didanosine, and stavudine are known to be the most hepatotoxic [21].
- Lactic acidosis is another adverse reaction of HAART caused by mitochondrial toxicity of nucleoside reverse transcriptase inhibitors such as didanosine and stavudine. Lactic acidosis usually presents with nonspecific symptoms such as fever, vomiting, and muscle pains with an increased serum lactic acid levels. Serum levels more than 10 mM/dL are dangerous and require prompt and aggressive treatment with hydration, mechanical ventilation, and dialysis. It is also associated with a prolonged recovery period which can last as long as 28 weeks [21].
- Enfuvirtide, a fusion inhibitor, can cause painful nodules at injection site, while maraviroc, an oral entry inhibitor, can produce postural hypotension.

See Table 47.3 for specific drugs causing adverse effects.

Table 47.2 Specific CD4 counts and diseases

CD4 count	Diseases
200–500	Lymphadenopathy, oral candidiasis, idiopathic thrombocytopenic purpura, or hairy leukoplakia. This stage also predisposes the patient to more virulent pathogens, such as *M. tuberculosis* or *S. pneumonia*
<200	*Pneumocystis carinii* pneumonia (PCP), tuberculosis (TB), toxoplasmosis, cryptosporidiosis, isosporiasis, esophageal candidiasis, cryptococcosis, and histoplasmosis
<50	Disseminated *Mycobacterium avium* complex (MAC) or cytomegalovirus (CMV)

Table 47.3 Adverse effects of specific HAART drugs

Drug	Adverse effects
Nucleoside reverse transcriptase inhibitors	
Abacavir	Hypersensitivity reaction (fever, rash, myalgias), Stevens-Johnson syndrome
Didanosine	Lactic acidosis, pancreatitis, peripheral neuropathy
Emtricitabine	Lactic acidosis/hepatic steatosis (rare), skin hyperpigmentation/discoloration
Lamivudine	Lactic acidosis/hepatic steatosis (rare)
Stavudine	Lactic acidosis, pancreatitis, peripheral neuropathy, ascending muscle weakness, dyslipidemia
Tenofovir	Renal failure, pancreatitis, headache, diarrhea, nausea, vomiting
Zidovudine	Bone marrow suppression
Non-nucleoside reverse transcriptase inhibitors	
Delavirdine	Rash (blisters), transaminitis, headache
Efavirenz	Psychosis, depression, suicidal ideation
Nevirapine	Hepatic failure, Stevens-Johnson syndrome
Protease inhibitors	
Amprenavir	Toxicity from propylene glycol diluent
Atazanavir	Increased indirect bilirubin, prolonged PR interval
Darunavir	Nausea, diarrhea, headache, rash
Fosamprenavir	Rash, hyperlipidemia
Indinavir	Nephrotoxicity, urolithiasis, indirect hyperbilirubinemia
Nelfinavir	Secretory diarrhea
Ritonavir	Nausea, vomiting, hyperlipidemia, hyperglycemia
Saquinavir (always given with ritonavir)	Lipodystrophy, hyperglycemia
Tipranavir	Hepatotoxicity, intracerebral hemorrhage
Entry and fusion inhibitors	
Enfuvirtide	Injection site reaction, pneumonia
Maraviroc	Postural hypotension, abdominal pain
Integrase inhibitors	
Raltegravir	Nausea, headache, increased CPK

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Chapter 48
Malaria

Menon Sachin Venugopal and B.L. Harikrishnan

Key Points
- Malaria is a disease with a wide spectrum of clinical manifestations.
- Majority of the infections are uncomplicated.
- Severe malaria is a multisystem disease.
- In uncomplicated cases chloroquine is still the drug of choice.
- Artemisinin combination therapy is used in complicated cases.

Introduction

- Malaria is a disease which is a burden on the public health system.
- The annual incidence of confirmed malaria cases reported by the National Vector Borne Disease Control Programme is around 1.5 million cases, 50 % of which are due to *Plasmodium falciparum* (Pf) [1].
- In 2014, the number of cases reported is 733,049, of which 472,906 cases are *Plasmodium falciparum* with 280 deaths [1].
- Early identification and prompt institution of treatment will prevent the morbidity and mortality due to malaria.
- Majority of the cases of malaria are uncomplicated and can be treated with appropriate oral therapy.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_48

- Severe malaria is a multisystem disease, which can present with many complications requiring specific treatment.
- In spite of massive control measures, there has been an increase in the resistance of the parasite to drugs and the vector to insecticides. The major contributory factors to this resurgence are human travel and migration.

Aetiopathogenesis

- Malaria is caused by obligate intra-erythrocytic protozoa of the genus *Plasmodium*.
- Nearly all human infections are caused by the following five species of the genus *Plasmodium* (Table 48.1):
- The vector involved in parasite transmission is the *Anopheles* mosquito.
- Transmission is also known with exposure to infected blood products (transfusion malaria) and also vertical transmission.
- *Premunity* is a term used to signify progressive development of immunity in individuals exposed to an infective agent. It is a phenomenon seen in hyper-endemic areas and holo-endemic areas, where immunity is developed among local inhabitants due to repeated encounters with the parasite.

Clinical Features

- Fever: high grade, intermittent, associated with chills and rigours followed by sweating.
- This pattern of fever occurs due to the rupture of large parasite-infected erythrocytes and high levels of circulating tumour necrosis factor alpha in erythrocytic cycle.
- For early diagnosis it is prudent to consider malaria in any patient presenting with fever with chills.
- In *P. vivax* infection, there is a 48 h cycle of fever.
- In *P. falciparum*, the periodicity of fever is more frequent.

Table 48.1 Species of malarial parasite

Species	Incubation period	Characteristic feature
P. falciparum	9–14 days	Causes majority of deaths due to malaria
P. vivax	12–17 days	Predominant infection worldwide 48 h cycle of fever
P. ovale	12–20 days	
P. malariae	18–40 days	
P. knowlesi	9–12 days	Predominant infection in Southeast Asia

- Headache, malaise and arthralgia are usually seen.
- Respiratory symptoms like cough and chest pain can be seen in repeated *P. vivax* infection.
- Abdominal pain, diarrhoea and vomiting can also be presenting complaints.
- Clinical examination usually reveals fever, tachycardia, pallor, jaundice, postural hypotension and organomegaly (liver and spleen).
- The presentation could also be with complications or severe infection.
- Clinical deterioration usually appears 3–7 days after onset of fever.
- Severe malaria can be diagnosed by using the WHO criteria (Table 48.2.)

Table 48.2 WHO criteria for severe malaria [2]

Manifestation	Definition
Cerebral malaria	Impaired consciousness or unarousable coma without a cause, with a GCS <9
	Prostration
	Failure to feed
	Convulsions – more than two episodes in 24 h
Severe anaemia	Haematocrit <15 % or Hb <5 g/dL with a parasite count >10,000/μl
Renal failure	Urine output <400 ml/24 h in adults (<12 ml/kg/24 h in children)
	Serum creatinine >265 μmol/l (>3.0 mg/dL) despite adequate volume resuscitation
Pulmonary oedema and ARDS	The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoxaemia and positive end-expiratory pressure
Hypoglycaemia	Blood glucose level <2.2 mmol/l (<40 mg/dL)
Circulatory collapse	Systolic BP <70 mmHg in patients >5 years of age
	<50 mmHg in children aged 1–5 years
	Cold clammy skin or
	Core-skin temperature difference >10 °C
Abnormal bleeding and/or disseminated intravascular coagulation (DIC)	Spontaneous bleeding from gums, nose, gastrointestinal tract or laboratory evidence of DIC
Repeated generalised seizures	>2 seizures observed within 24 h
Acidaemia/acidosis	Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l)
Macroscopic haemoglobinuria	Haemolysis not secondary to G6PD deficiency
Impaired consciousness	Rousable mental condition
Prostration or weakness	Generalised weakness so that the patient is unable to walk or sit up without assistance
Hyperparasitaemia	>2 % parasitized erythrocytes or >250,000 parasites/μl (in non-immune individuals)
Hyperpyrexia	Core body temperature >40 °C
Hyperbilirubinaemia	Total bilirubin >43 μmol/l (>2.5 mg/dL)

- *Cerebral malaria:*
  - Characterised by acute onset of altered sensorium with fever.
  - Untreated cases may show signs of meningeal irritation, coma and seizures.
  - Focal neurological deficits like cerebellar signs, extrapyramidal syndrome, stroke, etc. may be seen.
- *Gastrointestinal manifestations:*
  - Can present with nausea, vomiting or diarrhoea.
  - Jaundice is usually due to the haemolysis or hepatocellular involvement (hepatitis).
  - Can result in death due to hypovolaemic shock, acute renal failure or liver failure.
- *Pulmonary manifestations:*
  - Can present as acute respiratory distress syndrome (ARDS) or acute alveolar haemorrhage.
  - Aspiration pneumonia can occur due to the impaired consciousness.
- *Blackwater fever:*
  - Occurs because of intravascular haemolysis in patients with severe falciparum malaria.
  - Haemolysis could be due to inadequate or late initiation of antimalarials.
  - Onset is usually sudden with fever, rigours, anaemia, jaundice and haemoglobinuria.
  - Can be complicated by hypovolaemic shock and acidosis.
  - Death can occur due to renal or liver failure, severe anaemia, shock or secondary infection.

Investigations

Demonstration of Parasite

- Demonstration of asexual forms of parasite in stained peripheral blood smears.
- After a negative blood smear, repeat smears should be done if there is a high index of suspicion.
- Stains used are Romanowsky, Giemsa, Field's, Wright's or Leishman's stain.
- *Thin blood smear:*
  - Level of parasitaemia is indicated by a thin smear.
  - Expressed as number of parasitized erythrocytes per 1,000 RBCs.
  - The presence of >100,000 parasites/μl (approximately 2 % parasitaemia) is a predictor that the patient may be having severe malaria.

  - If there are >50 % tiny ring forms of parasite, at any level of parasitaemia, it indicates a better prognosis.
  - On the other hand the presence of visible pigment in >20 % of parasites or phagocytosed pigment in >5 % of neutrophils carries a worse prognosis as it indicates massive recent schizogony [3].

- *Thick blood smear:*
  - Has the advantage of increased diagnostic sensitivity compared to a thin film, as the parasites are concentrated 40 to 100-fold.
  - This happens because the erythrocytes lie over one another and are lysed during the staining procedure.
  - Both the parasites and the white blood cells are counted, and the number of parasites per unit volume is calculated from the total leukocyte count.

- *Quantitative buffy coat smear (QBC):*
  - Quantitative buffy coat is a highly sensitive (93.8 %) and specific test (99.8 %) for detection of malarial parasite [4].
  - Advantages [5]:
    (a) Low levels of parasitaemia can be detected.
    (b) Easy to perform and interpret.
  - Disadvantages:
    (a) Species identification is difficult (but possible and requires expertise).
    (b) Expensive.

- *Rapid diagnostic tests (RDTs):*
  - These are rapid, sensitive and specific antibody-based stick or card tests.
  - They detect *P. falciparum*-specific, histidine-rich protein 2 (PfHRP2) or lactate dehydrogenase.
  - The blood is collected by finger prick method.
  - But the PfHRP2-based tests can be positive for weeks after an acute infection.
  - In many places these RDTs are replacing the smear examination because of their ease and speed. The downside is that they are expensive and do not quantify the parasitaemia.

Other Laboratory Tests

- Normochromic normocytic anaemia or haemolytic picture can be seen.
- The leukocyte count is usually normal, but can be raised in severe infection.
- Acute phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated.

- Metabolic acidosis, hypoglycaemia, low sodium, bicarbonate, calcium, phosphate and albumin levels are common in severe malaria.
- There can also be elevated levels of lactate, blood urea nitrogen, creatinine, urate and muscle and liver enzymes, with conjugated and unconjugated hyperbilirubinaemia.
- In patients with cerebral malaria, lumbar puncture can reveal:
  - A mean CSF opening pressure of approximately 160 mm
  - Elevated protein <100 mg/dL
  - Cell count <20/μl.

Treatment

Refer to Fig. 48.1 for treatment approach to a patient with malaria.

1. *Uncomplicated P. falciparum infection:*
   - Artemisinin combination therapy (ACT) is preferred regimen in all diagnosed cases of uncomplicated *P. falciparum* cases. It can be safely combined with primaquine 45 mg on second day of treatment.
   - The ACT recommended by the National Program in India is artesunate+sulfa doxine+pyrimethamine (Table 48.2: ACT Regimen) [6] (Table 48.3).
   - Oral artesunate monotherapy is banned in India [6].
2. *Uncomplicated P. vivax infection:*
   - The treatment of choice is chloroquine.
   - Dose: 10 mg/kg (600 mg) on first and second day, 300 mg on day 3.
   - Primaquine in a dose of 15 mg/day for 14 days is given to prevent relapse. It is contraindicated in G6PD deficiency, infants and pregnant women.
   - If there is a mixed infection with *P. falciparum* and *P. vivax*, then artemisinin combination therapy is given with primaquine in the dose mentioned for *P. vivax* infection.
3. *Treatment of uncomplicated P. falciparum infection in pregnancy:*
   - The drug of choice in the first trimester is quinine, in a dose of 10 mg/kg three times a day PO for 7 days. ACT is recommended in the second and third trimester of pregnancy [6].
4. *Treatment of severe P. falciparum infection:*
   - Parenteral therapy either with artemisinin derivative or quinine should be instituted immediately to prevent mortality. Intravenous preparations are preferred.
   - *Artesunate:*
     - Drug of choice

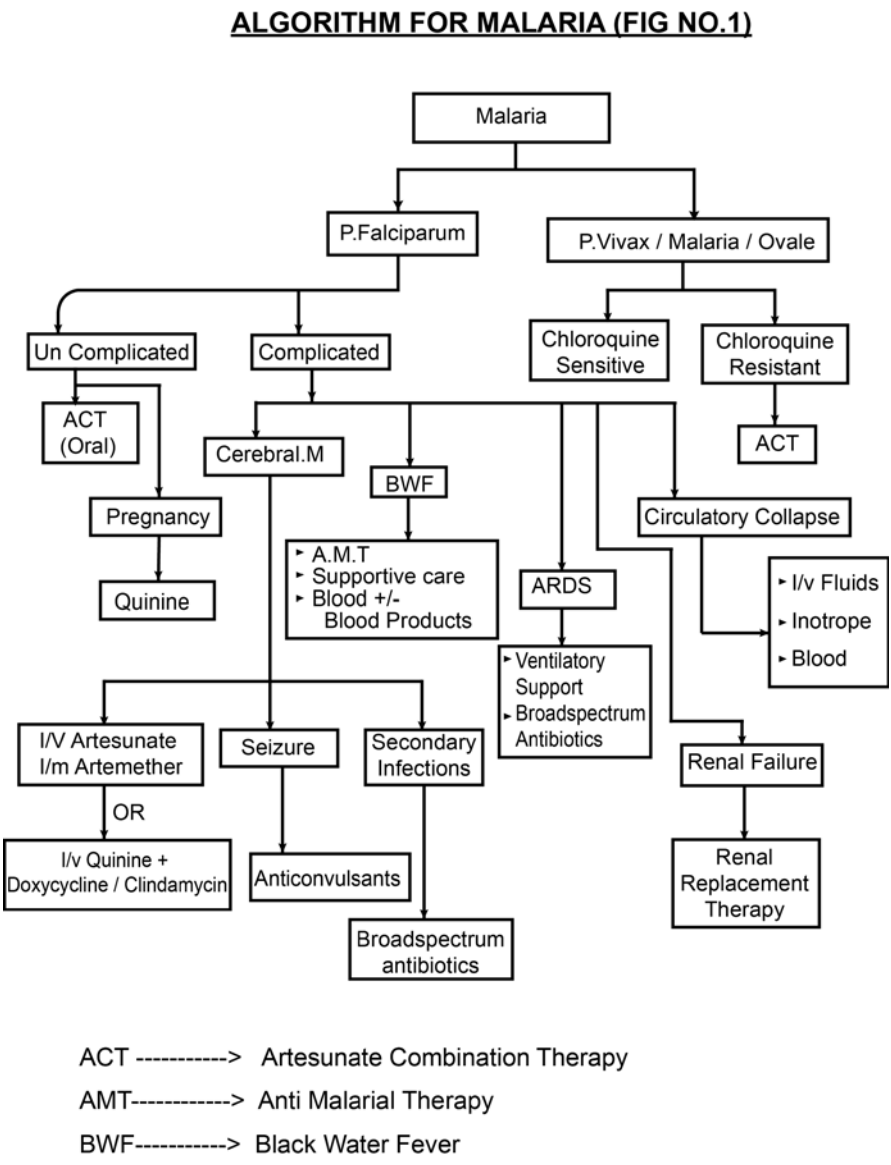

Fig. 48.1 Algorithm for malaria. *ACT* artesunate combination therapy, *AMT* antimalarial therapy, *BWF,* blackwater fever

Table 48.3 ACT regimen with dosages

	Day 1	Day 2	Day 3
Artesunate	200 mg	200 mg	200 mg
Sulfadoxine	500 mg/tab (3 tablets)		
Pyrimethamine	25 mg/tab (3 tablets)		

  - Dose: 2.4 mg/kg IV on admission, repeated at 12 and 24 h. It is then given once a day for 7 days or till the patient can take oral drugs. Once patient can take oral drugs, then they should be given full course of ACT for 3 days (refer Table 48.2).

- In patients with cerebral malaria, mefloquine-based regimens should be avoided as it can result in neuropsychiatric manifestations [6].
- *Quinine:*
  - Alternative drug to artesunate.
  - Dose: Initial loading dose of 20 mg salt/kg body weight, given slowly over 4–6 h. The vehicle used to administer quinine is 5 % dextrose or dextrose saline due to the risk of hypoglycaemia. This is followed by a dose of 10 mg/kg every eight hourly infusions. The initial loading dose is not needed if the patient has been on oral quinine. If an infusion is needed for more than 48 h, then the dose has to be decreased to 7 mg/kg eight hourly till it can be converted to oral tablets.
  - Oral quinine is also taken in the dose of 10 mg/kg thrice a day to complete total 7 days of therapy.
  - Doxycycline in the dose of 3 mg/kg per day for 7 days is added to quinine once the patient starts oral therapy. Contraindications to doxycycline are pregnancy and age less than 8 years.
  - Clindamycin is an alternative to doxycycline in a dose of 10 mg/kg twice a day for 7 days.
- *Artemether:*
  - Given intramuscularly.
  - Dose: 3.2 mg/kg on admission followed by 1.6 mg/kg once a day for four more days. This is followed by ACT for 3 days (refer Table 48.2) [6].
- *Alpha-beta artemether:*
  - Intramuscular injections
  - Dose: 150 mg/day for 3 days
  - Not used in children
  - Should be followed by ACT for 3 days (refer Table 48.2) [6]

5. *Treatment of severe malaria due to P. vivax or mixed infections:*
   - Treatment is same as for severe *P. falciparum* cases.
6. *Treatment of severe P. falciparum cases in pregnancy:*
   - Parenteral quinine is the preferred drug in the first trimester. In the event that quinine is not available, injectable artemisinin derivatives can be used. This is done to save the mother's life, accepting the risk to the foetus.
   - In the second and third trimester, the injectable artemisinin derivates are the preferred treatment.

7. *Basic supportive care:*

- Effort should be made to maintain the intravascular volume at the lowest level for adequate systemic perfusion.
- If patient is hypotensive, early use of inotropes is preferred rather than overhydration.
- The patient has to be maintained in a negative fluid balance so as to prevent acute lung injury. But this has to be done in a judicious way, so as not to precipitate acute renal failure [7].
- Mechanical ventilation with a low tidal volume and a high positive end-expiratory pressure to maintain optimal arterial oxygenation is associated with an improved clinical outcome [8].
- Frequent monitoring of serum sodium, arterial CO2, blood sugar and arterial lactate should be done.
- If there are seizures, then anticonvulsants should be given. There is no role of prophylactic use of anticonvulsants [9].
- The efficacy of the use of hypertonic mannitol in treatment of cerebral oedema is not proven.
- The early initiation of dialysis can help in preventing ARDS. If patient is hypotensive, then it is better to go for continuous renal replacement therapy than conventional haemodialysis [10].
- Blood transfusion should be done judiciously to avoid volume overload. It can be done if the haematocrit falls below 20 %.

8. *Antibiotics:*

- In patients with severe malaria, bacterial infections can occur as a complication.
- The common infections are aspiration pneumonia and sepsis.
- The clinical picture and investigations in severe malaria is similar to septicaemia, and hence it may be missed on initial evaluation.
- Therefore repeated examination of cultures from potential sites of infection should be done in patients with severe malaria, especially if they are not improving, and the appropriate antibiotic therapy has to be instituted.

9. *Corticosteroids:*

- Corticosteroids were used in the past for treatment of cerebral malaria. But now they have been proved to be harmful [11].

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Chapter 49
Standard Precautions Against Biohazardous Diseases

Sandeep Nathanael David

Abbreviations

BBV	Blood-borne virus(es)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCW	Healthcare workers
HIV	Human immunodeficiency virus
NSI	Needle-stick injuries
PEP	Post-exposure prophylaxis

Key Points

- Needle-stick injuries are to be considered as medical emergencies, and time is of the essence for notification of the same. Assume all patients as biohazardous unless proven otherwise.
- Implement Standard Precautions, especially wearing protective personal equipment, as mandatory for all.
- Hand hygiene should be meticulously followed, both as part of Standard Precautions, and for the benefit of infection control in patient care areas.
- Post-exposure prophylaxis is not 100 % effective. Prevention is far better than cure.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_49

Introduction

- Needle-stick injuries (NSIs) are defined as "a penetrating stab wound from a needle (or other sharp object) that may result in exposure to blood or other body fluids" [1].
- This is of major concern among hospital personnel due to risk of transmitting any of the major blood-borne viruses from an infected patient to a healthcare professional.
- The pathogens of note which are transmitted this way are the human immunodeficiency virus, hepatitis B virus and hepatitis C virus. Others include malarial parasites, hepatitis D virus, parvovirus B19, cytomegalovirus and Epstein-Barr virus [2].
- In 2002 the World Health Organisation reported that 37.6 % of hepatitis B, 39 % of hepatitis C and 4.4 % of HIV/AIDS in HCWs around the world are due to NSIs [3].
- In 2010, almost 80 % of HCWs had one or more NSIs in their career. More than half of them stated that fatigue was a cause of their injury and most of the injuries occurred during recapping of needles. Less than 10 % of the HCWs took post-exposure prophylaxis (PEP) against HIV/AIDS after their injury [4].

Mechanisms of Sustaining a NSI in the Emergency Department

1. Direct injury during venipuncture or blood gas analysis, especially from restless/non-cooperative/agitated/improperly anaesthetised patients.
2. While opening tightly applied dressings.
3. During invasive procedures such as central venous catheter insertions, emergency pericardiocentesis or suprapubic catheter insertion.
4. Although not technically a NSI, a splash or spurt of patients' body fluids onto any exposed skin or mucous membrane of the HCW is a potential portal of entry for blood-borne pathogens. Notable examples of this are during chest tube insertions, any open wound following major trauma, a patient with haematemesis, haemoptysis or any other bleeding manifestations.

Overview of Risk Assessment and Management

1. Identifying hazards and those at risk
2. Evaluating and prioritising risks
3. Deciding on preventive action
4. Taking action
5. Monitoring and reviewing

Personal Protective Equipment

- The term Standard Precautions is described as the "minimum infection prevention practices that apply to all patient care, regardless of suspected or confirmed infection status of the patient, in any setting where healthcare is delivered [6]".
- According to OSHA (Occupational Safety and Health Administration), blood and body fluids of all patients are considered potentially contaminated with blood-borne pathogens, and hence a "standardised" practice of self-protection for HCWs was necessary. Subsequently the term "Universal Precautions" was changed to Standard Precautions in 1996.
- With reference to NSIs, two aspects of the Standard Precautions are of utmost importance:

  (a) Usage of personal protective equipment (PPE)
  (b) Appropriate disposal of sharps

(a) Personal protective equipment (PPE)

  - This includes the wearing of disposable caps, masks, gowns and gloves.
  - These items of clothing are broadly divided into clean and sterile items, and the amount or type of PPE may vary depending on the area (i.e. operating rooms, intensive care units, delivery rooms) or the situation at hand.
  - Gloves must always be worn during activities involving vascular access like collecting blood samples or while touching any exposed body fluids or mucous membranes. The same pair of gloves must never be used for examining multiple patients, and gloves should never be washed and reused. Many studies have indicated that wearing an extra pair of gloves ("double-gloving") further reduces the risk of BBV transmission, either from NSIs or faulty glove material [8–10] by up to 87 % [11].

Gloves not needed	(a) Checking pulse
	(b) Measuring BP/temperature
	(c) Performing SC/IM injections
	(d) Any vascular line manipulation without blood leakage
Clean gloves needed	
(i) Direct exposure	(a) Contact with blood/faeces
	(b) Drawing blood, IV insertion and removal
	(c) Contact with mucous membrane/non-intact skin
	(d) Pelvic and vaginal examination
	(e) During any epidemic/emergency situation
	(f) Potential presence of contagious infection
(ii) Indirect exposure	(a) Handling instruments
	(b) Cleaning up body-fluid spills
Sterile gloves needed	(a) Any surgical procedure
	(b) Vaginal delivery
	(c) Inserting central venous catheters/arterial lines

Table 49.1 Usage and disposal of sharps

Do's	Don'ts
Immediately dispose all used sharps in the designated blue sharps disposal container	Recap, break or bend the needle by hand
Use forceps/clamp/kidney basin for transfer of all sharps	Transfer the needle or blade by hand
Empty the container when it is 3/4 full	Allow the container to fill up or overflow
Use a tourniquet for phlebotomy	Ask another person to proximally occlude the limb for phlebotomy
Inform the charge nurse immediately if the disposal container overflows	Discard used sharps along with other used dressings, gauze, etc.

- Surgical masks and goggles or face shields should be worn if there is a possibility of splash or spray of blood or body fluids from the patient. Face masks should also be worn during urinary catheterisation and lumbar puncture.
- Gowns should be worn if skin or clothing is likely to be exposed to blood or body fluids [7]. Examples of this are during evaluation and resuscitation of patients who have been involved in major trauma or for any highly invasive procedures like central venous catheter insertion, chest tube placement or emergency pericardiocentesis (Table 49.1).

(b) Post-exposure prophylaxis (PEP)

- In the event of NSI, the first and most important step is to wash the area well with soap and water. In case of body-fluid splash onto exposed mucosa or conjunctivae, the involved area is to be washed liberally under clean running water (Fig 49.1).
- There is no proven benefit from sucking the puncture wound or using antiseptics [12].
- The need for tetanus immune prophylaxis should be assessed.
- All cases of exposure to body fluids should be reported to the appropriate authority of the hospital and an occupational exposure report prepared (Table 49.2).
- Blood should immediately be drawn and sent for screening from the treating HCW and the source.
- All hospitals should have a rapid screening test for BBV which should yield results within 8–24 h, as PEP is not recommended after 72 h [13].
- It is important to note that due to several factors such as delayed initiation, viral resistance and difficulty in adhering to the PEP regimen, PEP is not 100 % effective in preventing the spread of BBV [14, 15].

Table 49.2 Rates of transmission of the major blood-borne viruses [2, 5]

Pathogen	Rate of transmission through needle-stick injury	Rate of transmission through mucocutaneous splash
HIV	0.3 %	0.1 %
HCV	3–10 %	(No quantifiable data)
HBV	30 % overall	(No quantifiable data)
HBsAg +ve, HBeAg –ve	2–6 %	
HBsAg +ve, HBeAg +ve	22–40 %	

Memory Pearl – 0.3, 3, 30 % for HIV, HCV, HBV accordingly

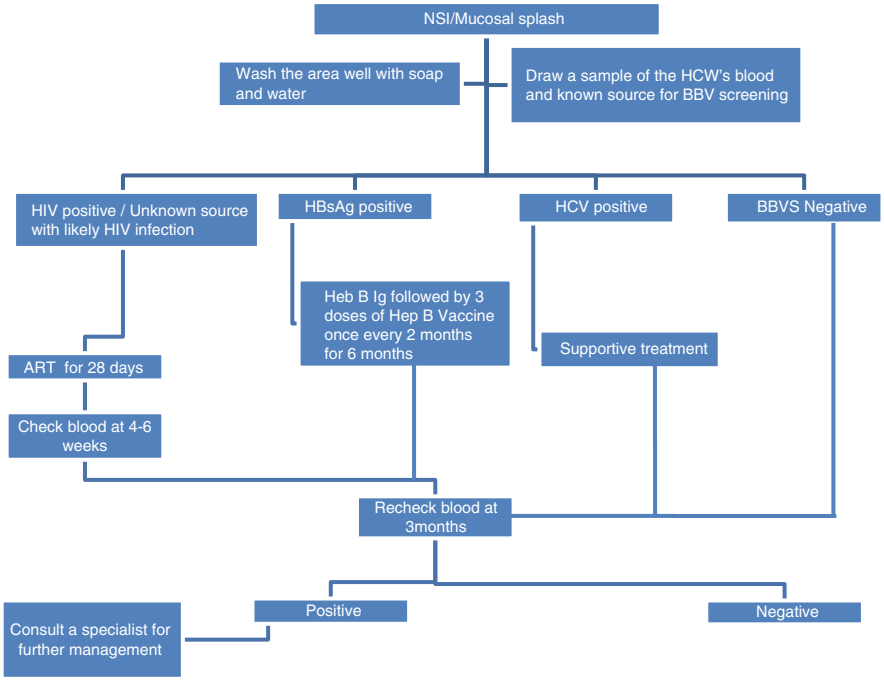

Fig. 49.1 Algorithm for needle-stick injuries

- Laboratory testing:
  - Viral serological testing is recommended for diagnosis and follow-up of any individual at high risk for BBV transmission [16].

    HIV – At exposure, after 4–6 weeks and after 3 months.
    Hepatitis B and C – At exposure and after 3 months.

– In the past, testing at 6 months was done as well. However, this has been proved unnecessary as of 2013 [17].

(a) *PEP for HIV*

This is a 28-day course of antiretroviral therapy, usually a combination of two or three drugs. As of December 2014, the recommended PEP regimens for HIV as per WHO guidelines [18] are as follows:

Adults: (Tenofovir) + (lamivudine/emtricitabine) + (ritonavir-boosted lopinavir)
Children: (Zidovudine) + (lamivudine) + (ritonavir-boosted lopinavir)

(b) *PEP for hepatitis B*

This is usually a stat dose of hepatitis B immunoglobulin IM, followed by three doses of hepatitis B vaccine, given as three injections over 6 months.

(c) *PEP for hepatitis C*

There is no vaccine for hep C, and the treatment is supportive.

- Missing even a single day of treatment greatly minimises the efficacy of the PEP.
- Side effects are frequent with PEP, especially with anti-HIV drugs. They include fatigue, malaise, nausea, vomiting, diarrhoea and headache.
- After completion, blood samples are again tested for BBV at 3 and 6 months to check for clearance.

Hand Hygiene

An important adjunct to NSI awareness and transmission of nosocomial infection is to understand the significance of proper hand hygiene. Both the WHO and CDC have run various trials and education programmes to determine the most effective way to prevent cross-infection between patients and HCWS.

Levels of Hand Hygiene [19]

Level I – social hand hygiene

– To render the hands physically clean and to remove microorganisms picked up during activities considered 'social' activities ("transient microorganisms").
– Perform for at least 15 s.

Level II – Aseptic hand hygiene

– To remove or destroy transient microorganisms. Also, to provide residual effect during times when hygiene is particularly important in protecting

yourself and others (reduces those "resident microorganisms" which normally live on the skin).
– Perform for at least 15 s.

Level III – surgical scrub

– To remove or destroy transient microorganisms and to substantially reduce resident microorganisms during times when surgical procedures are being carried out.
– Perform for at least 2–3 min.

In the emergency department, levels 2 and 3 are commonly encountered and must be accordingly followed.

Five Moments of Hand Hygiene

- Alcohol-based hand rub solutions are used to prevent spread of infection before, after and between examining patients, as well as for performing clean and low-risk procedures such as phlebotomies or starting peripheral lines.
- However they are not effective for:

  1. Visibly soiled hands with organic matter (blood, faeces, etc)
  2. Preventing spread of diseases by spore-forming organisms like tetanus or *Clostridium difficile* colitis
  3. Surgical scrub (level 3 exposure) or before any sterile procedure

- Hand wash with soap and water must be performed for any of the above.

Conclusion

NSIs and body-fluid splashes are a significant hazard in the emergency department. Every patient is a potential source of HIV, hep B or hep C to an unprepared or unsuspecting HCW. It is important to be aware and prepared against the spread of BBV and not become victims ourselves.

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Chapter 50
Varicella and Herpes Zoster Infections

Binod Basheer and Salish Varghese

Key Points
- Varicella zoster is a self-limiting illness.
- Systemic antiviral medication is recommended in immune-compromised individuals and other high-risk groups.
- Preexposure and postexposure vaccines are recommended for prevention of varicella disease.

Introduction

- Varicella (chickenpox) is an acute highly infectious disease caused by varicella-zoster virus.
- It is worldwide in distribution and occurs in both epidemic and endemic forms.
- In tropical countries the disease occurs mostly in the cooler months during the winter or spring [1].
- It is mainly a disease of childhood, as 90 % of cases occur in children younger than 13 years of age and 10 % older than 15 years of age [2, 3].
- About 10 % of the patients with chickenpox can have herpes zoster later in life, due to reactivation of the virus.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_50

Pathophysiology

Chickenpox

- Incubation period ranges from 10 to 21 days.
- Secondary attack rate in susceptible individuals is 70–90 % [2].
- Infectivity period is approximately 48 h before onset of vesicular rash, during the period of vesicle formation (4–5 days) and until all the vesicles are crusted.
- There is an initial viral replication in the nasopharynx and conjunctiva followed by infection of the reticuloendothelial system between days 4 and 6. The characteristic skin lesions appear at around 11–20 days due to secondary viremia and infection of the epidermis. Varicella-zoster virus subsequently travels from mucocutaneous lesions to dorsal root ganglion cells, where it remains latent until reactivation at a later date.

Herpes Zoster

- Appears on reactivation of VZV, which may occur spontaneously or be induced by stress, fever, radiation therapy, local trauma, or immunosuppression.
- During outbreak the virus continues to replicate in the dorsal root ganglion and produces a painful ganglionitis.
- Neuronal inflammation and necrosis can result in severe neuralgia that intensifies as the virus spreads down the sensory nerve into the skin.

Clinical Features

Chickenpox

- Varicella may begin as a prodrome of mild fever, malaise, and myalgia. This is followed by an eruption of pruritic, erythematous macules and papules, starting on the scalp and face and then spreading on to the trunk and extremities.
- Lesions rapidly evolve over 12–14 h into 1–3 mm clear vesicles surrounded by a narrow red halo. The number of vesicles varies from only a few to several hundred and there is often involvement of the oral mucosa. Sparing of the distal and lower extremities is common. Older lesions evolve to form pustules and crusts and heal within 7–10 days.
- The presence of lesions in all stages of development is a hallmark of varicella.
- The disease is self-limited and benign in healthy children.
- Secondary bacterial infection of the skin with subsequent scarring is the most common complication of varicella.
- The commonest neurological complication of varicella is a self-limiting cerebellar ataxia. Less common complications include meningoencephalitis and transverse myelitis.

- Varicella pneumonia is the most serious complication following chickenpox. It is more common in adults than in children and is particularly very severe in pregnant women. Pneumonia has its onset 3–5 days into the illness and resolves as the skin rash improves.
- Other complications include myocarditis, corneal lesions, nephritis, arthritis, bleeding diathesis, acute glomerulonephritis, and hepatitis.
- Perinatal varicella is associated with high mortality rate when maternal disease develops within 5 days before delivery or within 48 h thereafter. Maternal varicella during the first 20 weeks of pregnancy is associated with approximately 2 % risk of congenital varicella syndrome (varicella embryopathy).
- Varicella can lead to significant morbidity and mortality in immune-compromised individuals. The lesions are usually more extensive and atypical and often become hemorrhagic.
- HIV patients may develop chronic varicella which may be associated with acyclovir resistance.
- Elderly patients undergoing chemotherapy or bone marrow transplantation for bone marrow malignancies may develop recurrent varicella where all the lesions are in single stage of development and may appear similar to smallpox. Systemic findings are uncommon.

Herpes Zoster

- Occurs across all ages, but is commonest among people above 60 years of age.
- Recurrent herpes zoster is exceedingly rare except in the immune-compromised host.
- Herpes zoster occurs unilaterally along the distribution of a cranial or spinal sensory nerve which may overflow into the adjacent dermatomes.
- Lesions are usually painful. The pain develops few days before to few days after the appearance of cutaneous eruptions. The severity of pain increases with age.
- Rarely, patient may have pain but no skin lesions (zoster sine herpete).
- Eruptions initially present as papules and plaques of erythema and evolve into blisters within hours. The lesions continue to appear for several days.
- Lesions can occur in mucous membranes when maxillary and mandibular branches of the facial nerve or S_2–S_3 dermatome are involved.
- Old debilitated individuals, especially with lymphoreticular malignancy or AIDS, can develop disseminated herpes zoster where more than 20 lesions are found outside the affected dermatome. Visceral dissemination occurs to the lungs and central nervous system.
- Ophthalmic zoster follows involvement of the ophthalmic branch of trigeminal nerve. The most common lesions include uveitis and keratitis. Glaucoma, optic neuritis, encephalitis, and acute retinal necrosis are severe complications though these are less common.

If there is involvement of the external division of the nasociliary branch of ophthalmic nerve, vesicles appear on the side and tip of the nose (Hutchinson's sign). Eye involvement is usually seen in such cases.

Differential Diagnosis

Chickenpox

- Vesicular viral exanthems, disseminated herpes simplex infections, rickettsial pox, drug eruptions, bullous insect bite reactions, scabies, and PLEVA (pityriasis lichenoides et varioliformis acuta) are important differential diagnoses. Smallpox was another important differential until it was eradicated.

Herpes Zoster (Fig. 50.1)

- Differential diagnoses include localized contact dermatitis, phytophotodermatitis, and bacterial skin infections like cellulitis and bullous impetigo. These can be differentiated by clinical evaluation.

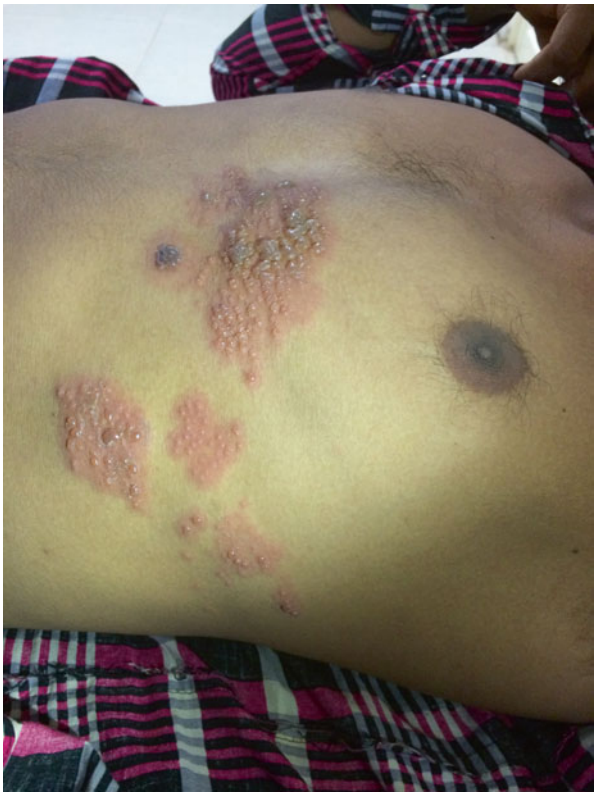

Fig. 50.1 Herpes zoster of thoracic dermatomes in a young male

- Herpes simplex and herpes zoster are confused if lesions of herpes simplex are linear (zosteriform HS) or if a number of zoster lesions are small and localized to one site and not along a dermatome. Direct fluorescent antibody test and viral culture can be used to differentiate the two.

Investigations

- Diagnosis is mostly clinical. Vesicles appearing in crops at various stages of development are characteristic of chickenpox. Clusters of vesicles and papules occurring in a dermatomal pattern are suggestive of herpes zoster.
- Laboratory diagnosis is required only in patients with atypical illness or when diagnosis is in doubt. This is accomplished by viral culture, antigen testing, or PCR testing of vesical fluid and Tzanck smear.
- The Tzanck smear prepared from scrapings at the base of vesicles shows giant cells with 2–15 nuclei but sensitivity of this test is only about 60 %.
- Fluorescent antibody to membrane antigen (FAMA) test and enzyme-linked immunosorbent assay (ELISA) are the most frequently done serological tests and are very sensitive.
- Diagnosis of varicella can be confirmed by isolation of VZV in culture.
- A chest X-ray should be obtained if varicella pneumonia is suspected.
- If neurological complications like encephalitis or myelitis are suspected, an MRI of the brain, lumbar puncture, and PCR testing for VZV should be considered.

Treatment (Fig. 50.2)

- Most healthy patients need only supportive care.
- The treatment is aimed at decreasing the severity and duration of illness and to prevent complications.
- In herpes zoster the goal is also to reduce the severity of postherpetic neuralgia.
- The patient's age, immune status, duration of symptoms, and presentation determine the management strategies for varicella.

Supportive Care

- Personal hygiene and close cropping of fingernails are important to prevent secondary bacterial infection. Secondary bacterial infection can be treated with antibiotics.
- Acetaminophen can be used as an antipyretic and antihistamines can be used for pruritus.

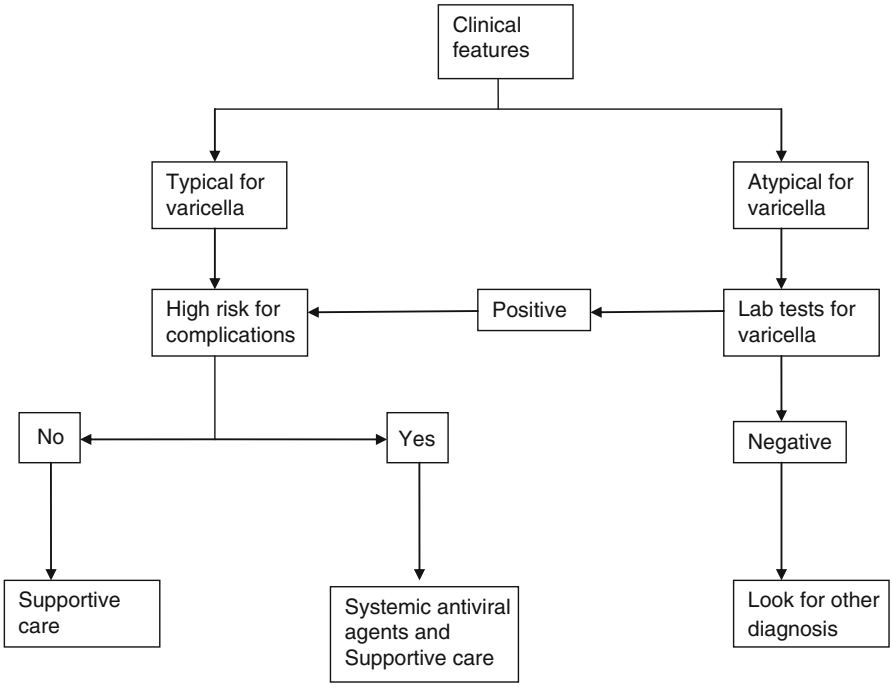

Fig. 50.2 Varicella disease treatment algorithm

- Aspirin should be avoided in children to prevent the possibility of development of Reye's syndrome [4].
- Judicious use of analgesics is important in relieving herpetic neuralgia. Medications that can be used to treat herpetic neuralgia include NSAIDs and opioids apart from drugs like gabapentin, pregabalin, amitriptyline, and fluphenazine. A short course of glucocorticoids offers significant pain relief but should only be used with systemic antivirals [5].

Antivirals

- In chickenpox antiviral medication should be considered for patients who are at risk for complications like adults and children >12 years of age, immune-compromised patients, those receiving long-term salicylate therapy, and patients with chronic skin or pulmonary disorders [6].
- Antiviral medications used for management of chickenpox and herpes zoster include acyclovir and newer medications like valacyclovir, famciclovir, and brivudin [7–10]. All of these drugs are safe and have low risk for adverse effects. Only acyclovir is available in an intravenous form.

- Oral acyclovir 800 mg five times daily for 7 days is recommended for individuals >12 years of age and should be started within 24 h of onset of rash. It may be of moderate benefit to children <12 years of age at a dose of 20 mg/kg every 6 h [7].
- The dose of oral valacyclovir in adults is 1 g eight hourly for 7 days.
- Systemic antiviral medications are effective especially in patients older than 50 years, for herpes zoster, when started within 72 h of the onset of rash and can also be offered beyond 72 h if new vesicles are still developing [11, 12].
- Treat immune-compromised patients regardless of the time since rash onset to reduce the risk of severe disseminated herpes zoster [5].
- IV acyclovir is indicated in immune-compromised people, disseminated herpes zoster, and those with CNS involvement. The dose is 10–12.5 mg/kg eight hourly for 7 days [13].
- When compared with oral acyclovir, the newer medications like valacyclovir may decrease the duration of the patient's pain and also have a lesser frequency of dosing [10].
- Herpes zoster ophthalmicus must be treated with oral antivirals and needs urgent evaluation by ophthalmologist.

Prognosis

- Usually self-limiting and rarely causes complications.
- About 10 % of the patients can have herpes zoster later in life due to reactivation of the virus. Herpes zoster usually subsides in 10–15 days and rarely recurs
- About 10–15 % of all patients with herpes zoster develop postherpetic neuralgia which can last for many months [14]. It is more likely to occur in persons over 50 years of age.
- Death due to herpes zoster is rare except in immune-compromised and severely debilitated patients.
- Disseminated zoster can develop causing encephalitis, hepatitis, or pneumonitis. Such cases have a mortality rate between 5 % and 15 % [5].
- In 3 % of patients delayed complications including vasculopathies affecting CNS or peripheral arteries and motor neuropathy can occur.

Prevention (Refer Fig. 50.3)

- Chickenpox and herpes zoster are prevented with vaccination although none of them is 100 % effective.
- Varicella virus vaccine can be administered after 1 year of age [15].
- Zoster vaccine is recommended for individuals who are 60 years or older (in some countries >50 years), irrespective of a previous history of herpes zoster [16, 17]. It also decreases the intensity of herpetic neuralgia.

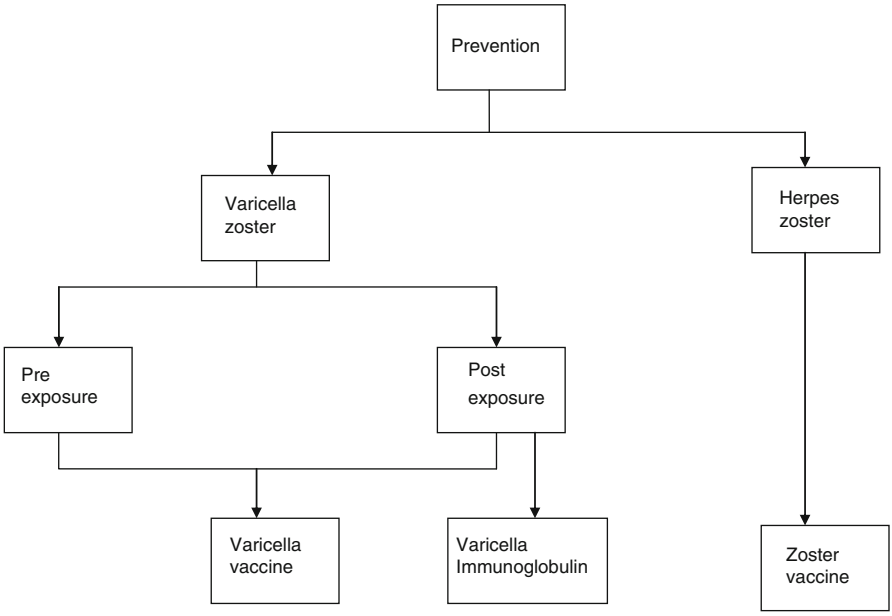

Fig. 50.3 Prophylaxis for chickenpox

Postexposure Prophylaxis

- Varicella vaccine is recommended for postexposure administration for unvaccinated persons without prior history of chickenpox.
- It should be administered within 5 days (ideally within 3 days) of exposure to rash and is effective in preventing varicella in 70–90 % cases and 100 % effective in modifying severe disease [18, 19].
- The vaccine is not recommended in pregnant women and infants.
- Varicella zoster immune globulin (VariZIG) is indicated for administration to individuals with contraindications for varicella vaccine or who are at high risk of developing complications. In such contacts the vaccine should be administered within 10 days (ideally within 4 days) of exposure to chickenpox [20].
- The high-risk group include:
  - Immune-compromised children and adults
  - Newborns of mothers with varicella shortly before or after delivery
  - Hospitalized premature infants born at ≥28 weeks of gestation whose mothers are not immune to varicella
  - Hospitalized premature infants born at <28 weeks of gestation or who weigh ≤1,000 g at birth, irrespective mother's varicella immune status.
  - Pregnant women
- There is no evidence for routine use acyclovir for postexposure prophylaxis of chickenpox.

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Part IX
Nephrology

Chapter 51
Acute Kidney Injury

Sreejith Parameswaran

Key Points
- AKI has significant short-term and long-term consequences.
- Active screening and monitoring of high-risk patients often with biomarkers help in early diagnosis.
- Follow-up of patients with AKI is necessary to screen for new onset or worsening CKD.

Introduction

Acute kidney injury (AKI) is an abrupt and potentially reversible decline in kidney function which has replaced the term "acute renal failure," emphasizing that even mild kidney injury (serum creatinine rise of 0.3 mg/dl from baseline) is also clinically significant.

Definition

Acute kidney injury is defined and classified as per the Acute Kidney Injury Network (AKIN) classification into three stages based on severity. Multiple studies have validated the AKI staging in both ICU and other hospitalized patients for predicting mortality and renal recovery.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_51

Table 51.1 Definition and staging of AKI [1]

Stage	Serum creatinine criteria	Urine output criteria
1	1.5–1.9 times baseline Or ≥0.3 mg/dl (≥26.5 mmol/L) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline Or Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/L) Or Initiation of renal replacement therapy Or, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h Or Anuria for ≥12 h

In AKIN criteria, patients are classified based on the worst stage attained in the clinical course.

AKI is defined as any of the following:

- Increase in SCr by 0.3 mg/dl (×26.5 μmol/L) within 48 h
- Increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine volume <0.5 ml/kg/h for 6 h (Table 51.1)

Epidemiology

- Overall, the incidence of dialysis requiring AKI is increasing and has from 40 per 1 million person-years in 1988 to 270 per 1 million person-years in 2002 [2].
- Up to two-third of patients admitted in the ICU in the high-income countries develop AKI and 4–5 % requires RRT [3].
- Highest incidence of AKI is in patients with sepsis, critical illness, and after cardiac surgery [4].

Etiology and Pathophysiology

- AKI is often multifactorial and is categorized into three broad types based on etiopathogenesis (Table 51.2):
  - Prerenal: AKI due to reduced effective circulatory volume or hypovolemia
  - Intrinsic renal (or renal): Due to pathological process affecting the kidney
  - Postrenal: AKI due to obstruction of the urinary tract from any cause
- Hypoperfusion AKI: Reduced renal perfusion from hypotension of any cause, if it is sustained and/or severe, can result in/aggravate AKI. Patients with AKI lose renal autoregulation of blood flow, with kidneys becoming susceptible to ischemic injury from reduced perfusion pressures.

- In the hospital setting, prerenal and intrinsic renal AKI from acute tubular injury accounts for the vast majority of cases.
- The term acute tubular necrosis (ATN) is commonly employed in clinical practice, often interchangeably with AKI, even though the term should ideally be restricted to cases where tubular injury is the predominant pathologic finding in kidney biopsy.

Risk Assessment

- The risk of developing AKI is determined by an interplay between the etiological exposures and the susceptibility factors (Table 51.3).

The risk assessment strategy in the emergency department should focus on screening all patients at admission to the emergency services for risk of AKI [5],

Table 51.2 Etiopathogenesis of prerenal, intrinsic renal, and postrenal AKI

Prerenal AKI	I. Hypovolemia	A. Excessive extracellular fluid loss: hemorrhage
		B. Gastrointestinal fluid loss: vomiting, diarrhea, enterocutaneous fistula
		C. Renal fluid loss: diuretics, osmotic diuresis, hypoadrenalism, nephrogenic diabetes insipidus
		D. Extravascular sequestration: burns, pancreatitis, severe hypoalbuminemia (hypoproteinemia)
		E. Decreased intake: dehydration, altered mental status
	II. Altered renal hemodynamics resulting in hypoperfusion	A. Low cardiac output state: diseases of the myocardium, valves, and pericardium (including tamponade); pulmonary hypertension or massive pulmonary embolism leading to right and left heart failure; impaired venous return (e.g., abdominal compartment syndrome or positive-pressure ventilation)
		B. Systemic vasodilation: sepsis, antihypertensives, afterload reducers, anaphylaxis
		C. Renal vasoconstriction: hypercalcemia, catecholamines, calcineurin inhibitors, amphotericin B
		D. Impairment of renal autoregulatory responses: cyclooxygenase inhibitors (e.g., nonsteroidal anti-inflammatory drugs), angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers
		E. Hepatorenal syndrome

(continued)

Table 51.2 (continued)

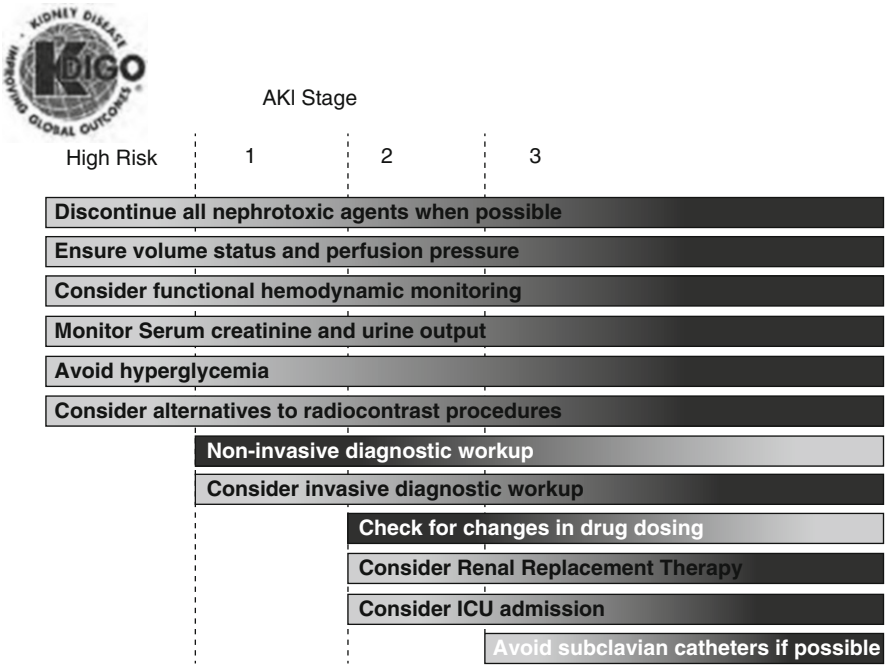
Intrinsic AKI	I. Renovascular obstruction (bilateral or unilateral in the setting of one kidney)	A. Renal artery obstruction: atherosclerotic plaque, thrombosis, embolism, dissecting aneurysm, large-vessel vasculitis
		B. Renal vein obstruction: thrombosis or compression
	II. Diseases of the glomeruli or vasculature	A. Glomerulonephritis or vasculitis
		B. Other: thrombotic microangiopathy, malignant hypertension, collagen vascular diseases (systemic lupus erythematosus, scleroderma), disseminated intravascular coagulation, preeclampsia
	III. Acute tubular necrosis	A. Ischemia: causes are the same as for prerenal ARF, but generally the insult is more severe and/or more prolonged
		B. Infection, with or without sepsis syndrome
		C. Toxins:
		1. Exogenous: radiocontrast, calcineurin inhibitors, antibiotics (e.g., aminoglycosides), chemotherapy (e.g., cisplatin), antifungals (e.g., amphotericin B), ethylene glycol
		2. Endogenous: rhabdomyolysis, hemolysis
	IV. Interstitial nephritis	A. Allergic: antibiotics (β-lactams, sulfonamides, quinolones, rifampin), nonsteroidal anti-inflammatory drugs, diuretics, other drugs
		B. Infection: pyelonephritis (if bilateral)
		C. Infiltration: lymphoma, leukemia, sarcoidosis
		D. Inflammatory, nonvascular: Sjögren's syndrome, tubulointerstitial nephritis with uveitis
	V. Intratubular obstruction	A. Endogenous: myeloma proteins, uric acid (tumor lysis syndrome), systemic oxalosis
		B. Exogenous: acyclovir, ganciclovir, methotrexate, indinavir
Postrenal AKI (obstruction)	I. Ureteric (bilateral or unilateral in the case of one kidney)	Calculi, blood clots, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
	II. Bladder neck	Neurogenic bladder, prostatic hypertrophy, calculi, blood clots, cancer
	III. Urethra	Stricture or congenital valves

Table 51.3 Risk assessment for AKI – exposures and susceptibilities for nonspecific AKI [1]

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

CKD chronic kidney disease, *CPB* cardiopulmonary bypass

followed by frequent monitoring of the renal function using serum creatinine at least daily in such patients.



Clinical Approach and Differential Diagnosis

- *The first step*: *Is the patient having AKI or CKD* (*or AKI superimposed on CKD*)?

  In general, a normal baseline renal function or a recent abrupt worsening of renal function indicates the presence of AKI.

  – Patients with AKI are highly symptomatic compared to patients with CKD for the same level of serum creatinine.
  – CKD itself is a risk factor for AKI and an acute process may be superimposed on preexisting CKD.
  – A good history and clinical examination can help recognize CKD, including:
  – Features that suggest CKD include:
  Previous high serum creatinine.
  Anemia.
  Mineral bone disease and hyperphosphatemia.
  Identifying shrunken kidneys in USG is suggestive of underlying CKD. However, normal or enlarged kidneys do not rule out CKD.

  – Early diagnosis of AKI is important to adopt preventive strategies to limit kidney injury.
  However serum creatinine is a poor marker for early detection of AKI.
    - Substantial kidney damage occurs without any appreciable change in serum creatinine values due to significant "renal reserve."
    - There may be delay of 48–72 h after kidney injury, before serum creatinine starts rising.
    - Serum creatinine levels are determined by many factors other than GFR.

  Many biomarkers were extensively studied for prediction of AKI following various renal insults (Table 51.4).

- *NephroCheck test*, recently approved by US FDA for marketing, is the first such test to be approved for clinical use, in prediction of risk of AKI in critically ill patients [6].

Table 51.4 Biomarkers extensively studied for early detection of AKI

Cystatin C
Neutrophil gelatinase-associated lipocalin (NGAL)
Interleukin 18 (IL-18)
Kidney injury 1 (KIM 1)
N-acetyl-beta-D-glucosaminidase (NAG)
Gamma-glutamyl transferase (GGT)
Glutathione S transferase (GST)
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Matrix metalloproteinase 9 (MMP 9)

- It detects the presence of the proteins insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases (TIMP-2) in the urine.
- Based on the amount of these proteins in the urine, the test gives a score within about 20 min, which correlates with the patient's risk of developing AKI within next 12 h.
- *Second step*: *What is the etiology of AKI*?
  - Identify reversible and treatable etiology. Presence of comorbidities may significantly influence the outcomes of AKI, and an attempt should be made to identify and address all the comorbidities.
  - The diagnostic approach in AKI involves a careful history taking, meticulous physical examination, and judicious interpretation of blood and urine laboratory reports (Tables 51.5 and 51.6).
  - Emergency imaging of the kidneys, usually by ultrasonography, is crucial not only in excluding postrenal AKI but also documenting shrunken kidneys which point to underlying CKD.
  - Kidney biopsy is usually reserved for patients with AKI where the etiology remains unclear.

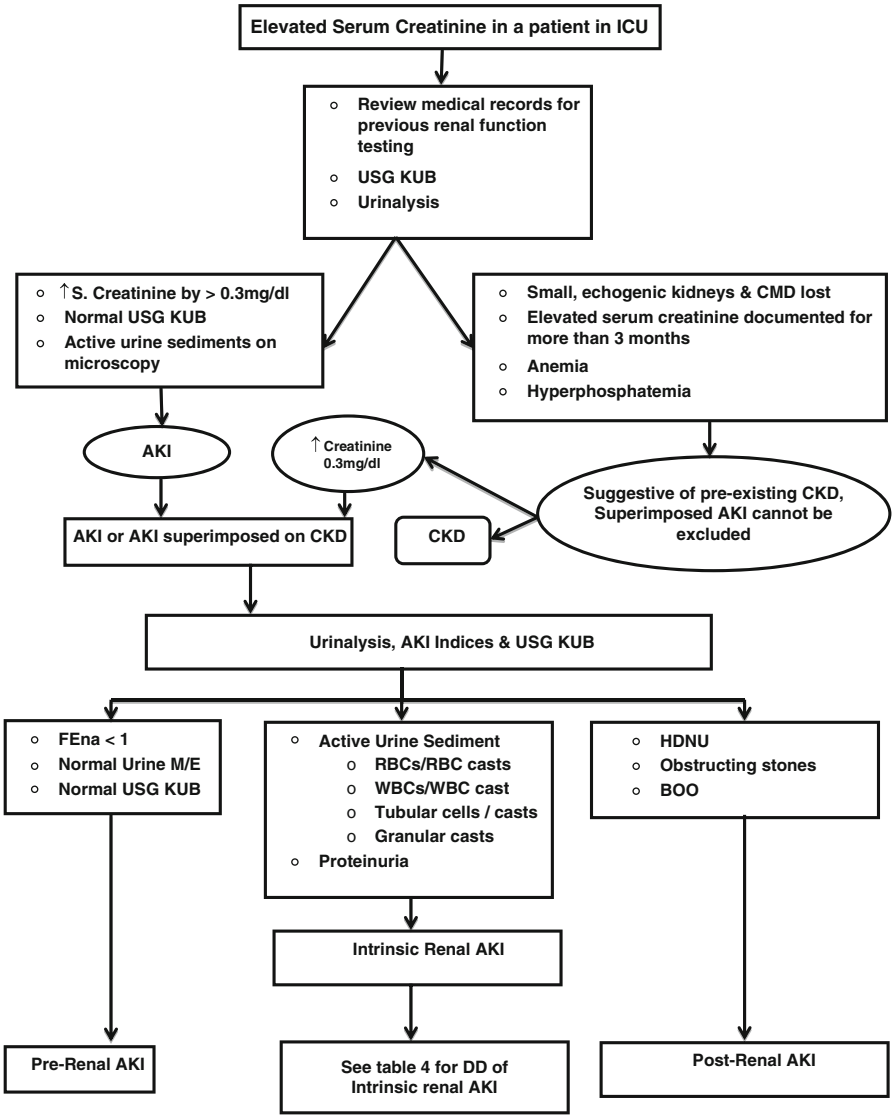
Table 51.5 Urinary sediment in AKI

RBCs, RBC casts	Glomerulonephritis, vasculitis, thrombotic microangiopathy, malignant hypertension
WBCs, WBC casts	Interstitial nephritis, pyelonephritis, malignant infiltration of the kidney, allograft rejection
Tubular epithelial cells, tubular epithelial cell casts, Pigmented casts	ATN, tubulointerstitial nephritis, myoglobinuria, hemoglobinuria
Granular casts	ATN, glomerulonephritis, tubulointerstitial nephritis
Eosinophiluria	Allergic interstitial nephritis, atheroembolic renal disease
Crystalluria	Acute uric acid nephropathy, ethylene glycol poisoning, drugs (acyclovir, indinavir, sulfadiazine, amoxicillin)

Table 51.6 Differential diagnosis between prerenal and renal AKI

Lab values	Prerenal	Renal
BUN/S_{cr}	>20	<20
Urine sediment	Normal of few casts	"Muddy brown" casts
Uosm (mmol/kg)	>500	<350
Proteinuria	None or trace	Mild to moderate
U_{Na} (mmol/L)	<20	>40
FE_{Na}	<1	>1
FE_{Urea} (%)	<35	>35
U_{cr}/S_{cr}	<20	>40
Novel biomarkers	None	KIM-1, Cystatin C, NGAL, etc.

BUN blood urea nitrogen, S_{cr} serum creatinine, *Uosm* urine osmolality, U_{Na} urine spot sodium, FE_{Na} fractional excretion of sodium, FE_{Urea} fractional excretion of urea, U_{cr} urine creatinine



Diagnostic Approach to elevated serum creatinine in a patient in a critically ill patient: Glossary: ***USG KUB*** ultrasonogram of Kidneys, Ureters and Bladder, ***CMD*** cortico-Medullary Differentiation, $\boldsymbol{FE_{Na}}$ fractional Excretion of Sodium, ***Urine M/E*** urine microscopy examination, ***HDNU*** Hydronephrouretterosis, ***BOO*** bladder outlet obstruction

Management

- The management of established AKI includes:
  - Optimizing volume status
  - Avoiding further renal injury
  - Nutritional considerations
  - Management of complications of AKI
  - Assessment of the need for RRT
- *Optimizing the hemodynamic status*: to avoid further renal injury.
  - *Aggressive volume resuscitation with crystalloids* is of proven benefit in prevention of AKI but not evidently in established AKI.
  - *Assessment of volume status* is difficult but important. Excess fluid accumulation (10 % more than baseline body weight) can contribute to excessive mortality [7].
  - *Early goal-directed therapy* in patients with sepsis and AKI:

    Proven to improve patient outcomes in patients with severe sepsis.
    Ideally should have an institutional protocol.
    The goals during the *first 6 h* of resuscitation of a patient with sepsis-induced tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L) are:

    - Central venous pressure 8–12 mmHg (12–15 mmHg in patients receiving mechanical ventilation)
    - Mean arterial pressure (MAP) ≥65 mmHg
    - Urine output ≥0.5 ml/kg/h
    - Central venous (superior vena cava) or mixed venous oxygen saturation 70 % or 65 %, respectively
    - In patients with elevated lactate levels targeting resuscitation to normalize lactate

    Crystalloids are recommended for initial fluid resuscitation in severe sepsis.
    Adequate initial resuscitation will require administration of a minimum of 30 ml/kg of fluids. Continue to administer fluids aggressively as long as patient continued to improve (except in oligo-anuric patients who are already volume overloaded).

Surviving sepsis campaign bundles
To be completed within 3 h:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad-spectrum antibiotics
4. Administer 30 ml/kg crystalloid for hypotension or lactate 4 mmol/L
To be completed within 6 h:

Surviving sepsis campaign bundles
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) _ 65 mmHg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dl):
Measure central venous pressure (CVP)[a]
Measure central venous oxygen saturation (ScvO2)[a]
7. Remeasure lactate if initial lactate was elevated[a]

[a]Targets for quantitative resuscitation included in the guidelines are CVP of _8 mmHg, ScvO2 of 70 %, and normalization of lactate.

- *Avoid nephrotoxic medications and radiocontrast* agents:
  - Discontinue potentially nephrotoxic agents like aminoglycoside antibiotics, amphotericin, acyclovir, etc. if possible
  - Avoid as far as possible the use of iodinated radiocontrast agents.
  - Avoid the use of other potentiators of AKI such as ACE inhibitors, angiotensin receptor blockers, and NSAIDs.
- Dietary support of AKI patients (Table 51.7):
  - AKI is associated with poor intake, dietary and fluid restrictions, and pro-inflammatory and high catabolic states, resulting in protein–energy malnutrition [8].
- Metabolic acidosis is the most common acid–base abnormality in patients with AKI.
  - Treat metabolic acidosis if pH <7.2 and there is cardiovascular compromise.

    Use sodium bicarbonate judiciously in severe metabolic acidosis till the primary process is addressed or a more definitive therapy like dialysis is instituted.

    Bicarbonate requirement = desired [HCO_3] – measured [HCO_3] × [HCO_3] space, where [HCO_3] space is [0.4 + (2.6 ÷ [HCO_3])] × lean body weight (in kg).

    Administer sodium bicarbonate slowly as isotonic solution and limit the initial dose not more than 1–2 mEq/kg body weight.

    Sodium bicarbonate is usually available as 8.4 % solution (50 mEq/50 ml) and is hypertonic (100 meq/50 ml = 2,000 mosm/L). Adding three vials (50 ml each) to 1 L of 5 % dextrose will generate an intravenous solution with approximately 150 meq/L of sodium bicarbonate.

Table 51.7 Diet recommendations in AKI [1]

Calorie	20–30 kcal/kg/day in patients with any stage of AKI
Protein	Not requiring dialysis, non-catabolic patient – 0.8–1.0 g/kg/day
	Requiring dialysis, non-catabolic patient – 1.0–1.5 g/kg/day
	CRRT and/or hypercatabolic patient – 1.7 g/kg/day
Enteral nutrition is preferred, whenever possible	
Avoid restricting protein intake in an effort to avoid RRT	

Bicarbonate therapy is not useful in circulatory shock and lactic acidosis.
Bicarbonate therapy may result in volume overload, carbon dioxide retention, worsening intracellular acidosis, and hypocalcemia.
Increasing alveolar ventilation temporarily may be considered for patients on ventilator support, especially if there is CO_2 retention.
Monitor acid–base status frequently, especially if there is circulatory shock.

- Fluid overload often accompanies AKI.
  - May necessitate institution of RRT if:

    Unresponsive to pharmacological measures and restriction of sodium and fluid intake

  - Loop diuretics may have a role if:

    The patient has volume overload and high fluid intake and low urine output and is symptomatic for volume overload (pulmonary oedema).
    Intravenous bolus administration of loop diuretics might be necessary for optimum response in these patients; there is no added benefit from using IV infusions.
    Maximum IV dose of furosemide: 16–200 mg administered over 20–30 min (torsemide 50–100 mg, bumetanide 8–10 mg).

- Hyperkalemia often accompanies AKI:
  - This can be life-threatening by producing cardiac asystole.
  - It is usually asymptomatic, thus screen all patients for hyperkalemia.
  - Identify and remove all sources of oral or intravenous potassium, if hyperkalemia is found.

    Effort should be made to identify drugs like ACE inhibitors and angiotensin receptor blockers, potassium-sparing diuretics, beta adrenergic antagonists, etc. which influence potassium handling and hence may aggravate hyperkalemia.

  - If ECG changes are present, administer IV calcium gluconate first, followed by insulin and glucose and salbutamol (Table 51.8).

Table 51.8 Management of hyperkalemia

Drug	Dose	Onset
IV calcium gluconate	10–30 ml, 10 %	1–3 min (immediate)
Insulin + glucose	50 ml 50 % glucose with 5–10 units regular insulin	5–10 min
Salbutamol	4 ml of 5 mg/ml (20 mg)	15–30 min
Sodium bicarbonate	50–150 mmol	15–30 min
K+ exchange resin	30–60 g in 70 % sorbitol as PO or enema	2 h
Hemodialysis	Removes 25–30 mEq/h of K+	

- Glycemic control:
  - At present, in critically ill patients, a more modest plasma glucose goal of 110–149 mg/dl (6.1–8.3 mmol/L) is recommended [1].
  - Start insulin when two consecutive blood glucose measurements are >180 mg/dl.
  - Target a maximum blood glucose of <180 mg/dl.
  - Keep monitoring blood glucose every 1–2 h till blood glucose and insulin administration rates are stable; subsequently monitor every 4 h.
  - Capillary blood glucose measurement may be misleading.
  - Use a protocolized approach to blood glucose management in the ICU.

Renal Replacement Therapy (RRT) in AKI

- The fundamental questions are:
  - When to start (timing)
  - Which modality to use
  - What the appropriate dose of RRT is and
  - When to stop RRT
- The optimal timing in the course of AKI to initiate RRT is not well defined.
  - Initiate RRT if any life-threatening complications of AKI are present, like severe hyperkalemia, fluid overload, acidosis, or azotemia.
  - Also consider the larger clinical context while deciding whether to initiate RRT or not.

    Conditions that may be modified with RRT need to be taken into account.
    Consider the trend of lab reports rather than relying on single test reports of blood urea or creatinine.
    Meeting nutritional requirement of the patient.

  - When such life-threatening features are absent and there are no other compelling reasons to offer RRT, it is better avoided, because of the well-known risks associated with RRT including hypotension, cardiac arrhythmias, and bleeding complications from anticoagulation.
- The role of timing of RRT initiation in determining outcomes has so far been studied only in one RCT and did not show any difference in ICU or hospital mortality or in renal recovery among the survivors [9] (Table 51.9).
- The RRT modalities available for AKI include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), sustained low-efficiency dialysis (SLED), and peritoneal dialysis (PD). The relative advantages and disadvantages of each is highlighted in Table 51.10.

Table 51.9 Indications for RRT

Indications for emergency RRT	Hyperkalemia
	Acidemia
	Pulmonary oedema
	Uremic complications: pericarditis, bleeding, encephalopathy
Non-emergent indications	Volume control
	Nutrition
	Drug delivery
	Regulation of acid–base and electrolyte status
	Solute modulation

Table 51.10 Theoretical advantages and disadvantages of CRRT, IHD, SLED, and PD [1]

Modality	Potential setting in AKI	Advantages	Disadvantages
IHD	Hemodynamically stable	Rapid removal of toxins and low molecular weight substances Allows for "downtime" for diagnostic and therapeutic procedures Reduced exposure to anticoagulation Lower costs than CRRT	Hypotension with rapid fluid removal Dialysis disequilibrium with risk of cerebral oedema Technically more complex and demanding
CRRT	Hemodynamically unstable Patients at risk of increased intracranial pressure	Continuous removal of toxins Hemodynamic stability Easy control of fluid balance No treatment-induced increase of intracranial pressure User-friendly machines	Slower clearance of toxins Need for prolonged anticoagulation Patient immobilization Hypothermia Increased costs
SLED	Hemodynamically unstable	Slower volume and solute removal Hemodynamic stability Allows for "downtime" for diagnostic and therapeutic procedures Reduced exposure to anticoagulation	Slower clearance of toxins Technically more complex and demanding
PD	Hemodynamically unstable Coagulopathy Difficult access Patients at risk of increased intracranial pressure Under-resourced region	Technically simple Hemodynamic stability No anticoagulation No need for vascular access Lower cost Gradual removal of toxins	Poor clearance in hypercatabolic patients Protein loss No control of rate of fluid removal Risk of peritonitis Hyperglycemia Requires intact peritoneal cavity Impairs diaphragmatic movement, potential for respiratory problems

Table 51.11 RRT dose in AKI [1]

Intermittent/extended dialysis	Kt/V of 3.9 per week
CRRT	Effluent volume of 20–25 ml/kg/h for CRRT[a]
Prescribe dose of RRT to be delivered before each session of RRT	
Frequently monitor the delivered dose of RRT	

[a]In order to achieve this dose, it is generally necessary to prescribe in the range of 25–30 ml/kg/h and minimize interruptions in CRRT.

- There is no "ideal" RRT modality suitable for all patients with AKI. The continuous and intermittent therapies need to be used as complimentary therapies in AKI patients. Transfer between RRT modalities may be necessary, dictated by changes in hemodynamic stability of the patient.
- CRRT is recommended as the modality of choice rather than IHD for hemodynamically unstable patients, patients with acute brain injury, increased intracranial pressure, or brain oedema.
- Defining an appropriate dose of RRT in AKI is difficult.
  - RRT dose should be sufficient enough to achieve adequate control of fluid, electrolyte, and acid–base and solute balance to meet the patient's requirements.
  - Beyond this, increasing dose of RRT to achieve better clearance of solutes has not been found useful and is not recommended (Table 51.11).
- The dose of RRT to be delivered should be prescribed before each RRT session, along with frequent monitoring of the delivered dose.
  - This will allow modification of the prescription to attain the prescribed dose in case the prescribed dose is not being delivered.
  - Despite optimization of RRT modality, if the prescribed RRT dose is not being achieved, switch RRT modalities or use a combination of different modalities (Table 51.12).

Follow-Up

There is accumulating evidence that AKI is not a onetime event and patients apparently recovering from AKI have higher risk of developing CKD [10]. Hence it might be prudent to evaluate patients who had AKI after a period of 3 months for resolution of AKI or new onset or worsening of preexisting CKD.

Prevention of AKI

- Optimizing volume and hemodynamic status is central to prevention of progression of all forms of AKI.

Table 51.12 Additional considerations in RRT for AKI [1]

Buffer solution in RRT	Bicarbonate instead of lactate to be used
Dialyzer membrane	Use biocompatible membranes for IHD and CRRT
Vascular access	Uncuffed nontunneled dialysis catheter to be preferred against tunneled catheter
	First choice: right jugular vein
	Second choice: femoral vein
	Third choice: left jugular vein
	Last choice: subclavian vein of the dominant arm
	Placing the catheter under USG guidance is recommended
	Obtain chest X-ray after catheter placement and before first RRT session
Anticoagulation	IHD with no increased bleeding risk: UFH or LMWH
	CRRT with no increased bleeding risk: regional citrate anticoagulation unless contraindication for citrate
	CRRT with no increased bleeding risk and contraindication for citrate: UFH or LMWH
	IHD or CRRT with increased risk of bleeding or active bleed: no anticoagulation

Table 51.13 Prevention of other specific forms of AKI [1]

Specific forms of AKI	Prevention measures
Contrast-induced AKI	Hydration
	Low risk – increase oral fluid intake
	High risk – IV hydration: 0.9 % saline 1–1.5 ml/kg/h for 3–12 h before and 6–24 h after contrast administration
	Iso-osmolal contrast agents
	Limit volume of contrast media used
Aminoglycoside nephrotoxicity	Avoid if less nephrotoxic alterative is available and suitable
	Administer a single-daily dose instead of multiple doses in patients in steady state and normal renal function
	Monitor aminoglycoside drug levels
	After 24 h if multiple daily dose
	After 48 h if single-daily dose
Amphotericin B nephrotoxicity	Use lipid formulations instead of conventional formulations
	Use azole antifungal agents or echinocandins if having equal therapeutic efficacy
ACEI, ARBs, and NSAIDs	Avoid in situations where renal perfusion and GFR are dependent on renal autoregulation, e.g., hypovolemia

- Invasive monitoring of hemodynamic and oxygenation parameters in high-risk patients and patients with septic shock.
- Protocol-based resuscitation strategy to achieve specific physiologic end points within 6 h of admission to the ICU (the early goal-directed therapy) may be useful in the prevention of organ injury including AKI.

Table 51.14 Drugs in the prevention of AKI

Drugs/treatment studied for prevention or treatment of AKI but *not recommended* for routine clinical use for lack of evidence [1]	
Dopamine	ANP
Fenoldopam	Calcium channel blockers
Loop diuretics	Adenosine antagonists
N-acetylcysteine	Erythropoietin
Statins	Multipotent stem cells

- In the absence of hemorrhagic shock, it is now recommended that crystalloids be used instead of colloids (albumin or hydroxyethyl starch) for volume expansion initially in patients with AKI or at risk of AKI (Tables 51.13 and 51.14).

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Chapter 52
Electrolyte Imbalance: Potassium, Magnesium, Calcium and Phosphorous

Jacob K. Addo

Key Points
1. Potassium and magnesium metabolism disorders are closely linked.
2. It is important to correct hypomagnesaemia when treating hypokalaemia.
3. Hypomagnesaemia is often associated with multiple biochemical abnormalities.
4. Most causes of hypermagnesaemia are predictable and preventable.
5. Calcium and phosphorus metabolism is closely interrelated.
6. Investigation of hypercalcaemia is best approached by considering whether it is related to a parathyroid hormone disorder.
7. Hypophosphataemia is often present in patients with chronic malnutrition and those on renal replacement therapy.

Introduction

Electrolyte balance is of vital importance in managing patients at all levels of healthcare delivery. It is of particular importance when managing patients who are critically unwell. Patients with cardiac arrhythmias, congestive cardiac failure, diabetes mellitus, acute and chronic kidney disease and hypertension are very likely to have electrolyte abnormalities, and careful anticipation and appropriate timely interventions can significantly improve outcomes.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_52

Potassium

Potassium is primarily an intracellular cation. Approximately 98 % of the total body potassium is intracellular. The intracellular potassium concentration is approximately 140 mmol/L, while the serum potassium concentration is approximately 4–5 mmol/L.

The ratio of the concentration of intracellular and extracellular potassium concentrations is the main determinant of the resting membrane potential which is essential for normal muscle and neuronal cell function. Significant derangements in potassium homeostasis can therefore cause muscle paralysis, nerve dysfunction and cardiac arrhythmias [1].

Hypokalaemia: (serum potassium <3.5 mmol/L)

Common causes include the following:

- Reduced oral intake
- Increased entry into cells (alkalosis, increased insulin availability, hypothermia)
- Increased gastrointestinal losses (diarrhoea and vomiting, laxative abuse)
- Increased urinary losses (diuretic use, salt-wasting nephropathies, renal tubular acidosis)

Clinical Features

The severity of symptom manifestation is often related to the degree as well as the rapidity of change of the serum potassium levels. Patients are generally asymptomatic until the potassium levels fall below 3.0 mmol/L.

Hypokalaemia results mainly in skeletal muscle weakness, myocardial excitability and arrhythmias.

ECG changes with mild to moderate hypokalaemia include T-wave flattening, ST-segment depression and prolongation of PR interval.

More severe hypokalaemia is characterised by development of a U wave (a positive deflection after the T wave) which progresses to fuse with the T wave and produces a pseudo-prolongation of the QT interval (Fig. 52.1). There may develop various tachyarrhythmias including ventricular tachycardia/fibrillation.

Treatment

Treatment goals should be to prevent life-threatening complications and identify the underlying cause.

It is important to have an accurate estimate of the potassium deficit in order to adequately correct this. In certain clinical situations, there is a transient increased potassium transfer into cells. It is very important to identify and treat the underlying cause rather than attempting to correct the deficit [2].

Increased insulin availability and increased beta agonist activity both promote the transfer of potassium into cells and can result in transient hypokalaemia.

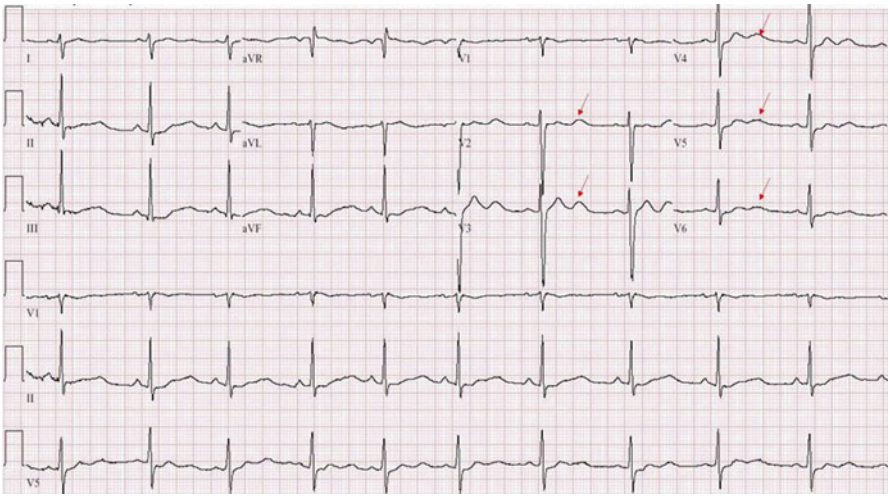


Fig. 52.1 U waves in hypokalaemia, indicated by *red arrows*

Patients with hypokalaemia often have hypomagnesaemia due to concurrent losses. Patients with primary hypomagnesaemia often have renal potassium wasting. It is important to treat the hypomagnesaemia as well in such cases.

Severity of hypokalaemia	Treatment options
Mild to moderate (2.5–3.4 mmol/L)	Often asymptomatic. Treat underlying cause
	Give oral potassium supplements if needed
Severe (<2.5 mmol/L)	Often symptomatic. Rapid correction of deficit is needed while addressing the underlying cause. Intravenous potassium replacement is preferred

Patients with diabetic ketoacidosis or hyperosmolar hyperglycaemic states with insulin deficiency require special consideration because rapid potassium redistribution does occur when treatment of the underlying cause is started.

Potassium preparations:

- Potassium bicarbonate is preferred in patients with hypokalaemia and metabolic acidosis.
- Potassium phosphate is preferred in patients with hypokalaemia and hypophosphataemia.
- Potassium chloride is the preferred preparation in all other cases of hypokalaemia.

For patients with severe symptomatic hypokalaemia, rapid correction with 10–20 mmol KCl/h can be given via peripheral veins. The maximum recommended infusion rate is 40 mmol/h via a central line and usually made up in infusion bags containing 20–60 mmol/L.

Serial monitoring of serum potassium levels is required when rapid correction is needed.

Patients with severe hypokalaemia should be managed in a high dependency area with full cardiac and respiratory monitoring. Remember to correct hypomagnesaemia concurrently if present.

Hyperkalaemia (serum potassium >5.0 mmol/L)

Mild hyperkalaemia 5.5–6.0 mmol/L
Moderate hyperkalaemia 6.0–7.0 mmol/L
Severe hyperkalaemia >7.0 mmol/L

In a patient with no clinical features and no ECG changes suggestive of hyperkalaemia, it is important to exclude pseudo-hyperkalaemia before considering any intervention.

Pseudo-hyperkalaemia refers to those conditions where the elevated serum potassium concentration is due to potassium movement out of cells during or after the sample has been taken. This is often the result of poor technique in obtaining the blood sample [3].

Causes of Hyperkalaemia

Increased potassium release from intracellular compartment	Reduced urinary excretion of potassium
Extreme exercise	Acute and chronic kidney disease
Insulin deficiency	Reduced aldosterone secretion
Increased tissue breakdown	Reduced response to aldosterone
Beta blockers	Reduced renal perfusion (low MAP)
Others (e.g. metabolic acidosis, hyperkalaemic periodic paralysis)	Others (e.g. Gordon's syndrome, ureterojejunostomy)

The main clinical features of hyperkalaemia are muscle weakness and cardiac arrhythmias.

ECG changes in mild to moderate hyperkalaemia include tall/peaked T waves (Fig. 52.2), widening/flattening of the P waves and PR prolongation. Severe hyperkalaemia is characterised by various types of AV conduction block, ventricular fibrillation, PEA and asystole.

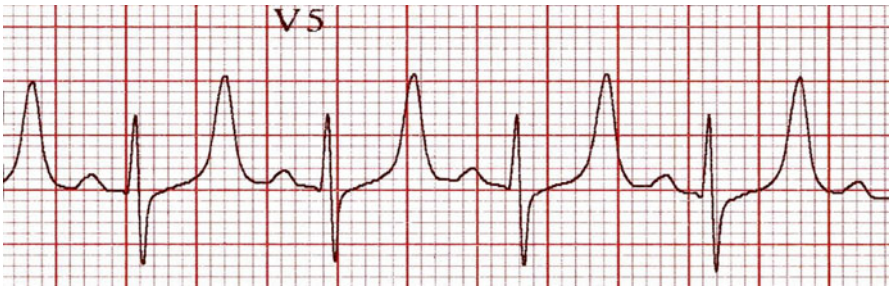


Fig. 52.2 ECG depicting tall/peaked T waves

Treatment of Severe Hyperkalaemia

Membrane action potential antagonists (calcium gluconate/calcium chloride). (Reduces the risk of ventricular fibrillation.) Give only in hyperkalaemia with significant ECG changes (Time to onset of activity is immediate)	Give 10 ml of 10 % calcium gluconate IV infused slowly over 10–15 min in a peripheral vein. Alternately give 10 ml of 10 % calcium chloride via a central line over 2–3 min Treatment may be repeated after 5–10 min if ECG changes persist
Agents that drive potassium from extracellular to intracellular compartment (insulin and dextrose, beta 2 agonists, correction of metabolic acidosis) Time to onset of activity is 15–30 min	Give rapid-acting insulin (e.g. Actrapid) 10 units and 50 ml of dextrose 50 % as a bolus intravenously. Start regular blood glucose monitoring and give a dextrose infusion if indicated Give beta 2 agonist (e.g. salbutamol 5 mg in 5 ml 0.9 % saline) via a nebuliser. Intravenous salbutamol infusion is an alternate option if indicated Sodium bicarbonate. Provides minimal benefit even in acidaemic patients. Give 50 mEq IV of the 8.4 % solution. Can be repeated if needed
Agents that facilitate potassium excretion	Give loop/thiazide diuretic (e.g. furosemide 20–40 mg IV); repeat if indicated but ensure careful fluid management. Benefits are short lived Cation exchange resin (e.g. Calcium Resonium 15 g TDS/QDS PO or 30 g PR as enema)
Haemodialysis	Haemodialysis is the most effective treatment for severe cases with renal impairment or those in whom pharmacologic treatment is inadequate

Magnesium

Magnesium homeostasis is a function of intake and excretion. Low oral intake is normally balanced by a reduction in renal excretion. Bone magnesium is the principal reservoir of magnesium [4].

There is however no hormonal mechanism regulating a ready exchange between bone magnesium deposits and circulating magnesium.

When there is a loss of renal excretory function, magnesium concentrations in the extracellular fluid increase.

Hypomagnesaemia

Hypomagnesaemia is present in approximately 12 % of hospitalised patients. This incidence rises to approximately 60–65 % of patients in ITU [5].

Symptomatic hypomagnesaemia is often associated with multiple biochemical abnormalities such as hypokalaemia, hypocalcaemia and metabolic acidosis [6].

Hypokalaemia is a common event in hypomagnesaemia patients. This relation is in part due to underlying disorders that cause both magnesium and potassium loss.

Clinical Manifestations

Neuromuscular hyperexcitability (tetany/convulsions and weakness).

Cardiovascular effects often manifested by ECG changes. Mild to moderate hypomagnesaemia is characterised by QRS widening and peak T waves. Widening of the PR interval and flattening of the T waves with various atrial and ventricular arrhythmias including Torsades de pointes have been noted in severe depletion (Fig. 52.3).

Treatment

Patients with symptomatic or severe hypomagnesaemia require ECG monitoring and intravenous magnesium. 4–8 mmol magnesium sulphate is given IV over 15 min. It is a good practice to measure magnesium levels 6–12 h after treatment to assess response [7]. In patients with minimal symptoms or moderate hypomagnesaemia, oral magnesium is preferred if well tolerated.

Hypermagnesaemia

Hypermagnesaemia in clinical practice is often seen in the context of patients with renal impairment or after the administration of a large dose of magnesium (IV/oral or enema).

Serum levels	Clinical features
Mild (2.0–3.0 mmol/L)	Headache, lethargy, drowsiness
Moderate (3.0–5.0 mmol/L)	ECG changes, absent deep tendon reflexes, hypotension
Severe (>5 mmol/L)	Complete heart block, muscle paralysis, respiratory failure

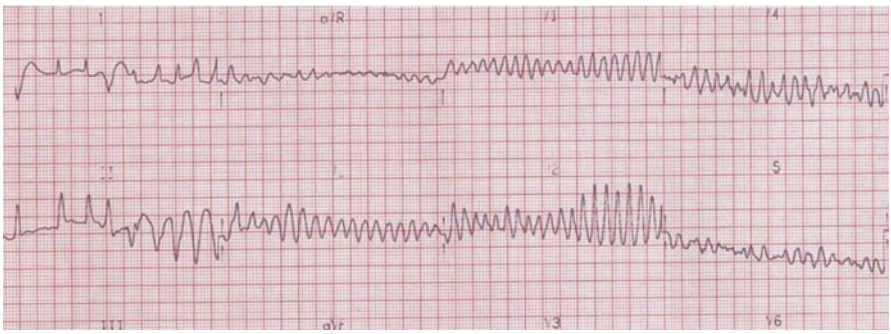


Fig. 52.3 Torsades de pointes

Treatment

Most causes of hypermagnesaemia are predictable and can be prevented by careful anticipation.

Patients with renal impairment should be closely monitored if on magnesium-containing medications and these should be avoided when possible.

Patients with normal renal function would normally excrete a large magnesium dose if adequately hydrated.

Patients with moderate renal impairment (eGFR 15–45) would often require isotonic IVF rehydration and loop diuretics to facilitate magnesium excretion.

Patients with severe renal impairment (eGFR <15) would require haemodialysis or haemofiltration.

In the acute setting, patients need to be given intravenous calcium as a magnesium antagonist while waiting for institution of haemodialysis. Give 10 ml of 10 % calcium gluconate over 10–15 min as an infusion [8].

Calcium and Phosphorous

The maintenance of calcium and phosphate homeostasis involves changes in bone, intestinal and renal function.

In contrast with the complete absorption of dietary sodium and potassium, the absorption of calcium and phosphate is incomplete [9]. This limitation is due to the requirement for vitamin D to facilitate absorption and the formation of insoluble salts in the intestinal lumen [10].

Most of the body calcium and much of the phosphate exist as hydroxyapatite, the main mineral component of bone. Phosphate is also present in high concentration in cells.

Only a small fraction of the total body calcium and phosphate is located in the plasma. It is however this small fraction of ionised calcium and inorganic phosphate that is under hormonal control. This is mediated primarily by parathyroid hormone (PTH) and vitamin D. The hormones affect intestinal absorption, bone formation and resorption and urinary excretion [11].

PTH is secreted by the parathyroid glands in response to a decrease in plasma concentration of ionised calcium. It acts to increase the plasma concentration via the following mechanisms:

- Works with vitamin D to stimulate bone resorption resulting in the release of calcium phosphate
- Promoting intestinal absorption of Ca2+ and phosphate by promoting the formation of calcitriol in the kidneys
- Promoting the active renal reabsorption of ionised calcium

Vitamin D (cholecalciferol) is a fat soluble steroid which is present in the diet and can also be synthesised in the skin in the presence of UV light. The hepatic

enzyme 25-hydroxylase places a hydroxyl group at the 25 position of the molecule to form 25-hydroxy vitamin D (calcidiol). This molecule can undergo further hydroxylation in the kidneys where another hydroxyl group is placed at the one position to form 1,25 dihydroxyvitamin D (calcitriol) which is the most active form of the vitamin.

Vitamin D acts to increase the plasma concentration of ionised calcium by:

- Increased intestinal absorption of calcium and phosphorous
- Works with PTH to promote bone resorption resulting in the release of calcium and phosphate
- Reduces urinary calcium excretion

Persistent vitamin D deficiency results in hypocalcaemia. Persistent hypocalcaemia results in secondary hyperparathyroidism which leads to phosphaturia, demineralisation of bones, osteomalacia in adults and rickets in children [12].

Calcium Homeostasis

Serum calcium concentration is normally maintained within a narrow range that is required for the optimal activity of the many intracellular and extracellular biochemical processes that it affects.

Serum calcium is partly protein bound. 45 % bound to albumin, 15 % bound to small anions (e.g. phosphate and citrate) and the remaining 40 % in the ionised state [9].

Only ionised calcium is metabolically active. Most laboratories however report total serum calcium concentrations. Concentrations of total serum calcium in normal serum generally range between 2.12 and 2.62 mmol/L. Levels below this are considered as hypocalcaemia and levels above this are considered hypercalcaemia. In patients with hypoalbuminaemia, there is a decrease in calcium binding with no net change in ionised calcium levels. The measured total calcium is however reduced, and there is a need to correct the measured calcium concentration by increasing by a factor of 0.8 mg/dL for each 1 g/dL fall in the plasma albumin concentration [13].

Acid-base disturbances alter the binding equilibrium of the albumin-calcium complex. Acidosis reduces the binding, while alkalosis enhances it. In clinical situations where acid-base equilibrium is impaired, it is better to directly measure the ionised calcium levels in order to determine hypocalcaemia [14].

Hypocalcaemia

(Corrected calcium levels <2.12 mmol/L)

Causes can be classified under low PTH hypocalcaemia, high PTH hypocalcaemia and others

Hypoparathyroid hypocalcaemia	Hyperparathyroid hypocalcaemia (secondary hyperparathyroidism)
Genetic disorders, e.g. abnormal PTH synthesis	Vitamin D resistance
Postsurgical, e.g. parathyroidectomy	Vitamin D deficiency
Autoimmune, e.g. autoimmune polyglandular syndrome	Parathyroid hormone resistance, e.g. (pseudohypoparathyroidism) and hypomagnesaemia
Infiltration of the parathyroid gland, e.g. granulomatous conditions	Chronic kidney disease
Radiation-induced damage	Rapid loss of calcium from the serum (e.g. acute pancreatitis and severe sepsis)

Other causes:

- Drugs that inhibit bone resorption (e.g. bisphosphonates, calcitonin, denosumab)
- Calcium-chelating drugs (citrate, phosphate, EDTA)
- Disorders of magnesium metabolism (hypomagnesaemia can reduce PTH secretion)

Clinical Features [15]

The main presenting feature of acute hypocalcaemia is tetany. This is characterised by neuromuscular irritability. Hyperexcitability of the peripheral nervous system is the main pathophysiologic effect.

Mild tetany is characterised by perioral numbness, paraesthesias of the hands and feet and muscle cramps.

Moderate to severe tetany manifests as carpopedal spasm, laryngospasm and focal or generalised seizures.

Management

Treatment varies depending on the severity and underlying cause. The severity of hypocalcaemia depends on the absolute serum levels of calcium and the rate of decrease in calcium levels.

Chronic hypocalcaemia is treated based on the underlying cause with oral calcium and/or vitamin D supplements.

Intravenous calcium is recommended for symptomatic patients with corrected calcium levels <1.9 mmol/L. 10 ml of 10 % calcium gluconate has 90 mg of elemental calcium. This can be given as an infusion over 10–20 min and repeated if necessary.

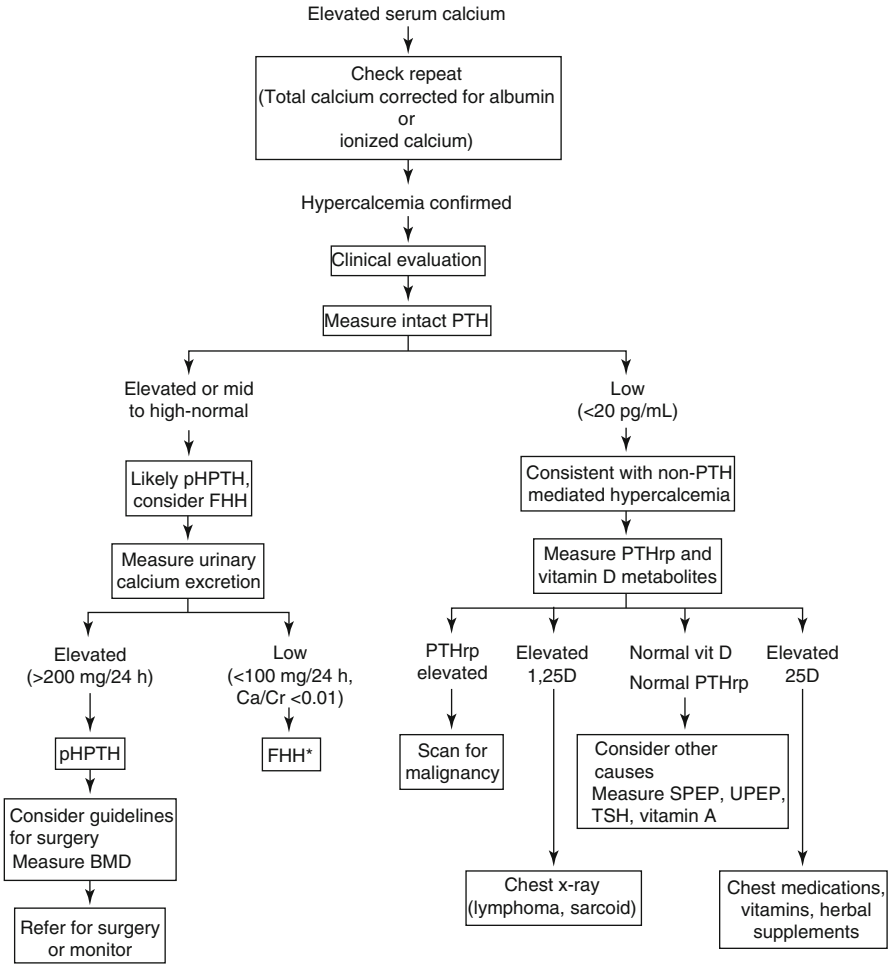
Hypercalcaemia

(Corrected serum calcium levels >2.62)

Causes can be classified under PTH-induced hypercalcaemia and PTH-independent hypercalcaemia

PTH-induced hypercalcaemia	PTH-independent hypercalcaemia
Primary hyperparathyroidism (idiopathic)	Paraneoplastic syndromes
Familial/genetic, e.g. (MEN-I and MEN-IIa)	Vitamin D intoxication
Tertiary hyperparathyroidism (CKD related)	Chronic granulomatous disorders
	Medications (e.g. vitamin A toxicity, theophylline toxicity, thiazide diuretics)

Diagnostic Approach to Hypercalcaemia [16]



PTH parathyroid hormone, *pHPTH* primary hyperparathyroidism, *FHH* familial hypocalciuric hypercalcaemia, *PTHrp* parathyroid hormone-related peptide, *1,25D* 1,25-dihydroxyvitamin D, *25D* 25-hydroxyvitamin D, *SPEP* serum protein electrophoresis, *UPEP* urine protein electrophoresis, *TSH* thyroid-stimulating hormone. * Further evaluation with measurement of 25-hydroxy vitamin D may be needed to differentiate FHH from primary hyperparathyroidism with concomitant vitamin D deficiency.

Clinical Features [17]

Clinical features depend on the severity of the hypercalcaemia and the rate of increase in calcium levels. Patients may be asymptomatic or have mild symptoms, e.g. constipation, fatigue and depression. More severe symptoms are multi-systemic.

Musculoskeletal system: muscle weakness
Cardiovascular system: shortening of the QT interval, supraventricular and ventricular arrhythmias
Neuropsychiatric: Anxiety, depression, cognitive impairment
Renal system: polyuria, nephrolithiasis, acute and chronic renal insufficiency, nephrogenic diabetes insipidus

Management

Severity	Treatment
Mild hypercalcaemia (<3.0 mmol/L)	Encourage increased oral fluid intake
Often asymptomatic	Avoid medications and promote hypercalcaemia, e.g. thiazide diuretics
Moderate hypercalcaemia (3.0–3.5 mmol/L)	Identify underlying cause and treat
	Simple measures as listed above if asymptomatic. If symptomatic, treat as per severe hypercalcaemia
Severe hypercalcaemia (>3.5 mmol/L)	Volume expansion with isotonic saline (200–300 ml/h aiming at a urine output of 100–150 ml/h) monitor fluid balance carefully
	Bisphosphonates (pamidronate 60–90 mg over 2 h) monitor serum calcium levels 4–6 hourly
	Calcitonin 4 IU/kg IM/SC 12 hourly increases renal calcium excretion

Hypophosphataemia (serum phosphate <2.5 mg/dL or 0.8 mmol/L)

Severe hypophosphataemia <0.3 mmol/L is often symptomatic and can cause significant physiological derangements [18].

True hypophosphataemia is generally caused by one or a combination of the following mechanisms:

- Decreased intestinal absorption
- Increased urinary excretion

- Rapid movement of extracellular phosphate into cells
- Removal associated with renal replacement therapy

The symptoms and clinical features depend mainly on the severity and chronicity of the phosphate depletion.

The major conditions associated with symptomatic hypophosphataemia include chronic malnutrition in the context of chronic alcohol abuse, total parenteral nutrition without adequate phosphate supplementation, urinary phosphate-wasting syndromes, Fanconi syndrome and renal replacement therapy [19].

The clinical features depend on the rate of phosphate depletion and the chronicity of the condition.

Symptoms are usually uncommon until the serum phosphate levels fall below 0.32 mmol/L.

The clinical manifestations are due to changes in mineral metabolism and adenosine triphosphate (ATP) depletion. The effects are multi-systemic.

Chronic phosphate depletion results in decreased renal distal tubular reabsorption of calcium and magnesium. There is also a persistent increase in bone resorption which results in osteomalacia and rickets [20].

Persistent decrease in intracellular ATP levels results in generalised muscle weakness, cardiomyopathy, respiratory failure due to muscle weakness, metabolic encephalopathy and various haematological disorders [21].

Treatment

Identify the underlying cause and treat appropriately.

Asymptomatic patients or those with mild symptoms with serum phosphate levels <0.62 mmol/L can be treated with oral phosphate supplements.

Symptomatic patients with serum phosphate between 0.32 and 0.62 mmol/L can also be treated with oral phosphate supplements.

Intravenous repletion should be reserved for patients with critical symptoms with serum phosphate below 0.32 mmol/L. This is due to a significant risk of developing complications of hyperphosphataemia with intravenous repletion. A change to oral repletion is therefore advised when serum phosphate levels reach 0.32 mmol/L and above [18].

Hyperphosphataemia

Hyperphosphataemia results when net phosphate entry into the serum exceeds renal excretion. The source of excess phosphate may be endogenous, e.g. cell lysis, or exogenous, e.g. phosphate-containing medications. It may also result from renal pathology, e.g. acute and chronic kidney disease or increased tubular reabsorption [22].

In patients with normal renal function, a large phosphate load is usually excreted by the kidneys. The phosphate excretion can be increased by administering saline infusions.

Acute severe hyperphosphataemia with hypocalcaemia can however be life-threatening. Saline infusion to promote phosphate excretion is the main intervention required. Patients with impaired renal function often require haemodialysis.

Chronic hyperphosphataemia requiring treatment occurs in patients with chronic kidney disease or familial tumoural calcinosis. The main treatment intervention is to diminish intestinal phosphate absorption by encouraging a low-phosphate diet and administering phosphate binders [23].

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Chapter 53
Electrolyte Imbalance: Sodium and Water

Gopal Basu

Key Points
- Sodium disorders are due to relative ECF water excess (hyponatraemia) or deficit (hyponatraemia) compared to sodium.
- Acute hyponatraemia is symptomatic and could be life-threatening, whereas chronic hyponatraemia is often asymptomatic despite severity.
- Rapid correction of serum sodium levels can result in central pontine myelinolysis.
- Hypovolaemia is managed with fluid therapy, while hypervolaemia is treated with diuretics.

Introduction

Disorders of water balance and sodium balance are commonly encountered in the Emergency Department. This chapter briefly describes the evaluation of hyponatraemia, hypernatraemia, hypovolaemia and hypervolaemia.

Sodium Imbalance

- Sodium plays an important role in fluid balance, acid base balance and neuromuscular function.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_53

- Serum sodium concentration is maintained within the narrow range of 135–145 mEq/L largely by antidiuretic hormone (ADH)-regulated thirst mechanism and renal handling of water and to a minor extent by renal handling of sodium.
- Thus, hyponatraemia is primarily due to the intake of water that cannot be excreted, while hypernatraemia is primarily due to loss of water that is inadequately replaced.

Hyponatraemia

Hyponatraemia, defined as a serum sodium <135 mEq/L, is the most common electrolyte abnormality, observed in about 3–5 % admissions to the Emergency Department (ED) [1]. Severe hyponatraemia is defined as serum sodium <125 mEq/L [2].

Aetiology

Hyponatraemia is a disorder of water balance with multifactorial aetiology, resulting when the free-water content exceeds the equilibrium with sodium, causing hypotonicity. Occasionally hyponatraemia could be observed in the presence of normal or even elevated measured plasma osmolality [3]. The aetiology of hyponatraemia is tabulated in Table 53.1.

Table 53.1 Aetiology of hyponatraemia

Hyponatraemia without true hypotonicity (plasma osmolality is normal/high)		
Increase in other osmoles: hyperglycaemia, mannitol infusion, glycine irrigation (transurethral resection of prostate)		
Interference (*pseudohyponatraemia*): hyperproteinaemia, hyperlipidaemia		
Hyponatraemia with true hypotonicity (measured plasma osmolality <290 mOsm/Kg)		
Reduced ECF volume	**Normal ECF volume**	**Increased ECF volume**
Na depletion ± relatively lesser water depletion	*Excess of water but with normal Na*	*Na excess with a relatively excess water*
Diarrhoea and vomiting or nasogastric suction/drainage, obstructed bowel Haemorrhage Insensible water losses (*skin and pulmonary losses*, *burns*) Fluid shifts into third space – *peritonitis*, *pancreatitis*, *muscle trauma* Renal losses – *salt-losing nephropathy*, *diuretic use*, *hypoadrenalism*, *osmotic diuresis*, *ketonuria*, etc. Cerebral salt-wasting syndrome (*CSW*)	Water intoxication (psychogenic polydipsia, beer potomania, iatrogenic hypotonic fluid therapy) Endocrine causes: syndrome of inappropriate ADH secretion (*SIADH*), *hypothyroidism*, *hypocortisolism* Pregnancy – reset osmostat Decreased salt intake Chronic kidney disease	Congestive heart failure Cirrhosis Nephrotic syndrome Acute or chronic renal failure

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

The most common cause of hyponatraemia in clinical practice in most hospitals is syndrome of inappropriate antidiuretic hormone (SIADH). The diagnosis of SIADH can be made with the criteria [4] given in Table 53.2.

The serum and urine chemistries in SIADH indicate inappropriately concentrated urine, due to "inappropriately" high plasma ADH activity, despite a hypotonic plasma. The various factors responsible for SIADH [5] are given in Table 53.3.

Clinical Features

- *Acute hyponatraemia* (*<48–72 h*): Rapid evolution of hypotonicity due to hyponatraemia results in cerebral oedema. It is often symptomatic and could be life-threatening. Children and young women are more symptomatic than adult males probably due to smaller CSF space between brain and skull.
  - *Mild symptoms* of nausea, malaise and hiccups [6] occur often at Na <125 mEq/L.
  - *Moderate symptoms* include headache, lethargy, confusion and obtundation.

Table 53.2 Criteria for SIADH

Essential criteria	Supplemental criteria
Normal adrenal and thyroid function Euvolaemic volume status Plasma osmolality <270 mOsm/Kg with hyponatraemia Urine osmolality >100 mOsm/Kg (usually 400–500 mOsm/Kg) Urine spot sodium >40 mEq/L	Abnormal water load test Inappropriately elevated plasma ADH levels despite hypotonicity

Table 53.3 Factors associated with SIADH

Malignancy central nervous system disorders	Pulmonary disorders	Drugs
Acute psychosis	Infections – pneumonia	Desmopressin
CNS tumours	Tuberculosis	Oxytocin
Encephalitis/meningitis	Lung abscess	Prostaglandin-synthesis
Inflammatory and demyelinating diseases	Cavitating lesions (e.g. aspergillosis)	inhibitors
Stroke, haemorrhage	Acute respiratory failure (hypoxia)	Carbamazepine
Trauma	Positive-pressure ventilation	Nicotine
Hydrocephalus	Miscellaneous	Chlorpropamide
	Postoperative state	Tricyclic antidepressants
	Pain	Serotonin-reuptake inhibitors
	Severe nausea	Monoamine oxidase inhibitors
	Infection with the HIV	Phenothiazines
	Acute intermittent porphyria	Opiate derivatives
		Clofibrate
		Cyclophosphamide, vincristine

  - *Severe hyponatraemia* manifests with stupor, seizures and coma, often at serum sodium <115 mEq/L.

- In *chronic hyponatraemia* (*>72 h*), adaptive osmolytes in the brain reduce the osmotic gradient preventing cerebral oedema. Thus, chronic hyponatraemia is *relatively asymptomatic*.

Management Approach

The first step is to confirm hypotonicity by (when possible) measuring (*not estimating/calculating*) the serum osmolality. The following laboratory investigations help delineate the aetiology and guide the therapy of hyponatraemia [7] (Table 53.4).

The simplified diagnostic approach of hypotonic hyponatraemia in the emergency setting is given in Fig. 53.1 and is further based on the history, clinical assessment of the patient's volume status and estimation of urinary electrolytes.

Key issues with diagnosis are to recognise the following:

1. It is important to note that in most cases, there is more than one factor responsible for hyponatraemia.

Table 53.4 Rationale of laboratory investigations in hyponatraemia

Lab investigation	Utility
Serum osmolality/plasma osmolality (P_{osm})	Helps in diagnosis of pseudohyponatraemia secondary to hyperlipidaemia, hyperproteinaemia, elevated glucose or mannitol-induced state
Urine osmolality (U_{osm})	Uosm reflects plasma ADH levels in most situations
	Uosm >100 mOsm/Kg: impaired diluting capacity of the kidney in the face of increased total body water (elevated ADH levels, appropriate or inappropriate)
	Usom <100 mOsm/Kg: urine is maximally dilute – normal water excretion and intact renal function (primary polydipsia, malnutrition)
Urinary sodium concentration: U_{Na}	*UNa >40 mEq/L* In SIADH and renal salt wasting
	UNa <20 mEq/L – extrarenal sodium loss
Serum urea and uric acid levels	Provide important supportive information (typically reduced in SIADH as well as CSWS)
Thyroid-stimulating hormone (TSH) and serum cortisol	Levels useful in euvolaemic hyponatraemia for diagnosing hypothyroidism and hypoadrenalism
Serum albumin, triglycerides, and a serum protein electrophoresis:	May be indicated for patients with suspected pseudohyponatraemia
CT head and chest radiograph	Useful in patients with suspected SIADH to ascertain the underlying aetiology

CSWS cerebral salt-wasting syndrome, *SIADH* syndrome of inappropriate ADH secretion

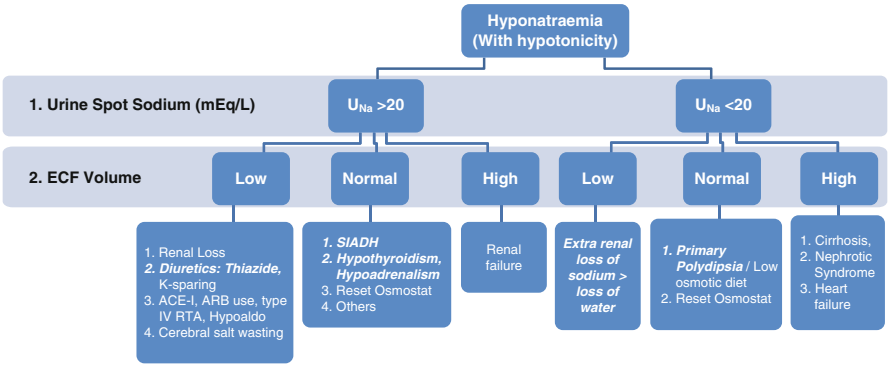

Fig. 53.1 Simplified and rapid diagnostic approach to hyponatraemia

2. Hyponatraemic encephalopathy is a medical emergency that should be diagnosed and treated promptly with hypertonic saline to prevent death or devastating neurological complications.
3. Patients who are asymptomatic do not require treatment with hypertonic saline, whatever their level of serum sodium.
4. Precipitating causes (e.g. thiazide diuretics) should be withdrawn when possible.

Management: Therapy of hyponatraemia depends on the *aetiology*, the *severity* (level of serum sodium), *rapidity* (acute or chronic) and the *symptomatology* of hyponatraemia. Therapy focuses on correcting hyponatraemia to prevent life-threatening complications as well as addressing the primary cause.

1. *Rule out pseudohyponatraemia* as it does not need any therapy.
2. *Address the hyperosmolar agent in hypertonic hyponatraemia*: For example, hyperglycaemic hyponatraemia needs insulin therapy to reduce blood glucose levels to correct hyponatraemia.
3. *In hypotonic hyponatraemia*, follow the steps:

   (a) *Correction of hypotonicity*

      (i) Choosing the *method* of correction
      (ii) Determining the sodium *deficit*
      (iii) *Monitoring the rate* of correction

   (b) *Correction of underlying cause*.

Step I. Choosing the Method of Correction

Clinical assessment and determination of the one or many aetiological factors are both important for choosing the method of serum sodium correction [8].

General principles of choice of agent:

Therapeutic options in hyponatraemia

1. *Fluid restriction*
   - Most important and relatively useful measure in almost all patients without obvious dehydration.
   - If patient has polyuria/dilute urine, additional measures are often unnecessary.
2. *Oral sodium replenishment lifting stringent sodium restriction*
   - As an adjunct measure useful in patients with sodium depletion (renal losses, extrarenal losses, third-space loss).
   - This could be used along with fluid restriction/diuretic therapy in patients with sodium excess as well (heart failure, cirrhosis, nephrotic syndrome, renal failure).
3. *Isotonic saline infusion*
   - Most useful in patients with sodium depletion (renal losses, extrarenal losses, third-space loss)
   - Can be used in euvolaemic hyponatraemia (SIADH) in combination with loop diuretics
   - Risk of overcorrection especially in hypovolaemic hypotonic hyponatraemia, or when used with loop diuretic
4. *Hypertonic saline infusion*
   - Indicated in hyponatraemic urgencies, especially in acute severe hyponatraemia.
   - Prescription is based on quantitative estimates.
   - In conditions with eu-/hypervolaemia, loop diuretics may be concomitantly used.
5. *Potassium repletion*
   - Often used in priority when hypokalaemia is present with hyponatraemia.
   - Correction of potassium does increase serum sodium to a limited extent. Thus, risk of overcorrection is present.
6. *Loop diuretic therapy*
   - Provides free-water clearance.
   - Often used as adjunctive measure in hypervolaemic states such as heart failure, nephrotic syndrome and cirrhosis.
   - Effective with fluid restriction, salt replenishment or parenteral saline infusion (isotonic or hypertonic)
   - Risk of overcorrection
7. *Glucocorticoid/thyroxine replacement*
   - Effective in specific deficiency states but with risk of overcorrection

8. *Discontinuation of offending drug/addressing primary cause*
9. *ADH antagonists* (*vaptans*): ADH receptor antagonists (vaptans) have emerged recently as therapeutic agents in hyponatraemia [9].

   (a) *Indications*:

   - Mild to moderate symptomatic hyponatraemia with hypervolaemia or SIADH
   - Resistant hyponatraemia (as adjunct Rx)
   - Chronic therapy in chronic/relapsing hyponatraemia
   - In cancer chemotherapy/surgical ICU patients with euvolaemic hyponatraemia

   (b) *Contraindications*:

   - Hypovolaemic hyponatraemia
   - Liver disease (risk of hepatic failure)
   - Renal failure (especially if GFR <30 ml/min/1.73sq.m. or creatinine >3 mg/dL)
   - Risk factors for overcorrection (Table 53.6)

   (c) *Dose*:

   - *Inj. Conivaptan* IV 20 mg loading dose followed by infusion of 20 mg/day. Can increase to 40 mg/day. Therapy for short term only – up to 4 days.
   - *Tab. Tolvaptan* 15 mg once daily. If insufficient increase in sodium, can increase dose up to 30–60 mg/day over intervals >24 h. Therapy can be extended for many days.

   (d) *Caveats*:

   - Vaptans should not be combined with hypertonic saline.
   - Vaptans should not be used in severely symptomatic hyponatraemia – It should be treated with hypertonic saline.
   - Vaptans are not useful in hyponatraemia due to nephrotic syndrome.
   - While on vaptans, patients should be:
     - Allowed to have normal fluid intake/drink according to thirst
     - Monitored regularly with serum Na every 4–6 h for the first few days of therapy and then less frequently
   - Vaptans should be stopped if rate of correction >8–12 mEq/L/day or >18 mEq/L/48 h

   (e) *Side effects of vaptans*: Thirst, dry mouth, headache, orthostatic hypotension, nausea, increased urinary frequency, hypokalaemia and hepatotoxicity

   (f) *Drug interactions*:

   - CYP3A4 inducers (i.e. rifampicin, barbiturates) reduce vaptan effect.
   - CYP3A4 inhibitors (i.e. macrolide antibiotics, diltiazem, ketoconazole) increase vaptan effect.
   - Tolvaptan increases serum digoxin concentrations.

Choosing the Appropriate Modality [10]

- *Hypovolaemic hyponatraemia correction*: Often involves *saline infusion* to replace the contracted intravascular volume. This reduces hypovolaemia-induced ADH release and thus effects free-water clearance and consequent sodium correction.
- *Hypervolaemic hyponatraemia correction*: *Fluid restriction with concomitant diuretic use*. Often salt restriction may be relaxed till when serum sodium reaches near normal range.
- *Euvolaemic hyponatraemia correction*: Therapy includes one or more of the following strategies: *free-water restriction*, *loop diuretic use* for free-water clearance, *sodium replacement* (oral or parenteral by saline infusion) and correction of the underlying condition.
- *Acute severe hyponatraemia* should be urgently treated with *hypertonic saline* (*although*, *any saline solution that is hypertonic to the urine can increase the serum sodium level*, *especially when oral water intake is restricted*) [11].
- In *SIADH*, normal saline infusion could potentially further reduce the serum sodium level by dilution, as the additional sodium gets excreted in the hyperosmolar urine. Hence, *fluid restriction and loop diuretic therapy* for free-water clearance is more effective in SIADH.

Step II: Determining Sodium Deficit

The *sodium deficit* is calculated by the following formula [8]:

$$\text{Na deficit}\left(\text{mEq}\right) = \left(\text{desired}\left[\text{Na}\right] - \text{current}\left[\text{Na}\right]\right) \times \text{TBW}$$

where TBW is the estimated total body water and desired [Na] is 140 mEq/L.

$$\text{TBW} = \text{Lean body weight} \times \left(0.5 \text{ for women or } 0.6 \text{ for men}\right)$$

This deficit needs to be corrected by choosing parenteral saline infusion as therapeutic strategy.

Step III. Monitored Correction of Serum Sodium

The sodium content of the infusion fluids varies (Table 53.5).

Using this table, the *approximate volume of fluid needed to correct the sodium deficit* could be calculated for each patient, preferably at every point when serum sodium is measured during the correction. The *rise in serum sodium resulting*

Table 53.5 Sodium content in 1 L of infusion fluids

Infusate	Infusate Na (mmol/L)	ECF distribution (%)
0.9 % NaCl	154	100
3 % NaCl	513	100
Ringer's lactate	130	97

from infusion of one litre of a given solution can be estimated from the following formula [8]:

$$\text{Rise in Serum}[\text{Na}] = \frac{(\text{infusate}[\text{Na}] - \text{baseline serum}[\text{Na}])}{(\text{TBW} + 1)}$$

However, in many situations, the actual rate of correction may be much faster (up to five times) than the one predicted by the formula. Hence, *frequent monitoring* remains important. Practical management algorithms, even if complex, cannot accurately predict a patient's response to treatment of hyponatraemia: *close monitoring of serum sodium* is essential.

The optimal rate of correction [10], for various categories of hyponatraemia includes:

- *Acute symptomatic hyponatraemia*
  - Initial therapy (often with hypertonic saline) to increase the serum sodium by 3–5 mEq/L in the first 3–6 h (~0.6–0.8 mEq/L/h at least for the first 3–6 h) or until the neurological symptoms remit.
  - Maximum increase of 10–12 mEq/L/day (if symptoms persist despite the correction, consider alternative causes for the symptoms).
  - Prompt correction recommended – risk of cerebral oedema outweighs risk of osmotic demyelination.
- *Chronic* (*severe*) *symptomatic hyponatraemia* (i.e. serum sodium <115 mEq/L)
  - Rapid correction only in the initial phase to improve symptoms
  - Initial rate of correction at 0.5–0.7 mEq/L/h to a maximum of 8–10 mEq/L/day
- *Severe but asymptomatic hyponatraemia*
  - Rapid correction not indicated as risk of CPM is high.
  - Correction is performed at ≤0.5 mEq/L/h, or, 6–8 mEq/L/day.
  - Often achieved with little or no use of parenteral saline infusion.
- *Immediate therapy*: Patients with suspected *hyponatraemic encephalopathy*, with either mild or advanced symptoms, children or adult, should receive *a 2 ml/Kg bolus of 3% NaCl with a maximum volume of 100 ml*. A single bolus would result in at most a 2 mmol/L acute rise in serum sodium, which would quickly reduce brain oedema. The bolus could be *repeated one to two times if*

symptoms persist. The advantage of this approach over a continuous infusion of 3 % NaCl is that there is a controlled and immediate rise in serum sodium, and there is little or no risk of inadvertent overcorrection, as can occur if a 3 % NaCl infusion runs at an excessive rate or for too long.

Caveats

1. A rapid increase in serum sodium in hyponatraemia could potentially result in *osmotic demyelination* or *central pontine myelinolysis* (*CPM*), a disabling life-threatening neurological syndrome characterised by osmotic demyelination of the pons [12, 13]. Symptoms range from dysphagia, dysarthria, paraparesis or quadriparesis, locked-in state (pseudocoma) and rarely even seizures or coma [15].
2. There are few important situations where despite appropriate calculations, overcorrection is common (Table 53.6). In these situations, it is important to be *conservative in the rate of correction* of serum sodium in these situations.

When encountered, *rapid overcorrection* (>10–12 mEq/L/day) should be immediately countered [14] by the following steps to prevent CPM:

- Discontinuation of all active therapy
- Infusion of electrolyte-free water in the form of 5 % dextrose (10 ml/Kg over 1–3 h)
- Injection desmopressin (DDAVP) 2 mcg subcutaneously. Can be repeated after 8 h

3. Slow correction fails to increase plasma tonicity quickly, which could result in persistent or worsening *cerebral oedema*, brain stem herniation and cardiopulmonary arrest.
4. As thiamine deficiency predisposes to osmotic demyelination, parenteral *thiamine replacement* at the beginning of sodium correction is prudent.

Table 53.6 Conditions where therapeutic strategies will result in rapid overcorrection of hyponatraemia

1. Primary polydipsia
2. Thiazide-induced hyponatraemia
3. Hypovolaemic hyponatraemia
4. Use of vaptans, especially in SIADH
5. Use of hypertonic saline in hyponatraemia
6. Haemodialysis with unadjusted dialysate sodium (often at 140 mEq/L)
7. Severe hypokalaemia when hypokalaemia is concurrently corrected
8. Adrenal insufficiency/hypothyroidism

Prevention of Hyponatraemia

- Hypotonic fluids should never be administered following surgery unless used to correct a free-water deficit. Instead, 0.9 % (normal) saline should be given post-operatively if parenteral fluids are indicated.
- All hospitalised patients should be considered at risk for the development of hyponatraemia and should not be given hypotonic fluids unless a free-water deficit is present or if ongoing free-water losses are being replaced.
- Those on thiazide diuretics, especially older people, should be weighed before and after starting therapy and serum electrolytes monitored to detect water retention and the development of hyponatraemia.

Hypernatraemia

Introduction

Hypernatraemia, defined as serum sodium >145 mEq/L, characterised by dehydration and hyperosmolality (plasma osmolality >290 mOsm/Kg), is observed in about 2 % of the patients presenting to Emergency Department (ED) [15].

Aetiology: The disorder is characterised by a relative free-water deficit and/or sodium excess. This is possible with failure of ADH-mediated thirst/renal water reclamation and/or restricted access to free water [16]. The broad groups of aetiology of hypernatraemia are listed in Table 53.7.

Assessment

- Obtain a detailed history regarding fluid intake and losses.
- Measure the urinary cationic electrolytes (sodium and potassium) and the urinary osmolality, remembering that the urinary osmolality alone cannot always determine the presence or absence of electrolyte-free water losses in the urine, the reason being that water can be excreted with nonelectrolyte osmoles or with electrolyte osmoles.

Table 53.7 Aetiology of hypernatraemia

Free-water deficit	Sodium excess
Renal	Chronic hyperaldosteronism
Diabetes insipidus	Salt loading
Central (low ADH secretion)	Parenteral hypertonic saline
Nephrogenic (ADH resistance – receptor defect)	Parenteral bicarbonate therapy
Osmotic diuresis (e.g. hyperglycaemia, mannitol, etc.)	
Extrarenal water loss (sweating, GI loss)	
Intracellular shift of water (trauma/seizures, rhabdomyolysis)	

Clinical features: Hypernatraemia causes hyperosmolality, thereby initiating neuronal dehydration and cell shrinkage, resulting in CNS symptoms [17].

- *Acute* (*<48–72 h*) *hypernatraemia* manifests with symptoms such as weakness, neuromuscular irritability, increased muscle tone, altered sensorium, CNS haemorrhage (subarachnoid, intracerebral or subdural due to rapid brain shrinkage resulting in tears in the bridging veins), focal neurologic deficits, seizures and coma.
- *Chronic* (*>72 h*) *hypernatraemia* is relatively asymptomatic.
- *Diabetes insipidus* presents with polyuria and polydipsia [18].
- *Hypovolaemia* is observed in patients with impaired thirst mechanisms or restricted access to water.
- *Hypervolaemia* and *hypertension* is seen in patients with sodium excess.

Diagnosis: Aetiological diagnosis has a significant impact on therapy of hypernatraemia. The important features/investigations that help in the diagnosis of the aetiology of hypernatraemia are given in Table 53.8.

The diagnostic algorithm for hypernatraemia is given in Fig. 53.2.

Management

This is facilitated through the following guidelines:

1. Correction of underlying deficits in circulatory blood volume by infusion of 0.9 % saline
2. Correction of chronic hypernatraemia
3. Administration of water by either oral, tube feeding or parenteral through intravenous fluids

Table 53.8 Investigations and their utility in diagnosis of hypernatraemia

Feature/investigation	Comment
ECF volume assessment	Hypervolaemia is often seen in conditions with sodium excess but not in water deficit
Urine volume	Polyuria is typically seen in diabetes insipidus and in osmotic diuresis
Urine osmolality	High urine osmolality in extrarenal free-water loss/osmotic diuresis Low urine osmolality is typical in diabetes insipidus
Daily osmolal excretion	High total osmolal excretion/day in urine is seen in osmotic diuresis
Response to DDAVP administration – by an increase in urine osmolality	Central diabetes insipidus – administration of 10 mcg intranasal DDAVP results in at least 50 % increase in urine osmolality. However, there is no/limited response in nephrogenic diabetes insipidus. Partial response could be observed in some cases of diabetes insipidus (partial DI)
Serum sodium (and osmolality)	Helps determine water deficit and rate of correction

Steps in management of hypernatraemia are:

I. *Ascertaining the need for correction*:

- Acute and symptomatic hypernatraemia requires urgent correction preferably with parenteral fluid therapy.
- Chronic/asymptomatic hypernatraemia will need a more conservative treatment to correct sodium level gradually

II. *Calculating the relative water deficit*:

- Water deficit is calculated approximately from the serum sodium as follows:

$$\text{Water deficit in Litres} = \text{TBW} \times \frac{\left(\text{current } [\text{Na}] \quad \text{desired } [\text{Na}]\right)}{\text{desired}[\text{Na}]}$$

- where TBW is the estimated total body water and desired [Na] is 140 mEq/L.

III. *Determining the method of correction*:

- Table 53.9 lists the several methods of correction of hypernatraemia [19] and their utility.
- *Hypovolaemic hypernatraemia* with tissue hypoperfusion: Isotonic saline is the fluid of initial choice with close monitoring of serum sodium till when tissue perfusion is restored. This should be followed by hypotonic fluids for decreasing serum sodium. A low urinary sodium (<10 mEq/L) will help uncover subclinical hypovolaemia, when isotonic saline infusion is advisable till when urine sodium is >20 mEq/L.
- *Hypervolaemic hypernatraemia*: combine free-water infusion with thiazide or potassium-sparing diuretic

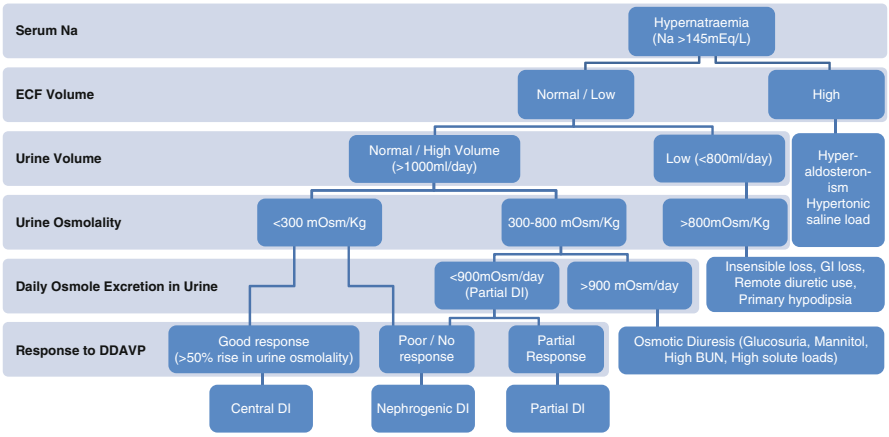

Fig. 53.2 Diagnostic approach to hypernatraemia

IV. *Determining the rate of correction*: Slow correction could result in cerebral dehydration, CNS haemorrhage, coma and death. Rapid correction can cause acute cerebral oedema due to sudden reduction of plasma osmolality [20].
- *Acute hypernatraemia*: Desired rate of correction is 0.5–1.0 mEq/L/h initially and <10–12 mEq/L/day.
- *Chronic hypernatraemia*: Desired rate of correction is 5–8 mEq/L/day. Total water deficit should be corrected in not less than 48–72 h.
- The expected fall in serum sodium with parenteral infusion of 1 L of a fluid is given by the formula:

$$\text{Decrease in } [\text{Na}] = \frac{(\text{Infusate } [\text{Na}] \quad \text{baseline plasma } [\text{Na}])}{(\text{TBW} + 1)}$$

- where TBW is the estimated total body water.

V. *Correction of the underlying cause*:
- In *central diabetes insipidus*: DDAVP administration (five units of aqueous vasopressin sc or 10 mcg of DDVAVP intranasally).
- In *nephrogenic diabetes insispidus*: A low-salt diet with low-dose thiazide diuretic will decrease polyuria.
- In *osmotic diuresis*: Control of the osmolyte will help – for example, glycaemic control, stopping mannitol, etc.
- In *hyperaldosteronism*: Aldosterone antagonists (spironolactone, eplerenone, amiloride, traimterene) are useful
- In *extrarenal water loss* – free-water infusion should be followed with addressing the underlying aetiology.

Table 53.9 Methods for correction of hypernatraemia

Modality	Oral/ nasogastric water	5 % dextrose	Hypotonic saline	
			0.45 % saline	0.225 % saline
Infusate [Na+]	0 mEq/L	0 mEq/L	77 mEq/L	39 mEq/L
ECF volume distribution	40 %	40 %	73 %	60 %
Advantages	Good safety profile Least invasive No additional Na delivered to patients	Indicated in conditions of water deficit not due to osmotic diuresis Complete parenteral free-water delivery No additional Na delivered to patient	Indicated in conditions with water loss and concurrent electrolyte loss (gastrointestinal loss, osmotic diuresis) Effective in ECF volume replacement in hypovolaemia Useful in hyperglycaemia	
Disadvantages	Gradual but unpredictable correction Not useful in gastrointestinal water losses	Not useful in severe hypovolaemia Watch for hyperglycaemia-induced osmotic diuresis which could aggravate hypernatraemia	Limited delivery of free water Not useful in hypervolaemia Net increase in Na delivered to patient	

VI. *Caveats*

- Glucose-containing solutions should be avoided if possible.
- As for the treatment of hyponatraemia, algorithms cannot accurately predict the response to treatment of hypernatraemia. Hence, regular monitoring of serum sodium with appropriate adjustment of treatment in response to the values obtained is mandatory.

Prevention

- Patients with impaired access to water (e.g. infants, elderly and hospitalised patients) should be considered at risk for the development of hypernatraemia.
- Urinary electrolytes should be measured in conjunction with urinary osmolality in patients with polyuria to assess water losses in the urine and urinary concentrating ability.

Hypovolaemia

Patients with reduced ECF volume present to Emergency Department (ED) often with hypotension.[1]

The common causes of hypovolaemia are listed in Table 53.10.

Clinical features: Symptoms of hypovolaemia can vary based on severity:

- *Mild volume losses* are often clinically silent – can be evaluated with capillary refill and passive leg-raising tests.
- *Moderate hypovolaemia* presented with signs such as tachycardia, postural hypotension, marginal weight loss, dry mucosa and diminished skin turgor.
- *Severe hypovolaemia* often manifests with tachycardia, hypotension, cool extremities, oligoanuria, cyanosis and syncope and coma.[2]

Evaluation and Management

- *Restoration of circulatory volume* is of utmost importance. Hence, urgent blood sampling for lab investigations should be followed by emergent intravenous fluid therapy.
- *Common laboratory abnormalities* providing corroborative evidence include elevated haematocrit, elevates serum albumin, increased serum and urine

[1] Exceptions to this include pre-eclampsia where patients present with hypertension but have hypovolaemia and congestive cardiac failure where patients have hypotension with hypervolaemia).

[2] Although oedema generally excludes hypovolaemia, an increased ECF volume may co-exist with reduced circulatory volume in situations like nephrotic syndrome, and cirrhosis).

Table 53.10 Causes of hypovolaemia

Renal fluid loss	Extrarenal fluid loss	Blood loss
Osmotic diuresis Diuretic use Salt-losing nephropathy Chronic interstitial nephritis Medullary cystic kidney disease Polycystic kidney disease and Sjogren's syndrome Renal tubular disorders Hypoaldosteronism Resolving acute tubular necrosis Postobstructive diuresis	Sweat loss (in hot environment) Insensible water loss (fever and tachypnoea) Burns Gastrointestinal losses (vomiting, diarrhoea, nasogastric aspiration and fistula drainage) Third-space losses (peritonitis, pancreatitis, ileus, intestinal obstruction, bacterial enterocolitis, portal vein thrombosis, serositis, crush injuries, rhabdomyolysis and sepsis-mediated endothelial dysfunction)	Gastrointestinal bleed Trauma Internal haemorrhage Bleeding disorder

osmolality, decreased urine sodium, contraction alkalosis and occasionally hypernatraemia.

- *Volume deficit assessment* is often clinical and based on severity of symptoms and signs. However, approximate empiric assessment could be performed using degree of weight loss or from change in haematocrit:

$$\text{ECF volume deficit} = 0.2 \times \text{LBW}(\text{kg}) \times \left[(\text{current Hct} \div \text{baseline or usual Hct}) - 1\right]$$

where LBW, lean body weight; Hct, haematocrit

- *Obtaining a venous access* and *immediate fluid resuscitation* are vital. Fluid replacement in the ED should begin with crystalloid infusions of either normal saline (0.9 % Na Cl) or Ringer's lactate. A *rapid infusion of 1 L of normal saline*, though initially fills up the intravascular space, eventually redistributes in the ECF to provide ~250 ml increase in circulatory volume.
- After immediate fluid infusion through a peripheral venous access, effort should be directed to obtain *large-bore central venous line* for rapid fluid therapy. Initial infusion should be followed by reassessment of volume status. *Persistent hypovolaemia* should prompt further boluses/continuous fluid infusion to rapidly achieve an effective circulatory volume (a mean arterial pressure of at least 70 mmHg).
- *Elderly and those with compromised cardiac function* should be managed with slower infusion rates of fluids and carefully monitored for signs of circulatory overload should be watched for, preferably with assessment of central venous pressure.
- Identifying the *addressing the cause of hypovolaemia* is important after initial resuscitation. Hypovolaemia due to haemorrhage requires blood transfusion. In case of severe haemorrhagic shock, rapid transfusion of O negative red cell units may be necessary to avoid delays. Protein loss-related hypovolaemia may need supplemental colloidal therapy.

Hypervolaemia

ECF volume increases are often related to:

- Increased fluid administration (self-induced or iatrogenic)
- Reduced renal excretion either due to renal dysfunction (acute kidney injury, chronic kidney disease, obstruction)
- Redistributed ECF volume with reduction in effective circulatory volume as in congestive heart failure, nephrotic syndrome and cirrhosis

Clinical features: Patient may present with dyspnoea, hypertension and bounding pulse, elevated jugular venous pressure, pulmonary crackles, S3 (if there is congestive cardiac failure), congestive hepatomegaly and peripheral oedema. Chest X-ray may confirm congested lung fields and often cardiomegaly.

Management

Initial step in management should focus on ensuring adequate *oxygenation*. Often, short duration of positive-pressure noninvasive ventilation may be required. While oxygenation is being restored, rapid *diuretic* boluses using loop diuretics are often effective in inducing venodilation and diuresis. *Blood pressure control* with parenteral vasodilator therapy may be required in hypertensive urgency. Careful addition of morphine may relieve symptoms in congestive heart failure. If large-dose loop diuretic boluses fail to induce diuresis, *ultrafiltration* may be necessary, especially in those with advanced renal failure.

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Chapter 54
Emergencies of End-Stage Renal Disease and Kidney Transplantation

Sishir Gang

Key Points
- Common problems in dialysis patients are cardiovascular disease, infections and electrolyte disorders.
- Fluid overload in end-stage renal disease should be urgently managed, and dialysis/ultrafiltration should be initiated early in severe cases
- Renal transplant patients often present to the emergency department with fever or graft dysfunction.
- Rejection is an important cause of graft dysfunction that needs immediate attention.

Introduction

End-stage renal disease (ESRD) is a stage of permanent loss of renal function which needs replacement by dialysis (haemodialysis or peritoneal dialysis) or kidney transplantation. The incidence of ESRD varies from 100 to 300 per million population [1].

Dialysis removes nitrogenous and other waste products and excess fluid and corrects electrolyte and acid-base abnormalities. However, it does not correct endocrine abnormalities associated with renal failure.

Chronic maintenance haemodialysis is an extracorporeal therapy which is typically done two or three times per week for approximately 4 h using haemodialysis machine. Blood is removed either by a temporary central venous catheter

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_54

or from an arteriovenous fistula. It is circulated through a dialyser which comprises of a membrane where in blood and dialysate flow in a counter current manner.

Chronic ambulatory peritoneal dialysis (CAPD) consists of instilling glucose-based dialysis fluid through a permanently placed catheter in the peritoneal cavity and removing it. The patient himself doses about three or four exchanges in a day. A typical exchange takes about 1 h and the remaining time the patient is ambulatory. The exchanges can also be done by an automated cycler throughout the night and disconnecting it in the morning. These therapies are remarkably well tolerated. However, they often present to emergency department with problem either related or unrelated to therapies. Few common problems are discussed below.

Shortness of Breath

The most common cause of ESRD patients presenting to emergency department is breathlessness. This is often due to volume overload leading to pulmonary oedema. Dialysis patients have reduced urine output. Any discretion in salt and fluid intake or missed dialysis schedule leads to fluid accumulation and breathlessness. However, other causes of shortness of breath like pulmonary infection, effusion, embolism, pneumothorax, acute cardiac failure and upper airway disease should be excluded.

Unlike patients with primary cardiac disease, patient on dialysis often has high blood pressure. They should undergo complete evaluation required of a dyspnoeic patient.

Management

The key to management is to quickly arrange for dialysis and prompt ultrafiltration. While dialysis is being arranged, the patient should be stabilised.

1. Oxygen support: Face mask or nasal cannula for oxygen supplementation should be started. If patient is severely breathless, continuous positive-pressure ventilation (CPAP) or bi-level positive airway pressure (BIPAP) is helpful.
2. Loop diuretics: They are generally not effective in ESRD patients. However, a large dose of furosemide (100 mg bolus) may provide symptomatic relief by decreasing pulmonary wedge pressure. The use of diuretic may just buy time, while arrangements for dialysis are being made.
3. Blood pressure control: Nitroprusside and nitroglycerine can be used to reduce afterload in severely hypertensive ESRD patients. However, because of risk of cyanate toxicity, nitroprusside should be used with caution in these patients.

Chest Pain

The two important causes of chest pain in dialysis patient are ischaemic heart disease and pericarditis. In view of early initiation and adequate dialysis, clinically significant pericarditis has now reduced in incidence.

Approach to Patient

The diagnosis of acute coronary syndrome (ACS) in patients on dialysis is particularly challenging because of the limited predictive value of the traditional triad of symptoms, ECG findings and cardiac biomarkers [2].

Chest pain is present in 50 % of the patients and they are more likely to present with symptoms of heart failure or syncope. Frequent presence of LVH with strain in these patients often masks ST segment depression on ECG. Myocardial injury biomarkers creatine kinase MB isoform and cardiac troponins (cTns) may be elevated in the absence of true myocardial necrosis, possibly because of myocardial apoptosis or small vessel disease. Cardiac troponin I is less elevated in renal failure in the absence of myocardial injury and is the preferred maker.

Treatment

There is little randomised data about the management of ACS in dialysis patient. Treatment approaches similar to non-CKD patients can be applied to patients with ESRD. Surgical and percutaneous intervention can be undertaken if deemed necessary.

Infections

Infections are a major cause of death in ESRD patients. ESRD patients have impaired granulocyte and lymphocyte function. They also have impaired humoral- and cell-mediated immunity.

Predominant causes of infection are access related especially tunnelled and non-tunnelled catheters in haemodialysis patients and peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD). The common organisms are *S. aureus*, enterococci, and gram-negative organisms.

Other important infections are pneumonia, urinary tract infection and septicaemia.

There is a several-fold high incidence of tuberculosis also. The disease is often extra-pulmonary.

They also have a high risk of nosocomial viral infections like hepatitis B and hepatitis C.

The workup of these patients is similar to other patients presenting with fever. The access sites should be thoroughly inspected for signs of local inflammation. In view of high incidence of MRSA, initially empirical treatment should include a combination of vancomycin 25 mg/kg IV and broad-spectrum cephalosporin (2 g IV ceftazidime IV) to cover for gram-negative organism. There should be low threshold for removing temporary catheters should the fever not respond quickly to antibiotics [3].

In patients on CAPD peritonitis should be suspected if they present with cloudy effluent, abdominal pain and fever. The whole CAPD bag should be sent to the lab for cell count and differential, gram stain and culture and sensitivity. Peritonitis is diagnosed if there are more than 100 white blood cells. Initial therapy consists of 2 g vancomycin and 1 g ceftazidime added to the next dialysate bag and allowed to dwell for 6 h [4].

Electrolyte Disorders

Electrolyte disturbances are more prevalent in haemodialysis patients compared to CAPD patients due to intermittent nature of its therapy. Hyperkalaemia is the most frequent electrolyte disturbance. Chronic dialysis patient tolerates hyperkalaemia better. However, they may present with weakness, acute flaccid paralysis or cardiac arrhythmias especially if the K^+ >6.5 mmol/L. They should be treated immediately with IV calcium gluconate, while arrangements are being made to initiate dialysis.

Hyperphosphataemia is common but patients are usually asymptomatic. However, if large volume of sodium phosphate is used for bowel preparation prior to colonoscopy, it leads to acute hyperphosphataemia which in turn causes hypocalcaemia. This can be life-threatening. Urgent prolonged dialysis along with administration of calcium gluconate should be undertaken [5].

Emergencies in Kidney Transplant Recipient

Kidney transplantation is the preferred treatment for patient with end-stage renal disease. It offers the greatest potential for restoring a healthy and productive life. Newer immunosuppressive therapies have reduced the incidence of rejection. There is now a large prevalent pool of patient with kidney transplant in the community. They are likely to present to the emergency department with medical problem which are both generic to general population and some which are unique to the transplant patients.

Kidney Transplant: Surgical Anatomy

The transplanted kidney is usually placed extra-peritoneally in the right or left iliac fossa. The transplant renal artery is anastomosed to either external or internal iliac artery. The vein is anastomosed end to side to the external iliac vein. The transplant ureter is anastomosed to the recipient bladder, less frequently to the ipsilateral native ureter. The transplant kidney is normally palpable and often a systolic bruit may be heard over the anastomotic site.

Post-transplant Immunosuppression

All transplant patients require immunosuppressive medications to prevent rejection. Post-transplant immunosuppression consists of induction phase and maintenance phase. Induction agent commonly used is either thymoglobulin or basiliximab. The maintenance therapy usually consists of corticosteroid, an anti-proliferative agent (azathioprine, mycophenolate mofetil or sirolimus/everolimus) agent and a calcineurin inhibitor (tacrolimus or cyclosporine). All these drugs increase the risk of infection and malignancy. Optimal dosing and prompt recognition of its side effects is crucial for obtaining long-term graft and patient survival [6] (Tables 54.1 and 54.2).

Presentation to the Emergency Department

The two common reasons for which renal transplant patients present to the emergency department are graft dysfunction and fever. A thorough history is important in any kidney transplant patient who presents to the ER.

- Current symptoms, especially fever, reduction in urine output, breathlessness, graft site pain
- History of pre-existing co-morbid conditions: diabetes, hepatitis B/C infection, cardiovascular disease
- Time interval since transplant (infection and malignancy often follow a timeline since transplant)
- Immunosuppressive therapy, their compliance and recent changes if any and the use of over-the-counter medications
- Episodes of antirejection treatment
- Previous infection, recent exposure to sick patients and history of travel

Table 54.1 Induction antibody agents

Induction agent	Adverse effect	Precautions/monitoring
Thymoglobulin	First-dose effects leucopenia, thrombocytopenia	Monitor CBC
Basiliximab	Similar rates to placebo	

Table 54.2 Maintenance immunosuppressive agents

Maintenance agent	Adverse effect	Precautions/ monitoring
Corticosteroids	Diabetes Hypertension Hyperlipidaemia Cushingoid Appearance peptic ulcer disease Cataracts Osteoporosis	Minimise dose
Anti-proliferative drugs		
Azathioprine	Leucopenia/anaemia/thrombocytopenia	Monitor CBC Avoid co-prescription of allopurinol
Mycophenolate mofetil	Nausea/diarrhoea/abdominal discomfort Leucopenia Thrombocytopenia	Monitor CBC Reduce dose
Sirolimus/everolimus	Impaired wound healing Acne Hyperlipidaemia Mouth ulcers Proteinuria	Switch if patient is undergoing major surgery
Calcineurin inhibitors		
Cyclosporine	Nephrotoxicity Hypertension Diabetes Hirsutism, gum hyperplasia Hyperlipidaemia	Monitor blood trough levels Significant drug interaction with drugs which induce and inhibit CYP3A4
Tacrolimus	Nephrotoxicity Tremors Diabetes Hyperlipidaemia	Monitor blood trough levels Significant drug interaction with drugs which induce and inhibit CYP3A4 Levels increase during diarrhoea
Co-stimulation blocker		
Belatacept	Post-transplant lymphoproliferative disease	Avoid in recipients who are Epstein–Barr virus (EBV) IgG negative prior to transplant

Adapted from Ref. [6]

Fever in Renal Transplant Recipient

Infection is the predominant cause of fever in kidney transplant patients. Knowledge about the risk factors helps in identifying the causative organisms [7].

1. The timing of infective episode after transplantation: As shown in Table 54.3, during the first month the predominant infection is one related to perioperative factor. After the first month as the intensity of immunosuppression takes its effect the infection is predominantly recrudescence of latent infection or opportunistic infections. After 6 months as the intensity of immunosuppression is reduced, most infections are community acquired.
2. The infection timeline may be altered depending upon the net state of immunosuppression. Net state of immunosuppression refers to the interaction of multiple factors such as dose, duration, intensity and sequence of immunosuppression. Furthermore, metabolic factor like hyperglycaemia, liver failure, malnutrition and infection with immunomodulatory virus also alter this net state of immunosuppressants.
3. Epidemiological factors also alter the likelihood of infection. In India malaria, dengue and leptospirosis should always be considered in the differential diagnosis.
4. The use of prophylactic medications may delay the onset of infection. Especially CMV normally occurs during the first 100 days. It may be delayed if prophylaxis with valganciclovir is administered for the first 90 days of transplantation.

Table 54.3 Assessing infection in renal transplant recipient

< 1 month	1–6 months	>6 months
Predominant infections are nosocomial, surgical procedure related, pre-existing infection in recipient or donor-derived nosocomial infection:	*Activation of latent infection (relapsed, residual, opportunistic). With PCP and antiviral Prophylaxis*:	*Community acquired*
Nosocomial infection: MRSA, VRE, Candida, resitanct GNB Aspiration pneumonia Bacteremia Urinary tract infection: catheter/sents related Wound infection Perigraft fluid collections Lymphocoele, seroma, hematoma, urinoma *Donor – derived infection* HSV, West Nile virus, HIV, bacterial Recipient – derived infection Aspergillus	*With PCP and antiviral Prophylaxis:* Polymavirus BK infection *C. difficile* colitis Hepatitis C virus Hepatitis B virus Adenovirus infection, influenza Cryptococcus neoformans infection Mycobacterium tuberculosis infection Anastomotic complications *Without prophylaxis*: Pneumocystis Infection with herpesviruses (HSV, VZV, CMV, EBV) Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania T, cruzi	*Bacterial* Pneumonia, urinary tract infection *Fungal* Aspergillus, Atypical molds, Mucor species Nocardia, rhodococcus species *Late viral infections:* CMV infection (colitis and retinitis) Hepatitis (HBV, HCV) HSV encephalitis BK virus nephropathy PTLD

Adapted from Ref. [7]

Investigations

Complete blood counts including peripheral smear for malaria, urine examination, urine and blood cultures, liver function tests, serum creatinine, chest X-ray and abdominal sonography should be done in all patients. Specific serology, nucleic acid testing and imaging should be done as deemed appropriate by clinical examination.

CMV infection should be suspected if patient has fever, low WBC counts and raised liver enzymes. Pneumocystis infection should be suspected in patients with fever, dyspnoea on exertion, minimal finding on chest examination and hypoxaemia. CT scan of the chest should be done; it would show ground-glass appearance even when chest X-ray appears normal.

Renal transplant patients often have extra-pulmonary tuberculosis. It should be suspected when patients have fever for more than 5 days, often appearing in the morning (unlike normal patients who get it in the evening). CT scan of the chest and abdomen should be done to look for lymph node enlargements.

Treatment

Empirical treatment should be initiated depending upon the clinical and initial laboratory workup. It should be modified once confirmatory diagnosis is established. Immunosuppressant needs to be modified depending upon the severity of infection. Anti-proliferative drugs may be temporarily reduced or stopped.

Renal Allograft Dysfunction

The approach to graft dysfunction in transplant patient is similar to acute kidney injury in native kidneys. It needs to be established whether the cause is prerenal, renal or postrenal. The common causes are listed in Table 54.4.

History and Evaluation

Haemodynamic instability would suggest prerenal decreased perfusion as a cause of graft dysfunction. Sudden drop in urine output or anuria is seen in patients with vascular occlusion or postrenal obstruction. Ultrasonography with Doppler should be done immediately to rule out these causes. Important parenchymal causes that need to be differentiated are acute rejection, drug toxicity especially calcineurin inhibitor (drug levels may be high) and infection. Often clinical clues are not sufficiently diagnostic and an early graft biopsy should be done.

Table 54.4 Common causes of acute graft dysfunction

Prerenal	Parenchymal	Postrenal
Functional Hypotension, hypovolaemia Sepsis Vascular occlusion Arterial thrombosis/ stenosis Venous thrombosis	Rejection Acute tubular injury Drugs: calcineurin inhibitors, thrombotic microangiopathy Acute pyelonephritis BK virus nephropathy Recurrent or de novo renal disease	Intrinsic obstruction Ureteral stenosis, blood clots Extrinsic obstruction Perigraft collections: lymphocoele, urinoma, haematoma Bladder outlet obstruction

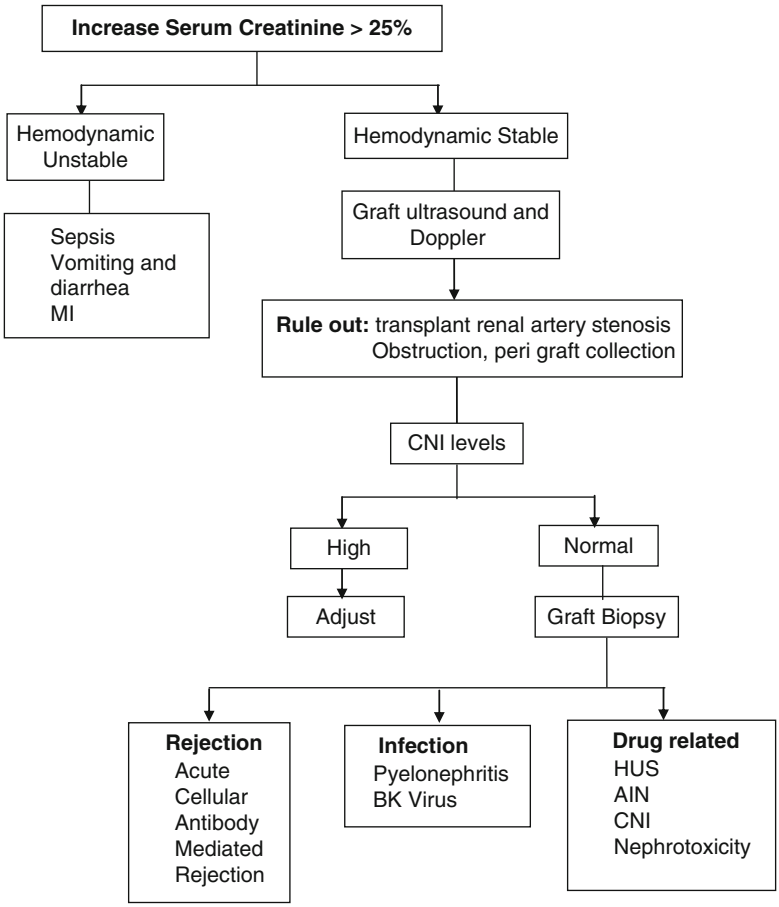

Fig. 54.1 Approach to a patient with renal allograft dysfunction

Approach to a patient with graft dysfunction is highlighted in Fig. 54.1.

Treatment is directed to the cause of graft dysfunction. Acute rejection requires emergent therapy with pulse corticosteroids (methylprednisolone) and further measures as directed by histopathological features to save the allograft.

Conclusion

Patients on renal replacement therapies are often likely to seek medical attention in the emergency department. Prompt thorough evaluation and coordinated care with specialist is essential to provide optimal treatment to these challenging patients.

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Part X
Neurology

Chapter 55
Altered Mental Status

Shakuntala Murty

Key Points
- Altered mental status encompasses a variety of clinical syndromes including delirium, coma, and psychiatric disorders.
- Use of a scoring system such as Confusion Assessment Method or Quick Confusion Scale is recommended to confirm presence of delirium.
- Treatment hinges on identification of the underlying cause. Hence early clinical pathway facilitates specific treatment.

Introduction

Altered mental status (AMS) is one of the most common presenting complaints to the emergency department and can also be one of the biggest challenges for an emergency physician. The challenge lies in identifying the anatomic basis for the altered mental state, the pathophysiology, and the underlying etiology and finally instituting appropriate initial treatment, all the while maintaining and supporting the patient's airway and hemodynamic status.

Elderly patients are particularly affected by AMS – one study reported that approximately 25 % of patients over 70 years of age presenting to an ED had some change in their mental status [1]. This chapter presents a simplified approach to a patient with altered mental status, highlighting the use of scoring systems, important differential diagnoses, and empirical treatment in the emergency department.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_55

Pathophysiology and Definitions

Consciousness is defined as the awareness of one's self and surroundings. Depression of consciousness can range along a spectrum of mild drowsiness, to stupor to frank coma. Alteration in consciousness can occur due to:

(a) Disorders of arousal including wakefulness and alertness
    Neurons responsible for arousal are located in the ascending reticular activating system (ARAS) which projects from the brain stem tegmentum through synaptic relays in the rostral intralaminar and thalamic nuclei to the cerebral cortex. Awareness is mainly a function of the cerebral cortex [2].
(b) Disorders affecting content of consciousness
    This includes cognitive functions such as attention, orientation, judgment, memory, and language.
(c) A combination of both

Delirium

This is primarily a dysfunction of arousal, but content of consciousness can be affected also. Delirium mainly causes difficulty in attention and concentration with associated cognitive defects. Symptoms are of acute onset, usually over hours to days, and often fluctuate. It is also referred to as "acute confusional state," or "acute encephalopathy." Delirium has been reported in 8–10 % of older ED patients [3]. The patient's activity levels may be increased or decreased, based on which delirium is classified into three subtypes. "Hyperactive" delirium is characterized by increased alertness, increased psychomotor activity, disorientation, and hallucinations. In contrast, in "hypoactive" delirium (also known as quiet delirium), the patient is confused, but there is a decrease in alertness and activity [4]. Hypoactive delirium is often missed by health-care providers and misdiagnosed as fatigue or depression [5]. One study found that emergency physicians missed delirium in 76 % of patients and suggested that using a delirium risk score would improve delirium screening efficiency in the ED setting [6].

Dementia

This indicates a loss of mental capacity and presents with various cognitive defects including language, memory, visual spatial, or executive function. Alertness and arousal are usually preserved, hence differentiating it from delirium (Table 55.1).

Table 55.1 Differentiation of delirium and dementia

Clinical feature	Delirium	Dementia
Onset	Acute	Chronic
Course	Fluctuating	Stable
Level of consciousness	Decreased or agitated	Normal
Attention	Abnormal	Normal
Orientation	Impaired	May be impaired
Hallucinations	Visual/auditory	Absent

Psychiatric Disorders

Patients with mood or psychotic disorders may present with a change in behavior and appear to be in altered mental status, but they are usually oriented and will have features of their primary psychiatric disorders.

An important point to note is that delirium, dementia, and psychiatric disorders may coexist or overlap, e.g., an elderly patient with dementia may present with new onset delirium due to an acute illness. Cognitive deficits like memory loss or lack of insight and judgment may occur in both delirium and dementia. The main difference is that in delirium, there is a change in arousal and alertness, whereas a patient with dementia will be normally alert.

Coma

Coma is a state in which the patient is unconscious, unaware, and unresponsive to external stimuli. It results from structural damage to the ARAS, anterior cingulate cortex, and association cortex (precuneus and cuneus) or from profound diffuse cerebral dysfunction. A patient in coma may have preserved response to painful stimuli to some extent, and brain stem reflexes also may be preserved [2].

Coma can result from a systemic disorder which deprives the brain of necessary substrates, such as hypoglycemia or hypoxia. Primary CNS causes are usually brain stem disorders such as infarction or hemorrhage, or any cause of bilateral cortical dysfunction. The etiology of coma often overlaps with that of delirium – the same underlying condition may begin as acute delirium and, if it gets worse or is untreated, can progress to coma.

Evaluation of AMS

In the ED, rapid assessment and stabilization of the patient should occur simultaneously with investigation and diagnosis of the cause of the altered mental status. Airway management takes priority and use of a scoring system such as the Glasgow

Coma Scale (GCS) helps to quickly determine the need for urgent endotracheal intubation. A GCS of 8 and below predicts the need for airway protection. Though it does not differentiate between the different causes of AMS, serial GCS scores are useful for monitoring depth of coma.

History

History should be obtained from family members, other caregivers, friends, or bystanders present at the scene and nursing home staff. If possible, previous medical records should be obtained and examined to identify past medical disorders and treatment. Important questions to be asked are:

1. Was the onset of altered mental state acute or insidious? What is the duration?
2. When was the patient last seen normal?
3. Were there any previous similar episodes?
4. Any history of alcohol or substance abuse or exposure to drugs or toxins?
5. History of hallucinations.
6. Past medication history and any recently added new medications.
7. History of fever, trauma, or seizures.
8. Past medical history including cardiac, respiratory, renal, hepatic, and CNS disease.

Physical Examination

General examination may reveal jaundice, pallor, cyanosis, clubbing indicating a chronic respiratory or cardiac disorder, or pedal oedema. Assessment of vital signs is paramount, particularly decreased oxygen saturation which may indicate acute respiratory failure or tachycardia and hypotension indicating shock of various causative factors. Any of these conditions can lead to altered mental status due to decreased cerebral oxygenation and perfusion. Fever may suggest infective pathology.

Systemic examination – relevant findings are summarized in Table 55.2.

Mental Status Examination

Alertness, attention, orientation, memory, and thinking are altered in delirium. An objective way to assess these parameters is useful to make a diagnosis and to monitor the patient over time. The Mini-Mental State Examination [7] has been widely used but is time consuming and difficult to perform in ED patients. A simplified but systematic method of bedside cognitive assessment has been suggested to differentiate between delirium and dementia [8] (Fig. 55.1).

Table 55.2 Systemic examination in altered mental status

Cardiovascular system	Tachycardia, S3 gallop, basal crepitations Murmurs	Congestive cardiac failure Infective endocarditis, valvular disease
Respiratory system	Diffuse wheezing Bronchial breathing/ crepitations	Acute severe asthma Acute exacerbation of COPD Pneumonia
Abdomen	Hepatosplenomegaly, ascites	Chronic liver disease, infection
CNS	Unilateral fixed dilated pupil Bilateral fixed dilated pupils Absent doll's eye reflex Any focal neurological deficit Meningeal signs	Brain stem herniation Brain stem pathology, drug/toxin ingestion Brain stem dysfunction Structural CNS lesion, e.g., hemorrhage, tumor Meningitis, subarachnoid hemorrhage
Skin	Injuries, skin lesions	Trauma, infection

Another simple scale which can be used is the Quick Confusion Scale (QCS) (Table 55.3). This has been developed and tested in ED patients and takes only 2 or 3 min to obtain [9]. It is a six-item battery of questions focusing on orientation, memory, and concentration weighted to yield a top score of 15. Comparison with the MMSE has shown that it is quicker to administer and the scores obtained correlate significantly with MMSE scores [10].

A third assessment tool for delirium, which is used most commonly, is the Confusion Assessment Method (CAM) (Table 55.4) [11].

Psychiatric Evaluation

The presence of any psychiatric symptoms and prior psychiatric history must be ascertained. It is important to verify that a patient's symptoms are psychiatric and not medical. Some predictors of medical conditions mimicking psychiatric illness are acute onset, age greater than 45 years, prior medical diseases, neurologic symptoms, new medications, abnormal vitals, and decreased level of consciousness [12].

If psychiatric illness appears likely, questions about mood, anxiety, psychotic, and substance abuse disorders should be asked. The patient's appearance, motor activity, speech, thought content, and thought process should be assessed. Auditory and/or visual hallucinations must be looked for, and if necessary, psychiatric consult should be obtained.

Differential Diagnosis

Following history, in physical examination and mental status examination, the most important question to be answered is – does the patient have a focal neurological deficit? If so, a structural CNS lesion must be excluded. Examples of deficits include

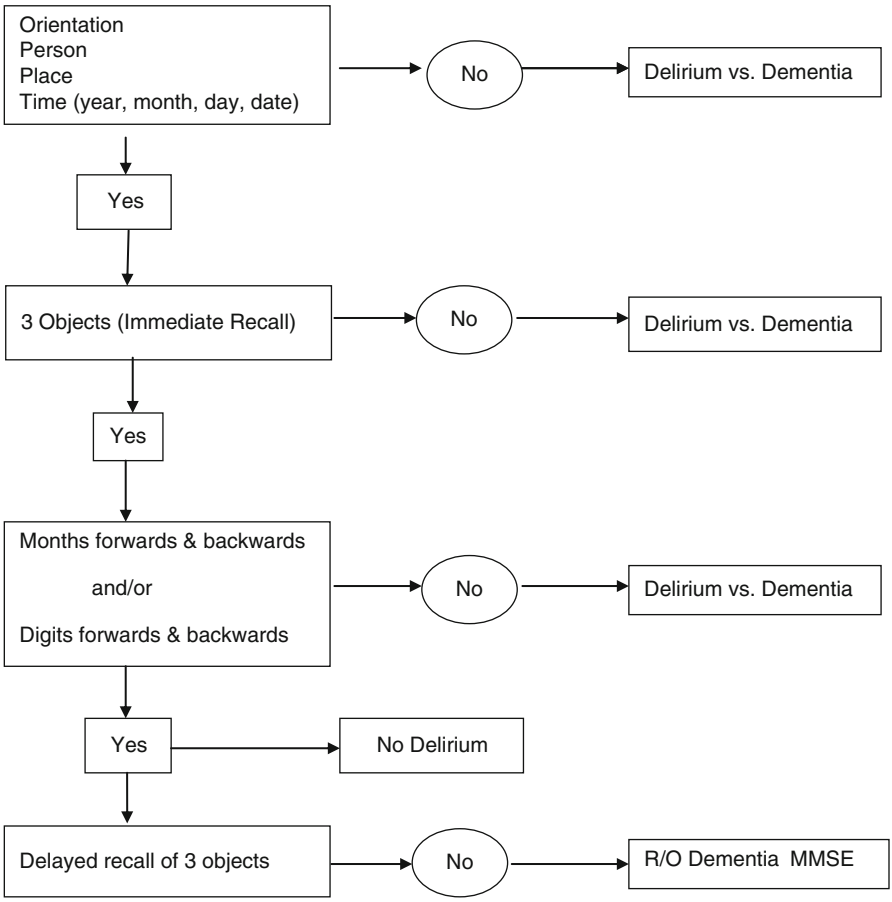


Fig. 55.1 Bedside cognitive assessment

aphasia, pupillary asymmetry, abnormal extraocular movements, hemiparesis or hemiplegia, cerebellar signs, or abnormal reflexes. Absence of focal deficits suggests that the altered mental status is due to diffuse cerebral dysfunction. There are exceptions to this rule – hypoglycemia may present with a focal deficit such as hemiparesis, whereas hydrocephalus, brain stem pathology, and cerebral venous thrombosis may present without obvious focal signs.

Causative factors can be classified broadly as:

1. Structural brain lesion
   (a) Brain stem pathology
   (b) Bilateral cerebral cortical dysfunction
2. Metabolic encephalopathy
3. Drug-induced or toxic encephalopathy

A more detailed list of differential diagnoses can be found in Table 55.5.

Table 55.3 Quick confusion scale

Item	No. correct	× Weight	Total score
What year is it now?	0 or 1 (score 1 if correct, 0 if incorrect)	×2	
What month is it?	0 or 1	×2	
Present memory phrase: "Repeat this phrase after me and remember it: *John Brown, 42 Market Street, New York*"			
Around what time is it? (answer correct if within 1 h)	0 or 1	×2	
Count backwards from 20 to 1	0, 1 or 2 1 (2 if no errors, 1 if one error, 0 if more than one error)	×1	
Say the months in reverse	0, 1 or 2 (2 if no errors, 1 if one error, 0 if more than one error)	×1	

Repeat memory phrase (each underlined portion is worth 1 point)
Final score is sum of the totals – score less than 15 suggests the presence of altered cognition and need for further assessment

Table 55.4 Confusion assessment method

Confusion assessment method (CAM) diagnostic algorithm[a]
1. Acute onset and fluctuating course
2. Inattention, distractibility
3. Disorganized thinking, illogical, or unclear ideas
4. Alteration in consciousness

[a]The diagnosis of delirium requires the presence of both features 1 AND 2, plus EITHER feature 3 or 4

Investigations

The most important immediate test to be done in the ED is the bedside finger-stick glucose, mainly to diagnose or exclude hypoglycemia which will need immediate treatment. Other investigations depend on the history and findings on physical examination. Any evidence of a structural CNS lesion merits immediate brain imaging, usually a non-contrast CT scan, which is quick and easy to perform even in a restless or agitated patient or a patient with borderline hemodynamics. A CT scan will identify hemorrhage, infarction, cerebral oedema, and traumatic lesions as well as hydrocephalus. The posterior fossa is difficult to image by CT scan, in which case MRI scanning may be required, which is usually not so easily available, is time consuming, and difficult to perform in a patient with altered mental state.

Other tests which should be performed in the ED are:

1. ECG – to look for acute coronary syndrome. Elderly patients may present only with altered mental status.
2. Complete blood count to screen for infection.
3. Arterial blood gas analysis – detects hypoxia, hypercarbia, and respiratory or metabolic acidosis.
4. Serum electrolytes.

Table 55.5 Common differential diagnoses of altered mental status

Category	Possible diagnosis
Structural CNS lesions	Intracerebral hemorrhage
	Subarachnoid hemorrhage
	Cerebral infarct
	Cerebral venous thrombosis
	Traumatic brain injury (causing extradural or subdural hematoma or cerebral contusions)
	Meningitis/encephalitis
	Cerebral abscess
	Acute hydrocephalus
	Neoplasm (primary or metastatic)
Diffuse CNS disease	Post-ictal state
	Non-convulsive status epilepticus
	Complex partial status epilepticus
Systemic infection	Pneumonia
	Urinary tract infection
	Sepsis
	Systemic febrile syndromes
Metabolic/endocrine	Hypo-/hyperglycemia
	Hypo-/hypernatremia
	Hypo-/hypercalcemia
	Hyperammonemia
	Hypo-/hyperthyroidism
	Acute liver failure
	Uremia
	Hypercapnia
	Wernicke's encephalopathy
Toxin/drug overdose	Benzodiazepine abuse/withdrawal
	Barbiturate abuse/withdrawal
	Alcohol intoxication/withdrawal
	Anticholinergic drug poisoning
	Opioids
	Organophosphates
	Tricyclic antidepressants
	Sympathomimetics
Cardiovascular	Acute MI
	Congestive heart failure
	Severe anemia

5. BUN and creatinine.
6. Coagulation profile.
7. Liver function tests and ammonia.
8. Urinalysis to look for evidence of infection or ketosis.
9. Urine drug screen.
10. Chest X-ray – to diagnose pneumonia and cardiac failure.

Other relevant investigations which may not always be possible in the ED include lumbar puncture and cerebrospinal fluid analysis for diagnosis of neuro-infections and electroencephalography, especially if non-convulsive status epilepticus is suspected.

Treatment

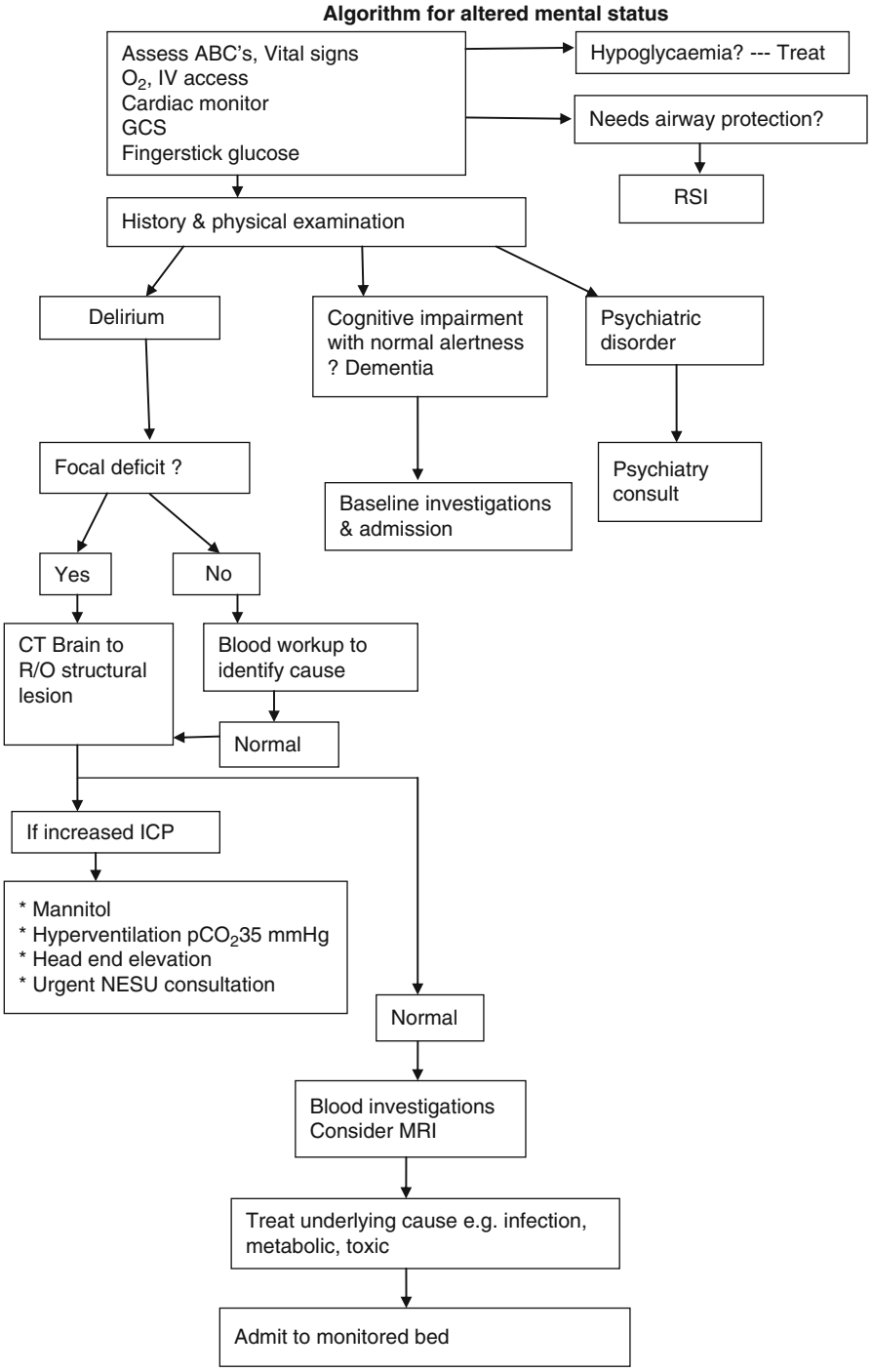
The initial actions of the emergency physician must be to stabilize the airway, breathing, and circulation. Oxygen should be administered and intravenous access obtained within the first few minutes of the patient's arrival, along with cardiac monitoring. A Glasgow Coma Scale of 8 or less is an indication for urgent endotracheal intubation to protect the airway, unless the cause of altered mental state is quickly reversible.

Treatment can be classified under three headings:

1. Treatment of the underlying cause – this should be initiated in the ED, e.g., correction of metabolic abnormalities, treatment of infection, and appropriate management of toxidromes. Presence of an abnormality on CT head particularly signs of raised intracranial pressure or cerebral herniation should prompt urgent neurosurgical referral. Definite evidence of impending cerebral herniation, e.g., unilateral dilated pupil or Cushing's reflex (bradycardia and hypertension) should be empirically treated with mannitol, 2 g/kg intravenously, head-end elevation to 30° to help in venous drainage, and hyperventilation to maintain $PaCO_2$ at 35 mmHg.
2. Pharmacological treatment
   (a) Thiamine 100 mg intravenously in alcohol withdrawal states may help prevent Wernicke's encephalopathy.
   (b) Naloxone should be considered in possible opiate overdose.
   (c) In agitated patients, sedation may be required though it may further confound the clinical picture. The usual initial drug used is haloperidol, 5–10 mg PO, IM, or IV, which can be repeated at 20–30 min intervals as required. Lorazepam, 0.5–2.0 mg PO, IM, or IV may be added to haloperidol. Atypical antipsychotics such as risperidone, olanzapine, and quetiapine have also been used to treat delirium. A comparative study which used low-dose haloperidol found no difference in the efficacy and safety of haloperidol compared to these drugs [13]. A systematic review also found haloperidol in low dose (<3 mg/day) to be as efficacious as olanzapine and risperidone, without a higher incidence of side effects. Dose of haloperidol >4.5 mg per day in one study was associated with an increased incidence of extrapyramidal adverse effects, compared with olanzapine [14].
3. Non-pharmacological treatment – a calm environment, adequate lighting, and presence of family members may have an ameliorating effect on agitated patients. If absolutely necessary, physical restraints may be used, keeping in mind the safety of the patient.

Both drug treatment and restraint are only temporizing measures. Appropriate diagnostic testing must continue to establish the cause of altered mental status, so that specific treatment can be started.

Algorithm for altered mental status



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Chapter 56
Dizziness and Syncope

Girish Narayan

Key Points
- Dizziness and syncope are common symptoms that have multiple differential diagnoses.
- History and clinical examination are crucial to determine the aetiology of dizziness or syncope.
- Directed and focussed investigations are required to ascertain the diagnosis.

Introduction

Dizziness is a frequent but complex symptom that patients present with to the emergency department. The term "dizziness" is used by patients to describe a wide-ranging group of symptoms from the benign to the life threatening. Hence, the determination of aetiology and management requires precision.

The prevalence of dizziness and syncope among patients varies with age. Approximately 3 % of patients present with dizziness and the incidence of syncope vary from 1 to 5 %, with an increasing prevalence among patients aged greater than 50 years, along with more likelihood of dangerous causes [1, 3, 5].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_56

Definitions

(A) **Syncope**
Syncope is defined as a transient loss of consciousness accompanied by loss of postural tone followed by recovery to a normal neurological state [4–6].

(B) **Dizziness**
Dizziness as a symptom is often vague and inexact. From a patient's point of view, it can be difficult to explain and for a physician its analysis can be vexing.

Generally, the term dizziness is used to describe one or a combination of the following [7, 8, 10]:

1. Vertigo: An illusory rotatory or a spinning sensation
2. Light-headedness/presyncope: An impending sensation of faintness or feeling woozy
3. Imbalance/disequilibrium: A sensation of unsteadiness while walking or loss of posture

Pathophysiology

Syncope occurs due to cerebral or brainstem hypoperfusion resulting in the sequelae of loss of consciousness and loss of postural tone.

The perception of balance is maintained by sensory input from visual, proprioceptive and vestibular systems which are integrated via the cerebrum, cerebellum and brainstem to the subsequent motor outflow. Any disturbance in any of these systems or their connections can result in the symptom of dizziness or vertigo [3, 5, 7, 11].

Aetiology

The causes of dizziness and syncope are many (Table 56.1). The mechanisms through which they occur may overlap. Vestibular and otologic causes usually cause vertigo. Vertebrobasilar insufficiency and stroke like lateral medullary and anterior inferior cerebellar artery syndromes and cerebellar haemorrhage/infarction may present with vertigo, imbalance or even syncope at times. Cardiovascular causes usually cause symptoms as a result of decreased perfusion. Systemic causes and medications result in dizziness or syncope by a number of mechanisms, and there may be an overlap as with hypoglycaemia secondary to Addison's disease or drugs. Medications and toxins will usually cause symptoms through various pathophysiological mechanisms but may precipitate other aetiologies, especially in the elderly [2–5, 10, 12].

Table 56.1 Causes of dizziness and/or syncope [2–5, 10, 12]

Vestibular or otologic[a]	Neurologic	Systemic	Drugs and toxins
(a) Benign paroxysmal positional vertigo (b) Vestibular neuronitis (c) Labyrinthitis (d) Meniere's disease (e) Foreign body in ear (f) Otitis media (g) Otosclerosis (h) Perilymphatic fistula (i) Ramsay Hunt syndrome (j) Concussion (post-head trauma) (k) Motion sickness	(a) Acoustic neuroma (b) Cerebellopontine angle tumours (c) Migraine (d) Stroke (e) Subarachnoid haemorrhage (f) Multiple sclerosis (g) Seizure/postictal (h) CNS infections (i) Peripheral neuropathy (j) Myelopathy **Cardiovascular** (a) Acute coronary syndromes (b) Hypertensive emergency/urgency (c) Aortic dissection (d) Angina (e) Arrhythmias (f) Valvular lesions (g) Cardiomyopathy (h) Pulmonary embolism/ hypertension (i) Subclavian steal syndrome	(a) Anaemia (b) Orthostatic hypotension (c) Blood loss (d) Polycythaemia (e) Hyperviscosity syndrome (f) Dehydration (g) Chronic renal failure (h) Vasovagal (i) Trauma (j) Concussion (k) Cervical spine disorders (l) Addison's disease (m) Hypothyroidism (n) Diabetes insipidus (o) Hypoglycaemia (p) Hyperventilation (q) Psychogenic (anxiety, stress)	(a) Aminoglycosides[a] (b) Erythromycin (c) Minocycline (d) Fluoroquinolones (e) Antimalarials (f) Diuretics (g) Beta blockers (h) Vasodilators (i) Sympatholytics (j) Digoxin (k) Salicylates (l) NSAIDS (m) Cisplatin (n) Vincristine (o) Phenytoin (p) Antidepressants (q) Anticonvulsants (r) Antipsychotics (s) Anxiolytic/sedative (t) Mood stabilizers (u) Insulin (v) Oral hypoglycaemic agents (w) Substances of abuse (alcohol, cannabis, cocaine) (x) Carbon monoxide

[a]Aetiologies particularly presenting with the symptom of vertigo

Clinical Features (Tables 56.2 and 56.3)

Physical examination remains the backbone of evaluation of dizziness and syncope. Patients may have returned to their presymptom state at the time of examination; therefore, a thorough examination is required to establish differentials.

Neuro-cardiogenic or vasovagal syncope is a type of situational syncope which can be precipitated by number of triggers. Emotion, pain and uneasy high-stress situations can be the inciting factor. There may be a prodrome of light-headedness, blurring of vision or diaphoresis. The event occurs when the patient is in upright posture, gradual in onset followed by a rapid recovery once the patient is supine. The pathogenesis is due to increased sympathetic outflow and sudden vagal modulation [4, 11].

Benign paroxysmal positional vertigo (BPPV) is the most common aetiology of vertigo. It occurs when otoconia (crystals of calcium carbonate) are dislodged from the utricle and drift into the semicircular canals, usually the posterior. The patient will experience vertigo when turning the head towards the affected side and it is

Table 56.2 Symptomology [3, 7, 9, 11]

	Syncope	Dizziness
Preceding event	Exertion, heat exposure, micturition, defecation, emotional stress	Prior history of an ear disorder may be present if a peripheral cause
Event	Patients will usually describe it as fainting or passing out with loss of muscle strength Position: standing/supine/sitting Onset: abrupt/gradual	Patients will describe it as a feeling of unsteadiness on standing or walking or whirling or spinning when stationary which may be aggravated on head movement Duration: several hours to days
Post-event	Spontaneous recovery, duration and rate to be inquired to rule out postictal state	Maybe episodic with spontaneous recovery with symptom-free intervals. Can be persistent also
Associated symptoms	Chest pain, dyspnoea, palpitation, sweating	Nausea, vomiting, ear disturbances, head or neck injury, neurologic symptoms
Past history	Coronary artery disease, CVA/TIA, diabetes, hypertension, arrhythmias	Coronary artery disease, CVA/TIA, diabetes, hypertension, arrhythmias, trauma, ENT disorders, drugs

Table 56.3 Examination of patients with dizziness or syncope [3–5, 7, 10, 11]

System	Signs	Possible aetiology
General physical examination		
Pulse: rate and rhythm (all peripheral pulses to be examined)	Tachycardia, bradycardia, arrhythmias, pulse volume, asymmetrical pulses, carotid bruits	Cardiac, vascular, fluid overload, hypovolemia, infective
Respiratory rate and volume	Tachypnea	Hyperventilation, hypoxia, pulmonary embolus, AMI, heart failure
Blood pressure	Hypotension, hypertension, orthostatic hypotension, variation in limbs	Shock, hypertensive crisis, hypovolemia, vascular
Temperature	Increase or decrease	Fever, infection, shock
Appearance	Pallor	Anemia, shock, blood loss, heart failure
	Cyanosis	
Neurological system	Higher mental functions	Stroke, raised ICP, localization of neurological lesion (cerebrum/cerebellar/brainstem/spinal cord)
	Papilloedema	
	Focal neurological deficits	
ENT	Peripheral nystagmus: horizontal, sudden, episodic, short duration, fatigable, triggered by head movement	Peripheral or central vertigo Otitis media, trauma, BPPV
	Central nystagmus: Any direction, insidious, constant , sustained duration, nonfatigable, nonprovocative	
	Tympanic membrane abnormalities, deafness, Dix Hallpike Test	

Table 56.3 (continued)

System	Signs	Possible aetiology
Cardiovascular system	Raised JVP	Heart failure, pulmonary embolus, tamponade, cardiomyopathy, valvular pathology, pericarditis
	Apical impulse displaced	
	Heart sounds muffled, rubs, murmurs, S3, S4	
Respiratory system	Crepitations	Pneumonia, pulmonary oedema, haemothorax
	Decreased breath sounds	
Abdomen	Pulsatile mass	Aortic aneurysm, abdominal or pelvic trauma, GI bleed
	Tenderness, abrasions	
	Melaena	
Genitourinary	Bleeding per vagina	Ectopic pregnancy, genitourinary trauma
Extremities	Pedal oedema	Fluid overload, heart failure, trauma
	Swelling, tenderness	

usually episodic. It is diagnosed with Dix-Hallpike test which is done by placing the patient in a supine position with his head hanging off the edge of the examination table. The patient's head is then turned to either side rapidly and held in that position and is observed for nystagmus which confirms BPPV. The nystagmus usually starts after a few seconds of latency and will reduce with repeat testing and time. In central causes, there will be no latency or reduction with time. Meniere's disease is poorly understood pathophysiologically. Increased endolymph production resulting in elevated pressure is suspected. Episodes of rotational vertigo lasting for hours accompanied with nausea, vomiting, hearing loss and tinnitus can occur. Nystagmus will be present but it will not be related to position.

Vestibulitis typically presents with severe vertigo peaking in hours, plateauing over the next few days and may persist for weeks. Symptoms can worsen with change in position. Associated symptoms such as nausea and vomiting may be present but auditory symptoms are absent. When hearing loss is present, labyrinthitis is to be considered. Nystagmus will be spontaneous towards the affected side [3, 7, 10, 13].

Investigations

Studies estimate that physical examination and history are able to potentially diagnose 40 % of causes of syncope and dizziness. Therefore, investigating patients becomes imperative in most emergency rooms. Judicious and targeted investigations

Table 56.4 Directed investigations in patients with dizziness or syncope [4, 5, 7, 10, 11, 13]

Investigation	Possible diagnosis
ECG	Ischaemia, arrhythmias
Blood sugar	Hypo-/hyperglycaemia
Haemoglobin, haematocrit	Blood loss, anaemia
WBC count	Infection, sepsis
Urine pregnancy test	Pregnancy, ectopic
Beta HCG	
Blood gas	Hypoxia
Electrolytes	Metabolic abnormalities, hypo-/hyperkalaemia, kidney injury
Cardiac enzymes	Acute coronary syndromes
B-natriuretic peptide	Heart failure
D-dimer	Pulmonary embolism
Drug screen (urine/blood)	Medication/toxin identification
X-rays	Trauma, pneumonia, aortic aneurysm
USG (FAST, RUSH)	Trauma, shock, ectopic pregnancy
ECHO	Acute myocardial infarction, valvular pathologies, tamponade
Doppler	Aneurysm, DVT in a suspected case of PE
CT	Trauma
	Pulmonary embolism
	Stroke, subarachnoid haemorrhage
MRI	Stroke (particularly posterior cranial fossa and brainstem pathologies), space-occupying lesions

complimenting a thorough examination are essential for a quick diagnosis and to limit costs for a patient (Table 56.4).

When investigating patients in the emergency department, life-threatening causes need to be identified quickly. Without a supportive history or positive clinical examination, diagnostic tests can have a low yield. An ECG is still recommended though yield is low. It is used extensively in most risk stratification guidelines. ECG in addition to history and examination helps increase the yield of laboratory investigations in particular cardiac enzymes [4, 5].

Ultrasound has proven to be a very useful tool in identification of free fluid in trauma. Echocardiography is useful in patients with structural heart disease presenting with syncope or dizziness. Identification of impaired ejection fraction helps manage patients at serious risk. Other investigations help an emergency physician risk stratify the patient after a cause has been determined by a clinical examination or by radiological evaluation [5, 7].

Neuroimaging in patients with dizziness and syncope should be guided by clinical examination. During evaluation of a possible cerebellar stroke, imaging is vital. Though CT scan is the most frequently used modality due to its easy availability, it cannot be used conclusively to rule out certain pathologies. Physicians should

recognize the limitations of CT in evaluation of acute strokes particularly in the posterior cranial fossa or brainstem. When available, MRI with diffusion weighted imaging should be performed as it provides a higher sensitivity than CT [7, 10, 11, 13].

Treatment and Disposition

Management of patients with dizziness and syncope will essentially be directed by the diagnosis. Treatment will also be dictated by the patient's haemodynamic status. Primary stabilization of vital parameters with identification of risk factors will begin in the emergency department. Strokes, acute coronary syndromes, arrhythmias and suspected vascular emergencies will require intensive care management after stabilization in the emergency room. Unambiguous diagnoses will usually follow definitive management pathways [4, 7, 11].

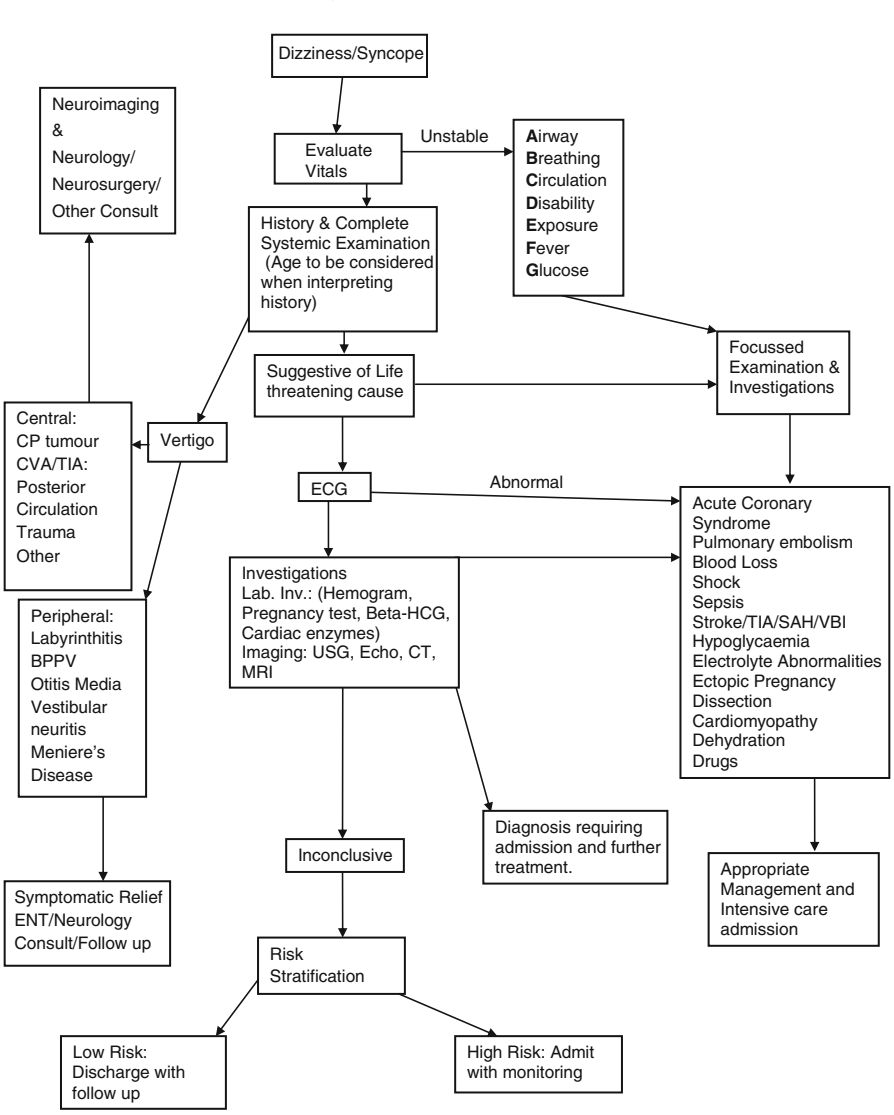
Benign paroxysmal positional vertigo can be cured by Epley's particle repositioning manoeuvre along with vestibular suppressants for acute symptoms of nausea and vomiting. Intravenous ondansetron is considered safe and effective for these symptoms. For patients presenting with severe vomiting, promethazine and benzodiazepines can be considered, but sedation is a frequent side effect. For other causes with acute symptoms, short-term therapy with these agents can be considered till definitive treatment for the cause is implemented [3, 7].

Patients in whom the diagnosis is elusive will require risk stratification and then appropriate disposition. A number of syncope risk stratification guidelines have been developed, but no set of rules have achieved complete validation to rely on. The focus of these rules is to admit high-risk patients and minimize admissions in low-risk patients. Currently, all rules either inadvertently miss risk stratifying some high-risk patients to reduce inpatient numbers or unnecessarily identify many patients as potential dangerous outcomes resulting in over admission. The various rules suggested are the San Francisco Syncope Rule (SFSR), the Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score, the European Guidelines in Syncope Study (EGSYS) score and the Risk Stratification of Syncope in the Emergency Department (ROSE) score. None of these rules have been completely validated. However, the common minimum criteria that have been present across all rules are the following:

- Older age
- History suggestive of structural heart disease or arrhythmias
- Unrelenting abnormal vitals
- Abnormal ECG [4–6, 11]

Patients who are discharged after evaluation for dizziness or syncope should be asymptomatic at discharge and advised follow up with appropriate departments.

Clinical pathway to manage dizziness and syncope



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Chapter 57
Headache

Thomas Mathew and Sagar Badachi

Key Points
1. It is prudent to perform imaging of the brain – either CT scan or MRI scan for patients presenting to the ED with headache.
2. "Time is brain". Early and appropriate management reduces mortality and morbidity.

Introduction

Headache can be the presenting feature of many medical and neurological disorders. Headache, or cephalalgia, is the fifth most common primary complaint of patients presenting to an emergency department (ED), representing more than three million patients each year, or 2 % of all ED visits [1]. The field of headache medicine is so

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_57

vast that it takes many years for any physician to diagnose and manage all different types of headache. In this context it is right to say that the role of an emergency physician is to diagnose the dangerous causes of headache as early as possible and institute timely and appropriate treatment to prevent devastating consequences.

Pathophysiology

It is interesting to note that brain parenchyma is insensitive to pain. Pain-producing structures in the head are scalp, dural sinuses, middle meningeal artery, falx cerebri and proximal segments of major arteries. Injury or inflammation to these structures results in pain.

Approach to a Patient with Headache in the Emergency Setting

Any patient presenting to the ED with headache should be evaluated carefully as it may be the manifestation of a serious underlying neurological disorder. The physician attending to the patient should *elicit a proper history* from the patient or the close relative (if the patient is in altered sensorium or in coma) to understand the nature of the illness causing the headache. This step is the first and the most important step in the diagnosis of the headache disorder. The general principle of neurological medicine – "Talk, Talk, Talk, Touch, Test and Treat" – should not be forgotten. The emergency physician evaluating a patient with the complaint of headache should be able to differentiate primary from secondary headache (Fig. 57.1). Primary headaches are those in which headache is the disorder, whereas secondary headaches are presenting symptom of exogenous disorders. Primary headaches are classified based on symptoms, while secondary headaches are classified according to causes [2]. The aim of the emergency physician should be to rule out any secondary causes of headache and refer to a physician/neurologist or neurosurgeon for further management.

The Important Questions to Be Asked in History in a Patient Presenting to Emergency with Headache

1. When did the headache start?
2. How did it start?
3. Since when have you been having headache?
4. How severe is the headache?
5. Is this the worst headache of your life?
6. Is there any head trauma, fever, vomiting, diplopia or neck stiffness?
7. Is the patient conscious or unconscious?
8. Does the patient have seizures?
9. Is the patient on oral contraceptive medication ?
10. Does the headache change with posture ?

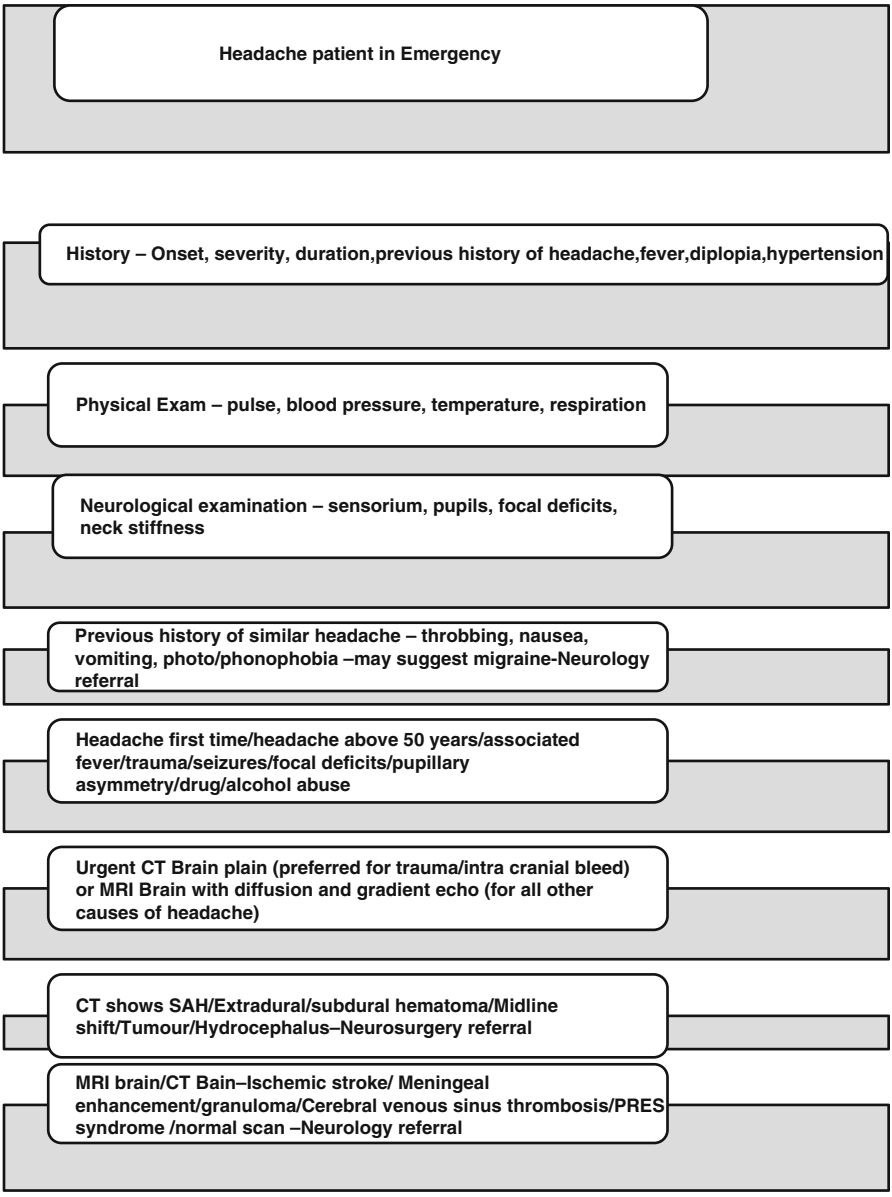

Fig. 57.1 Algorithm for workup of patients with headache presenting to emergency

The Important Signs to Be Checked in Physical Examination

1. Vital signs – pulse and blood pressure
2. Sensorium
3. Pupils
4. Focal deficit

The Most Important Investigations to Be Ordered in All Patients Presenting to the Emergency Department with Severe Headache

Neuroimaging of the brain – either a CT scan or MRI scan of the brain is the most important investigation in patients with headache in the emergency room. A CT scan is ideal for patients with head trauma and those suspected to have intracranial bleed as blood and bone is best made out in plain CT brain (both are white/hyperdense on plain CT brain). In all other patients, an MRI of the brain is preferable (ischaemic stroke, meningitis/encephalitis/metastasis/CVT). In those suspected to have meningitis, an MRI of the brain with contrast is the best modality of imaging. Magnetic resonance angiography (MRA) is indicated for subarachnoid haemorrhage, dissection of the carotid or vertebral artery and arteriovenous malformations. In patients with suspected CVT, we should ask for an MR venogram.

Most Important Steps to Be Taken for Treating Acute Headache Patients

- Treatment depends on the aetiology of the headache.
- Stabilise the vital parameters.
- Anti-oedema measures to be started in case of raised intracranial pressure.
- Antiepileptics to be started in case of seizure.

Red Flags

Red flags refer to specific warning signs or clinical circumstances in which a more ominous cause of headache should be ruled out.

1. Abrupt onset of headache
2. New headache pattern
3. Change in existing pattern of headache [3]
4. Postural change of headache
5. Presence of neurologic signs or symptoms
6. Fever
7. Weight loss
8. Presence of a systemic disease such as HIV/SLE/nephrotic syndrome/malignancy
9. Headache during pregnancy and postpartum period
10. Headaches triggered by exertion, sexual activity, cough or Valsalva manoeuvre
11. Age more than 50 years

Comfort Signs in Headache

The presence of the following comfort signs indicates a benign type of headache:

1. Established stable pattern of headache >6 months
2. Long-standing history of similar headache

3. Exacerbation with menses/travel/sunlight/fasting
4. Variability of headache location
5. Return to baseline function between headaches
6. Positive family history of primary headache disorder
7. Normal physical and neurological examination

Aetiologies for Various Patterns of Headache

1. *Abrupt onset of headache*: CNS haemorrhage (subarachnoid haemorrhage), ischaemic stroke, cerebral venous sinus thrombosis, meningitis (pyogenic/viral), hypertensive encephalopathy, reversible cerebral vasoconstriction syndrome
2. *New headache*: CNS haemorrhage (subarachnoid haemorrhage), ischaemic stroke, cerebral venous sinus thrombosis, meningitis (pyogenic/viral), reversible cerebral vasoconstriction syndrome
3. *Change in existing headache*: Medication overuse headache or any of the secondary causes
4. *Neurologic signs or symptoms*: Mass lesion – primary or metastatic, CNS infection, connective tissue disease, intracranial hypertension
5. *Head or neck trauma*: Haemorrhage/dissection
6. *Fever*: Systemic infection, meningoencephalitis
7. *Weight loss*

   Malignancy
   Systemic disease
   HIV

8. *Systemic disease*

   HIV
   Inflammatory and rheumatological disease
   Hypertensive crisis

9. *Pregnancy/postpartum*

   Toxaemia
   Pituitary apoplexy

10. *Headaches triggered by exertion*, *sexual activity*, *cough or Valsalva manoeuvre*

    - Mass lesion
    - Subarachnoid haemorrhage
    - Vertebral or carotid dissection
    - CV junction anomaly

11. *Postural headaches*

    Post-lumbar puncture headache
    Idiopathic intracranial hypotension

12. *Age more than 50 years*: Temporal arteritis/subdural haematoma/metastasis

Table 57.1 Secondary causes of thunderclap headache

Arterial dissection: cervical, vertebral and carotid
Arteriovenous malformations
Aneurysmal bleed
Altitude sickness
Acute stroke
Acute myocardial infarction
Cerebral venous thrombosis
Cerebral vasculitis
Glaucoma
Intracranial haemorrhage
Malignant hypertensive crisis
Meningitis
Pheochromocytoma
Pituitary apoplexy
Posterior reversible leukoencephalopathy syndrome
Reversible cerebral vasoconstriction syndrome
Spontaneous intracranial hypotension
Sentinel bleed
Third ventricular occlusion from colloid cyst

Thunderclap Headache

Abrupt onset severe headache reaching maximum intensity in <1 min and lasting for at least 5 min is called thunderclap headache [4]. Thunderclap headache can be primary or secondary. In primary thunderclap headache, there is no demonstrable aetiology after extensive investigation. An emergency physician should be aware of the secondary causes of thunderclap headache which are given in Table 57.1. In this article we will be concentrating more on the common causes of acute severe headache.

The most common causes of acute severe headaches are:

- Subarachnoid haemorrhage
- Intraparenchymal/intraventricular/extradural/subdural bleed
- Meningitis/encephalitis – pyogenic/viral
- Malignant hypertension
- Cortical venous sinus thrombosis
- Eclampsia
- Status migrainosus

Subarachnoid Haemorrhage

Patients presenting with sudden onset of severe headache should be evaluated to rule out subarachnoid haemorrhage (SAH) and intraparenchymal bleed. Patients with SAH will have the worst headache of their life which is maximal at the onset.

They may have associated neck stiffness and photophobia and may lose consciousness at the onset [5]. Symptoms and signs of meningeal irritation and raised intracranial pressure may be evident. Temperature elevation can be seen due to chemical meningitis from subarachnoid blood products and is common after the fourth day following bleeding. Tachycardia may be present for several days after the occurrence of a haemorrhage. Papilloedema may be evident on fundoscopy. Focal neurologic deficits may be seen.

Sentinel Leaks/Warning Leaks

Minor loss of blood from the aneurysm is reported to occur in 30–50 % of aneurysmal SAHs. These may cause sudden onset of severe headache and serve as harbinger of imminent complete rupture. Nausea, vomiting, photophobia or, occasionally, neck pain may be associated with headache. However, signs of meningeal irritation and raised intracranial tension may not be present during sentinel leak. Therefore, emergency physicians should have the acuity to recognise this entity to prevent catastrophic events caused due to delay in timely diagnosis. Any patient of sudden onset of severe headache must be investigated with non-contrast CT scan of the brain and, if needed, a CT angiogram to check for aneurysms.

Clinical Grading of SAH

The World Federation of Neurological Surgeons (WFNS) Grading System

- Grade 1 – Glasgow Coma Score (GCS) of 15, motor deficit absent
- Grade 2 – GCS of 13–14, motor deficit absent
- Grade 3 – GCS of 13–14, motor deficit present
- Grade 4 – GCS of 7–12, motor deficit absent or present
- Grade 5 – GCS of 3–6, motor deficit absent or present

The Hunt and Hess Grading System

- Grade 0 – Unruptured aneurysm
- Grade I – Asymptomatic or mild headache and slight nuchal rigidity
- Grade Ia – Fixed neurological deficit without acute meningeal/brain reaction
- Grade II – Cranial nerve palsy, moderate to severe headache, nuchal rigidity
- Grade III – Mild focal deficit, lethargy or confusion
- Grade IV – Stupor, moderate to severe hemiparesis, early decerebrate rigidity
- Grade V – Deep coma, decerebrate rigidity, moribund appearance

(The lower the grade, the better the prognosis.)

Investigations

Non-contrast CT Scan

CT without contrast is the most sensitive imaging study in SAH. CT has 100 % sensitivity and specificity when done within 6 h. Sensitivity is 93 % within 24 h of onset [6]. The location of blood within the subarachnoid space correlates directly with the location of the aneurysm. It is valuable to note that blood localised to the basal cisterns, the sylvian fissure or the inter-hemispheric fissure indicates rupture of a saccular aneurysm, while blood lying over the convexities or within the superficial parenchyma of the brain is indicative of arteriovenous malformation (AVM) or mycotic aneurysm rupture or cerebral venous sinus thrombosis.

Lumbar Puncture

Lumbar puncture (LP) is usually done as a follow-up test when a CT scan fails to reveal SAH. It should not be performed if the CT scan demonstrates SAH because of the minor risk of aggravating intracranial bleeding precipitated by a drop in intracranial pressure. Contraindications to LP include significant intracranial mass effect, elevated ICP, obstructive hydrocephalus or obvious intracranial bleed.

Cerebrospinal fluid is analysed for the presence of red blood cells (RBCs) and xanthochromia. LP may be negative if performed less than 2 h after an SAH occurs. LP is most sensitive 12 h after onset of symptoms. RBCs in the CSF can reflect a traumatic LP. SAH often can be distinguished from traumatic LP by comparing the RBC count of the first and last tubes of CSF. In traumatic LP, the RBC count in the last tube is usually lower, but in SAH the RBC typically remains consistently elevated. The most reliable method of differentiating SAH from a traumatic tap is to centrifuge the CSF and examine the supernatant fluid for the presence of xanthochromia, a pink or yellow coloration caused by the breakdown of RBCs and subsequent release of haem pigments.

Xanthochromia typically will not appear until 2–4 h after the seizure. In nearly 100 % of patients with an SAH, xanthochromia is present 12 h after the bleed and remains for approximately 2 weeks.

Principles of Treatment

Emergency management of blood pressure, airway, breathing, circulation and urgent referral to neurology department may improve the final outcome.

Table 57.2 Causes of intracranial bleed

Hypertensive bleed
Trauma
Infarct with haemorrhagic transformation
Cerebral venous sinus thrombosis
Antiplatelet agents, anticoagulants, thrombolytic agents
Tumour with bleed
AV malformation, cavernous angioma
Cocaine/amphetamine abuse
Sympathomimetic drugs

Headache due to Intracranial Bleed

Hypertension is the most common cause of intracranial parenchymal bleed. The typical sites of hypertensive bleed are putamen, thalamus, cerebellum and pons. Headache is maximal at the onset and may be localised to the site of bleed. Signs depend on the site of bleed, the commonest being hemiparesis/hemisensory symptoms, cranial nerve palsies and ataxia. If atypical sites are involved, other causes of intracranial bleed should ruled out (Tables 57.2).

Extradural haematomas are usually traumatic. Subdural haematomas are common in elderly, alcoholics and those on antiplatelet agents and anticoagulant drugs.

Headache due to Cerebral Venous Thrombosis (CVT)

Sudden severe headache can be the initial manifestation of CVT. Focal neurological deficits and seizures may be present. Headache followed by seizures is the classical presentation of CVT. Fundus examination may show papilloedema. Diagnosis should be strongly suspected in patients presenting with headache in the postpartum/postabortion period, women on oral contraceptive pills and men with chronic alcohol intake. Infarctions in non-arterial territories may provide clue to diagnosis. Unusual location of parenchymal bleeds which are uncommonly seen in hypertensive bleeds should alarm the emergency physician to suspect CVT. MR venogram will confirm the diagnosis. Anti-coagulation, anti-epileptic and anti-oedema measures are the mainstay of treatment.

Headache due to Meningitis

Association of fever, neck stiffness and headache with/without focal neurological deficits constitutes the clinical picture of meningitis. MRI of the brain with contrast followed by lumbar puncture is diagnostic. Lumbar puncture should be avoided in

patients with low GCS and focal deficits. Once a provisional diagnosis is made, blood should be drawn for bacterial culture followed by 10 mg of IV dexamethasone and 2 g IV ceftriaxone and 1 g IV vancomycin. Patient should be referred to physician/neurologist for further management.

Malignant Hypertension/Eclampsia

Patients with malignant hypertension may present with headache with or without altered sensorium/seizures. Females during their third trimester of pregnancy and in the first 2 weeks of postpartum period can present with eclampsia. Neurological manifestations include headache, blindness, altered sensorium, seizures and focal neurological deficits. Fundoscopy will reveal papilloedema. Neuroimaging should be done to rule out intracranial bleed, infarct and posterior reversible encephalopathy syndrome (PRES). Prompt and careful reduction of blood pressure forms the mainstay of treatment. In all these patients, blood pressure should be controlled as per standard protocols.

Status Migrainosus

Headache lasting for more than 72 h in a known patient of migraine is called status migrainosus. MRI of the brain should be done in such cases, to rule out any ominous causes. IV dexamethasone and IV valproate can be used for immediate treatment. Neurology opinion should be taken for planning further management.

Carotid Artery Dissection

Headache is usually described as constant and severe and is commonly ipsilateral to the dissected artery. It usually precedes a cerebral ischaemic event. Associated symptoms may include transient episodic blindness (amaurosis fugax), partial Horner syndrome (may be painful), neck swelling, pulsatile tinnitus and focal neurological deficits. Diagnosis is confirmed by CT or MR angiography. Most ischaemic cerebral symptoms arise from thromboembolic events; therefore, early institution of antithrombotic treatment provides the best outcome. Neurologist, neurosurgeon and endovascular consultants should act in concert to facilitate management decisions.

Vertebral Artery Dissection

Headache may be associated with symptoms and signs of posterior circulation stroke. Diagnosis is confirmed by CT or MR angiography. Input from

neurologist, neurosurgeon and endovascular expert is needed for appropriate treatment decisions.

Headache due to Ruptured Arteriovenous Malformations

Thunderclap headache may be the initial manifestation of rupture of AV malformations which may be associated with focal neurological deficits. MR or CT angiogram will confirm the diagnosis. Prompt referral to neurointervention expert should be done.

Headache due to Ischaemic Stroke

Headache may be very rarely a presenting or a prominent feature of ischaemic stroke especially in posterior circulation strokes. Diagnosis is confirmed by MRI of the brain with diffusion and gradient echo sequences. A neurologist should be called for further expert management.

Headache due to Acute Myocardial Infarction

Acute coronary syndrome may very rarely present with severe headache. Neurological examination and neuroimaging will be normal. Electrocardiogram may depict ischaemic changes. Elevation of cardiac enzymes will confirm the diagnosis. Twelve-lead ECG in all patients of sudden severe headache must be done mandatorily to prevent misdiagnosis.

Headache due to Glaucoma

The key feature is associated ocular symptoms and signs. Raised intraocular pressure is diagnostic. Neuroimaging will be normal. Prompt referral to ophthalmologist needs to be done.

Headache due to Pituitary Apoplexy

Pituitary apoplexy is characterised by a sudden onset of headache, visual symptoms, altered mental status and hormonal dysfunction due to acute haemorrhage or infarction of a pituitary gland. Diagnosis is confirmed by MRI of the brain/pituitary.

Referral to neurologist/neurosurgeon/endocrinologist should be done for further management.

Conclusion

Headache can be a symptom of serious neurological and systemic disorders. All patients presenting to emergency room with headache should leave the ER only after a proper diagnosis is reached. The main task of the emergency physician is to differentiate benign causes from serious causes. In this article we have given a brief outline of the more ominous causes of headache which no physician should miss in the emergency room. Almost all patients may require a scan of the brain and appropriate referral to the internist/neurologist/neurosurgeon for further management.

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Chapter 58
Neurosurgical Emergencies

Ruth-Mary deSouza and Tony Elias

Introduction

Treatment of neurosurgical diseases is often time dependent, and early intervention may lead to favourable outcomes. This chapter discusses some of the common neurosurgical emergencies.

The concept of secondary brain injury is now well established. It refers to cerebral damage occurring after the initial insult by effects dependent on and independent of the primary mechanism. There is compelling research that preventing hypoxia, hypotension and seizures and ensuring normal blood sugar and normal temperature reduce secondary brain injury and improve patient outcome. Although the initial research into secondary brain injury was in the setting of trauma, the principles of ensuring normal physiological parameters are applicable to all neurosurgical emergencies.

Neurosurgical History

Key points for history taking are shown in Table 58.1.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_58

Table 58.1 Neurosurgical history

Events/mechanism/trauma leading to neurological deterioration
Time course of events
If the patient is intubated, pre-intubation Glasgow Coma Scale (GCS) with breakdown and indication for intubation
Static, episodic or progressive problem
Quantify any neurological deficit and the impact on the patient
Signs of raised ICP (headache, nausea and vomiting, visual disturbance, confusion, alteration in consciousness)
Seizures
Systemic history suggestive of infection or malignancy
Known HIV and recent travel
Smoking/drugs/alcohol
Medical history
Medications including any antiplatelet and anticoagulant agents within the last 7–10 days
Patient's baseline function – living independently/residential care/nursing home, ability to mobilise, package of care, and activities of daily living
For a paediatric patient, the following information are required:
Head circumference and centile
Growth chart and centile
State of the fontanelles (if not fused)
Any changes in head or growth centiles
Feeding/thriving
Vomiting
Irritability
Crying/agitated/listless/drowsy
Milestones achieved
Regression in milestones
Difficulties at school
Vaccination status up to date
Clumsiness
Abnormal posture
Headaches
Lumps/bumps noted by parents

Neurosurgical Examination

The following are general components of examining the neurosurgical patient. Scenario-specific assessment information will be given in the relevant sections.

- Airway, breathing and circulation
- Temperature, blood sugar and presence of seizure activity
- Glasgow Coma Scale with breakdown of each component
- Ventilation status and any adjuncts
- Haemodynamic status and any measures being taken for cardiovascular support

Table 58.2 Age-appropriate GCS from birth to age 5

Modified paediatric GCS (Adelaide system)		
Eye opening	Verbal response	Best motor response
Spontaneous	Talks normally	Obeys commands
To sound	Words	Localises to pain
To pain	Vocal sounds	Flexes to pain
None	Cries	Extends to pain
None	None	None

- Pupillary size and response
- Cranial nerve examination with focus on eye movements, visual fields and acuity
- Fundoscopy for papilloedema
- Signs of meningism
- Cerebellar signs
- Focal deficit – e.g. limb weakness, speech disturbance

The GCS [1] is suitable for use in patients over the age of 5. Paediatric GCS is shown in Table 58.2.

A unilateral painless enlarged and unreactive pupil may suggest life-threatening brainstem compression. Bilateral fixed and dilated pupils are associated with an extremely poor prognosis and death. The timing of any pupillary changes is critical information as the neurosurgeon can use this information to decide on the nature and appropriateness of any temporising measures such as the use of mannitol/hypertonic saline and any surgical procedure.

Aneurysmal Subarachnoid Haemorrhage

Introduction

Aneurysmal subarachnoid haemorrhage (SAH) is a neurosurgical emergency as the blood load within the brain may cause acute deterioration in consciousness, rebleed and other complications.

Pathophysiology

- Risk factors for SAH in a patient with an aneurysm are hypertension, female gender, smoking, previous SAH and two first-degree relatives with SAH [2].
- Intracranial aneurysms associated with conditions including autosomal dominant polycystic kidney disease and connective tissue disorders.
- SAH is usually due to a ruptured intracranial aneurysm leaking blood into the subarachnoid spaces and the cerebrospinal fluid (CSF) cisterns.

- Early complications of aneurysmal SAH include rebleed, acute hydrocephalus, seizures, electrolyte abnormalities and cardiorespiratory instability.
- There are non-aneurysmal causes of subarachnoid haemorrhage, which are investigated and managed differently.

Clinical Features

- SAH typically presents with a characteristic sudden onset of headache that starts at maximal intensity. It is often described as being "like an explosion/kick/axe in the head". This may be accompanied by vomiting, meningism, seizures and alterations in consciousness. Patients may be in a coma before arriving in the emergency department.
- In a conscious patient, establish the time of ictus, associated symptoms, SAH risk factors and neurological deficits. Fundoscopy can identify papilloedema and vitreous bleeds (Terson's syndrome).
- In patients with known headache disorders, do not write off a potential SAH.
- A new onset *painful* oculomotor nerve palsy is, until proven otherwise, due to a posterior communicating artery aneurysm with impending rupture and should be referred as a neurosurgical emergency. Assess for pain, ptosis, restricted eye movements and a non-reactive pupil.

Investigations

- CT is the first-line investigation. Look for blood in the subarachnoid spaces and cisterns (Fig. 58.1), intraventricular haemorrhage, intraparenchymal haemorrhage, hydrocephalus (often subtle) and loss of sulcal definition.
- A negative CT does *not* exclude SAH.
- Lumbar puncture (LP) is the definitive diagnostic investigation for SAH. If the clinical history is suspicious for SAH and the CT is negative with no contraindications to LP, an LP may be performed *12 h or more* after the ictus [3]. The definitive test is CSF bilirubin, which indicates blood breakdown products. The CSF should be inspected for xanthochromia, protected from the light and sent to the lab for cell counts, microscopy, culture, protein and spectrophotometry for bilirubin. The opening pressure should be measured. Occasionally, the results from the LP may read as "unable to comment on the presence of bilirubin as large amount of oxyhaemoglobin masking bilirubin peak". Such results should be discussed with neurosurgery.

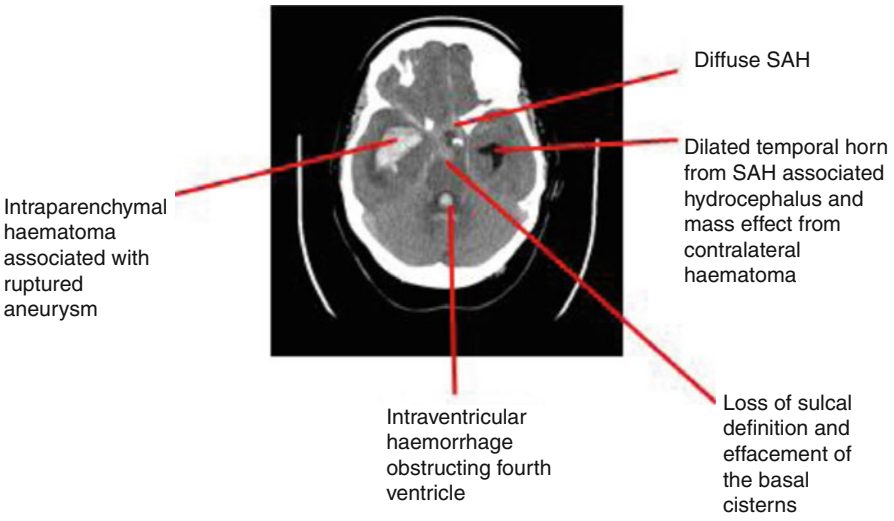

Fig. 58.1 Axial CT brain demonstrating SAH, a right temporal haematoma and hydrocephalus

Treatment

- Definitive treatment of SAH is securing the ruptured aneurysm, either by surgical clipping or by endovascular methods and treating/preventing associated complications of SAH in a neuro-intensive care/high dependency unit.
- Some patients may need urgent CSF diversion.
- Ensure normotension, normoxia and normoglycaemia. Treat any seizures.
- Obtain urgent neurosurgery advice regarding the next steps in management.

Prognosis

- SAH is graded 1–5 by the World Federation of Neurosurgeons. Grade 1 is a neurologically intact patient, and grade 5 is a moribund patient.
- Prognosis depends on the initial grade, treatment-related complications and the patient's baseline status.

Intracranial Sepsis

Introduction

Cerebral abscesses and empyema are neurosurgical emergencies as the pus collection needs to be decompressed and washed out and systemic sepsis treatment commenced whilst the source is sought.

Pathophysiology

- Intracranial infections that require neurosurgical intervention include abscess or an empyema in the subdural spaces.
- The source of infection may be from direct spread from locally infected tissues, haematogenous spread or related to a traumatic or iatrogenic dural breach.
- Risk factors for intracranial sepsis are immunocompromised state, sinus infection, ear infection, dental infection, congenital cyanotic heart disease, pulmonary vascular malformations and recent head and neck procedures.
- The most common organisms are *Streptococci* species. Gram-negative organisms and anaerobes are rarer. Immunocompromised patients may have toxoplasma, nocardia, and fungal and mycobacterial abscesses, not all of which require neurosurgical treatment.

Clinical Features

- Intracranial sepsis usually presents with rapid onset (hours to days) of headache, seizures, altered consciousness, focal neurology, meningism, pyrexia and signs of systemic sepsis.
- Cortical venous sinus thrombosis may result from infective thrombophlebitis.
- The underlying source of intracranial infection may not be obvious. History should focus on recent infections, travel, intravenous drug use, recent surgery and other CNS infection risk factors.
- Examine the teeth, ears, chest and skin.
- The abscess may rupture into the ventricular system, a rare complication with 80–90 % morality.

Investigations

- Initial investigations are blood cultures, inflammatory markers, chest x-ray, urine dip and a contrasted CT scan. LP is contraindicated in suspected intracranial abscess or empyema.

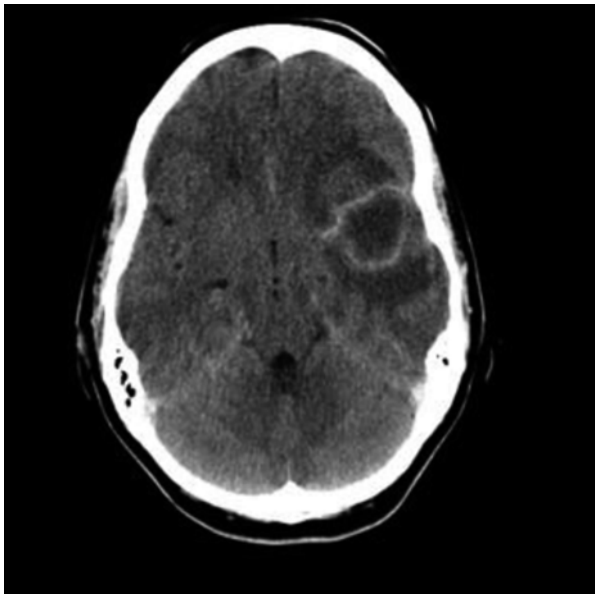

Fig. 58.2 Axial contrast enhanced CT showing a ring-enhancing lesion with surrounding oedema and mass effect

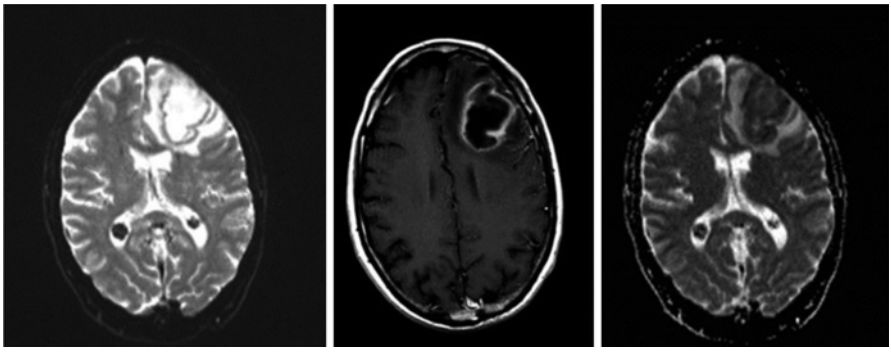

Fig. 58.3 The T2 weighted image on the left demonstrates a left frontal mass. The T1 MRI with contrast in the centre panel shows rim enhancement which can represent abscess or tumour. The image on the right is an ADC map indicating restricted diffusion, suggesting an abscess

- CT may demonstrate a ring-enhancing lesion (Fig. 58.2), enhancing subdural collections (often subtle) and generalised meningeal enhancement.
- There are multiple differential diagnoses for ring-enhancing lesions on imaging, including tumours and inflammatory pathologies [4]. When the CT is not characteristic of an abscess, there is a role for MRI (Fig. 58.3). Before embarking on MRI, the neuroradiologist/neurosurgeon should be made aware of the patient's condition and advice sought regarding MRI.

Treatment

- Management priorities are sepsis, seizures, prevention of secondary injury and identification of any obvious source.
- Steroids are not usually administered, unless the patient has severe neurological symptoms or signs.
- Definitive treatment involves drainage of the pus and sepsis treatment.
- If the source of the sepsis is surgically remediable (e.g., sinusitis or mastoiditis), this may be dealt with at the same sitting.
- If the source is not identified early, postoperative investigations include cardiac ECHO, ENT review, maxillofacial review and other imaging as directed by clinical findings.
- Treatment is at least 6 weeks of targeted antibiotics and continued monitoring with inflammatory markers and CT scans for resolution.

Prognosis

- Good for localised collections that respond to treatment.
- Poor for associated ventriculitis.
- Eradicating any source of infection is important in ensuring effective treatment.

Hydrocephalus

Introduction

Hydrocephalus is an imbalance between CSF production and absorption. It can present to the emergency department as a new diagnosis or as a shunt malfunction in a patient with known hydrocephalus. Untreated acute hydrocephalus can be rapidly fatal due to a rise in intracranial pressure.

Pathophysiology

- Hydrocephalus can be communicating or noncommunicating. Noncommunicating hydrocephalus is when there is an obstruction to the CSF outflow pathways. Noncommunicating hydrocephalus cannot safely be managed by LP.
- The aetiologies of hydrocephalus can be diverse. Some causes are SAH, tumours, haematomas, infection, cysts and congenital abnormalities.

- In patients with a CSF shunt in situ, the patient is dependent on it to drain CSF from the ventricles to another body cavity, usually the peritoneum. Shunts can become infected, blocked, and disconnected or overdrain/underdrain CSF.
- In idiopathic intracranial hypertension (IIH), the problem is chronically raised ICP in the absence of any mass lesion, and the main danger of this condition is ICP-related chronic visual failure and not acute hydrocephalus.

Clinical Features

- Acute hydrocephalus presents with features of raised ICP. Ask about headache, nausea, vomiting and visual disturbance. As ICP rises, the patient's conscious level can deteriorate, with confusion, drowsiness and coma. On examination, false localising signs, restricted eye movements and papilloedema may be seen.
- Specific points when assessing a child with hydrocephalus: In children with an open anterior fontanelle (closes at 12–18 months), assess whether the fontanelle is tense or bulging. Look for splaying of the skull sutures, dilated scalp veins, "sunsetting" of the eyes, enlarged head circumference, head circumference crossing centiles, drowsiness, irritability, vomiting, failure to feed, respiratory difficulties and bradycardias.
- Patients with a shunt in place that may be malfunctioning present in a similar manner to hydrocephalus without a shunt. They may describe that they feel the same way they did when the shunt malfunctioned previously. Ask about the indication for the shunt, shunt revisions and the reason for these and recent infections.

Investigations

- First-line investigation is a CT scan (Fig. 58.4). Features of hydrocephalus are enlarged ventricles, rounding of the frontal horns, enlarged temporal horns, a ballooned third ventricle and transependymal exudation of CSF into the parenchyma. Sulcal definition will be lost as the ICP rises. The aetiology of the hydrocephalus may be apparent on the scan.
- In a patient with a shunt, obtain a new CT scan and compare with previous CT scans from when the shunt was functioning. Obtain a shunt series (series of x-rays to demonstrate any breakages, disconnections or kinks in the shunt tubing). For a ventriculo-peritoneal shunt, this would be skull, neck, chest and abdominal x-rays.
- Inflammatory markers
- Fundoscopy.
- Inspect the skin over the shunt tubing.

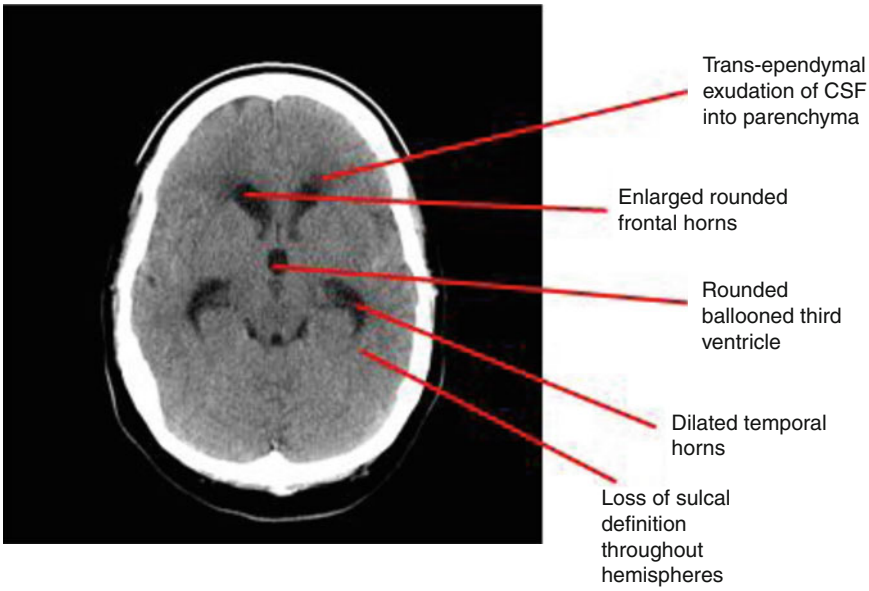

Fig. 58.4 Axial CT showing acute hydrocephalus

Treatment

- Acute hydrocephalus with clinical compromise requires emergency CSF diversion. Options for CSF diversion include external ventricular drainage, shunting (or shunt revision), endoscopic third ventriculostomy, LP, lumbar drainage, shunt taps and in young children, fontanelle taps. The choice of CSF diversion depends on the aetiology of the hydrocephalus and the patient's clinical condition.
- In patients with IIH and a known shunt, CT is of limited value as the ventricles do not tend to expand. In this group of patients, ophthalmology assessment (acuity, fields and fundoscopy) and a shunt series are required.

Prognosis

- Depends on the aetiology of the hydrocephalus and shunt function

Brain Tumours

Introduction

Brain tumours can present for the first time to the emergency department, or patients with a known tumour can present with new complaints. Brain tumours

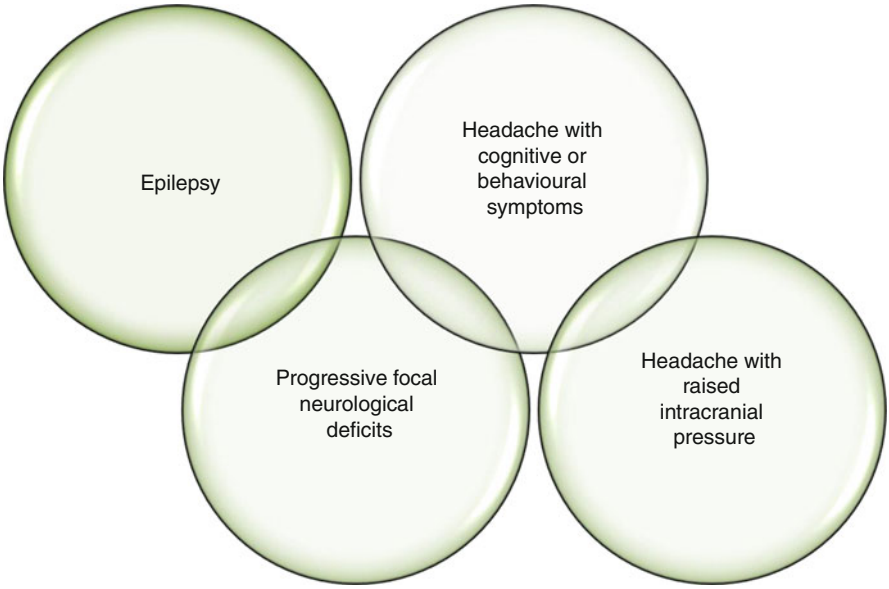

Fig. 58.5 Presenting features of brain tumours

can be difficult to detect and should be considered in patients with unexplained neurological deficits or signs of raised ICP.

Pathophysiology

- Brain tumours can be primary or secondary, benign or malignant.
- The aetiology of primary brain tumours is poorly understood. Known risk factors are a history of ionising radiation and inherited tumour syndromes.
- Cancers that commonly metastasise to the brain are lung, breast, kidney and melanoma.

Clinical Features

- The presenting features largely conform to the patterns in Fig. 58.5, regardless of the tumour type. Pituitary tumours are an exception. Tumours can obstruct CSF pathways and cause hydrocephalus [5].
- Patients with a known brain tumour may present with symptoms related to progression of the tumour, postoperative complications, haemorrhage within the tumour or associated hydrocephalus. In known tumour patients, establish the type of tumour, any secondary sites involved, surgical treatments and presence of a shunt, oncological treatments, steroid doses and the patient's current management plan.

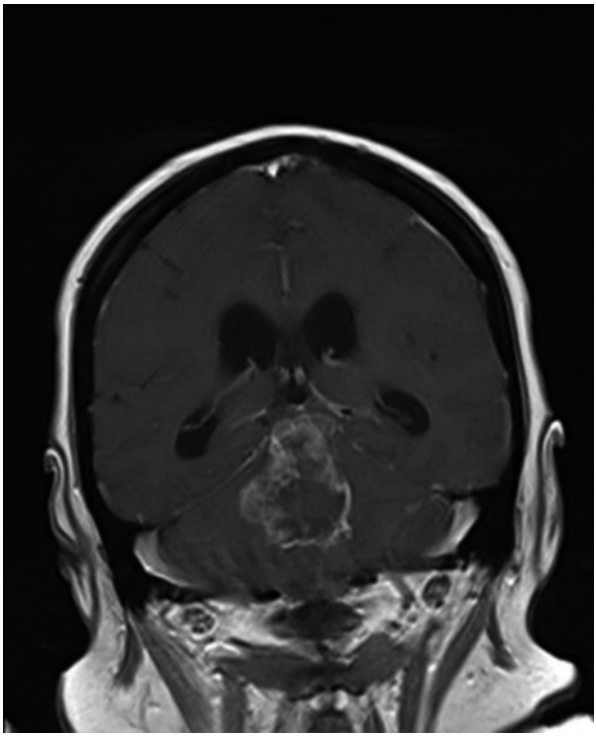

Fig. 58.6 T1-weighted coronal MRI with gadolinium demonstrating a midline peripherally enhancing posterior fossa mass with associated ventriculomegaly from effacement of the fourth ventricle. This was a glioblastoma

Investigations

- The first-line investigation is contrast enhanced CT scan. Once tumour is a differential, the next investigations are a contrast enhanced MRI scan of the brain (Fig. 58.6).
- Whole-spine MRI for certain tumour types as directed by the neurosurgeon.
- CT of the chest/abdomen/pelvis, tumour markers and fundoscopy.

Treatment

- Treatment plans are typically made for stable patients by a specialised neuro-oncology multidisciplinary team (MDT). Options include surgical resection, tumour biopsy, radiotherapy, chemotherapy and palliative care [5].
- Neurosurgical advice on dexamethasone, which reduces peri-tumoral oedema but has significant side effects. Treat any seizures

Chronic Subdural Haematoma

Introduction

Chronic subdural haematoma (CSDH) is usually a problem of elderly patients who may have serious comorbidities and need to be considered holistically. CSDH in young patients is unusual and may be the consequence of another pathology.

Pathophysiology

- The initial insult in CSDH is a bleed from tearing of bridging veins in the subdural space.
- Brain atrophy due to age and alcoholism can predispose to this process.
- Once blood has entered the subdural space and is not of sufficient volume to declare an acute subdural with neurological compromise at that time, the clot degrades and draws in fluid over weeks. The gradual increase in the size of the CSDH may cause neurological compromise.

Clinical Features

- CSDH can present with focal neurology from mass effect, confusion and/or with signs of raised ICP.
- Bilateral CSDH are a particular concern. As there is compression from both sides, the scan may not demonstrate obvious midline shift, even when the amount of mass effect is significant.

Investigations

- Plain CT scan is the investigation of choice for CSDH (Fig. 58.7).
- On CT scan, CSDH is a hypodense, isodense (easy to miss) or mixed density extra-axial unilateral or bilateral collection. In bilateral CSDH, loss of sulcal definition and effacement of the ventricles can occur. Differentials of subdural haematoma are empyema and hygroma.

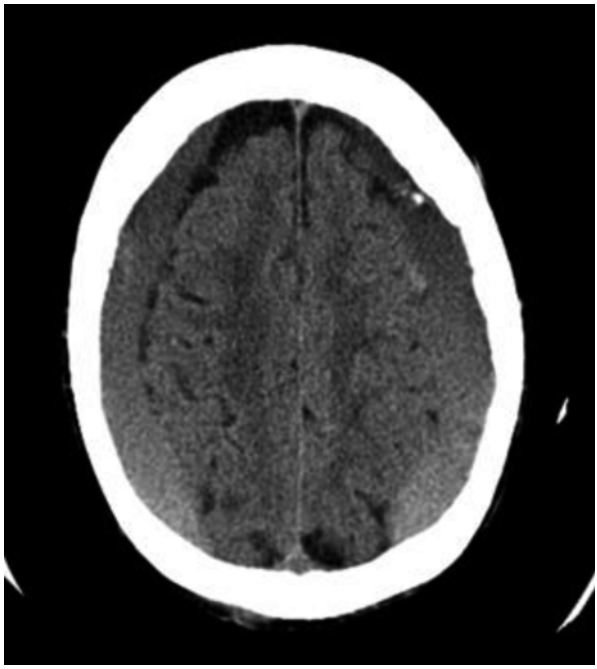

Fig. 58.7 Axial CT scan showing bilateral extra-axial collections with effacement of the sulci. These are chronic subdural haematomas

Treatment

- Treatment of symptomatic CSDH, in patients who are appropriate for operation, is typically with burr-hole drainage [6].

Prognosis

- Recurrence is a significant risk. Outcome is dependent on preoperative neurological status and postoperative recovery and on the patients' general medical condition.

Pituitary Apoplexy

Introduction

Pituitary apoplexy (PA) is a differential diagnosis for sudden onset of severe headache and/or neuro-ophthalmological deficits

Pathophysiology

- PA is due to haemorrhage or infarction of a pre-existing pituitary mass which leads to rapid expansion of sellar contents, causing compression on the optic chiasm, the gland itself and cranial nerves within the cavernous sinus.
- PA leads to a triad of visual deficits, headache and endocrinopathy.
- PA may be the first presentation of a pituitary tumour.
- Predisposing factors for PA include pregnancy, hypertension and abnormal coagulation

Clinical Features

- Sudden onset of severe headache occurs in almost all cases of pituitary apoplexy. Other features are visual field/acuity loss, ophthalmoplegia, cranial nerve (3, 4, 5, 6) dysfunction, vomiting, reduced consciousness and haemodynamic instability and electrolyte disturbance

Investigations

- CT head to rule out other differentials such as SAH. Look for haemorrhagic mass in the sellar region. This is followed by an urgent MRI [7].
- Urea and electrolytes, renal function and full pituitary profile [7].
- Bedside assessment of visual fields, eye movements and acuity. Formal ophthalmological assessment including perimetry within 24 hours [7].

Treatment

- Corticosteroid replacement [7].
- Optimise fluid balance and electrolytes [7].
- Management can be conservative with endocrine replacement and visual monitoring or can be surgical (usually trans-sphenoidal approach) in cases of deteriorating vision or consciousness [7].

Prognosis

- Long-term endocrine, ophthalmological and radiological follow-up are required. Stress dose of corticosteroids during intercurrent illnesses. [7]

Spontaneous Intracerebral Haemorrhage

Introduction

Intracerebral haemorrhage (ICH) can be superficial, deep or in the posterior fossa. It can extend into the ventricles, blocking CSF pathways. Treatment may be conservative or operative management of the haemorrhage and to establish the aetiology of the bleed if possible.

Pathophysiology

- ICH may be due to hypertension, recreational drug use, trauma, amyloid angiopathy, venous or arterial infarction, anticoagulation, vascular malformations and tumours or cysts.
- In children, they may be associated with prematurity and vascular malformations.

Clinical Features

- Sudden onset of neurological deficit, vomiting, seizures and if there is significant mass effect, alterations in consciousness.
- The haematoma may rupture into the ventricles, causing hydrocephalus.

Investigations

- Plain CT is the first-line investigation.
- Further imaging to establish aetiology on neurosurgery advice.

Treatment

- Reverse any anticoagulation and treat seizures.
- Blood pressure management in ICH is controversial [8] and should be discussed with the stroke or neurosurgery team first. Do not rapidly lower BP to avoid ischemia.
- Surgery for selected cases of superficial lobar ICH [9], ICH causing significant mass effect (Fig. 58.8) with clinical compromise and relief of hydrocephalus related to ICH.
- Management of the underlying cause.

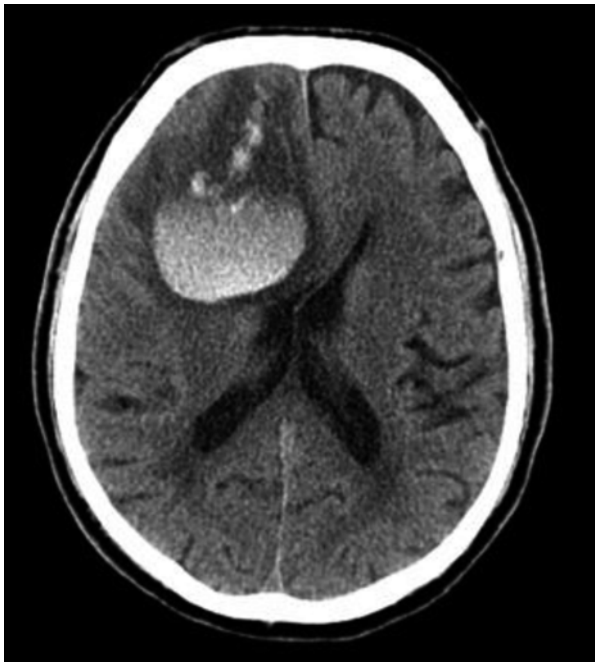

Fig. 58.8 Axial XT scan showing right frontal haematoma with mass effect. This was evacuated as the patient progressively dropped his conscious level due to the mass effect

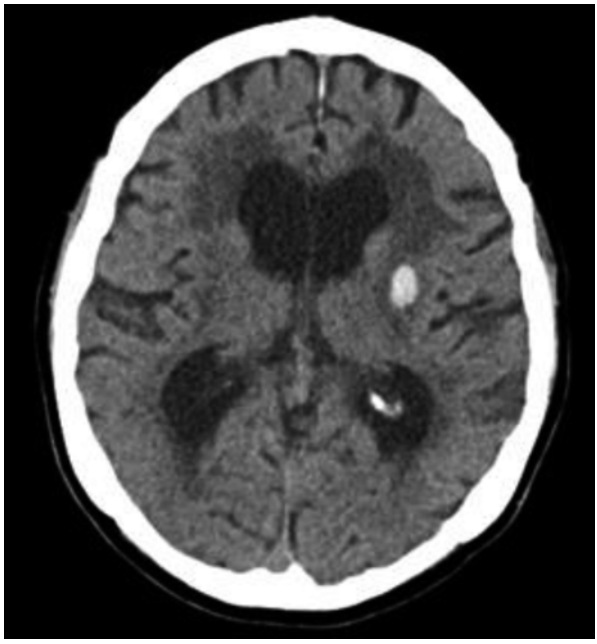

Fig. 58.9 Axial CT scan showing small deep-seated haematoma with no mass effect and no intraventricular extension. This was in a hypertensive patient, needed no neurosurgical input and is typically managed by the stroke services

- Conservative management for deep haematomas (Fig. 58.9) and selected superficial ICH.
- Basal ganglia haematoma in known hypertensives and elderly rarely needs further investigation. In patients without hypertension and in young patients, discuss with neurosurgery regarding further neurovascular investigations for an underlying malformation.

Prognosis

- Likely fixed neurological deficit.
- Recurrence depends on underlying cause.

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Chapter 59
Seizures

Raghunandan Nadig

Key Points
- The differential diagnosis of a seizure is wide; accurate and detailed history is an important tool for appropriate management.
- Acute or subacute neurological insult or metabolic disturbances can potentially cause seizures.
- 'Time is brain' in the management of status epilepticus as seizure activity itself can damage the brain.

Introduction

Seizures are one of the common neurological symptoms with which a patient presents to the emergency room. Patients with seizures can present with different manifestations like jerky movements of limbs, transient loss of consciousness or transient sensory symptoms. Status epilepticus is a life-threatening neurological emergency where early management can prevent permanent disability. In the past decade, there have been changes in classification of seizures, epilepsy and also approval of newer antiepileptic drugs. This chapter addresses these aspects and also discusses the evaluation of a patient with seizures in the emergency room and management of status epilepticus.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_59

Definition

- Seizure is a transient neurological symptom or sign developing secondary to paroxysmal burst of abnormal, excessive and synchronous discharges of neurons in the brain.
- Provoked or acute symptomatic seizures are episodes occurring secondary to an acute central nervous system insult which may be metabolic, toxic, structural, infectious or due to inflammation (e.g. febrile seizure, hypoglycaemic seizure, head injury, etc.).
- Epilepsy is defined as a brain disorder having any of the following conditions [1, 2]:

  (a) Two unprovoked seizures occurring more than 24 h apart (multiple seizures occurring in 24 h should be considered as the first attack)
  (b) Diagnosis of an epilepsy syndrome (e.g. juvenile myoclonic epilepsy)
  (c) One unprovoked seizure and a probability of further seizure similar to the general recurrence (at least 60 %) after two unprovoked seizures, occurring over the next 10 years:

    - Convulsion: motor manifestation of a seizure.
    - Epilepsy resolved: a person is seizure-free since the past 10 years and also off antiepileptic medication since the past 5 years.
    - First unprovoked seizure: is defined as one occurring in a person over 1 month of age without any past seizures and not due to an acute CNS insult. An episode of status epilepticus is considered to be a single event.

Epidemiology

According to the World Health Organization (WHO), of the 50 million people with epilepsy worldwide, 80 % reside in low-income countries [3, 4], and about 16 million people live in Western Pacific region [5]. Acute symptomatic seizure accounted for 22.5 % of seizure disorders as found in a hospital-based study from South India [6]. Prevalence reports as high as 20–30 per 1,000 have been reported [3–7]. In the United States 1–2 % of all ED visits were patients with seizures or presenting complaints related to seizures [8].

Aetiology

Aetiologies for the first seizure in adults/children include:

(i) Idiopathic – e.g. epilepsy syndromes, genetic epilepsy.
(ii) Acute or subacute neurological insult or injury such as stroke, head injury and infection (meningitis, encephalitis, subdural empyema and cerebral abscess).

Table 59.1 Metabolic derangements causing seizures

Serum glucose <36 mg/dl (2.0 mM) or >450 mg/dl (25 mM)
Serum sodium <115 mg/dl (<5 mM)
Serum calcium <5.0 mg/dl (<1.2 mM)
Serum magnesium <0.8 mg/dl (<0.3 mM)
Urea nitrogen >100 mg/dl (>35.7 mM)
Creatinine >10 mg/dl (>884 mM/dl)
Hepatic encephalopathy

(iii) Structural CNS diseases – Tumours (primary or metastatic), vascular malformations and dysplasia.
(iv) Autoimmune disorders like SLE, vasculitis, autoimmune encephalitis.
(v) Metabolic disturbances [9]: Common metabolic derangements with proposed cut-off values where seizures can be precipitated are indicated in Table 59.1.
(vi) Toxin, illicit drug or medication related, including alcohol withdrawal or excess.
(vii) Hypertensive emergencies like eclampsia and malignant hypertension.

In children between 6 months to 6 years of age, the first seizure may be due to a fever, so-called febrile convulsion. It could be idiopathic or provoked due to electrolyte disturbance or meningitis

Pathophysiology

- Seizure occurs when a group of neurons become hyperexcitable and fire an action potential which spreads uninhibited to other neurons in the cerebral hemisphere.
- This occurs due to either increased excitatory and/or decreased inhibitory influences from other neurons. This process is known as epileptogenesis.
- Various CNS insults like vascular, trauma, infections, etc. lead to epileptogenesis. Ions and neurotransmitters play an important role in neuronal depolarisation and repolarisation.
- Seizures cause a number of physiologic changes due to the catecholamine surge.
- During a generalised seizure, there can be a period of transient apnoea and subsequent hypoxia, hypertension, hyperglycaemia and lactic acidosis.

Classification

International League Against Epilepsy (ILAE) task force on classification and terminology has revised terminology and approaches for classifying seizures and epilepsy in 2010 [10]. The detailed classification of epilepsy is beyond the scope of the

Table 59.2 Classification of seizures

Generalised seizures
Tonic-clonic (in any combination)
Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Without impairment of consciousness or awareness
With impairment of consciousness or awareness
Evolving to a bilateral, convulsive seizure (involving tonic, clonic or tonic and clonic components)
Unknown
Epileptic spasms

book. Recent classification of seizures is mentioned in Table 59.2. Seizures are broadly classified into two groups, focal and generalised.

- Focal seizures are considered to be originating within the networks of brain limited to one hemisphere. They can be described by their clinical manifestation (semiology).
- Generalised seizures are considered to be originating at some point within and rapidly engaging bilaterally distributed networks (both hemispheres). The location and lateralisation are not consistent from one seizure to another.

Many clinical situations are encountered by emergency physicians involving seizures like new-onset seizures, breakthrough seizures in patients with known epilepsy and various conditions that can mimic seizures. The detailed clinical history and correlation with examination findings and investigations remains the most important tool in distinguishing seizures from their mimickers.

Evaluation of First Seizure

Although there is no standardised algorithm for the evaluation of a patient with first-onset of seizures, the following steps are recommended:

Step 1:

When evaluating a patient who has just experienced a seizure, the emergency physician should first verify that the patient has normal airway, breathing and circulation and that there is no active seizure occurring at that point of time.

Step 2:

A. The history should initially focus on determining whether a seizure actually occurred and evaluating the circumstances and characteristics of the event. Detailed seizure semiology should be determined including aura, onset (focal or generalised), progression, duration, tongue bite, urinary incontinence and postictal period.
B. Every attempt should be made to interview the witness of the event to obtain a clear description of the seizure to avoid misdiagnosing non-seizure events/mimic (Tables 59.3 and 59.4).
C. An important part of the history is determining whether this was truly a first seizure or patient previously had brief transient neurological symptoms suggestive of seizures.
D. Emotional stress, sleep deprivation, medications reducing the seizure threshold (fluoroquinolones, tramadol, tricyclic antidepressants, etc.),flickering light, hyperventilation(e.g. in case of absence seizures) and missing

Table 59.3 Differential diagnosis of seizure

Mimics of seizure	Cause
Syncope	Vasovagal, micturition, carotid sinus
Cardiac	Arrhythmogenic
	Structural: aortic stenosis, hypertrophic cardiomyopathy
Orthostatic hypotension	Autonomic failure
Psychogenic non-epileptic attack disorder	Panic disorder (especially in people with epilepsy)
	Dissociative
	Factitious and malingering
Sleep disorders	Narcolepsy syndrome and cataplexy
	Parasomnias
Paroxysmal symptoms of structural brain disease	Multiple sclerosis
	Tumour
Vascular	Migraine (hemi-paretic, occipital, 'basilar artery')
	Shaking transient ischaemic attack (critical bilateral stenosis)
	Subclavian steal syndrome
Hypoglycaemia	Behaviour disturbance
	Hemiparesis
Movement disorder	Paroxysmal kinesigenic dystonia/dyskinesia
	Myoclonus following hypoxia
Hydrocephalus	Colloid cyst
	Arnold-Chiari malformation
Drop attacks	Postural instability
	Psychogenic

Table 59.4 Distinguishing features between syncope and seizure

	Seizure	Syncope
Gradual onset	Focal onset possible (aura, duration typically <30 s)	Common (pre-syncopal symptoms, duration often minutes)
Motor activity	Typical seizure patterns (tonic, clonic, tonic-clonic)	Myoclonic jerks common (short duration, rapid recovery) after loss of postural tone
Skin	Cyanosis common	Pallor, sweating
Ictal incontinence	Common	Rare
Postictal reorientation	Mostly over minutes	<1 min (exception: head injury caused by collapse/patient maintained in upright position)
Tongue biting	Frequent (lateral)	Occasional (tip)
Injury	Common	Rare
Seizures at night (from 'sleep')	Common	Rare

antiepileptic medication dose, drug withdrawal like benzodiazepine and alcohol withdrawal are the most common triggers/precipitant for seizures.

Step 3:

The physical examination should include a detailed general and neurological examination. Examination of cardiovascular system is essential to rule out valvular heart disease or rhythm disorders. Clinical evidence that a seizure has occurred are presence of any of the following:

- Tongue bite
- Urinary or faecal incontinence
- Conjunctival haemorrhage
- External injury
- Fractured bone
- Shoulder dislocation

Step 4: Diagnostic testing

Diagnostic testing can be helpful in corroborating the diagnosis and establishing an aetiology. The evaluation of the first seizure is outlined in the bulleted points that follow, but all studies need not be done in the emergency department.

- CBC, serum chemistry, including sodium, calcium, magnesium and phosphate levels, renal function tests, a toxicology screen, ABG (for hypoxia/hypercapnia which may precipitate seizures) and urine analysis.
- ECG (screen for prolonged QRS or QTc interval, arrhythmias, ACS).
- Brain imaging, at least a CT head to rule out structural lesions. Best neuroimaging for seizures is MRI brain.
- Lumbar puncture, if CNS infection suspected.
- EEG (to differentiate focal vs. generalised seizure, to predict recurrence and to rule out non convulsive status).

Treatment of First Seizure

- Stabilisation of the patient and taking care of airway, breathing and circulation.
- A seizure evolving into convulsive status epilepticus should be treated aggressively following pre-established protocols.
- Identifying precipitating insults. Treatment should be started promptly whenever possible and supportive measures taken whenever necessary (e.g. antibiotics in case of infection, correction of metabolic derangement appropriately, etc.).
- As a rule, anticonvulsant drugs are indicated in a long-lasting attack.
- In some conditions, such as head trauma and acute ischemic stroke, the use of prophylactic anticonvulsant treatment may be warranted for the prevention of early seizures although this practice is not universal.
- If a patient has had a single seizure, long-term therapy with an AED is often not necessary unless there is an obvious structural lesion or overt epileptogenic abnormalities on the EEG, such as a focal or generalised interictal sharp/spike wave.
- If the patient has an active seizure in the emergency department or there is history of more than one seizure, therapy should be initiated immediately with either lorazepam (0.1 mg/kg IV) or diazepam (0.3 mg/kg IV).
- In the emergency department, if decision is made to treat with an AED, then an intravenous AED in loading dose is appropriate, such as fosphenytoin, phenobarbital, valproic acid, levetiracetam or lacosamide, as oral administration will take a few days to reach therapeutic levels. Phenytoin is an extremely common antiepileptic medication and is classically given as '1 gm' in the ED. Oral absorption of phenytoin can be erratic, but when the agent is given in the appropriate doses (15–20 mg/kg PO either as a single dose or divided into 400–600 mg per dose every 2 h), it can achieve therapeutic serum levels. Fosphenytoin is a phenytoin precursor and water soluble, causes less hypotension and can be administered faster and also IM. This is an advantage for patients without IV access.

(a) Provoked seizure

Treatment of an isolated provoked seizure should be directed at the cause. AED therapy may be avoided if the cause is readily reversible, unless the seizure was prolonged or a recurrence is likely, for example, with a new CNS mass lesion.

(b) In a person with epilepsy

The management of a single, isolated seizure in a patient with known epilepsy should include a brief observation period to be sure there is no recurrence. Any precipitating factors should be addressed. Measure the AED drug level which the patient was taking, if found low give a half loading dose of the drug. If levels are normal, then add a new drug appropriate for the type of seizure/epilepsy.

(c) Unprovoked seizure

The decision to start an antiepileptic drug (AED) after a first isolated, unprovoked seizure is controversial. AED treatment reduces the risk of recurrent seizures in the near future, but does not change the long-term prognosis or decrease

the risk of developing epilepsy. Most experts recommend waiting for a second seizure before starting AEDs, as AEDs can have side effects and might be unnecessary. However, AED is recommended if there are risk factors for recurrence of seizure (Table 59.5). AED is also indicated following first unprovoked seizure if in an individual, risk of injury due to recurrence of seizure is high (in elderly, those with osteoporosis or fracture/dislocation following first seizure, those on anticoagulation, etc.). AED is also recommended in those where risk of economic hardship from recurrence is high.

Treatment

Choice of AED depends on the efficacy, tolerability, side effects, interactions and type of seizure [11, 12]. Table 59.6 lists the recent ILAE recommendations of AED based on type of seizure and dosages (Table 59.7).

Table 59.5 Risk factors for recurrence of seizure after a first unprovoked seizure

Remote symptomatic aetiology (pre-existing static brain abnormality)
Focal neurological findings
Focal seizure phenomenology/Todd's palsy
Focal/generalised epileptiform activity on EEG
Tumours/progressive lesions on imaging
Status epilepticus
Family h/o seizures
Past h/o febrile seizures

Table 59.6 Selection of antiepileptic drug

Generalised tonic-clonic	Focal	Typical absence	Atypical absence, myoclonic, atonic
First line			
Valproic acid	Lamotrigine	Valproic acid	Valproic acid
Lamotrigine	Carbamazepine	Ethosuximide	Lamotrigine
Topiramate	Oxcarbazepine		Topiramate
	Phenytoin		Zonisamide
	Levetiracetam		
	Zonisamide		
Alternatives			
Zonisamide	Topiramate	Lamotrigine	Clonazepam
Phenytoin[a]	Valproic acid	Clonazepam	Felbamate
Carbamazepine[a]	Tiagabine		
Oxcarbazepine[a]	Gabapentin		
Phenobarbital	Lacosamide		
Primidone	Phenobarbital		
Felbamate	Primidone		
	Felbamate		

[a]May aggravate myoclonic seizures

Table 59.7 Dosage of commonly prescribed antiepileptic drugs

Drug	Initial dose	Average adult daily dose
Carbamazepine (CBZ)	100 mg hs or b.i.d	600–1,800 mg (15–25 mg/kg)
Clonazepam	0.5–1.0 mg hs or b.i.d.	1–5 mg (0.03–0.3 mg/kg)
Ethosuximide	250 mg hs	500–1,000 mg (10–30 mg/kg)
Gabapentin	300 mg b.i.d.	1,800 mg
Lacosamide	50 mg b.i.d.	200–400 mg
Lamotrigine	50 mg/day if added to PHT/CBZ: 25 mg q.o.d. if added to VPA 250–500 mg b.i.d.	300–500 mg with PHT/CBZ; 100–150 mg with VPA
Levetiracetam	250–500 mg b.i.d.	1,000–3.000 mg
Oxcarbazepine	150–300 mg b.i.d.	900–1,800 mg
Phenobarbital	90 mg hs	90–180 mg (2–4 mg/kg)
Phenytoin (PHT)	300 mg/day in 2 doses	300–500 mg (3–7 mg/kg)
Primidone (Mysoline)	125 mg hs	750–1,500 mg (10–20 mg/kg)
Valproate/divalproex sodium (VPA)	250 mg hs or b.i.d,	1,000–3,000 mg (15–60 mg/kg)
Topiramate	25–50 mg/day	200–400 mg/day
Zonisamide	100 mg	200–400 mg

Status Epilepticus (SE)

Definition

- In 1994 Shorvon defined SE as two or more sequential seizures without full recovery of consciousness between seizures or more than 30 min of continuous seizure activity [13].
- Operational definition that is being considered in day-to-day management and also in studies define status as continuous seizures lasting at least 5 min or two or more discrete seizures between which there is an incomplete recovery of consciousness [14], the reason being that most clinical and electrographic seizures last less than 5 min and seizures that last longer often do not stop spontaneously.
- Animal data suggest that permanent neuronal injury and pharmacoresistance may occur before the traditional definition of 30 min of continuous seizure activity has passed.

Causes

CNS infections (encephalitis, meningoencephalitis) and febrile convulsions are common causes in children, accounting for 49 % of SE treated in a tertiary hospital in North India [14]. Other causes include vascular episodes, trauma, metabolic derangement and toxins. In a person with epilepsy, SE can occur due to non-compliance or withdrawal of antiepileptic therapy. Intercurrent infections and stress may predispose to status epilepticus.

Pathophysiology

Status epilepticus develops due to failure of mechanisms that usually abort isolated seizure and/or due to excess excitation or ineffective inhibition. Any factor which increases glutamate activity and decreases GABA activity can trigger SE.

In SE CNS damage can occur due to uncontrolled neuronal firing leading to excess glutamate. This causes sustained high influx of calcium ions into neurons and leads to cell death ("excitotoxicity"). GABA is released to counteract this, but in prolonged seizures, GABA receptors gets downregulated; hence, exitotoxicity continues. These effects are worsened if there is hyperthermia, hypoxia, hypotension and hypo- or hyperglycaemia. In status epilepticus, there is pronounced systemic decompensation, including hypoxaemia, hypercarbia, hypertension followed by hypotension, hyperthermia, depletion of cerebral glucose and oxygen, cardiac dysrhythmias and rhabdomyolysis.

Management of Generalised Status Epilepticus

Time is brain in the management of SE as seizure activity itself can damage the brain. Metabolic consequences due to seizures cause further damage, and treatment is more likely to work earlier on than later.

Patients must be brought to the hospital at the earliest, and every hospital should have a protocol.

There are four stages that are considered in the management of SE based on time of seizure occurrence [14].

Premonitory Stage: Prolonged Seizure at Home/Before Hospitalisation (5 min)

- General Measures: Airway, breathing and circulation
- Drugs: Diazepam 0.5 mg/kg rectally and buccal/intranasal midazolam 0.2 mg/kg or IM midazolam
- Investigation: Glucometer blood glucose

First Stage: At Hospital (5–20 min)

- *General measures*

  Airway; oxygen, cardiorespiratory function and regular monitoring; ECG, blood pressure and SpO2

- *Drug treatment*

  Lorazepam IV 0.1 mg/kg (max 4 mg) or
  Diazepam IV 0.3 mg/kg (max 10 mg)
  Intravenous access; IV glucose, thiamine and pyridoxine; treat acidosis

- *Emergency investigations*

  Glucose, Na, K and Ca levels of AEDs; toxicology screening; kidney and liver function tests
  If seizure continues, proceed to management of established status epilepticus and consult neurologist

Second Stage: Established SE (20–60 min)

- *Drug treatment*

  Fosphenytoin IV 20 mg phenytoin equivalent (PE)/kg at maximum rate of 150 mg PE/min

  Phenytoin 20 mg/kg at maximum rate of 50 mg/min. Monitor ECG and blood pressure.
  Phenytoin should be avoided in patients with hypotension, heart block and in hepatic failure.
  If seizures persist after 10 min of phenytoin administration, then repeat half loading dose (10 mg/kg) of phenytoin.
  If seizure persists, then consider:

  Option 1: Valproate sodium 20–40 mg/kg IV at 3–6 mg/kg/min
  Option 2: Phenobarbital 15–20 mg/kg IV at maximum rate of 100 mg/min
  Option 3: Levetiracetam 20–60 mg/kg IV at 2–5 mg/kg/min

- *General measures*

  Endotracheal intubation, monitoring of blood pressure, SpO2 and vasopressors if needed

- *Investigations*

  CT scan of brain for aetiology and CSF for CNS infection. EEG for pseudo-status.

  If seizure continues, proceed to refractory status epilepticus management.

Third Stage: Refractory Status Epilepticus (>60 min)

Refractory SE is diagnosed after failure of first-line therapy, and treatment should be protocol driven. Choice of medication is dependent on availability, ED capability

and hemodynamic status of the patient. Coma is initiated with either pentobarbital 5 mg/kg loading then infusion 0.5–5 mg/kg/h, propofol 1 mg/kg then 2–4 mg/kg/h or midazolam 0.2 mg/kg then 0.05–0.5 mg/kg/h, and patient should be admitted to an ICU. Further management could be done in due consultation with neurologist and intensivist.

Disposition is based on the severity and underlying cause of the patient's seizures.

- Most patients will be admitted for monitoring, further work-up and treatment of their underlying condition.
- Any patient with SE, severe alcohol withdrawal or underlying conditions (e.g. diabetic ketoacidosis) requiring intensive monitoring and care is best treated in an ICU setting.

Outpatient Care

- First-time generalised tonic-clonic seizures with no concerning features, i.e. clinically fully recovered, a normal ED work-up and not at risk for repeat seizure can be discharged home advising urgent consultation with the patient's primary care physician or a neurologist.
- Patients who are found to have subtherapeutic levels of medications may be given loading doses orally or parenterally as indicated and should undergo follow-up with their primary physician or neurologist on an urgent basis.

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Chapter 60
Stroke

Praveen Kumar B. Gowder

Key Points
- Stroke is a clinical diagnosis.
- As time directed therapy is available for stroke, undue delay in diagnosis and thereby delay in administration of appropriate treatment should be avoided as TIME IS BRAIN.
- Stroke mimics should be excluded by a diligent history and examination.

Introduction

Non-communicable diseases (NCDs), which include stroke, currently constitute the primary cause of morbidity and mortality worldwide [1]. Stroke is a leading cause of disability-adjusted life-years (DALYs) lost, and the majority of stroke DALYs are from developing countries [2].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_60

Definition of Ischaemic Stroke [3]

An episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction resulting from cell death attributable to ischaemia, based on:

1. Pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischaemic injury in a defined vascular distribution
2. Clinical evidence of cerebral, spinal cord or retinal focal ischaemic injury based on symptoms persisting ≥24 h or until death and other aetiologies excluded

Pathophysiology of Ischaemic Stroke

Acute occlusion of an intracranial vessel causes focal cerebral ischaemia and post-ischaemic reperfusion. This leads to cerebral capillary dysfunction resulting in a progressive alteration in the permeability of the blood-brain barrier, leading to formation of ionic oedema and vasogenic oedema [4]. The ultimate consequence is oncotic death of neurons.

Tissue surrounding the core region of infarction is ischaemic but reversibly dysfunctional and referred to as the *ischemic penumbra* which will eventually infarct if no change in flow occurs, and hence saving the ischaemic penumbra is the goal of revascularisation therapies.

Physical Examination

Assessments of the airway, breathing and circulation (ABCs) are the top priorities.

Airway – Can get compromised because of hypotonia of pharyngeal muscles, pooling of oral secretions because of impaired gag reflex or altered mental state as in brainstem stroke

Breathing – Can be altered due to a large hemispheric infarct or intracerebral haemorrhage causing decreased consciousness or vertebro-basilar artery territory stroke involving the brainstem or cerebellum causing altered conscious level and bulbar dysfunction as well

Circulation – Can be compromised because of unstable tachyarrhythmias (most commonly atrial fibrillation) or coexisting myocardial infarction and congestive heart failure (look for elevated JVP, S3 gallop and bi-basal crackles) (Table 60.1)

Table 60.1 General physical examination in a suspected case of ischaemic stroke

Clinical parameter	Cause	Intervention
Pulse	If irregular, suggest atrial fibrillation	Perform cardiac monitoring for at least the first 24 h to screen for atrial fibrillation and other potentially serious cardiac arrhythmias
Blood pressure	Is often higher in acute ischaemic stroke patients with a history of hypertension than in those without premorbid hypertension. Blood pressure typically decreases spontaneously starting within 90 min after the onset of stroke symptoms	Control of blood pressure carefully to <185/110 mmHg in patients who have elevated blood pressure and otherwise eligible for treatment with intravenous fibrinolysis
		In patients with markedly elevated blood pressure who do not receive fibrinolysis, withhold medications unless the systolic blood pressure is >220 mmHg or the diastolic blood pressure is >120 mmHg
Temperature	If there is hyperthermia (temperature >37.6° C), think of a stroke mimic like the central nervous system infections (meningitis, encephalitis) or a complication of the stroke (e.g. aspiration pneumonia)	Hyperthermia increases energy requirements of the brain. Hence administer antipyretic medication to lower temperature
Pulse oximetry	Hypoxia is present frequently after stroke due to partial airway obstruction, hypoventilation, aspiration, atelectasis and pneumonia. In patients who are able to maintain oxygenation while lying flat, a supine position is recommended. For patients at risk for airway obstruction or aspiration and those with suspected elevated intracranial pressure (ICP), the head of the bed should be elevated 15–30°	Administer oxygen to hypoxaemic patients to maintain oxygen saturation >94 % [5] using nasal cannula, venturi mask, non-rebreather mask, bilevel positive airway pressure, continuous positive airway pressure or endotracheal intubation with mechanical ventilation
Extremities	Examine the extremities for injuries	
Fundoscopy	Papilloedema (suggests raised ICT – a mass lesion, cerebral vein thrombosis or hypertensive crisis). Preretinal haemorrhage (suggests subarachnoid haemorrhage)	Identify the cause
		Institute anti-oedema measures
Look for	Meningismus, signs of emboli (Janeway lesions and Osler nodes) and bleeding diathesis (ecchymoses or petechiae) [6]	Identify bacterial endocarditis as the cause of cardioembolic stroke

Neurologic Examination

Should be done using National Institutes of Health Stroke Scale (NIHSS).

The goal is to confirm the diagnosis of stroke, localise the stroke lesion, identify the culprit vessel, provide early prognosis, help select patients for various interventions and identify the potential for complications (Tables 60.2, 60.3 and 60.4).

Table 60.2 National Institutes of Health Stroke Scale [7]

Tested item	Title	Responses and scores
1A	Level of consciousness	0-alert, 1-drowsy, 2-obtunded, 3-coma/unresponsive
1B	Orientation questions (2)	0-answers both correctly, 1-answers one correctly, 2-answers neither correctly
1C	Response to commands (2)	0-performs both tasks correctly, 1-performs one task correctly, 2-performs neither
2	Gaze	0-normal horizontal eye movements, 1-partial gaze palsy, 2-complete gaze palsy
3	Visual fields	0-no visual field defect, 1-partial hemianopia, 2-complete hemianopia, 3-bilateral hemianopia
4	Facial movement	0-normal, 1-minor facial weakness, 2-partial facial weakness, 3-complete unilateral palsy
5	Motor function (arm)	0-no drift, 1-drift before 5 s, 2-falls before 10 s, 3-no effort against gravity, 4-no movement
	(a) Left	
	(b) Right	
6	Motor function (leg)	0-no drift, 1-drift before 5 s, 2-falls before 5 s, 3-no effort against gravity, 4-no movement
	(a) Left	
	(b) Right	
7	Limb ataxia	0-no ataxia, 1-ataxia in one limb, 2-ataxia in two limbs
8	Sensory	0-no sensory loss, 1-mild sensory loss, 2-severe sensory loss
9	Language	0-normal, 1-mild aphasia, 2-severe aphasia, 3-mute or global aphasia
10	Articulation	0-normal, 1-mild dysarthria, 2-severe dysarthria
11	Extinction or inattention	0-absent, 1-mild (one sensory modality lost), 2-severe (two modalities lost)

NIHSS score >/25 indicates severe stroke.
Most patients with disabling symptoms will have NIHSS score >/4.
But patients with isolated gait disturbance, isolated aphasia or isolated hemianopia may have potentially disabling symptoms although their NIHSS score is just 2.

History

Imaging Appearance of Acute Infarction [9]

A hyper-dense vessel corresponding to intravascular thrombus is seen in approximately one-third of patients with an MI occlusion (Fig. 60.1) and less commonly in patients with MCA insular branch, ICA or basilar artery occlusion. Early parenchymal CT findings in MCA stroke (Fig. 60.1) include:

- Blurring of the grey-white matter junction
- Loss of the insular ribbon
- Obscuration of the lentiform nucleus
- Cortical sulcal effacement

CTA identifies thrombus as a filling defect within proximal intracranial arteries.

Table 60.3 History taking in stroke

Time of onset	It is defined as the time when the patient was last seen normal (that is at his or her previous baseline) or in a symptom-free state. For a patient who wakes up with stroke symptoms, the time of onset is defined as the time the patient was last awake and symptom-free. For patients with stroke symptoms that completely resolve and reappear, the time of onset begins anew
Enquire about hypertension and diabetes mellitus	Risk factors for atherosclerotic thrombus
Previous atrial fibrillation, valve replacement or recent myocardial infarction	Suggest embolism
Previous TIA or stroke, ischaemic heart disease and atrial fibrillation	Increase the risk of stroke
Medication history – antihypertensives, antidiabetics, antiarrhythmics, antithyroid, anticoagulants, antiplatelet therapy, antiepileptics	May give a clue about the possible stroke aetiology or a stroke mimic
A history of drug abuse (cocaine, amphetamines), oral contraceptive use and pregnancy	Risk factors for stroke
History of seizures, diabetes mellitus, infection, trauma or migraine particularly in young patients	May be markers for stroke mimics

Table 60.4 Emergency diagnostic tests in suspected TIA or acute stroke patients [7, 8]

In all patients
1. Brain imaging: CT or MRI (if MRI is used, the inclusion of diffusion-weighted imaging (DWI) and T2-weighted gradient echo-sequence is recommended)
2. ECG
3. Laboratory tests
Complete blood count and platelet count, prothrombin time or INR, partial thromboplastin time (PTT)
Serum electrolytes, blood glucose
C-reactive protein (CRP) or erythrocyte sedimentation rate
Hepatic and renal chemical analysis
When indicated
Extracranial and transcranial Duplex/Doppler ultrasound
MR angiography (MRA) or CT angiography (CTA) in patients with TIA, minor stroke or early spontaneous recovery
Diffusion and perfusion MR or perfusion CT
Echocardiography (transthoracic and/or transesophageal)
Chest X-ray (if lung disease is suspected)
Arterial blood gas analysis (if hypoxia is suspected)
Lumbar puncture (if meningitis is suspected or if subarachnoid haemorrhage is suspected and CT scan is negative for blood)
EEG
Toxicology screen
Pregnancy test
Blood alcohol level

MRI – With acute ischaemia, there is rapid decrease in water diffusion, reflecting cytotoxic oedema, which produces marked hyperintensity on diffusion-weighted imaging (DWI) (Fig. 60.2) and hypointensity on the apparent diffusion coefficient (ADC) map (Fig. 60.3). In contrast, there is frequently insufficient accumulation of tissue water for reliable detection of acute infarction on fluid-attenuated inversion recovery (FLAIR) (Fig. 60.4) or T2-weighted images within the first 6 h.

Fibrinolysis

Note: Administer intravenous rtPA 0.9 mg/kg (10 % as bolus, remaining dose over 1 h, maximum dose 90 mg) to eligible patients who may be treated within 3 h of onset of ischaemic stroke (refer Table 60.5).

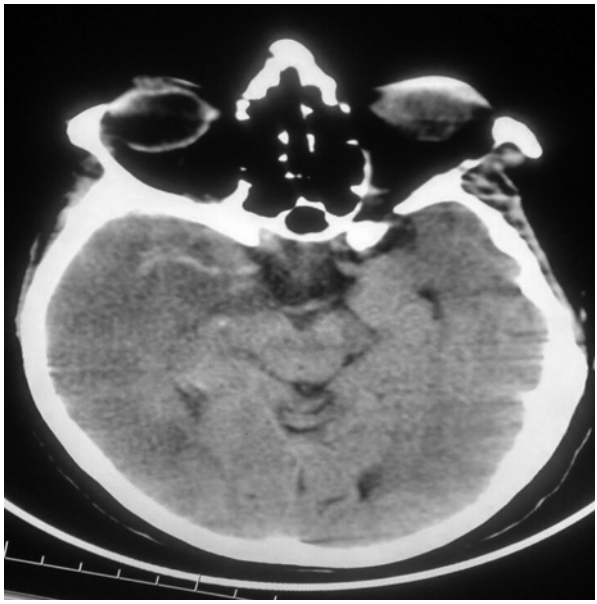


Fig. 60.1 Acute ischaemic stroke. Noncontrast CT at the level of temporal lobes reveals sulcal effacement, loss of grey-white differentiation and 'dense MCA' sign on the *right side*

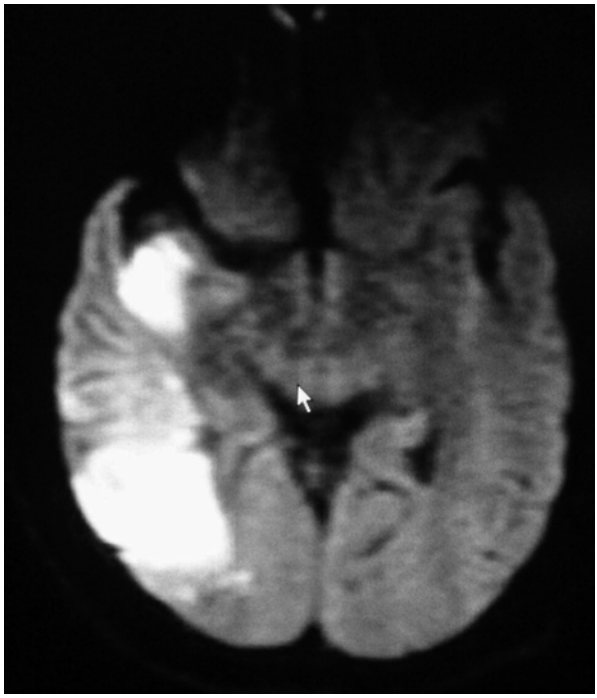


Fig. 60.2 DWI map reveals diffusion restriction reflecting cytotoxic oedema within the right temporal lobe consistent with acute right MCA territory infarction

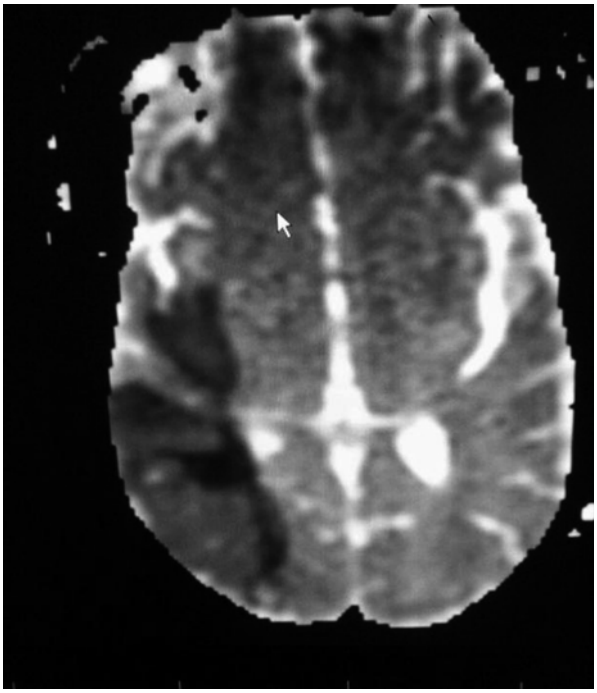


Fig. 60.3 ADC map reveals hypointensity within the acute right MCA territory infarction confirming restricted diffusion

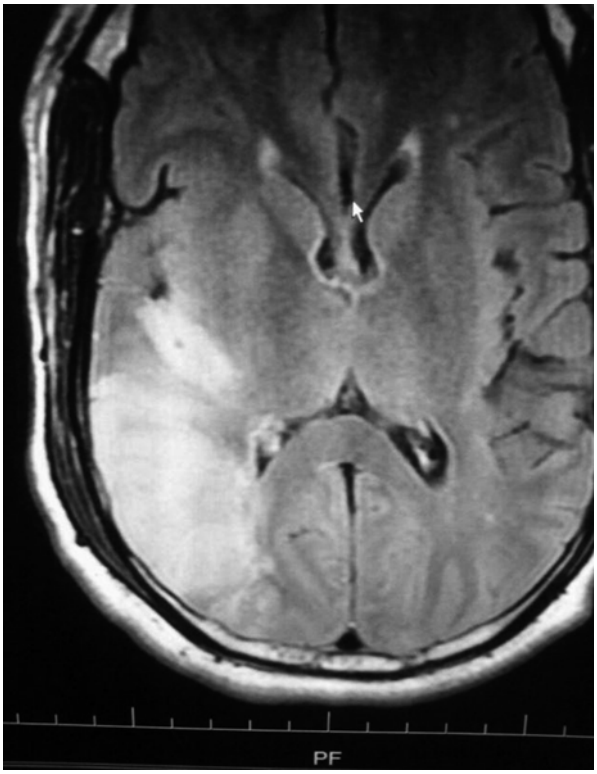


Fig. 60.4 FLAIR demonstrates minimal hyperintensity corresponding to the acute right MCA infarction

Table 60.5 Inclusion and exclusion characteristics of patients with ischaemic stroke who could be treated with IV rtPA within 3 h from symptom onset [7]

Inclusion criteria
Diagnosis of ischaemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid haemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial haemorrhage
Intracranial neoplasm, arteriovenous malformation or aneurysm
Recent intracranial or intra-spinal surgery
Elevated blood pressure (systolic >185 mmHg or diastolic >110 mmHg)
Active internal bleeding
Acute bleeding diathesis
Platelet count <100,000/mm^3
Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory test results (such as aPTT, INR, platelet count and ECT, TT or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairment
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract haemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Goal: door to needle time (i.e. time interval from arrival to administration of the drug) should be less than 60 min

Administer intravenous rtPA 0.9 mg/kg, maximum dose 90 mg, to eligible patients who can be treated within the time period of 3–4.5 h after stroke onset. The eligibility criteria are similar (refer Table 60.5), with the additional exclusion criteria (refer Table 60.6).

In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.

Table 60.6 Additional exclusion characteristics of patients with ischaemic stroke who could be treated with IV rtPA within 3–4.5 h from symptom onset [7]

Age >80 years
Severe stroke (baseline NIHSS score >25)
Taking oral anticoagulants regardless of INR
History of both diabetes and prior ischaemic stroke

It is recommended that intravenous rtPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischaemia.
The use of intravenous fibrinolysis in patients with mild neurological deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months and recent myocardial infarction may be considered, and the potential increased risk should be weighed against the anticipated benefits.
IV indicates intravenous, *rtPA* recombinant tissue plasminogen activator, *NIHSS* National Institutes of Health Stroke Scale, *INR* international normalised ratio

Table 60.7 Other drug therapies

Type	Intervention	Caveat
Anticoagulants (unfractionated heparin, low molecular weight heparin or heparinoids)	As an adjunct in addition to mechanical or pharmacological fibrinolysis *is not recommended*	
Antiplatelet agents	Oral administration of aspirin (initial dose 325 mg) within 24–48 h after stroke is recommended for most patients	If fibrinolysis is planned or given, aspirin should not be given within 24 h
Vasopressor	May be used in exceptional patients with systemic hypotension producing neurological sequelae	Close neurological and cardiac monitoring needed
Statins	Continue if patient was already taking statins at the time of onset of ischaemic stroke	
Neuroprotective agents	Not recommended	

In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count results but should be discontinued if platelet count is <100,000/mm^3.

aPTT indicates activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time; INR, international normalised ratio; IV, intravenous; PT, partial thromboplastin time; rtPA, recombinant tissue plasminogen activator; and TT, thrombin time (Table 60.7).

Table 60.8 Medical management of cerebral oedema

Intervention	Effect
Avoid dextrose-containing fluids, minimise hypoxia and hypercarbia	
Treat hyperthermia	Hyperthermia increases metabolic demands of the brain, release of neurotransmitters and free radicals
Elevate the head of the bed to 20–30°	Assists venous drainage
When oedema produces raised ICP. Hyperventilation of intubated patients Target (pCO2 30–35 mmHg)	Induces cerebral vasoconstriction causing a reduction in cerebral blood volume thus lowering ICP
Hypertonic saline	Causes a rapid decrease in ICP
Mannitol	0.25–0.5 g/kg IV administered over 20 min and every 6 h. Maximum dose is 2 g/kg
Steroids	Not recommended because of the potential risk of infections
Decompressive surgery for malignant oedema of the cerebral hemisphere	Effective in preventing and treating herniation and brainstem compression
Ventriculostomy or decompressive surgical evacuation of a space-occupying cerebellar infarction	

Treatment of Acute Neurological Complications after Acute Ischaemic Stroke

1. *Ischaemic brain oedema* – Early reperfusion of a large volume of necrotic tissue can accelerate the oedema to a potentially critical level within the first 24 h, a circumstance termed malignant oedema (Table 60.8).
2. *Haemorrhagic transformation* – Symptomatic haemorrhage occurs in 5–6 % of patients after use of intravenous rtPA. Most symptomatic intracerebral hemorrhage (sICHs) occur within the first 24 h after intravenous rtPA (Fig. 60.5). Signs and symptoms resemble those of patients with spontaneous ICH, such as worsening neurological symptoms, decrease in mental status, headache, increased blood pressure and pulse and vomiting.
3. *Seizures* – An increased incidence is reported in patients with haemorrhagic transformation. Recurrent seizures after stoke should be treated similarly to other acute neurological conditions. Prophylactic use of anticonvulsants is not recommended.
4. *Acute hydrocephalus* – Placement of a ventricular drain is useful.

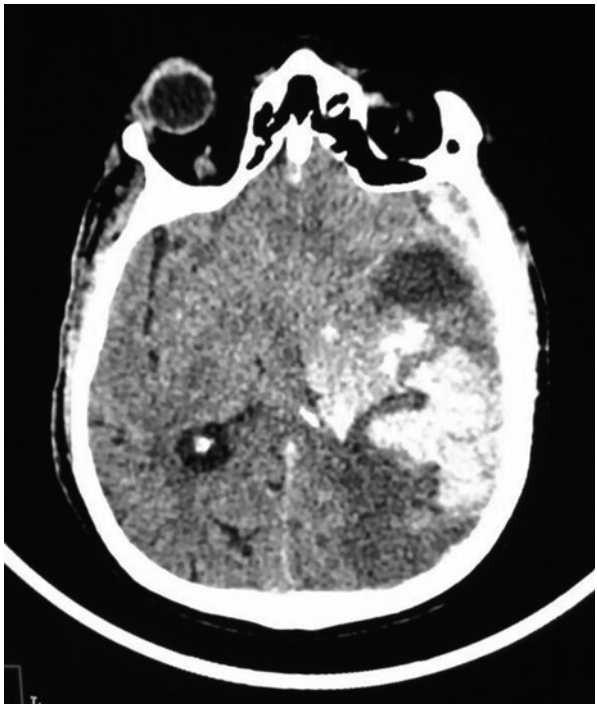


Fig. 60.5 Post-fibrinolysis bleed

Haemorrhagic Stroke

Intracerebral haemorrhage (ICH) caused by bleeding, primarily into parenchymal brain tissue (Fig. 60.6), is responsible for 9–27 % of all strokes worldwide. Underlying pathologies can be differentiated into arterial small and large-vessel disease, venous disease, vascular malformation, haemostatic disorders and cryptogenic.

Definition of Stroke Caused by Intracerebral Haemorrhage [3]

Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma (Table 60.9).

There is no role for prophylactic anticonvulsant treatment. If the patient presented with/has a seizure, anticonvulsants should be initiated (Table 60.10).

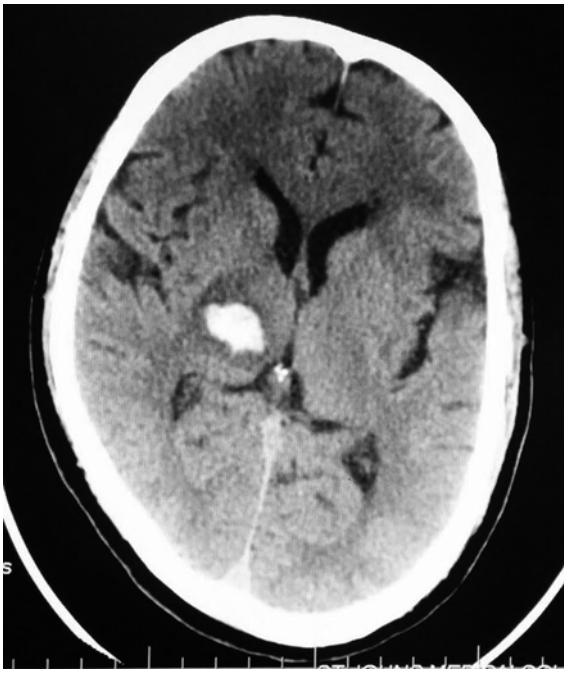


Fig. 60.6 Noncontrast CT brain showing right thalamic bleed

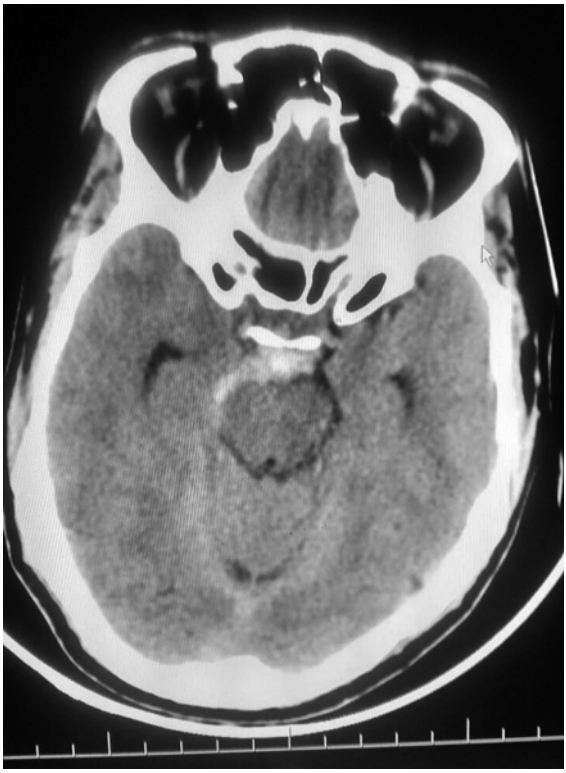


Fig. 60.7 Noncontrast CT brain showing prepontine subarachnoid haemorrhage

Table 60.9 Initial assessment of a patient with ICH

Clinical parameter	Intervention
Determine baseline severity of neurological impairment	Awake or drowsy patients – use NIHSS
	Obtunded, semi or fully comatose patients – use GCS
Suspected ICH	CT/MRI immediately to confirm diagnosis, location and extent of haemorrhage
Confirmed acute ICH	CTA/MRA or catheter angiography to exclude an underlying lesion such as aneurysm, arteriovenous malformation or tumour
Patients with ICH	Ask about anticoagulant therapy. Measure platelet count, PTT and INR
Assess for clinical signs of increased ICP	Neurological assessment should be conducted every 30–60 min depending on stability of patient
Blood pressure	Assess every 15 min until BP has stabilised. Close BP monitoring (Q30–60 min if above target) should be continued for at least first 24–48 h

Table 60.10 Management of ICH

Type of ICH	Management	Rationale
In acute ICH within 6 h of onset	Intensive blood pressure reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg	Blood pressure reduction decreases haematoma expansion but does not affect peri-haematoma blood flow
	Labetalol is an acceptable choice if there are no contraindications	
Acute ICH associated with antiplatelet use	Platelet transfusion has no effect on platelet function or ICH progression	
ICH associated with anticoagulant drug use	Stop anticoagulants	
	Reverse the effects of vitamin K antagonists	
	For patients with elevated INR – give intravenous vitamin K 5–10 mg, as well as fresh frozen plasma (20 ml/kg) or prothrombin complex concentrate (25–40 IU/kg) to prevent haematoma expansion	
	Intravenous protamine sulfate for patients on heparin	
ICH associated with the use of novel oral anticoagulants (NOACs – apixaban, dabigatran, edoxaban, rivaroxaban)	No specific antidote available	

Subarachnoid Haemorrhage (SAH) [10]

There is a high early risk of rebleeding in SAH patients. Patients with SAH should have urgent consultation with a neurosurgeon.

Table 60.11 Evaluation of patients with suspected subarachnoid haemorrhage

Evaluation	Indication
Noncontrast CT scan (Fig. 60.7)	
CSF analysis	In patients with a strongly suggestive clinical history of SAH but negative noncontrast CT scan as reported by radiologist
Vascular imaging of the brain in patients with SAH	CT angiography preferred to catheter angiography as an initial investigation, but catheter angiography should be considered as 'gold standard' when initial CT is negative

Definition of Stroke Caused by Subarachnoid Haemorrhage [3]

Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma (Table 60.11).

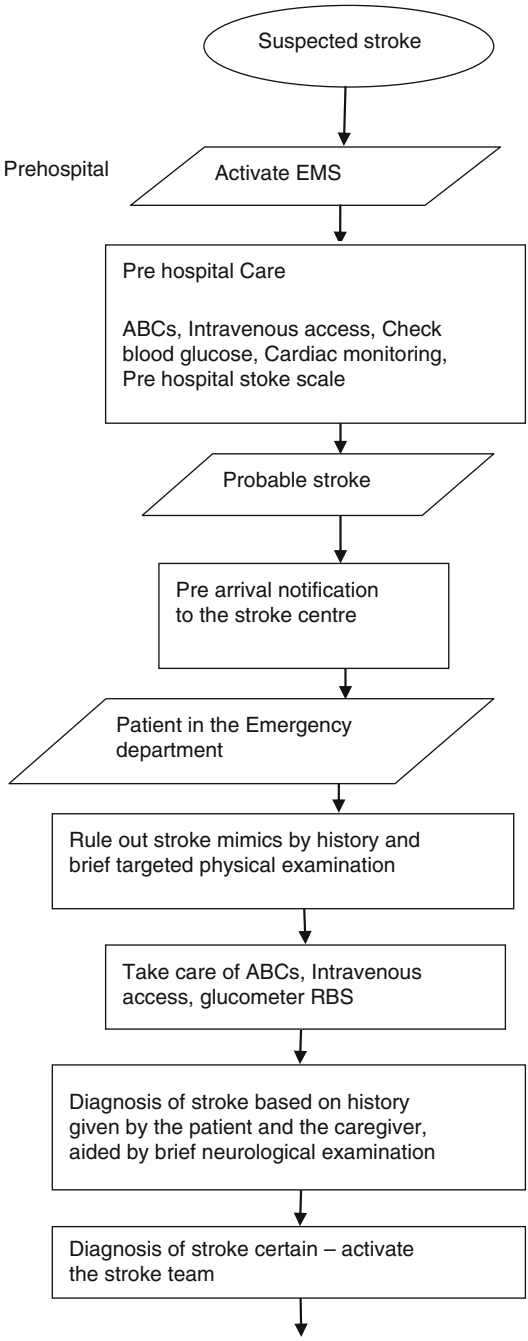
Interventions for Patients with SAH

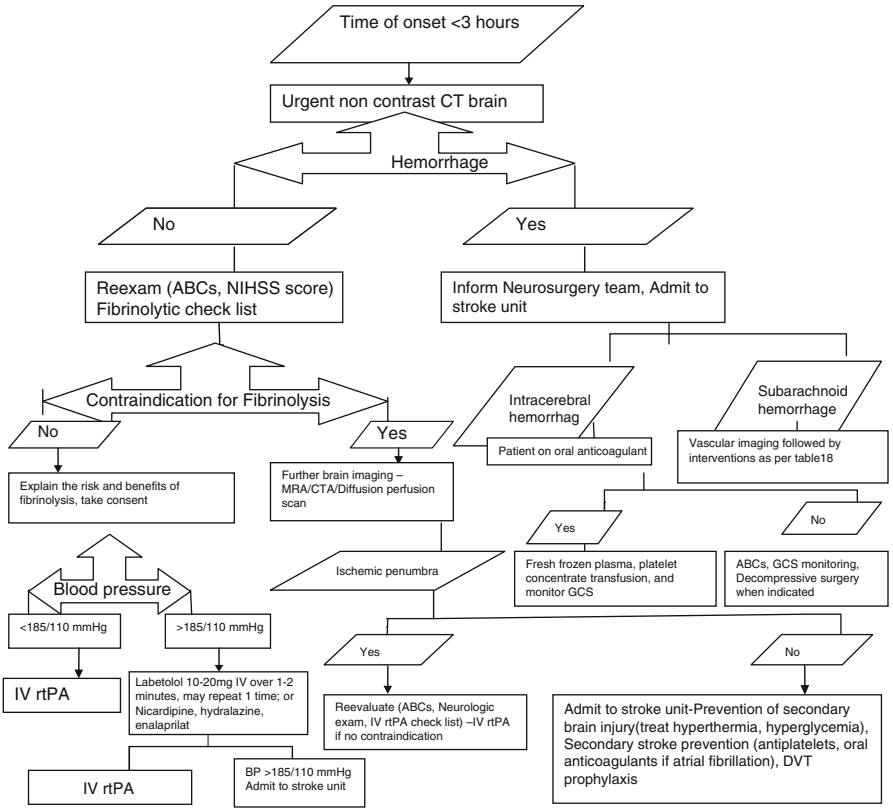
- Patients who present within 96 h of SAH and an adequate BP should be started immediately on nimodipine 60 mg Q4 h by mouth for 14–21 days. Treatment for high blood pressure should be initiated, while the aneurysm is unsecured to reduce the risk of hypertension-induced rebleeding and to maintain cerebral perfusion pressure.
- Neurological assessment should be conducted using standardised assessment tools (GCS, NIHSS) throughout the course of stay to monitor changes and ideally Q2–4 h until patient is stable.

Summary and Algorithm

1. In case of ischaemic stroke if inclusion criteria are met, intravenous rtPA should be administered as quickly as possible in consultation with the neurologist, after having explained the risks and benefits of therapy and obtaining an informed consent.
2. If the patient is not a candidate for intravenous rtPA and interventional modalities of treatment have to be considered, consider referral to a centre which offers the same.
3. In case of haemorrhagic stroke and subarachnoid haemorrhage, consult neurosurgeon at the earliest, recognise/anticipate complications and manage accordingly.

Algorithm for stroke management – early phase





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Part XI
Obstertics and Gynaecology

Chapter 61
Abnormal Uterine Bleeding

Devendra Naik

Key Points
- Abnormal uterine bleeding is a disorder of menstruation and represents a change in the menstrual pattern.
- Abnormal uterine bleeding has a number of structural and hormonal causes. A careful, relevant history and thorough physical examination along with required imaging can help in determining the likely cause.
- Dysfunctional uterine bleeding is a diagnosis of exclusion.
- Different treatment options are available for the control of acute uterine bleeding.

Introduction

Vaginal bleeding is one of the most frequent reasons for women to present at the emergency department. An estimated 5 % of women aged 30–49 years will consult a physician for the treatment of abnormal uterine bleeding. The figures vary from 20 % in premenopausal women [1] to 70 % in the peri- and postmenopausal years [2]. Abnormal uterine bleeding is one of the commonest causes of iron deficiency anaemia in Western women [3]. It occurs in women of all age groups. Vaginal bleeding as a complication of pregnancy can be life threatening for the mother and

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_61

foetus. Premenarchal or postmenopausal vaginal bleeding is rarely life threatening. This chapter deals with non-pregnant women visiting emergency department (ED) with complaints of abnormal vaginal bleeding.

Pathophysiology

An understanding of the normal menstrual cycle is valuable in the causes of abnormal uterine bleeding. The normal menstrual cycle is 28 days and is divided into four phases: follicular, ovulation, luteal or secretory and menses. It starts on the first day of menses. The endometrium thickens under the influence of oestrogen during the first 14 days (follicular phase) of the menstrual cycle. In response to rising oestrogen levels, the pituitary gland secretes follicle-stimulating hormone (FSH) and luteinising hormone (LH), which stimulate the release of an ovum at the midpoint of the cycle. The residual follicular capsule forms the corpus luteum.

After ovulation, the luteal phase begins and is characterised by production of progesterone from the corpus luteum. Progesterone matures the lining of the uterus and makes it more receptive to implantation. If implantation does not occur, in the absence of human chorionic gonadotropin (hCG), the corpus luteum dies, accompanied by sharp drops in progesterone and oestrogen levels. Hormone withdrawal causes vasoconstriction in the spiral arterioles of the endometrium. This leads to menses, which occurs approximately 14 days after ovulation when the ischemic endometrial lining becomes necrotic and sloughs.

The mean menstrual blood loss per menstruation in a healthy Western European population ranges between 37 and 43 ml; 70 % of the loss occurs in the first 48 h [4]. The upper limit of normal menstruation is thus taken as 80 ml per menses [5].

The history of excessive blood loss is subjective, but it has been found to correlate with objective measurement of menstrual bleeding. Table 61.1 compiles the various terminologies used to describe abnormal patterns of menstrual bleeding.

The aetiology of abnormal uterine bleeding may be classified as:

1. Organic causes
    - Systemic diseases (idiopathic thrombocytopenic purpura, leukaemia, liver and renal diseases, von Willebrand's disease or hypothyroidism)
    - Pregnancy
    - Trauma
    - Reproductive tract lesions
    - Iatrogenic
    - Foreign bodies in genital tract

Table 61.1 Definitions

Menorrhagia	Regular, heavy menstrual bleeding
Metrorrhagia	Irregular bleeding of variable volume and duration
Hypermenorrhoea	Heavy menstrual bleeding but of normal duration
Menometrorrhagia	Irregular non-cyclical excessive bleeding
Polymenorrhoea	Frequent menstrual cycles ≤21 days' intervals
Polymenorrhagia	Frequent cycles ≤21 days' intervals with heavy menstrual bleeding
Postmenopausal bleeding	Any bleeding that occurs more than 6 months after cessation of menstruation
Dysfunctional uterine bleeding	This term is used where no organic cause can be found for the abnormal bleeding pattern

2. Non-organic causes (DUB)
   - Ovulatory
   - Anovulatory

Systemic Diseases

Abnormal menstrual bleeding is the commonest symptom in women with coagulation disorders. About 5–20 % of adolescents visiting the hospital with abnormal uterine bleeding have blood dyscrasias [6]. Hence, when an adolescent presents with acute bleeding per vagina, an appropriate haematological evaluation needs to be done.

Hypothyroidism is also associated with abnormal uterine bleeding. This has been attributed to a decrease in certain coagulation factors and to infrequent ovulation. Reduction in menstrual blood loss has been noticed following the treatment of hypothyroidism. Liver dysfunction, chronic renal disease and connective tissue disorders like SLE have also been known to cause abnormal uterine bleeding.

Pregnancy

The risk of spontaneous abortion (20 %) and ectopic pregnancy (2 %) in adolescents is similar to that in adults [7]. A urine pregnancy test has to be performed, and when uncertainty exists, β-HCG test may also be necessary. Ectopic pregnancy has to be ruled out in women who have undergone tubectomy because it has been seen that sterilisation fails in 0.13–1.3 % of procedures [8].

Reproductive Tract Lesions

There is a steep rise in incidence of benign, premalignant and malignant lesions which cause abnormal bleeding from genital tract. Though majority of them are uterine in origin, careful examination is necessary to rule out bleeding due to cervical or vaginal lesions.

Trauma

Another cause of genital bleeding could be accidental or coitus-related genital trauma. The possibility of sexual assault or vigorous consensual sex should also be considered.

Iatrogenic

All the methods of hormonal contraception have been known to cause irregular uterine bleeding. Nonhormonal drugs like those used in the treatment of depression and hirsutism, anticoagulants, digitalis and anticonvulsants may also cause abnormal uterine bleeding.

Foreign Bodies

Abnormal bleeding can also be caused by intrauterine contraceptive devices, retained pessaries and tampons.

Dysfunctional Uterine Bleeding (DUB)

Abnormal uterine bleeding is termed as DUB when no systemic or organic cause can be identified for the bleeding. DUB is mainly a diagnosis of exclusion. It is mainly attributed to hormonal dysfunction.

Anovulatory DUB is the most common cause of abnormal uterine bleeding (up to 90 %) in adolescents. Polycystic ovarian disease (PCOD) is the predominant cause of reproductive age. The perimenopausal period has another peak of anovulatory DUB.

Ovulatory DUB occurs between adolescence and menopause. The cause has been attributed to changes in local haemostasis.

Clinical Features

A systematic history and physical examination can help narrow down the possibilities. Management of AUB is summarised in the algorithm (Fig. 61.1).

- A brief history should focus on the age and sexual history. This should include use of any contraceptive agents and any current medical conditions or medications.
- History should also include any history of preceding amenorrhoea which may give a clue about anovulation or pregnancy.
- Patient should be asked about the duration, amount in terms of number of sanitary pads, passage of clots and passage of fleshy tissue suggestive of products of conception.
- A general physical examination should include looking for *pallor* which is a sign of severe acute bleeding or prolonged heavy bleeding.
- Physical findings suggestive of PCOD include obesity, acne, hirsutism and hyperpigmentation typically seen in the folds of the skin in the neck, groyne or axilla.
- An examination of external genitalia may help in assessing the extent and also possible source of bleeding. Per speculum examination may reveal any cervical or vaginal lesions, any products of conception or local trauma and infections. Bimanual examination may tell about the presence of a fibroid or any adnexal masses.
- Adequate examination of a young female or an apprehensive patient may necessitate anaesthesia or sedation.

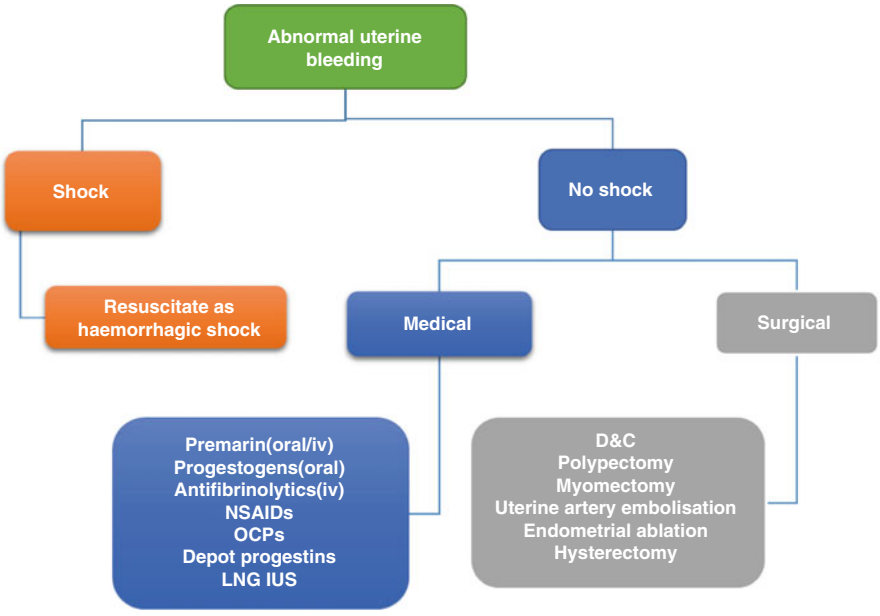

Fig. 61.1 Algorithm: abnormal uterine bleeding

Investigations

Laboratory Studies

- A urine pregnancy test is essential in evaluating a woman in reproductive age group.
- Haemoglobin, haematocrit, platelet count and peripheral smear.
- Thyroid profile.
- Dilatation and curettage (D&C) can be performed as a diagnostic procedure and sometimes used as a haemostatic procedure in cases of acute bleeding [1].

Imaging

- Ultrasonography – trans-abdominal is preferred in adolescents, whereas trans-vaginal is more sensitive in sexually mature women. The ultrasonography may reveal a fibroid, endometrial thickening or a focal mass. Thickened endometrium may indicate an underlying lesion [9]. The decision to perform ultrasound imaging in the ED will depend on the urgency to determine the aetiology of bleeding.
- MRI scanning may help in planning the further management of lesions like leiomyomas and adenomyomas.
- Hysteroscopy allows the direct visualisation and identification of intrauterine lesions like polyps or leiomyomas, and biopsy can be taken at the same time [10].

Treatment

The cause of the abnormal bleeding and amount of bleeding will guide the ED management. An initial appraisal is important to rule out haemodynamic instability. A gynaecologist has to be involved in the treatment of women with significant and continued bleeding.

- *Nonsteroidal anti-inflammatory drugs* (NSAIDs): These are generally effective for the relief of associated cramping pain. The most commonly used NSAIDs are mefenamic acid and naproxen. Mefenamic acid is used in the dose of 500 mg thrice daily and naproxen as 275 mg administered every 6 h. Naproxen and mefenamic acid have both been found to be equally efficacious [11].
- *Antifibrinolytics*: These act as inhibitors of plasminogen activator and can reduce the bleeding by 40–60 % [12]. Tranexamic acid may be administered in doses of 1–1.5 g orally, four times a day, or parenterally in a dose of 10 mg/kg given every 6 h.

- *Oestrogen*: The administration of oestrogen alone in acute bleeding causes rapid proliferative changes, capillary haemostasis and stoppage of bleeding from small vessels [13, 14]. The bleeding is usually controlled within 24 h of initiation of oestrogen therapy, which can be followed by progesterone or combined OC pills.
- *Cyclical and oral progestogens*: Progestogens inhibit the endometrial growth in the endometrium that has been primed with oestrogen. Progestogens also promote the formation of arachidonic acid in the endometrium which decreases bleeding [10, 13].
- *Combined oral contraceptive pills* (COCs): For anovulatory bleeding, COCs can help regulate the cycle. In a patient who wants to continue contraception and not heavily bleeding, a COC with 20–30 μg of ethinyl estradiol may be prescribed. For a patient with heavy bleeding, an oral contraceptive with 35 μg of oestrogen can be given twice a day for 5–7 days until the bleeding stops, and then the dose is decreased to once a day until the pack is completed [9].
- *Levonorgestrel-releasing intrauterine system* (LNG IUS): It acts by a direct effect on the endometrium. It causes decidualisation of stroma with inflammatory infiltrate and atrophy of the endometrial glands [12].
- *Danazol*: It is a 17-α-ethinyl testosterone derivative with antioestrogenic, antiprogestogenic and androgenic properties. It is used in doses of 200–400 mg over a duration of 12 weeks in women with heavy bleeding [15].
- *GnRH analogues*: They have been mainly used in the treatment of endometriosis and fibroids or prior to minimally invasive surgery. They produce more effective control of bleeding in cases of heavy menstrual bleeding. Their adverse effects are hot flushes, night sweats, vaginal dryness and temporary reduction in bone density [12].
- *Surgical therapy*: Hysteroscopic resection of polyps and myomectomy are done for pedunculated fibroids up to 3 cm in size [16].

Embolisation of uterine fibroid is usually done in women who carry high risk for surgery. It is not recommended in women who want to preserve their fertility [17].

Endometrial ablation techniques are minimally invasive surgical techniques. It is done in cases where medical therapy has failed. They are more effective and safe than conventional hysterectomy [18].

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Chapter 62
Assessment of Sexual Assault

Shweta Tyagi

Key Points
- Compassionate medical care should precede forensic examination.
- Assessment of sexual assault should be performed after valid consent. The procedure should be conducted as early as possible.
- Appropriate collection and preservation of evidence is mandatory.
- Post-assault management includes emergency contraception as well as definitive management of injuries.
- Emergency psychiatric referral should be offered, if needed.

Introduction

Definition

The World Health Organization (WHO) defines sexual violence as "Any sexual act,[1] attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic or otherwise directed against a person's sexuality using coercion, by any

[1] A sexual act [2] includes rape, which is defined as sexual intercourse by a man of a woman against her will or without her consent. The term rape is limited to penetration of the genitalia of the woman by the penis of the accused. The "slightest penetration of the penis with the vulva, such as minimal passage of the glans between the labia with or without emission of semen or rupture of the hymen constitutes rape." Other sexual acts include non-consensual sexual touching involving genital, anal, or oral penetration by the penis, fingers, or other objects.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_62

person regardless of their relationship to the victim, in any setting, including but not limited to home and work" [1].

In addition, sexual violence may also take place when someone is not able to give consent – for instance, while intoxicated, drugged, asleep, or mentally incapacitated [1].

Morbidity and Mortality

The course of sexual assault can inflict overwhelming impact on the victim ranging from life-threatening polytrauma, unwanted pregnancy, unsafe abortions, and sexually transmitted diseases to posttraumatic stress disorder which can significantly contribute to burden of disease and injury [3].

Epidemiology

The prevalence data on sexual assault is obtained mainly from population-based surveys, police reports, and case studies from hospitals and nongovernment organizations. However the prevalence is underestimated as a large proportion of such cases remain unreported [4].

According to WHO multi-country study [4], lifetime prevalence of sexual partner violence is 10–50 % and non-partner 0.3–12 %, and childhood sexual abuse is 27 % in girls and 14 % in boys.

Role of Emergency Physician

Principles of good practice for addressing sexual assault [5]:

(a) Compassionate healthcare facilities

- Specific treatment as per clinical condition
- Emergency contraception and information on safe abortion
- Treatment and prophylaxis for STDs
- Prophylaxis of HIV
- Psychiatric referral

(b) Medicolegal services

- Forensic examination and collection of evidence.
- Can be done on request of survivor, her relatives, or representatives of law enforcement agencies.
- Consent of woman or parents in case of minor should be taken in writing.

- Statement of the victim to be documented.
- Examination to be carried out without delay in comfortable and optimum conditions in the presence of a third person, preferably female nurse/relative.

Apart from providing treatment, care, and appropriate referrals, the purpose of examination in ED is also to confirm

- Whether a sexual act has been attempted/completed
- Whether woman has not given consent, which can be mostly inferred from injuries inflicted on her
- Whether the given consent was valid (e.g., under influence of drugs, mentally incapacitated, minor)
- To verify age of the patient in case of minor

History

The initial history should be intended to obtain information regarding injuries and to stabilize any life-threatening condition.

SAMPLE history format with following additions:

- Events history [6]:

  When – date/time
  Where – place of incident
  Who – assailant: known/unknown; single/multiple
  What – specifics of rape including
  Whether – sucking/licking/fondling/penetration

    Vaginal/anal/oral
    Ejaculation, use of foreign objects, use of condom,
    Use of physical force with what and where
    Drug facilitated

- Details pertaining to last meal, menstrual period, consensual intercourse, shower, change of clothes, passage of stools and urine

General and Evidential Examination

- Assessment of vital signs with primary survey of trauma.
- Examination may have to be performed under GA in cases of minor or severe injuries.
- Secondary survey should include head to toe examination for marks of violence like scratches/bruises/bites, petechiae on face/conjunctiva which indicates partial asphyxia, and gait.

– Genital examination should include careful inspection of the perineum, vulva, labia, and vagina for injury, bleeding, and seminal stains.
– Assessment of mental and emotional state of the patient should be made.

Collection of Specimen [2]

– Patient should be made to stand on a clean sheet of paper and anything that falls (hair, fibers, leaves, gravel, etc.) should be preserved.
  All clothes are to be removed by the patient and preserved.

  • Smears are to be collected by means of moistened swabs from the oral cavity, blood, semen, or any other stains and preserved.

– Any loose hair or debris should be collected from the head after combing. To serve as control samples, five to ten, scalp hair should be cut and preserved too.
– Debris from under the nails collected by pointed moistened swab along with nail clippings should be preserved.
– Blood of 7 ml is to be collected, 2 ml in EDTA bulb for blood grouping and DNA analysis and 5 ml in bulb (sodium fluoride and potassium oxalate) for assessing alcohol and drug levels.
– Urine sample for alcohol and drug screening.
– Following genital examination:

  • Pubic hairs are to be combed and any loose hair and debris to be collected. To serve as control sample, five to ten hairs are to be cut and preserved.
  • Any matted pubic hair should also be cut and preserved.
  • Two swabs each should be taken from the anterior and posterior vaginal wall, vulva, and anal opening.
  • One vaginal smear should be prepared on glass slide.

All specimens should be air-dried and preserved in clean paper bags, labeled, sealed, and handed over to police. They should not be left unattended and ensure that chain of custody is maintained at all times.

Emergency Treatment Guidelines

– Priority-based management of medical problems and sustained injuries
– For prophylaxis against infections [7]:

  • IM ceftriaxone 125 mg single dose
  • Oral metrogyl 2 g single dose
  • Oral azithromycin 1 g single dose or oral doxycycline, 100 mg BD for 7 days

  Do not use doxycycline and metrogyl if pregnant.

– For prophylaxis against specific sexually transmitted infections:

  Syphillis: Benzathine penicillin 2.4 million IU IM given as 1.2 million IU dose in each buttock. If allergic, use oral erythromycin, 500 mg q.i.d. for 15 days.
  Hepatitis B: Immunoglobulin, 2.5 mcg (children), 5 mcg (adolescents), and 10 mcg (adults) to be administered IM in the deltoid within 72 h of assault. Provide post-exposure hepatitis B vaccination stat and follow-up doses.
  Gonorrhea: IM ceftriaxone 125 mg single dose.
  Chlamydial infection: Oral azithromycin 1 g single dose or oral doxycycline, 100 mg BD for 7 days.
  Trichomoniasis and bacterial vaginosis: Oral metronidazole 2 g single dose.
  HIV: Post-exposure prophylaxis for HIV should be considered similar to needle-stick injury.

– For pregnancy prophylaxis:

  Two tablets of levonorgestrel 750 μg (Norlevo), within 72 h. If vomiting occurs, within 3 h repeat
  Combined estrogen-progestin, two doses of 100 mcg ethinyl estradiol plus 0.50 mg levonorgestrel 12 h apart

– For injuries:

  Clean and dress.
  Surgical referral if necessary for suturing.
  Consider TT immunoprophylaxis if not previously immunized.

– Consider psychiatric referral.
– Consider admission and/or follow-up after 72 h.

Excellent care for sexual assault victims involve coordinated approach of clinical and forensic medicine, law enforcement agencies, and social organizations. A well-structured sexual assault policy should be formulated in every healthcare facility, meeting the above guidelines and taking into account the state laws and community resources.

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Chapter 63
First and Second Trimester Emergencies

Rachel Gnanaprakasam

Key Points

- Rule out ectopic gestation in any woman in the reproductive age group, presenting with abdominal pain and/or vaginal bleeding or any atypical symptom.
- There is no symptom or sign that can differentiate between ruptured and unruptured ectopic gestation in the ED.
- The 'classic triad' of amenorrhoea, vaginal bleeding and abdominal pain seen in Ruptured Ectopic pregnancy can be as low as 56 % [1].
- Hyperemesis gravidarum (HG) is a diagnosis of exclusion and based on clinical presentation. Ensure that other possibilities for recurrent vomiting in pregnancy are ruled out, especially if onset is greater than 10 weeks.

Introduction

Treating pregnant women in the emergency department is part of the daily routine of an ED clinician. Early identification and efficient management of pregnancy-related emergencies are of prime importance. Some of the common presentations are dealt with, in this chapter.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_63

Ectopic Pregnancy

Introduction

The commonest life-threatening emergency in the first trimester, ectopic pregnancy is the implantation of the fertilised ovum outside the uterine cavity. Tubal gestation is the most common form, constituting nearly 97 % of all ectopic pregnancies [2]. Heterotopic pregnancy is the simultaneous existence of both intrauterine and extra-uterine gestation which is very rare in natural conception (i.e. nearly 1 in 30,000 pregnancies) [4].

Pathophysiology

Abnormal paracrine interactions between tubal smooth muscle, epithelial, immune cells and embryonal cells cause disturbed embryo-tubal transport. Factors favouring tubal implantation affect tubal smooth muscle contractility, ciliary motility or the inflammatory milieu. Some of them are inducible nitric oxide synthase, interstitial cells of Cajal, activated macrophages, interleukin-8, mucin and endocannabinoid receptors (CB1) [3].

Risk Factors [5, 6]

- Previous ectopic pregnancy
- Documented tubal pathology
- Previous tubal surgery
- In vitro fertilisation
- Previous genital infections (e.g. *Chlamydia trachomatis*, *Neisseria gonorrhoeae*)
- Cigarette smoking
- Current intrauterine contraceptive device use
- Previous medical termination of pregnancy

Clinical Features (Table 63.1)

Clinical signs include cervical motion tenderness, adnexal tenderness, abdominal tenderness, adnexal mass, sinus tachycardia, shock and pallor. The presentation depends on whether the tubes are intact or ruptured.

Table 63.1 Symptoms

Symptoms [7–9]	Incidence
Abdominal/pelvic pain	(80–95 %)
Amenorrhoea	(79–87 %)
Dizziness/fainting attack	(37–60 %)
Vaginal bleeding	(65 %)
Shoulder-tip pain	(8 %)
Atypical symptoms – urinary symptoms, diarrhoea	4 %

The 'classic triad' of amenorrhoea, vaginal bleeding and abdominal pain can be as low as 56 % [1]. Mean gestational duration at presentation is 7 weeks with a range between 5 and 11 weeks.

Differential diagnosis: Pelvic inflammatory disease, endometriosis, gastroenteritis, appendicitis, ovarian torsion, ovarian cyst rupture, mittelschmerz, splenic rupture

Investigations

- *Urine beta-hCG*: Point-of-care beta-hCG testing should be part of initial patient assessment. If the test is negative but there is clinical suspicion of ectopic pregnancy, result should be correlated with serum beta-hCG as urine tests can be negative in 3 % of ectopic pregnancies [1].

Ultrasonography:

- Around 90 % of patients with ectopic pregnancy can be diagnosed by visualising an adnexal mass in a transvaginal sonogram (TVS) [6].
- Haemoperitoneum should be looked for, both by TVS (free fluid above the level of uterine fundus or around the ovary) and in transabdominal scan (free fluid in Morison's pouch).

Serum beta-hCG:

- Serial monitoring can be helpful in evaluating the trophoblastic proliferation and thereby guide the subsequent management.
- In case of pregnancy of unknown location (PUL), measure serum levels of hCG both at 0 and 48 h. If hCG rises greater than 63 %, it is more likely to be a continuing intrauterine pregnancy, whereas a decline of more than 50 % shows that it's unlikely to continue [10].

Culdocentesis: In case of a ruptured ectopic pregnancy, blood inside the peritoneal cavity collects in the Douglas space which should appear as non-clotting (due

to the presence of fibrinolytic proteins in the peritoneum) blood on aspiration. However, this invasive method has been largely replaced by ultrasound and serial hCG estimation (Fig. 63.1).

MRI: It can be used in patients in whom the above investigations fail to give a clear diagnosis.

Management – Fig. 63.1 – Algorithm for Suspected Ectopic Pregnancy

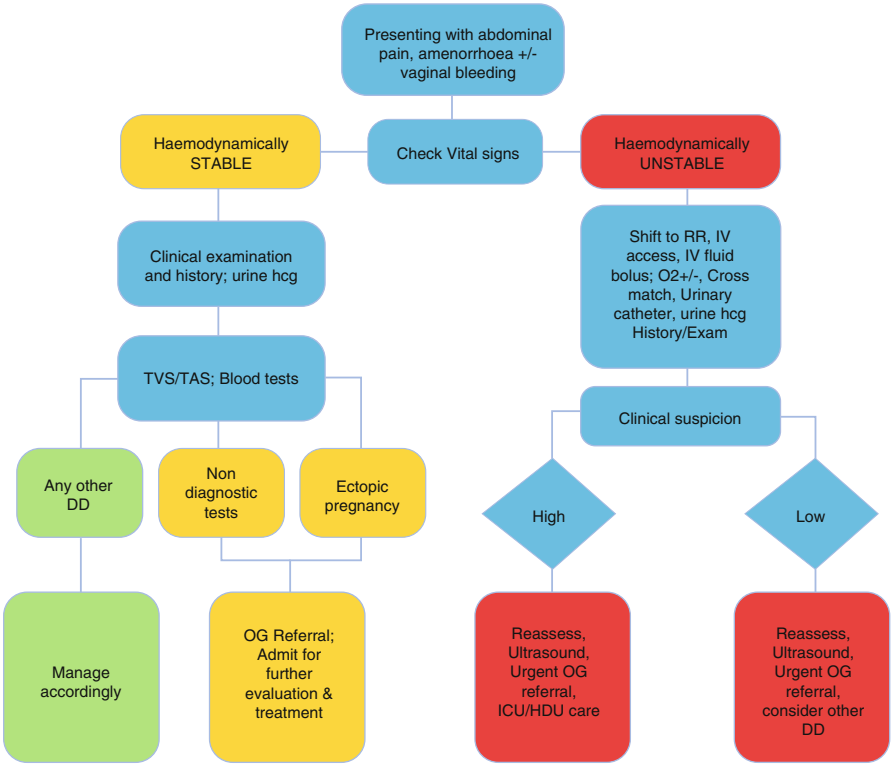

Fig. 63.1 Algorithm for ED management of ectopic pregnancy. *RR* resuscitation room, *IV* intravenous, *TVS* transvaginal sonography, *TAS* transabdominal sonography, *DD* differential diagnosis, *OG* obstetrics and gynaecology, *ICU* intensive care unit, *HDU* high dependency unit

Management of Ectopic Pregnancy

Laparoscopic management by salpingectomy or salpingotomy is the usual surgical approach to a patient with ectopic gestation (Image 63.1). However, the use of medication in treating ectopic pregnancy has increased by leaps and bounds in the last decade [11]. Methotrexate is given either intramuscularly or injected locally with ultrasound guidance. The National Institute of Clinical Excellence (NICE) recommends systemic methotrexate as the treatment of choice for women who fit the criteria [10] below:

- Unruptured ectopic pregnancy with adnexal mass <35 mm and no visible foetal heartbeat
- Serum hCG <1,500 IU/l
- No significant abdominal pain
- Compliant and able to come for review

Immunoprophylaxis: 250 IU of anti-D immunoglobulin should be administered to all RhD-negative, unsensitised women diagnosed with ectopic pregnancy, regardless of the duration of pregnancy or the mode of treatment chosen [11]. This prophylactic administration of immunoglobulin prevents the development of harmful antibodies in the mother and hence protects the foetus against RhD haemolytic disease or erythroblastosis foetalis.

Pregnancy Loss

Miscarriage is the most frequent complication of pregnancy. It is defined as foetal death before 20 weeks of gestation after which the term 'stillbirth' is used. Incidence of first trimester pregnancy loss is 10–15 % of all pregnancies among patients who sought medical treatment [12].

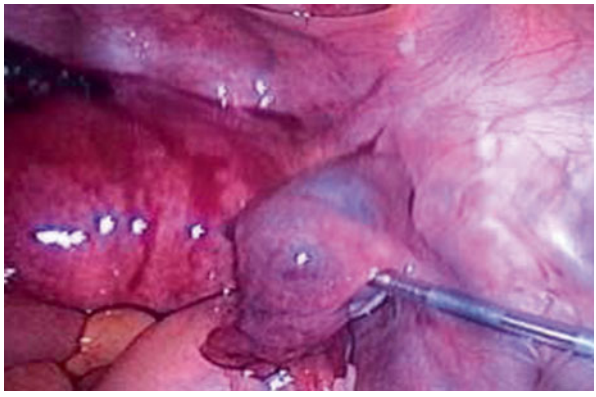

Image 63.1 Tubal ectopic pregnancy (unruptured) during laparoscopic removal (Courtesy: Dr. C. Prabakar, Maimonides Medical Center, New York City)

Definitions

Threatened miscarriage: Vaginal bleeding before the 20th week of gestation but accompanied by signs of foetal life and no dilation of cervix. Nearly 14–26 % progress to complete miscarriage [13].

Inevitable miscarriage: Products of conception still inside the uterus along with intrauterine bleeding and cervical dilation.

Complete miscarriage: Spontaneous loss of pregnancy with complete emptying of uterus.

Incomplete miscarriage: Spontaneous loss of pregnancy with partial retention of products of conception within the uterus and a closed cervix.

Missed miscarriage (blighted ovum or anembryonic pregnancy): Spontaneous death of foetus without expulsion of the products with no symptoms of miscarriage.

Septic abortion: Abortion or miscarriage complicated by secondary genital tract infection.

Aetiopathogenesis

First Trimester Causes

S. no.	Causes	Examples
1.	Genetic	Translocations, inversions, recurrent aneuploidy, etc.; chromosomal abnormalities are responsible for nearly half the first trimester miscarriages
2.	Hormonal imbalance	Luteal phase defect, thyroid abnormalities, diabetes mellitus with uncontrolled sugars
3.	Anatomical	Intrauterine adhesions, uterine anomalies, leiomyoma
4.	Maternal infections	*Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Treponema pallidum*, *Salmonella typhi*, *Vibrio fetus*, Malaria, *Toxoplasma gondii*, etc.
5.	Toxic	Maternal alcoholism or exposure to cigarette smoking, x-radiation, cosmic radiation, chemotherapeutic drugs, toxic chemicals, etc.

Second Trimester Causes

- *Anatomical:*
  - Uterine anomalies – uterus didelphys, bicornuate uterus, arcuate uterus, septate uterus, etc.

  - Leiomyomas or fibroids complicating pregnancy – cause thinning of endometrium, red degeneration or less uterine space as the foetus continues to grow
  - Incompetent internal cervical os – acquired due to cervical procedures in the past or inherited connective tissue disorders
- *Thrombotic:* Acquired thrombophilia (e.g. antiphospholipid antibody syndrome) and inherited thrombophilia (e.g. factor V Leiden) – due to placental thrombosis
- *Major foetal malformations*
- *Others:* Include those listed as first trimester causes

Clinical Features

- Vaginal bleeding or spotting is the most common presenting symptom.
- Abdominal pain.
- Amenorrhoea or positive pregnancy test.
- Passage of products of conception.
- Dizziness, pre-syncope or syncope.
- Hyperventilation/anxiety.

Risk Factors

- Increasing maternal age
- Low BMI ($\leq$20 kg/m^2) and lower progesterone levels ($\leq$12 ng/ml)
- Primary antiphospholipid antibody syndrome
- Polycystic ovarian syndrome
- Previous spontaneous miscarriage, multiple previous elective abortions, IUCD use

Differential diagnosis
Ectopic pregnancy
Molar pregnancy
Degeneration of fibroids
Endometriosis
Genital tract infections
Subchorionic haemorrhage
Implantation bleeding
Genital tract trauma
Cervical pathologies, e.g. polyps, malignancy, excessive friability

Investigations

- Urine beta-hCG (if pregnancy not confirmed prior to ED presentation)
- Serum beta-hCG (quantitative) – can serve as baseline to correlate subsequent test values which can indicate whether the pregnancy is progressing as usual or not
- Complete blood count, clotting screen, blood grouping and typing, crossmatch if necessary, blood urea, serum creatinine – if patient is bleeding heavily or has signs of haemodynamic instability
- Vaginal examination – helpful in determining the amount of vaginal bleeding, presence of blood clots or products of conception in the cervical os or vagina
- Transvaginal ultrasound – favoured in first trimester scanning
- Vaginal swabs for culture – if evidence of infection on examination

Treatment *(Fig. 63.2)*

Supportive Measures

- Reassurance.
- Explain prognosis and treatment options.
- Supportive counselling – if needed.
- Provide patient information leaflet.

Anti-D Prophylaxis

Indications for administration of anti-D immunoglobulin in non-sensitised rhesus D-negative women are as follows:

- Any type of miscarriage ≥12 weeks of gestation.
- Before surgical evacuation of uterus, regardless of gestational age.
- Consider giving anti-D immunoglobulin prior to medical evacuation of uterus as well.

However, if the gestational age is less than 12 weeks and the symptoms have completely resolved, there is no need for immediate administration of anti-D immunoglobulin.

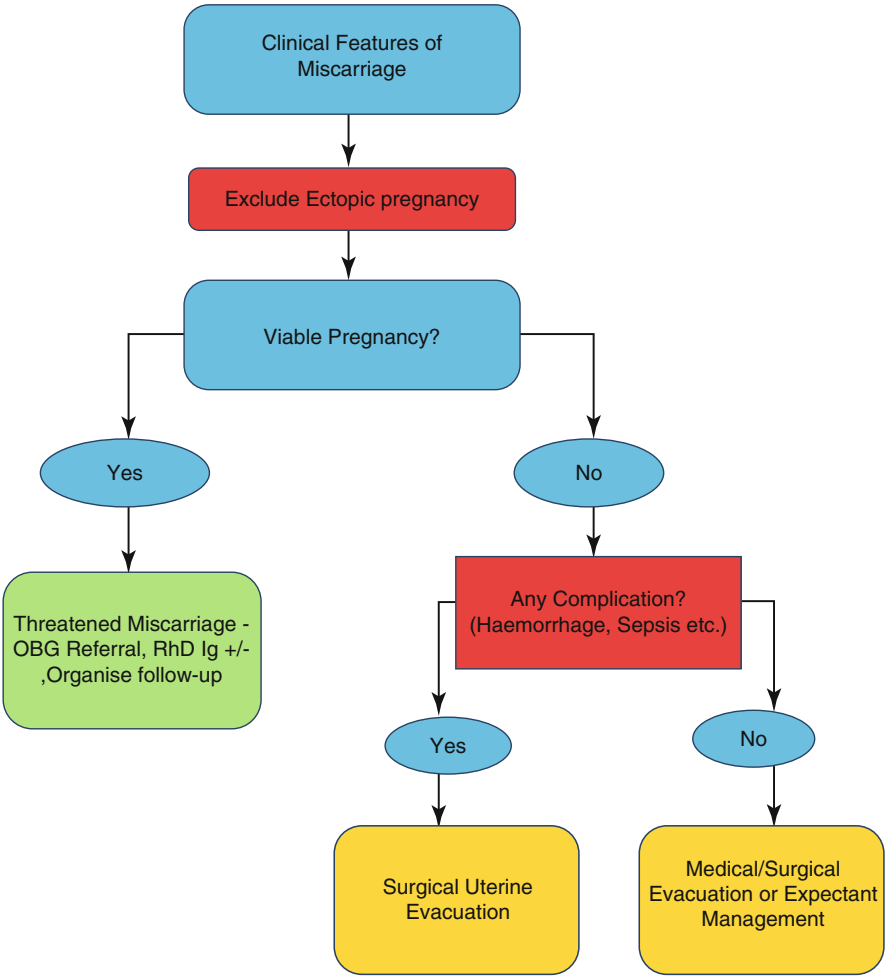

Fig. 63.2 Algorithm for ED management of suspected miscarriage

Definitive Management

Treatment modalities commonly used for expelling the retained products of conception could be surgical, medical or the expectant method.

Expectant Management

- Involves observing the patient with serial ultrasound scans and serum hCG measurements

- Supplemented with medical or surgical evacuation as needed according to patient's symptoms
- '2-week rule' has been validated and shows nearly 70 % resolution by the end of 2 weeks with the rate of unplanned dilatation and curettage being as low as 2.5 %. Incomplete miscarriage carries the best prognosis by this 'expectant' method [14].

Medical Management

- Induction of abortion is required for those presenting with incomplete and missed miscarriage. Strict patient selection criteria based on gestational age, contraindications, etc. and also access to emergency medical services should be followed.
- The commonest regime is a combination of mifepristone (progesterone receptor antagonist) and oral or vaginal misoprostol (prostaglandin analogue).
- Patients need to watch for bleeding and passing products of conception with subsequent follow-up with gynaecologist within a couple of weeks.

Surgical Management

Surgical options for uterine evacuation include:

- Dilatation and curettage (D&C) – most common procedure done to evacuate the uterus of the products of conception
- Dilatation and electric vacuum aspiration
- Manual vacuum aspiration
- Emergency cervical cerclage is indicated in case of cervical insufficiency. In a recent Indian study, mean prolongation of pregnancy was 7.4 weeks and 42 % delivered after 28 weeks [15].

Hyperemesis Gravidarum

- Defined as recurrent vomiting in pregnancy which has no other medical cause apart from pregnancy and also associated with varying combination of dehydration, ketonuria, electrolyte imbalance and weight loss (>5 % as compared to pre-pregnancy body weight) [16].
- Nausea and vomiting of pregnancy (NVP) is the milder and more common form of vomiting in pregnancy associated with good foetal outcomes.
- Hyperemesis gravidarum (HG) is quite rare (nearly 1 % of all pregnancies) when compared to NVP which has a global incidence of 70 % [17, 18].

Pathophysiology

The exact pathophysiology of hyperemesis still seems to be vague, and various factors have been associated with its occurrence. *Human chorionic gonadotropin* (hCG) is the commonest hormone pointed to as a causal factor, and studies prove that higher levels escalate the severity of HG. Greater than usual levels of *oestradiol* have been observed in HG and attributed to the effect of hCG on steroidogenesis. *Psychological* factors may also add to the others causing hyperemesis. *Helicobacter pylori* infection might also aggravate the symptoms of hyperemesis. On the whole, HG can be considered as a result of a complex interaction between biological, sociocultural and psychological influences.

Risk Factors

- Family history
- Small pre-pregnancy body habitus
- Multiple pregnancies and pregnancies with female foetus
- HG in previous pregnancy
- Foetal abnormalities like triploidy and hydrops foetalis

Clinical Features

- Nausea and vomiting – Usual onset of symptoms is by 4–6 weeks of gestation and reaches a peak between 8 and 12 weeks. Hence, other causes of vomiting should be ruled out before labelling as HG, in those patients with onset >10 weeks.
- Heartburn and acid reflux symptoms are commonly associated with HG.
- Ptyalism or excessive salivation.
- Signs of dehydration – Dry mucous membranes, sunken eyes, decreased skin turgor, tachycardia.
- Weight loss – Both due to dehydration and decreased food intake. Document the body weight on each visit to assess progress.

Differential Diagnosis

- Nausea and Vomiting of Pregnancy (NVP)
- Gastrointestinal causes: Acute gastroenteritis, peptic ulcer disease, viral hepatitis, biliary tract disease, appendicitis, intestinal obstruction, pancreatitis

- Genitourinary causes: Pyelonephritis, ovarian cyst rupture/torsion, degeneration of fibroids, molar pregnancy, renal calculi
- Endocrine: Diabetic ketoacidosis, hyperthyroid crisis, parathyroid adenoma – hypercalcaemia
- Neurologic: Intracranial mass lesions, pseudotumour cerebri
- Toxic: Ingestion of toxic substances

Investigations

- CBC (complete blood count).
- Serum electrolytes.
- Renal function tests – serum creatinine, blood urea.
- Serum amylase – mildly elevated in HG due to raised salivary secretion of amylase.
- Liver function tests – elevation of AST and ALT up to three to four times can be safely observed after ruling out other causes, e.g. viral hepatitis.
- Urine: Ketones – helpful in assessment but does not contribute to making the diagnosis; specific gravity and urinalysis.
- Thyroid function tests.
- Abdominal ultrasonography – to rule out other conditions if considering any of the differentials.

Taper the tests according to individual patient presentation.

Treatment

Non-pharmacologic Measures

Dietary modification should include a bland diet, avoiding fatty foods, strong-smelling foods and iron supplements. Taking solids and liquids separately and also eating small and frequent amounts of food during the day can be helpful. Ginger capsules, protein meals or snacks can help in controlling the symptoms of NVP.

Pharmacologic Therapy

- *Vitamin B6:* Pyridoxine is found to be effective in controlling symptoms even in severe NVP.
- *Prokinetic agents:* Metoclopramide works by increasing the gastric motility and also raising the lower oesophageal sphincter pressure. It is used widely in the treatment of NVP and HG and is safe for both mother and foetus.

- *Antihistamines:* Doxylamine, dimenhydrinate and meclizine are some of the commonly used ones in this group.
- *Phenothiazines:* Anecdotal reports of malformation are associated with first trimester exposure to phenothiazine intake [19], but majority of evidence points towards a good safety and efficacy profile.
- *Serotonin antagonists:* Ondansetron, a 5-HT3 antagonist, seems to be safe for use in HG and is commonly used due to its effectiveness in controlling vomiting. Nevertheless, it is recommended as a second-line agent, as it is linked to minor birth defects if used in the first trimester [20, 21].
- *H2 blockers/PPIs:* H2 blockers and proton pump inhibitors are quite safe to be used in pregnancy if required to control heartburn, acid reflux and peptic ulcer disease or for *H. pylori* treatment as the above can aggravate HG symptoms (Fig. 63.3).

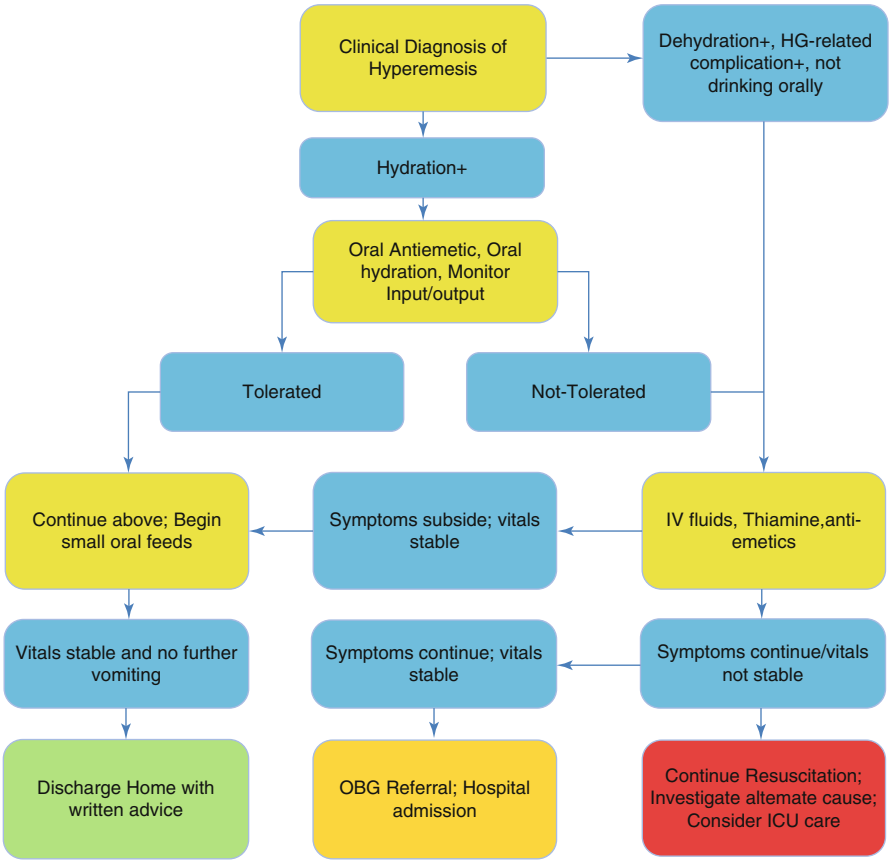

Fig. 63.3 Algorithm for management of hyperemesis gravidarum

Hydration and Nutrition Support

- *Intravenous fluids* act as volume expanders and also supply the essential electrolytes.
- *Thiamine supplementation* is recommended with severe symptoms.
- *Parenteral nutrition* is recommended for those who continue to lose weight despite adequate treatment to control emesis. Nasogastric and nasojejunal gastrostomy, feeding jejunostomy and total parenteral nutrition (TPN) are some of the options available.

Complications

Some of the common complications are described below and mentioned as either maternal or foetal:

Maternal

- Dehydration
- Dyselectrolytaemia
- Acute kidney injury
- Osmotic demyelinating syndrome
- Placental dysfunction disorders – pre-eclampsia, placental abruption
- Wernicke's encephalopathy
- Oesophageal rupture and pneumomediastinum – due to forceful vomiting
- Anxiety/depression

Foetal

- Small-for-gestational-age babies and low birth weight infants – only in severe HG as a result of poor maternal weight gain due to hyperemesis
- Vitamin K deficiency in the newborn manifesting as intracranial haemorrhage – very rare

Disposition

If symptoms resolve with treatment and patient can tolerate orally, there is no need for hospital admission. But if the initial anti-emetic treatment does not help, hospital admission is recommended.

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Chapter 64
Gynaecological Infections

Benita Florence

Key Points
- Gynaecological infections may present to the emergency department with vague non-specific lower abdominal pain.
- Inadequately managed PID can lead to significant complications.
- Genital TB should be kept in mind while dealing with women in the reproductive age group with vague complaints of pelvic pain.
- Proper follow-up is mandatory for patients being treated with STIs and on prolonged treatment regimens.

Introduction

Female reproductive tract infections may be endogenous, sexually transmitted or iatrogenic. They need to be promptly diagnosed and treated, as the sequelae may lead to significant complications. Good communication, accompanied with professional behaviour, is essential to maintain cordial patient-physician relationship. It is prudent to ensure privacy and avoid being judgmental.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_64

Pathophysiology

The female genital tract is conventionally divided into the upper (body of the uterus, fallopian tubes, ovaries and pelvic peritoneum) and lower genital tract (vulva, vagina and cervix). This chapter endeavours to describe commonly encountered gynaecological infections in the non-pregnant female presenting to the ED. It is divided into four parts.

Part 1 Upper genital tract infections which include:

(a) Acute and chronic endometritis
(b) Pelvic inflammatory disease

Part 2 Lower genital tract infections which include:

(a) Infection of the vulva
(b) Infection of the vagina

Part 3 Sexually transmitted diseases of the female genital tract
Part 4 Tuberculosis of the female genital tract

Upper Genital Tract Infections

Acute Endometritis

Acute endometritis is defined as five or more neutrophils per 400 power fields in the superficial endometrium with one or more plasma cells per 120 power fields in the endometrial stroma. It commonly occurs post-partum (puerperal endometritis), secondary to acute gonorrhoeal infection and also due to the use of intrauterine contraceptive devices (IUCDs). It is defined as five or more neutrophils per 400 power fields in the superficial endometrium with one or more plasma cells per 120 power fields in the endometrial stroma [1].

Chronic endometritis seen in the reproductive age groups is commonly due to tuberculosis, retained products of conception (post delivery or abortion) and IUCDs(usually low grade). In the postmenopausal women senile endometritis may present as postmenopausal bleeding.

Pyometra (collection of pus inside the uterine cavity) is usually seen in post-menopausal women.

Puerperal endometritis is caused by organisms from the normal vaginal flora by ascending into the uterine cavity during childbirth.

Clinical Features [2]

- Persistent fever ≥38.0 °C (100.4 F)
- Foul-smelling vaginal discharge
- Leucocytosis
- Tachycardia
- Uterine tenderness

Management

- Cultures of vaginal samples are of less importance, as there is often contamination with the local flora.
- Treatment consists of antibiotics, drainage of pus and specialist obstetric consultation.
- Patients who do not show signs of sepsis and those without risk factors (diabetes mellitus, obesity and hypertension) can be treated with oral antibiotics with regular follow-up.

  Clindamycin 300 mg three times a day for 10 days
  Or
  Doxycycline 100 mg twice a day for 10 days (avoid in breastfeeding women).
  Inpatients can be treated with ampicillin or clindamycin plus gentamicin.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) includes infection of the endometrium, fallopian tubes, ovaries and pelvic peritoneum either in isolation or in any combination, commonly referred to infections involving the female upper genital tract [3]. The disease may range from a spectrum of asymptomatic infection to severe life-threatening disease. PID is a clinical diagnosis and imaging and laboratory investigations are reserved for in patients whom the diagnosis is uncertain or in those who do not respond to treatment [4].

Pathophysiology

Exogenous pathogens acquired through sexual intercourse cause acute inflammation and colonisation of the upper genital tract with endogenous organisms. Intrauterine contraceptive device (IUCD) and operative interventions lead to the ascent of endogenous organisms.

PID is polymicrobial in nature. *C. trachomatis* and *N. gonorrhoea* are the common sexually transmitted organisms causing infection in PID. PID in a virgin female is usually tubercular in nature [5].

The risk factors for PID are listed in Table 64.1 [6] and the Gainesville clinical classification of PID in Table 64.2 [7]. This was developed to bring about a stan-

Table 64.1 Risk factors for PID

1	Sexually transmitted infections
2	Previous PID
3	Many sexual partners
4	Sexual abuse
5	Alcohol abuse
6	Recent intrauterine device insertion

Table 64.2 Gainesville clinical classification of PID

Stage	Features	Disposition
I	Acute salpingitis without peritonitis	Treated on outpatient basis
II	Acute salpingitis with peritonitis	Hospitalisation and IV antibiotics
III	PID with a pelvic mass	Hospitalisation, IV antibiotics and appropriate surgery if required
IV	Ruptured tubo-ovarian abscess	Hospitalisation, IV antibiotics and appropriate surgery if required

dardised approach to the disease progression and its management. Since it is based on clinical signs, PID can be diagnosed, the progression of the disease can be assessed and the disposition can be planned even in a place where resources are limited. Health-care workers can be trained easily to assess patients and identify the stage of the disease.

Clinical Features

- Signs and symptoms of PID can range from being subtle and silent to severe ones.
- Sexually active young women with pelvic or lower abdominal pain without any cause for another illness should be empirically treated for PID if one or more of the following criteria are present on pelvic examination [3]:
- Cervical motion tenderness (chandelier sign) or uterine tenderness or adnexal tenderness
- Additional criteria include:
  - Oral temperature >101 F (>38.3 °C)
  - Abnormal vaginal mucopurulent discharge
  - Presence of leucocytosis on saline microscopy of vaginal fluid
  - Elevated erythrocyte sedimentation rate
  - Elevated C-reactive protein
  - Laboratory investigation suggestive of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

More specific criteria include:

- Endometrial biopsy (histopathology suggestive of endometritis)
- Transvaginal sonography or magnetic resonance imaging (thickened or fluid-filled tubes)
- PID abnormalities detected on laparoscopy

Hospitalisation should be considered if the patient fits any of the below situations [3]:

- Surgical emergencies (e.g. appendicitis) cannot be excluded.
- Pregnant patient.

- Failed oral antimicrobial therapy.
- Tubo-ovarian abscess.
- Severe illness.

Differential Diagnosis

Young female patients presenting to the ED with lower abdominal pain can fall into a wide range of differential diagnosis suggestive of acute appendicitis, ectopic gestation, diverticulitis, twisted ovarian cyst, ruptured endometriotic cyst, septic abortion, etc.

Management

- The goal in treating PID is to prevent the sequelae of the disease which may lead to infertility, ectopic pregnancy or chronic pelvic pain.
- Negative endocervical screening of *N. gonorrhoeae* and *C. trachomatis* does not rule out upper reproductive tract infection; hence, regimens used to treat PID also should be effective against these organisms.

Randomised trials have demonstrated that the clinical efficacies of both oral and parental regimens are the same. Patients on parental regimens, showing improvement within 24–48 h of treatment, can be discharged on oral medications [8–10].

Inpatient (Admission for Minimum 48 h)

Cefoxitin 2 g IV six hourly
Plus
Doxycycline 100 mg IV and then 100 mg orally or IV 12 hourly followed by 100 mg orally 12 hourly as outpatient for 14 days
Doxycycline IV discontinued for the entire hospital stay as there was high incidence of phlebitis

Outpatient

Cefoxitin 2 g IM
Plus
Probenecid 1 g orally
Plus
Doxycycline 100 mg orally 12 hourly for 14 days

Oral Regimens [3, 8, 10]

Ceftriaxone 250 mg IM single dose
Plus
Doxycycline 100 mg orally 12 hourly for 2 weeks
With/without
Metronidazole 500 mg orally 12 hourly for 2 weeks

Follow-Up

Patients should show improvement in clinical features within 3 days of treatment.

Those not improving require hospitalisation, further additional diagnostic tests and surgical intervention [3].

Sexual Partner Treatment

Sexual partners of women diagnosed with PID, who have had intercourse 60 days preceding the onset of symptoms, should be treated empirically for gonococcal and chlamydial infection.

Abstinence from sexual intercourse should be advised for both the partners until treatment course is complete and they are asymptomatic [3].

Complications

Sequelae of PID may lead to [11]:
Fitz-Hugh-Curtis syndrome:

- It is common in women of childbearing age presenting with complaints of right upper quadrant abdominal pain.
- Perihepatic inflammation with pelvic inflammation is characteristic of this syndrome.
- Diagnosis is challenging, though symptoms of PID are usually present. Pathogenesis is not very well understood.
- It may result from direct, haematogenous spread and lymphatic or hyperimmune response to the organism C. *trachomatis*.
- Diagnosis is made by clinically eliminating other causes of right upper quadrant as this may mimic cholecystitis, pyelonephritis, hepatitis, etc.
- Chest X-ray should be done to rule out pneumonia and air under the diaphragm; ultrasound also is useful to rule out other causes.
- Patients are treated with the standard PID regimens and show improvement in 24–48 h.

Prevention

Sexually active women should be screened and treated for chlamydia, which reduces their risk for PID.

Lower Genital Tract Infections

Bartholin Cyst and Abscess

Bartholin's glands are found posterolaterally on either side of the vaginal opening.

The glands and ducts become palpable when infected. Patients present to the ED with complaints of a painless lump at the lateral introitus.

A Bartholin cyst on secondary infection becomes a Bartholin abscess, which is painful.

The causative organisms include anaerobic and aerobic bacteria of the normal vaginal flora. It may also be due to sexually transmitted organisms like *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or other gram-negative organisms.

Examination may reveal a swollen and tender labium.

Treatment usually requires an incision and drainage, with sitz baths and follow-up for wound re-examination. Pus culture is recommended for testing STDs and if required to be started on antibiotics covering *Chlamydia* and *N. gonorrhoea* [12].

Vulval Pain Syndrome

The term vulvodynia or vulval pain syndrome was used to describe women with chronic vulval discomfort. Some of the causes are:

Some of the causes are: Skin infections (Human papilloma virus, fungal infections, herpes), urinary oxalate excretion, autoimmune disease, iatrogenic (topical agents, deodorants), psychological and hormonal (low oestrogen and oral contraceptives). The treatment depends on the cause identified.

Bacterial Vaginosis (BV)

The normal hydrogen peroxide-producing *Lactobacillus sp*. in the vagina is replaced with anaerobic bacteria and fastidious or uncultivated anaerobes resulting in a polymicrobial syndrome [13].

Amsel's diagnostic criteria [14] are clinical criteria used for diagnosing BV, when gram stain is unavailable. Three of the following signs or symptoms are suggestive of the disease:

1. Thin white discharge that coats the vaginal walls
2. Clue cells present on microscopic examination

3. pH of vaginal fluid >4.5
4. The whiff test (fishy odour of vaginal discharge before or after adding 10 % KOH)

Gram stain is the gold standard test in diagnosing BV.

Treatment

Metronidazole 500 mg orally twice a day for 7 days
Or
Clindamycin cream 2 % intravaginally at bedtime for 7 days
Other causes of vaginal infection may be due to gonococcal, trichomonal, monilial, chlamydial, etc.

Sexually Transmitted Diseases of the Female Genital Tract

A variety of clinical syndromes caused by various organisms that are transmitted through sexual activity describe the term sexually transmitted diseases (STDs). These include gonorrhoea, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, trichomoniasis, candidiasis, chlamydia, herpes genitalis, molluscum contagiosum, AIDS, genital warts, etc.

These diseases were previously termed as 'venereal diseases', later on termed as 'sexually transmitted diseases' (STDs) and more recently termed as 'sexually transmitted infections' (STIs). The terms STI and STD are used synonymously [15, 16].

Sexually transmitted diseases have caused a worldwide problem in the health industry with the increase in promiscuity and sex partners. The epidemiology varies from country to country and from different regions within countries.

Gonorrhoea

Gonorrhoea was described by Hippocrates as 'strangury' and it was Galen who gave it its present name. Male to female transmission rate is 75 % and female to male is 25 % with one sexual intercourse [17]. This is caused by *Neisseria gonorrhoea*, a gram-negative diplococcus found intracellularly. Incubation period varies from 2 to 10 days.

Pathogenesis

Squamous epithelium in an adult female is resistant to gonococcal infection. Columnar epithelium is susceptible for the organism to penetrate, and it affects the Skene and Bartholin glands, urethra, cervix and fallopian tubes and rectum in some cases. It spreads in a piggyback form attached to sperms.

Signs and Symptoms

Fifty percent of the affected women may not show any signs of local infection.

Urethritis, skenitis, bartholinitis, vulvitis, cystitis, proctitis, vaginitis, cervicitis and pharyngitis (oral sex) are the common localised presenting signs.

These infections if left untreated may lead to salpingitis with tubo-ovarian abscess, hydrosalpinx, pyosalpinx and pelvic abscess and may be a cause for infertility.

Women with chronic infection may have lower abdominal pain, low backache and menstrual irregularities.

The disease may spread via direct, lymphatic or haematogenous route causing gonococcal arthritis, bacterial endocarditis, perihepatitis (Fitz-Hugh-Curtis syndrome), meningitis, pericarditis, septicaemia and ophthalmitis.

Common risk factors are listed in Table 64.3.

Investigations

Gram stain of cervical discharge showing polymorphonuclear leucocytes with intracellular gram-negative diplococcic may be considered as a positive test for the infection.

NAAT (nucleic acid amplification test), cultures and nucleic hybridization tests can be used for the detection of N. *gonorrhoea* [18].

Women detected with gonorrhoea should be screened for other STDs – chlamydia, syphilis and HIV.

Treatment [3]

Quinolones are no longer used in the treatment of gonorrhoea due to development of resistance. *Chlamydia trachomatis* may be a coinfection with *N. gonorrhoea*; hence, it is advised to treat patients with a regimen that treats both the infections.

Uncomplicated Gonococcal Infection

Ceftriaxone 250 mg IM single dose

Or

Cefixime 400 mg orally single dose

Table 64.3 Risk factors for gonorrhoea

1	Age less than 25 years
2	History of STIs
3	Multiple sex partners
4	Homosexuals
5	Drug abuse

Or
Cephalosporin single-dose injection
Plus
Azithromycin 1 g orally single dose
Or
Doxycycline 100 mg orally twice daily for 7 days

Tuberculosis of the Female Genital Tract

Pulmonary tuberculosis being the primary and most common presentation, extra-pulmonary causes also form a significant number. Genital tract TB is difficult to diagnose as it is either asymptomatic or has different presentations. It affects the fallopian tubes, endometrium, ovary, cervix, vagina and vulva.

Clinical Symptoms

Most of them may be asymptomatic:

- Infertility
- Pelvic pain
- Menstrual disorders

Other Signs

Patient may look stable, afebrile and asymptomatic. In peritoneal TB, the abdomen may be doughy with straw-coloured tubercular ascites. 'Frozen pelvis', a condition where the pelvic masses are matted and fixed to the pelvis, may be noticed. Pelvic inflammatory masses in virgin girls are usually tuberculous.

Diagnosis and Treatment

A high erythrocyte sedimentation rate and positive Mantoux test are non-conclusive. Chest X-ray may be normal. Pelvic ultrasound may be helpful.
Features suggestive of tubercular salpingitis on hysterosalpingogram are [19]:

1. 'Lead pipe appearance' – rigid, non-peristaltic tube
2. Beading and variation in filling density
3. Calcification of tube
4. Lymphatic intravasation of the dye
5. Cornual block
6. Tobacco pouch

Hysterosalpingography is contraindicated in a proven case of genital TB.

In clinically suspected cases, a positive PCR (polymerase chain reaction) in an infertile woman should be suspected as genital TB and treated accordingly [20].

Imaging modalities and PCR may help us in diagnosing and treating the disease. Early treatment with antitubercular drugs and appropriate surgery remain the treatment for genital TB.

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Chapter 65
Third Trimester Emergencies

Suresh S. David and Harshil Mehta

Key Points
- The third trimester is the period of mainly "big 4" – conditions which result in maternal deaths – PIH, eclampsia, placenta praevia and abruptio placenta.
- Vaginal examination is contraindicated in antepartum haemorrhage.
- Severe PIH and eclampsia are best treated with injection magnesium sulphate.
- Early delivery is often the corrective intervention.

Hypertension in Pregnancy

- Hypertension is one of the most common presentations in pregnancy and contributes largely to maternal and foetal health.
- It is seen in 6–8 % of pregnancies [1].
- Hypertension in pregnancy is divided into several categories:
  - Gestational hypertension: Hypertension (>140/90 mmHg) without proteinuria developing after 20 weeks of gestation till puerperium in a previously normotensive woman.

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_65

- Chronic hypertension: Hypertension that is present before pregnancy or 20 weeks and persists after 6 weeks postpartum.
- Pregnancy-aggravated hypertension: Chronic hypertension with new-onset proteinuria.
- Pre-eclampsia.
- Eclampsia.

Pregnancy-Induced Hypertension (PIH)

- *Definition*:
  - PIH is a multisystem disorder of unknown aetiology characterized by development of hypertension to the extent of 140/90 mmHg or more on at least two occasions at least 6 h apart with proteinuria (more than 300 mg/day) after 20th week.
  - It can be noticed up to 5–6 weeks postpartum.
  - It is known as pre-eclampsia or toxaemia.
  - If a baseline BP is available, then rise of at least 30 mmHg in systolic pressure and 15 mmHg in diastolic pressure, along with proteinuria (more than 300 mg/day), defines PIH.
- *Incidence*: Around 3.2 % of live births globally [2].
- *Risk factors* [3]:
  - Primigravida
  - Previous hypertension
  - Diabetes/chronic hypertension/renal disease
  - Twin pregnancy
  - Polyhydramnios
  - Anti-phospholipid antibody syndrome
- *Pathophysiology* [4, 5]:
  - Abnormal placental perfusion and placental syncytiotrophoblast stress have demonstrated evidences that suggest its contribution in pathogenesis.
  - The histologic feature of pre-eclampsia is acute atherosis of decidual artery. This leads to ischaemia and infarction of the placenta that causes development of free radicals and oxidative stress [6].
- *Clinical types*:
  - Mild: SBP <160 mmHg and DBP <110 mmHg without any signs or symptoms of severe pre-eclampsia
  - Severe [7]:

    SBP >160 mmHg, DBP >110 mmHg
    Proteinuria ≥5 g/day on two random samples collected at least 4 h apart

Oliguria <500 ml/day
Cerebral or visual disturbances
Pulmonary oedema
Upper abdominal pain
Abnormal liver functions
Thrombocytopenia
Foetal growth impairment

- *Clinical features*:
  - Symptoms: pedal oedema, pedal swelling, headache, disturbed sleep, decreased urinary output, epigastric pain, nausea, vomiting, blurring of vision, dimness and scotoma
  - Signs:

    Abnormal weight gain: 2 kg/week in later part of pregnancy (normal: 0.5 kg/week)
    Increased blood pressure
    Oedema: facial and pedal oedema in morning time, not relieved by rest
    Pulmonary oedema
    Brisk deep tendon reflex

- *Investigations*:
  - Laboratory:
    - Coagulation profile: thrombocytopenia, raised plasma fibrinogen levels
    - Urine tests: proteinuria with few red cells
    - Altered renal functions: *raised serum uric acid level* [8] (biochemical marker of pre-eclampsia), serum creatinine and BUN levels
    - Changes in liver functions: raised AST, ALT and LDH levels
  - Ophthalmic examination: papilloedema, haemorrhage and constriction of arterioles
  - Ultrasonography: Accurate determination of gestational age

- *Treatment*:
  - Initial documentation of blood pressure, reflexes and weight are helpful to monitor course of illness.
  - Patients with mild illness can be discharged after obstetrician consultation with the following general instructions:

    Bed rest, high-protein diet
    Follow-up instructions (red signs: headache, scintillating scotoma, abdominal pain, vaginal bleeding, decreased foetal movement)

  - Hospitalization is required for sustained high blood pressure (>140/90 mmHg) and severe pre-eclampsia with end-organ failure.
  - Patients with fulminant hypertension (BP >160/110 mmHg) with signs of severe pre-eclampsia should be treated as eclampsia to prevent seizures.

Table 65.1 Antihypertensive medicines

Drug	Mechanism of action	Onset of action	Dose
Hydralazine	Arterial vasodilator	10–20 min	5 mg i.v., repeat at 20 min, max dose 20 mg
Labetolol	Selective alpha and non-selective beta-blocker	5 min	10–20 mg i.v., repeat at 10 min, infusion at 1–2 mg/min, max dose 300 mg/day
Nifedipine	Calcium channel blocker		10 mg oral, repeat at 30 min
Sodium nitroprusside	Vasodilator	Less than 1 min	0.25 μg/kg/min to max 5 μg/kg/min

– Antihypertensive:

  Treatment goal is a diastolic pressure of 90–105 mmHg.
  IV drugs (Table 65.1) are indicated in hypertensive crisis (BP >160/110 mmHg or MAP >125 mmHg).
  Angiotensin-converting enzyme inhibitors are contraindicated in the second and third trimester [10].

– Magnesium sulphate:

  For seizure prophylaxis with same dose as in eclampsia

– Diuretics: Furosemide (IV/Oral) can be given with cautions in mild pre-eclampsia with sign of fluid overload. Do not give before delivery in severe pre-eclampsia and with signs of maternal fluid or foetal growth restriction [9].
– Foetal Monitoring
– Delivery: Indications

  Severe pre-eclampsia (BP > 160/100) even after medical management
  Oliguria (<400 ml/day)
  Thrombocytopenia (<50,000/mm^3)
  Deteriorating renal functions
  Raised liver enzymes
  Worsening of symptoms
  Oligohydramnios

Eclampsia

- *Definition*: New onset of generalized tonic clonic movements and unexplained coma during pregnancy or postpartum in a female with features of pre-eclampsia [11]
- *Incidence*: 1.4 % of all deliveries globally [12]
- *Risk factors*: Same as pre-eclampsia

- *Clinical features*:
  - Premonitory symptoms of severe pre-eclampsia.
  - The most common symptoms that precede seizure are neurological (headache and/or visual disturbance) [13].
  - Eclamptic convulsions: Generalized tonic-clonic fits with unconsciousness. Seizures may be divided into two phases:

    Phase 1: Lasts for 15–20 s, starts with facial twitching; body becomes rigid; generalized muscular contraction

    Phase 2: Lasts for 60 s. Starts with the jaw, spreading to muscles of face and eyelids. Body involves later with alternating contraction and relaxation.

- *Differential diagnosis*:
  - Hypoglycaemia
  - Epilepsy
  - Encephalitis/meningitis
  - Cerebral thrombosis/cerebral vascular accident
  - Poisoning
  - Intracranial tumours
  - Hypertensive encephalopathy
  - Hysteria

- *Diagnosis*:
  - Presence of seizures, proteinuria and hypertension (triad).
  - Laboratory investigations are same as pre-eclampsia.
  - Ultrasonography: to rule out molar pregnancy and/or hydropic or cystic degeneration of the placenta.
  - CT scan/MRI – to rule out any intracranial structural pathology.
  - Eclampsia should be the first diagnosis unless proven otherwise if seizures develop in the first half of pregnancy with hypertension and proteinuria [11].

- *Treatment*:

  Prevention of maternal injury and her cardiovascular and respiratory stability should be the first priority.
  - Seizure management:

    General measures:

    - Place patient in lateral decubitus position.
    - Ensure airway protection. Clean the mouth, nose and throat regularly to remove secretions.
    - Administer oxygen – 8–10 L/min.
    - Ventilator support if required.
    - Intensive monitoring: pulse, BP, respiratory rate, SpO_2, urine output.
    - Prevention of secondary injuries.
    - IV fluids at 80 ml/h.

- Organize investigations.
- Prevention of complications.
- Rule out other causes if possible.

Anticonvulsants and sedative agents:

- Inject magnesium sulphate [14] (drug of choice) 4–6 g i.v. over 15–20 min and then 1–2 g/h i.v. infusion for 24 h.
- Insert a Foley catheter to monitor urine output hourly as well as BP, respiratory rate and presence of knee jerk (see below).
- Continue treatment with magnesium as long as the following criteria are met:
  - Patellar reflexes are present.
  - Urine output is at least 25 ml/h.
  - Respiratory rate is at least 12/min.
- If patellar reflexes disappear, respiratory rate is <12 per minute or urine output is <30 ml/h, then patient should be treated for magnesium toxicity with calcium gluconate in a dose of 10 ml of a 10 % solution, given over 3 min.
- Thiopentone sodium 0.5 g dissolved in 5 % dextrose IV for status eclampticus.
- Continue anticonvulsant therapy, 48 h after delivery.
  - Antihypertensives (Table 65.1)
  - Perform a computed tomography scan of head if consciousness is decreased or seizures persist, lateralizing signs are present or there are other concerns.
  - Delivery: Caesarean section is preferred (definitive treatment for eclampsia).

Antepartum Haemorrhage

- Bleeding from or into the genital tract after 24 weeks of pregnancy and prior to the birth of the baby is considered as antepartum haemorrhage (APH) [15].
- Two common conditions:
  - Placenta praevia (until proven otherwise)
  - Abruptio placenta
- It complicates 3–5 % of pregnancies and is a leading cause of perinatal and maternal mortality worldwide [16].
- Cannot be reliably predicted.

- Domestic violence and trauma should always be suspected as an aetiology of APH.
- Per vaginal digital examination should not be done in patients who present with bleeding in the second half of pregnancy.
- As blood loss is often underestimated, clinical signs of shock should always be correlated. Presence of foetal compromise is a helpful indicator of volume depletion [17].
- Decision over aggressive management requires proper history, thorough clinical examination of mother, estimation of amount of vaginal bleeding and foetal well-being.

Placenta Praevia

- *Introduction*:
  - It is defined as the placenta is being implanted partially or completely over the lower uterine segment [18].
  - Dilatation of the lower uterine segment due to foetal growth causes premature separation of the placenta and subsequent bleeding.
- *Incidence*: 0.4–0.5 % of all deliveries [19]
- *Clinical types*: four types of placenta praevia depending on the degree of extension of placenta to the lower segment [18]
  - Low lying – In lower segment, not touching internal os
  - Marginal – Touching the margin of internal os, not covering it
  - Partial complete – Covering some part of internal os
  - Central (total) – Covering internal os completely
- *Risk factors* [20]:
  - Advanced maternal age (>40 years)
  - Illicit drug use
  - Previous caesarean section
  - Multiparity
  - Previous placenta praevia
  - Previous termination of pregnancy
  - Smoking
  - Assisted conception
- *Clinical features*:
  - Vaginal bleeding: Sudden, painless, causeless and recurrent
  - No uterine contractions
  - Symptoms frequently preceded by coitus

- *Signs*:
  - Anaemia
  - Abdominal examination:

    Size of uterus is proportionate to gestational age.
    Uterus feels relaxed and soft.
    Foetal parts can be felt easily.
    Malpresentation like breech or diagonal is observed.
    Foetal sounds can be present.

  - Digital examination (vaginal and rectal) is contraindicated in APH.
  - Signs of shock according to amount of blood loss.
- *Diagnosis*:
  - Ultrasonography: Transvaginal sonography is gold standard. It confirms placement of placenta as well as foetal well-being [21].
  - Laboratory investigations:

    Haemoglobin, coagulation profile, blood group and cross-match, Rh compatibility

- *Treatment*:
  - Always anticipate massive bleeding and preterm delivery.
  - Expectant management at home is considered in patients without active bleeding and foetal reassurance is noted. However, if patients develop active bleeding and contractions with foetal compromise, they should be admitted.
  - General measures:

    Bed rest
    Estimate the amount of blood loss
    Gentle abdominal palpation
    Inspection of vulva for active bleeding

  - Haemodynamic management:

    Two large-bore IV lines.
    Blood sample for blood group and cross match and routine investigations (grouping, cross matching and routine).
    Infusion of normal saline.
    Consider blood transfusion if needed (Hb <8 g/dl).

  - Definite management:

    Obstetrician involvement for urgent delivery.
    Consider admission for observation if bleeding subsides and gestation <34 weeks.

– Hysterectomy:

Severe case of placenta praevia and placenta accreta, which is co-existent with placenta praevia in significant proportion, warrants obstetric hysterectomy occasionally [22].

Abruption Placenta

- *Introduction*:
  - This term refers to the bleeding at the decidual-placental interface that causes partial or total placental detachment prior to delivery of the foetus.
  - It must be considered whenever bleeding is encountered in the second half of pregnancy [23].
  - More common in older women with preceding pre-eclampsia or chronic glomerulonephritis.
  - Perinatal mortality is directly proportional to the percentage of separation.
- *Incidence*: 0.4–1 % of total deliveries [24]
- *Clinical varieties*: three varieties
  - Revealed – blood comes out from the separation site
  - Concealed – blood gets collected between the placenta and membrane
  - Mixed – combination of the above mentioned types
- *Risk factors*:
  - Multigravida
  - Advanced age
  - Pre-eclampsia and chronic hypertension
  - Thrombophilia
  - Maternal trauma
  - Poor socio economic class and malnutrition
  - Smoking/tobacco use
  - Previous abruption placenta
- *Clinical features*:
  - Symptoms:

    Vaginal bleeding: painful (due to uterine contractions, tetany, pre-eclampsia, trauma), dark coloured, continuous revealed/concealed/mixed
    Uterine contractions present
    Decreased foetal movement

  - Signs:

    Anaemia, sometimes out of proportion of bleeding
    Signs of pre-eclampsia may be present

Abdominal examination:

- The uterus may be disproportionately enlarged.
- Board-like rigidity of the uterus.
- Tender uterus.
- Foetal parts are rarely palpable.
- Foetal heart sounds may be absent.

- *Classification*: It is based on extent and location of separation.
  - Grade 0: asymptomatic; retrospective diagnosis after delivery
  - Grade 1: mild features with unaffected foetus
  - Grade 2: moderate clinical symptoms with foetal distress and DIC
  - Grade 3: severe symptoms with foetal death and multiple complications
- *Investigations*:
  - It is a diagnosis of exclusion. Other causes of APH need to be ruled out in order to diagnose abruption [25].
  - Ultrasonography: It is not diagnostic for abruption. Its main use is to rule out other causes of bleeding, e.g. placenta praevia [26].
  - Laboratory investigations: haemoglobin, coagulation profile, renal function test, Rh compatibility, Kleihauer-Betke test.
- *Management*:
  - General measures:

    Complete bed rest
    Continuous vital checks: pulse, blood pressure, respiratory rate, saturation of oxygen, urine output and abdominal girth every half hourly
    Oxygen at 8–10 l/min
    Monitoring of amount of vaginal bleeding
    Monitoring of foetal heart rate
  - Haemodynamic measurement:

    Two large-bore IV lines
    Blood samples for group and cross match and routine investigations
    Infusion of IV crystalloids
    Blood transfusion as required
  - Pain management

    IV opiate is preferable.
  - Definitive management:

    If the baby is alive, then plan for an early caesarean section.
    With obstetric consultation, the membranes should be ruptured to reduce intra-uterine pressure and the risk of further separation.

Amniotomy is advisable to decrease extravasation of blood into myometrium and entry of trophoblastic substance into the circulation [27].

If the baby has died and if contractions have not already started, oxytocin stimulation can be commenced.

The primary objective is to complete foetal delivery within 6 h.

– Couvelaire uterus, also known as uteroplacental apoplexy, is a life-threatening condition in which abruptio placentae results in bleeding into the uterine myometrium. This is a life-threatening obstetric emergency requiring urgent foetal delivery (Table 65.2).

Table 65.2 Third trimester emergencies in a nut shell

	Pre-eclampsia	Eclampsia	Placenta praevia	Abruptio placenta
Definition	After 20 weeks of pregnancy, BP >140/90 mmHg on 2 different occasions	Features of pre-eclampsia with new-onset GTCS and altered sensorium	Placenta is implanted over lower uterine segment	Partial or total detachment of placenta before delivery of the foetus
Incidence	3.3 % of total live births	3–4 % of total live births	0.4–0.5 % of all deliveries	0.4–1 % of all deliveries
Classification	Mild Severe		Low lying Marginal Partial central Central (total)	Revealed Concealed Mixed
Risk factors	Primigravida, previous HT, DM, twins, polyhydramnios	Ill treated pre-eclampsia	Previous placenta praevia/abruption placenta, multiparity, multiple pregnancy, advanced age	Multigravida, advanced age, malnutrition, smoking
Symptoms	Pedal oedema, headache, epigastric pain, blurring of vision, scotoma	GTCS with symptoms of pre-eclampsia	Painless vaginal bleeding, bright red coloured	Painful vaginal bleeding, dark coloured
Signs	BP: >140/90 mmHg, weight gain, pulmonary oedema , brisk tendon reflex	Post-ictal confusion, tongue bite +,	Pallor Uterus: relaxed, proportionate height, palpable foetal parts, malpresentation, FHS +	Pallor Uterus: tender, disproportionately enlarged rigid Foetal parts impalpable, FHS absent
Laboratory	RFT (serum uric acid levels), LFT, haemoglobin, coagulation profile, urine routine		Haemoglobin, coagulation profile	Haemoglobin, coagulation profile, RFT
Radiology	Ultrasonography		Ultrasonography	Ultrasonography

BP blood pressure, *DM* diabetes mellitus, *FHS* foetal heart sound, *GTCS* generalized tonic clonic seizures, *HT* hypertension, *LFT* liver function test, *RFT* renal function test

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6

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