VOLUME 2
SEARO IMAI
District Clinician Manual:

Hospital Care for Adolescents and Adults

GUIDELINES FOR THE MANAGEMENT OF COMMON ILLNESSES AND NOTIFIABLE DISEASES

Integrated Management of Adolescent and Adult Illness (IMAI)
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9.1 Referral and transport of the severely ill patient

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Good clinical care is a core component of effective public health, and is essential to achieving universal health coverage, one of the Region’s eight Flagship Priorities. This Manual is written for clinicians who diagnose and manage sick adolescents and adults at district hospitals that do not have an ICU. Its target audience includes the full range of clinicians working at the district hospital level – medical officers, general practitioners and other doctors; health assistants; and senior clinical nurses working in the emergency department and adult wards.

Simplification and standardization of case detection and first-line treatments support decentralization and expand access to care. Within a district network, the district clinician receives referred patients who have not responded to first-line treatment or who require emergency treatment and hospitalization for severe illness. The ability to provide effective emergency care for severely ill patients, establish a likely differential diagnosis, promptly report notifiable diseases, provide appropriate and effective clinical management, and then monitor the patient’s response to treatment, can contribute substantially to the health of the community.

Work on adapting this Manual to the epidemiology of communicable diseases in the WHO South-East Asia (SEA) Region, emphasizing severe acute respiratory infections (SARIs) and other diseases with epidemic potential such as Nipah virus disease, had begun at the beginning of 2020, when the COVID-19 pandemic struck. Management of COVID-19 as well as other SARIs in a district hospital without an ICU is based on the current WHO COVID-19 clinical and infection prevention and control (IPC) guidelines and has required many iterative changes over the past year. This edition is current with WHO’s COVID-19 Clinical management: living guidance (25 January 2021).

The Manual aims to provide an effective clinical approach and protocols for the management of common and serious or potentially life-threatening conditions at district hospitals. It supports clinical reasoning, with an emphasis on communicable diseases through an integrated approach to the patient. The Manual is a regional adaptation and updates portions of the generic WHO IMAI district clinician manual published in 2011. All sections of the Manual have been updated with new, relevant WHO evidence-based guidelines. The Manual supports the clinician’s role in communicable disease surveillance and response, emphasizing recognition and immediate reporting of priority diseases with epidemic potential. This can contribute to early detection and timely reporting and correct IPC
precautions to prevent amplification of infectious diseases with epidemic potential within the hospital.

Most emphasis to date in clinical training and manuals has been on children, pregnant women, reproductive health, and leading killers across age groups, such as HIV and tuberculosis (TB), which are supported by strong international and national programmes. It is important to also improve the broader quality of adult clinical care by addressing, in an integrated fashion, other leading killers of adults such as sepsis and severe pneumonia, as well as the management of the common illnesses of adolescents and adults. This integrated clinical Manual supports the implementation of the clinical components of multiple disease-control strategies.

The Manual can serve as an effective tool to manage illness promptly when the adult patient reaches the emergency department of the district hospital and is managed in the ward if severely ill or receives appropriate pre-referral treatment before transfer to an ICU. It complements the WHO *Pocket Book of Hospital Care for Children*¹ and the SEA Regional Office’s manual for the management of pregnancy.² The Manual also addresses the management of important severe infectious diseases in pregnant women, especially maternal sepsis, pneumonia and malaria. Severe disease conditions related to pregnancy are included in the Quick Check emergency algorithm and differential diagnoses tables. The detailed clinical care instructions are relevant to providing the skilled care required to manage critical conditions such as sepsis and severe pneumonia during pregnancy. The Manual is applicable to most areas of the SEA Region and may be adapted by countries to suit their specific circumstances.

Dr Poonam Khetrapal Singh  
Regional Director  
WHO South-East Asia Region

² Pocket Book of Hospital Care for Mothers. New Delhi: WHO Regional Office for South-East Asia; 2017.
Preface

This is an integrated clinical manual for managing adolescents and adults in hospitals at the district level, which do not have an intensive care unit (ICU). It has been adapted to the epidemiology and health system of the WHO South-East Asia (SEA) Region.

The major sections in this Manual include the following:

- Quick-check algorithm and emergency treatment guidelines, including the management of non-severe COVID-19 (Section 2).
- Management of severely ill patients with shock at the district hospital (without an ICU). These would include severe respiratory distress; chest pain; altered consciousness; seizures; intoxication, overdose or withdrawal from opioids, amphetamines or alcohol; poisoning; snake-bites; and burns (Section 3).
- Infection prevention and control for the clinician (Section 6).
- Clinical procedures, both diagnostic and therapeutic, commonly used in emergency and acute care and the steps necessary for infection control (Section 7).
- Summaries of the management of key acute and subacute illnesses by syndrome (Sections 8 and 10).
- The clinician’s role in disease surveillance at the health facility, priority diseases for immediate notification, and standard case definitions (Section 9). Timely recognition and reporting of notifiable diseases is also supported by their inclusion throughout the syndromic sections of the manual and in all relevant differential diagnoses tables, marked with an icon (small trumpet).
- Clinical summaries of the management of common diseases that affect multiple systems of the body with a focus on communicable diseases, including their clinical diagnoses, use of laboratory investigations and treatment, adapted to diseases in the SEA Region. Nipah virus disease, chikungunya, COVID-19 and Lyme disease have been added (Section 11).
- Palliative care – symptom management and end-of-life care (Section 12).

In adapting each section of the Manual, revisions have been based on all new, relevant WHO evidence-based guidelines; these as well as the original WHO and other sources for the 2011 edition are referenced as footnotes in each section.

This Manual is used as an integral component and resource during “Quick Check+” training using the SEA Regional Office Integrated Management of Adolescent and Adult Illness (IMAI) and severe acute respiratory infection (SARI) tools. The Manual supports ongoing learning after training through mentoring and practical use in providing clinical care.

This Manual is also the basis for the Regional Office IMAI SARI training tools which cover emergency triage, assessment and emergency treatments; management of severely ill
patients with respiratory distress and shock; and the clinician’s role in disease surveillance and response. The latter includes infection prevention and control for the clinician, including standard and transmission-based precautions by suspected disease.

The SEA Region’s adaptation process has focused on communicable diseases while presenting them in the context of the full differential diagnoses for key signs and symptoms. These include the full range of possible communicable and noncommunicable diseases.

Although this Manual does not include the clinical management of HIV, TB, sexually transmitted illnesses, reproductive health or pregnancy, and the long-term care of noncommunicable diseases and alcohol and other substance use disorders (which are covered in other SEA Region publications and guidelines), it does address these conditions in the differential diagnoses tables when they present acutely, alongside other causes. The emergency management of intoxication and acute withdrawal and ongoing ward management of the acute clinical conditions caused by alcohol and other substance use disorders are included but not long-term management of substance use disorders, which can be found in mental health Gap Action Programme (mhGAP) materials. Future editions and country adaptations could incorporate the chronic management of noncommunicable diseases.

Although not aimed at ICU intensivists, internists or other specialists, the operational guidelines for district-level management of sepsis, severe respiratory distress and other severe diseases as well as other common adult diseases are based on WHO current guidelines for critical care relevant to a district hospital. These have been simplified and operationalized for use at a district hospital within the realm of available resources. Even when transfer or referral to an ICU is feasible, it is important to support district hospital clinical teams to provide effective initial management of patients presenting with severe respiratory distress or septic shock or other severe diseases. These are life-saving interventions that must be provided within the first hour or at the earliest after arrival at the hospital.
Acknowledgements

This adaptation by the WHO Regional Office for South-East Asia (SERO) of this manual was prepared by the Infectious Hazards Management (IHM) unit of the Health Emergencies Department of the WHO Regional Office, through a contract with the IMAI-IMCI Alliance. The SEARO adaptation was further modified to support practical management of COVID-19 patients, based on the WHO COVID-19 interim guidelines.

The contributions of the following are gratefully acknowledged:

WHO SEARO: Regional Adviser (Malaria) and the team of the Department of Communicable Disease (CDS); Regional Adviser (Vector-Borne and Neglected Tropical Diseases) and the team (CDS); Coordinator (Health through the life course) and the Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCAH) team; and the Regional Advisers for Occupational and Environmental Health and Mental Health in the Department of Health Promotion and Noncommunicable Diseases (HPN).

WHO headquarters: Teams from the Universal Health Coverage/Communicable Diseases and Noncommunicable Diseases departments and the WHO Global Malaria Programme

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Special thanks to Robert Thatcher for design and illustrations and to Sarah Brandt for her review and formatting of the materials. The Reports and Documentation team at the WHO Regional Office is also acknowledged for its editorial review of the compendiums. The contribution of Drs Bhagteshwar Singh and Ravikar Ralph is also acknowledged.

The SEARO IMAI District Clinician Manual is a regional adaptation and updates portions of the generic WHO IMAI District Clinician Manual published in 2011 (see this version for acknowledgements of the original writers and reviewers). Based on the guidelines in this Manual, the original development of the Quick Check+ training curriculum by the IMAI-IMCI Alliance with WHO Pandemic and Epidemic Diseases (PED) was supported by funding from the Government of the United States of America (DOD DTRA) and the Government of Japan through grants to WHO/HSE/PED (project manager Nahoko Shindo), with the support of the WHO Regional Office for Africa and the WHO country offices in affected countries. This SEARO version of the Manual and Quick Check+ training curriculum builds on the Nepal adaptations in 2019 that were supported by the Nepal WHO Country Office, Nepal Ministry of Health, and Patan Academy of Health Sciences as well as developmental work in Uganda (Walimu, MoH) and Sierra Leone (MoHS).

This activity was executed with funding support provided through the cooperative agreement between the WHO Regional Office for South-East Asia, New Delhi, and the United States Centers for Disease Control, Atlanta, No. IP 16-1606, titled ‘Strengthening and integrating surveillance and response to seasonal and pandemic influenza in Member States of the WHO South-East Asia Region 2016-2021’.
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- Table: How to choose antibiotics for skin and soft tissue infections
- Complicated skin and soft tissue infections (including necrotizing fasciitis)

10.1.3 Papular lesions (with DDx tables)
- Syndromic management of itchy papular lesions in PLHIV
- Tungiasis (jiggers, sand flea disease)
- Furuncular myiasis
- Molluscum contagiosum
- Talaromycosis
- Viral warts
- Eosinophilic folliculitis
- Pityrosporum folliculitis
- Papular urticaria
- Drug reactions
- Scabies
- Cutaneous tuberculosis
- Cutaneous histoplasmosis
- Cutaneous cryptococcosis
- Acne

10.1.4 Vesicular or bullous lesions (with DDx table)

10.1.5 Nodular lesions (with DDx table)
- Erythema nodosum
- Yaws

10.1.6 Maculopapular rash (with DDx table)
- Viral exanthems
- Viral haemorrhagic fever

10.1.7 Plaques (with DDx tables)
- Eczema
- Dermatophytosis (ringworm)
- Pityriasis versicolor
- Psoriasis
- Cutaneous leishmaniasis

10.1.8 Pruritus (with DDx table)
- Xeroderma
- Pediculosis
- Cimicosis (bed bug infestation)
- Symptomatic management of itching

10.1.9 Urticaria

10.1.10 Skin ulcers (with DDx table)
- Diabetic ulcers
- Venous ulcers
- Arterial ulcers
- Buruli ulcer
- Pressure sores (bed sores)
- Tropical ulcers
- Anthrax

This Section provides an approach to the diagnosis and management of common skin and soft tissue conditions. For anorectal and genital lesions, see sexually transmitted infection guidelines.

Skin lesions may be due to primary skin conditions, or may be a sign of a multisystem disease. Most skin problems can be diagnosed based on clinical examination. If a patient is HIV-infected, skin problems are very common, but the clinical presentation may be atypical.

When using skin ointments or creams, follow the medication instructions. Avoid use of potent topical steroids on the face.

10.1.1 Clinical approach to a patient with a skin disorder

Step 1: Perform Quick Check
Use the Quick Check and ensure that there are no serious or life-threatening conditions. Exclude sepsis, anaphylaxis or severe drug reactions, bleeding disorders, and snake-bites.

Step 2: Take a history and examine the patient
Take a thorough history specific to the skin lesions and a general history.
Perform a complete cutaneous and systemic examination.

Step 3: Assess the patient’s HIV status. Is the patient COVID-19 positive?

Step 4: Classify the skin problem and work through the DDx table(s):
- red, tender, warm with pus or crusts
- papular lesions
- vesicular or bullous lesions
- nodular lesions
- maculopapular rash
- plaques and patches
- generalized itching
- skin ulcers.
Step 5: Perform investigations if required  
Step 6: Initiate management and monitor the response

**History**
A good medical history is important in the evaluation of cutaneous disorders.

**Specific history**
- What is the duration of the skin problem?
- What is the mode of onset and progression of symptoms?
- Site on the body – extensor versus flexor, skin creases, exposed areas?
- What are the associated symptoms: pain, itching, bleeding, discharge?
- Are there any triggering, relieving factors:
  - seasonal
  - exposure to sun
  - foods, cosmetics, drugs
  - insect bites?
- Is there a past history of similar rashes or lesions?

**General history**
- Is there evidence of systemic disease:
  - constitutional symptoms (fever, night sweats, malaise, lymphadenopathy)
  - specific system involvement (CNS signs, cough, abdominal complaints)?
- Is there a history suggestive of co-morbidities:
  - HIV status, clinical stage, or CD4 count
  - autoimmune conditions, diabetes, rheumatoid conditions, any infectious diseases?
  - COVID-19?

A variety of skin lesions have been reported in COVID-19 cases in adults and children. More date is required to understand skin involvement – is it from viral infection, systemic consequences of the infection or from medication?¹

Signs which may appear early in the disease have been included in the differential diagnosis tables below. This may change with more published data.

Note: Because of the need and duration of wearing personal protective equipment (PPE) during this pandemic, health workers have also themselves experienced skin problems such as pressure injury, contact dermatitis, pressure urticaria, and exacerbation of pre-existing skin diseases.²

- Is there a past history of atopy, allergies, or any other skin disease?
- Medications – review all prescribed medications (IV, oral, and topical) including traditional medications.
- Substance use – injecting drug use?
- Sexual history – high risk behaviour, signs or symptoms of STIs now or in the past?
- Family history – skin disorders, arthritic conditions, allergic conditions?
- Travel history – the patient travels to or lives in an area endemic for relevant infectious diseases?

¹ BMJ Best Practice June 11

10. Acute and subacute by symptom: SEARO 2021

- Outbreak history – suspected or confirmed outbreak of COVID-19, VHF, measles or other diseases with skin manifestations in the area where the patient lives.
- Consider endemic neglected tropical diseases (NTDs). WHO has produced a training guide for recognizing skin signs of NTDs.³

### Examination

Perform a full general physical examination to look for signs of multisystem disease (particularly lymphadenopathy, hepatosplenomegaly, fever, CNS, and respiratory signs).

#### Examine the lesions

**Characteristics:**
- type of lesion – macule, papule, maculopapule, vesicle, bulla, plaque, patch, nodule, or tumour;
- size;
- shape – flat-topped, umbilicated, cuniform, rough or verrucous, annular, round, oval, linear, irregular;
- number – single or multiple;
- colour – hyperpigmented, hypopigmented, depigmented, erythematous, black, blue.

**Distribution (map anatomically, noting the pattern of distribution):**
- unilateral;
- dermatome;
- sun-exposed areas, dust-exposed areas, covered areas;
- generalized, localized;
- specific areas spared, e.g. palms and soles;
- mucosa – oral, conjunctival, vulval, vaginal, penile;
- skin appendages – hair, nails;
- consistency – hard, irregular.

Assess for involvement of:
- hair, nail, mucous membranes;
- lymphadenopathy;
- joints.

### Definitions or descriptions of skin lesions according to characteristics

<table>
<thead>
<tr>
<th>Blister</th>
<th>A collection of fluid underneath the top layer of skin (epidermis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicle</td>
<td>A raised lesion of &lt;1 cm that is filled with clear fluid</td>
</tr>
<tr>
<td>Bullae</td>
<td>Bullae are circumscribed fluid-filled lesions that are &gt;1 cm in diameter</td>
</tr>
<tr>
<td>Erythema</td>
<td>Redness or inflammation of the skin or mucous membranes</td>
</tr>
<tr>
<td>Nodules</td>
<td>A raised solid lesion of &gt;1 cm, and may be in the epidermis, dermis, or subcutaneous tissue</td>
</tr>
<tr>
<td>Papule</td>
<td>A discrete, solid, elevated lesion usually &lt;5 mm in diameter; further classified by shape, size, colour, and surface change</td>
</tr>
<tr>
<td>Macule</td>
<td>A flat, colour change of the skin with a size of &lt;1 cm</td>
</tr>
<tr>
<td>Plaque</td>
<td>A solid, raised, flat-topped lesion &gt;1 cm</td>
</tr>
<tr>
<td>Patch</td>
<td>A macule &gt;1 cm in size; may be referred to as a patch</td>
</tr>
<tr>
<td>Pustule</td>
<td>A small elevated skin lesion containing pus</td>
</tr>
<tr>
<td>Scale</td>
<td>Flakes or plates that represent compacted, desquamated layers of the superficial layer of the skin</td>
</tr>
</tbody>
</table>

³ NTD skin reference
<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crust</td>
<td>Dry small plates of plasma or exudates over the skin</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Discontinuation or break in the skin or mucosa</td>
</tr>
<tr>
<td>Lichenification</td>
<td>Characterized by an increase in pigmentation, prominent skin markings and thickening of skin due to chronic scratching</td>
</tr>
<tr>
<td>Excoriation</td>
<td>Traumatized or abraded skin caused by scratching and rubbing, usually superficial and linear</td>
</tr>
</tbody>
</table>

**Investigations**

The diagnosis of skin lesions usually is clinical, but if it is unclear or confirmation is required, consider the following investigations (see Section 7).

**Skin scrapings and smears** – microscopy or culture:
- with KOH (potassium hydroxide) – useful for identifying causative organisms which directly infest the skin, e.g. mite or mite parts in scabies; yeasts or fungal filaments in fungal diseases; molluscum bodies in molluscum contagiosum;
- slit skin smears – with appropriate staining to identify AFB or Leishman Donovan bodies in leishmaniasis or *Mycobacterium leprae* (see Section 11.20);
- Tzanck smears – to identify viral giant cells.

**Skin biopsy:**
- histology – to identify dysplasia or malignancy;
- microscopy or culture;
- Gram stain of fluid or pus and sometimes culture.

**10.1.2 Skin and soft tissue infections**

**DDx: Skin lesions: red, tender, warm with or without pus or crusts**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| Impetigo (superficial bacterial skin infections) | Initially a vesicle or blister that ruptures to form small, superficial ulcers  
Honey-coloured crusts  
Little or no surrounding erythema  
Pruritic  
No lymphadenopathy |
| Ecthyma a variant of impetigo | Lesions extend deeper into the dermis  
Dry, black, tightly adherent crust common  
Heals with scarring  
Often occur on the legs of children  
Predisposing – pruritic lesions (insect bites, scabies, or pediculosis); poor hygiene; malnutrition |
| Folliculitis                  | Superficial, painful, yellow pustules  
Associated with hair follicle  
Localized  
No lymphadenopathy |
| Furuncle (boil)               | Painful, tender, warm, erythematous nodule  
Surrounding inflammation  
Fluctuation (soft, with or without pus) |
| Carbuncle                     | Large, inflamed, boggy swelling studded with pustules or cluster of furuncles  
With or without central ulceration  
Systemically ill |
| Cellulitis                    | Fever and systemically ill  
Ill-defined diffuse swelling of the skin and subcutaneous tissues with redness, tenderness, and warmth – may ooze serous fluid  
Spreads to involve significant body surface area |
<p>| Erysipelas                    | Lesions are more superficial than cellulitis |</p>
<table>
<thead>
<tr>
<th>Necrotising fasciitis</th>
<th>Characteristics of cellulitis plus central area showing a blistering and greyish necrotic tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blistered area with lack of sensation under blister</td>
</tr>
<tr>
<td></td>
<td>Intense pain or pain out of proportion to visible skin lesions</td>
</tr>
<tr>
<td></td>
<td>Systemically ill</td>
</tr>
<tr>
<td></td>
<td>X-ray – gas in soft tissue (only occasionally seen)</td>
</tr>
</tbody>
</table>

| Other conditions to consider in DDx | Deep vein thrombosis, gout, drug reactions, insect bites or stings, dermatitis linearis, malignant lesions, bursitis, osteomyelitis |

Infections can develop on previously healthy skin, in pre-existing lesions, or lesions from other causes (such as impetiginized scabies). Potentially fatal systemic toxaemia may occur in patients with cellulitis, erysipelas, or other soft tissue infections that remain untreated.

**Impetigo**

Impetigo is contagious.

**Treatment**

- Soak and gently scrub crusts to clear collections of pus underneath.
- For single lesions of impetigo or small areas of involvement, local treatment with topical mupirocin ointment thrice daily for 7 days may suffice.
- For more extensive lesions, oral cotrimoxazole or doxycycline (effective against some MRSA) or amoxicillin for 7 days.

**Complications**

Glomerulonephritis may occur as a complication of impetigo caused by nephritogenic *Streptococcus pyogenes*. This occurs within 1–3 weeks (average 7–10 days).

**Prevention of spread**

- Add a spoonful of potassium permanganate into bathwater to make it pale pink. The family should bathe in this solution 2–3 times per week.
- Clean shower and bath with bleach.
- Do not share towels.
Management of skin and soft tissue infections

If a patient is systemically ill, parenteral antibiotics should be administered.

Figure: Flowchart for the management of soft-tissue infections
Abscesses, furuncles, carbuncles, cellulitis (with or without purulent drainage)

Assess for signs of severity or risk factors:
- severe or extensive disease;
- significant immunosuppression including AIDS, poorly controlled DM;
- very young or old age;
- difficult area to drain, such as face, genitals, hands;
- lack of response to incision and drainage alone.

Treatment
- Incision and drainage is the mainstay of treatment and is often all that is required.
- Treatment in the absence of severe sign and risk factors, for 7–10 days:
  - oral cloxacillin 500 mg 4 times daily (preferred); OR
  - alternatives if allergy to penicillin or high rate of methicillin-resistant *Staphylococcus aureus* (MRSA):
    - cotrimoxazole 1–2 DS tablets twice daily (if suspect MRSA, use higher dose); OR
    - doxycycline 100 mg twice daily; OR
    - clindamycin 300–450 mg 3 times daily.
- Give parenteral therapy such as ceftriaxone if any of these severe signs or risk factors. Switch to oral options after significant improvement, for total treatment of 7–10 days.
- Patients who have diabetes or are immunocompromised require particularly careful management as carbuncles with multiple openings sometimes form as a result of invasion and necrosis of the dermis. See management of complicated skin infections below.

Erysipelas

Patients with classic signs and symptoms of erysipelas who are not systemically ill and have small lesions may be managed with oral phenoxyethyl penicillin 500 mg every 6 hours for 5 to 10 days. If there are any systemic signs (fever, malaise), treat with IV antibiotics as for cellulitis above.

Table: How to choose antibiotics for skin and soft tissue infections

<table>
<thead>
<tr>
<th>Antibiotics with reliable coverage against group A Beta-haemolytic streptococci</th>
<th>Penicillin, ampicillin, amoxicillin, cloxacillin, flucloxacillin, all cephalosporins, clindamycin. Clindamycin is preferred in case of penicillin allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics with reliable coverage against <em>Staphylococcus aureus</em> (methicillin-susceptible strains only)</td>
<td>First-line: cloxacillin, flucloxacillin, nafcillin, oxacillin, 1st generation cephalosporins (e.g. cefazolin or cephalaxin), ampicillin/sulbactam, amoxicillin/clavulanate Second-line or penicillin allergic: clindamycin, ceftriaxone, cotrimoxazole, doxycycline Note: Vancomycin has activity against all <em>S. aureus</em>, but is reserved for use against MRSA (methicillin-resistant <em>Staphylococcus aureus</em>)</td>
</tr>
<tr>
<td>Antibiotics with activity against many MRSA strains</td>
<td>Clindamycin, cotrimoxazole, doxycycline, vancomycin</td>
</tr>
<tr>
<td>Antibiotics with activity against Gram-negative organisms occasionally encountered in skin-related infections</td>
<td>Note: Gram-negative organisms are not routinely associated with skin and soft tissue infections but, in some cases such as infected ulcers, necrotizing fasciitis, or penetrating injuries, Gram-negative coverage may be appropriate Ceftriaxone, ciprofloxacin in higher doses (also has activity against <em>Pseudomonas</em>), gentamicin, and amoxicillin/clavulanate, cotrimoxazole</td>
</tr>
</tbody>
</table>
Complicated skin and soft tissue infections (including necrotizing fasciitis)

Treatment
Antibiotic treatment should be based upon Gram stain, culture and sensitivity where possible. Early empirical treatment should cover both aerobic and anaerobic organisms. IV antibiotics are the mainstay of therapy, there is no place for oral agents.

- Treat with:
  - cloxacillin 1 to 2 grams every 6 hours and clindamycin 900 mg IV every 8 hours; OR
  - ampicillin 2 g IV every 6 hours and clindamycin 900 mg IV every 8 hours.
- If previously hospitalized, consider adding Gram-negative coverage such as ceftriaxone, a fluoroquinolone, or an aminoglycoside.
- If MRSA is prevalent and clindamycin is not available, consider adding MRSA coverage with vancomycin, cotrimoxazole, or doxycycline.

Consider surgical intervention, with debridement. If necrotizing fasciitis is suspected, this is mandatory.

10.1.3 Papular lesions

Ask:
- Is there an itch?
- Look for mouth lesions
- Is there a fever, or is the patient systemically ill?
- Are others in the home affected?
- Distribution of the lesions?
- HIV status?
- Drug history?
- Recent introduction of ART?
### DDx: Papular lesions with itching

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insect bite or contact reaction (papular urticaria) (very common)</td>
<td>Scattered over exposed area; some insects such as the blister beetle or Nairobi fly cause a linear rash Small papules and central crust Scratch marks mostly on exposed areas – face, arms, legs Exaggerated response in HIV – vesicular or bullous lesions</td>
</tr>
<tr>
<td>Chiggers</td>
<td>Itching occurs several hours after bites of mites found in grassy fields, forests, parks, and gardens and the moist areas along lakes and streams. Severe itching with red pimple-like bumps Distribution rash on legs and waist line or parts of the body exposed to the sun; it may stop where the underwear meets the legs Secondary infection common following intense scratching</td>
</tr>
<tr>
<td>Body louse infestation or pediculosis corporis (Vagabond’s disease)</td>
<td>Itching where clothing makes direct contact with the body Heavy infestations can cause intense irritation and severe itching The white eggs or nits are found on fine threads of clothes</td>
</tr>
<tr>
<td>Sand flea disease (tungiasis, jiggers)</td>
<td>Itching in soft areas of skin – cracks on feet, between toes, under toenails Pale round lesion with a central black spot Dark crust or oozing fissure An ulcer crater left after sand flea extraction</td>
</tr>
<tr>
<td>Pruritic papular eruption of HIV (PPE)</td>
<td>Hyperpigmented papules and nodules Occasionally hyperkeratotic Symmetrical – affects arms, legs, lower back, and buttocks Residual hyperpigmentation after healing Resolves with ART</td>
</tr>
<tr>
<td>Eosinophilic purulent folliculitis</td>
<td>Extremely itchy – resembles insect bites with a tendency to group Urticarial papules (wheel-like) Seborrheic areas – face, neck, scalp, chest, trunk (vs PPE) Residual hyperpigmentation Occurs commonly as IRIS</td>
</tr>
<tr>
<td>Pityrosporum folliculitis</td>
<td>Numerous follicular papules or pustules Mostly on upper trunk and arms; may be extensive – affecting the scalp and face Gram stain: Gram-positive budding yeast cells</td>
</tr>
<tr>
<td>Scabies Crusted scabies (Norwegian scabies)</td>
<td>Papules and burrows – on torso, web-space of hands and feet, wrist and ankles, elbows, axilla, umbilical and groin areas Itching worse at night Similar problem in family or other close contacts Clinical diagnosis or microscopy of skin scrapings – mites (KOH or mineral oil preparations) Crusted scabies (Norwegian scabies) has widespread, scaly patches and crusted lesions. The fingernails can be thickened and discoloured. Itching may be minimal or absent in this form of scabies. Occurs with weakened immune system or elderly or debilitated persons.4</td>
</tr>
<tr>
<td>Drug reactions</td>
<td>Sudden onset involving the trunk, extremities and face History of starting on a new drug in recent past Mild or severe if mucosal involvement (Stevens-Johnson Syndrome) With or without fever</td>
</tr>
<tr>
<td>Myiasis (blowfly strike) infection with the tumbu fly larvae</td>
<td>Lump will develop in subcutaneous tissue as the larva grows. Develops into purulent lesion (furuncular myiasis) Sensation of movement under skin Stabbing pain May involve skin sores and open wounds May involve nasopharyngeal, genitourinary or rectal space</td>
</tr>
</tbody>
</table>

---

### Syndromic management of itchy papular lesions in PLHIV

- Document distribution, duration, involvement of palms or soles or mucosal surfaces.
- Ask if anyone else at home is itching
- Are there other symptoms of STI?
- Obtain VDRL or RPR (if sexually active, if involvement of palms soles, or if mucosal lesions).

It is often difficult to make a specific diagnosis. An example of an approach to empirical treatment follows.

#### Stage I empirical treatment:
- anti-scabetic or mite topical treatment (see scabies management below);
- potent topical steroid with antifungal cream(s);
- oral antipruritic agents:
  - chlorphenamine 4 mg every 4 to 6 hours;
- oral antibiotic (e.g., erythromycin or doxycycline).

#### Stage II empirical treatment if no response to Stage I:
- continue Stage I regimen (including possible re-treatment for scabies or mites);
- add systemic oral antifungal (fluconazole or griseofulvin).

#### Stage III Refer or biopsy.

### Chiggers

#### Treatment
- Vigorous cleansing with soap and water may help to remove the mites.
- Topical antipruritics, such as menthol, calamine lotion, or topical corticosteroids, and oral antihistamines may help relieve the itching.
- The condition heals without treatment.
- Treat secondary bacterial infection with topical or oral antibiotics (see impetigo above).

### Sand flea disease (tungiasis, jiggers)

#### Treatment
- Wash the body part with clean water and soap (can use savlon or hibitane disinfectant)
- Dry the body part with a clean towel
- Extract the sand flea using a clean safety pin (DO NOT use this on other persons)
- Immerse the body part in water with disinfectant for about 5 minutes then leave to dry
- Apply vaseline or antibiotic ointment to the body part
- May cover the ulcer left after extraction with gauze dressing
- Ensure adequate antitetanus coverage
- Treat secondary bacterial infection

#### Monitoring
- Regular inspection of the feet and hands and early extraction of sand fleas
- Regular washing with thorough cleaning of the extremities
- Application of vaseline to the extremities after washing
### DDx: Papular lesions – without itching

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molluscum contagiosum</strong></td>
<td>Dome-shaped lumps with a dimple in the centre&lt;br&gt;Involving, face, neck, armpits, hands and genitals&lt;br&gt;Lesions may be chronic and numerous&lt;br&gt;In PLHIV – may be large &gt;1 cm and coalesce</td>
</tr>
<tr>
<td><strong>Talaromycosis</strong>&lt;br&gt;(see Section 11.36)</td>
<td>Papules on face, chest and extremities&lt;br&gt;Centre of papule becomes necrotic – appears umbilicated</td>
</tr>
<tr>
<td><strong>Common warts (verruca vulgaris)</strong></td>
<td>Small raised lesions with rough surface.&lt;br&gt;Commonly involving the extremities&lt;br&gt;Can appear anywhere&lt;br&gt;May be recurrent and persistent in HIV&lt;br&gt;May be very large, recurrent, and persistent in patients with HIV</td>
</tr>
<tr>
<td><strong>Genital warts</strong></td>
<td>Variable sizes, shapes and number – from small, flat to large and polypoid&lt;br&gt;May be seen on any part of the genitalia, including intravaginal and intra-anal&lt;br&gt;May be recurrent and persistent in patients with HIV</td>
</tr>
<tr>
<td><strong>Secondary syphilis</strong>&lt;br&gt;(see Section 11.34)</td>
<td>Multiple lesions – papular or macular&lt;br&gt;Generalized involving the palms and soles&lt;br&gt;Dusky red-coppery&lt;br&gt;Mucocutaneous lesions – moist erythematous patches over genital and oral mucosa&lt;br&gt;Generalized lymphadenopathy&lt;br&gt;Diagnosis – blood VDRL/RPR/TPHA</td>
</tr>
<tr>
<td><strong>Cutaneous leishmaniasis</strong>&lt;br&gt;(Aleppo boil, Oriental sore)&lt;br&gt;(see Section 11.19)</td>
<td>Erythematous papule (at the site of a sandfly bite)&lt;br&gt;Enlarges to a painless ulcerated nodule&lt;br&gt;Raised and well-demarcated border&lt;br&gt;Single or multiple lesions&lt;br&gt;Touch preparation, lesion aspirate and tissue biopsy show amastigotes</td>
</tr>
<tr>
<td><strong>Cryptococcosis</strong>&lt;br&gt;(see Section 11.8)</td>
<td>Generalized raised umbilicated, fleshy lesions (similar to molluscum contagiosum)&lt;br&gt;Develops rapidly (within days)&lt;br&gt;Fever&lt;br&gt;Signs and symptoms of disseminated cryptococcosis, e.g. meningitis, lung infection&lt;br&gt;Serum or CSF CrAg or CSF India ink</td>
</tr>
<tr>
<td><strong>Histoplasmosis</strong>&lt;br&gt;(see Section 11.17)</td>
<td>Erythematous maculopapular lesions with ulceration and purpura&lt;br&gt;Oropharyngeal lesions&lt;br&gt;Systemic involvement: lung, CNS, gastrointestinal, or eyes&lt;br&gt;Diagnosis – tissue biopsy or microscopy: yeast forms on haematoxylin and eosin staining&lt;br&gt;Endemic&lt;br&gt;Blood or tissue culture</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Single or multiple purple-coloured lesions&lt;br&gt;May be papular, nodular, patches, or plaques&lt;br&gt;Can involve any part of the body including palate&lt;br&gt;Lymphoedema may occur if on limbs</td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex</strong>&lt;br&gt;(MAC)&lt;br&gt;(see Section 11.25)</td>
<td>Papulo-pustular eruptions on trunk and extremities&lt;br&gt;Fever&lt;br&gt;Lymphadenopathy&lt;br&gt;Pulmonary symptoms, diarrhoea, weight loss, night sweats&lt;br&gt;Acid-fast bacilli on skin biopsy; blood culture&lt;br&gt;The patient has advanced HIV</td>
</tr>
<tr>
<td><strong>TB verrucosa cutis</strong></td>
<td>Warty papules (may be nodular or an irregular plaque)&lt;br&gt;Localized to 1 area – often the hands or extremities&lt;br&gt;Often mistaken for verruca vulgaris&lt;br&gt;Lesions may evolve and persist for years</td>
</tr>
<tr>
<td><strong>Papulo-necrotic tuberculides</strong></td>
<td>Multiple papules with black necrotic centres&lt;br&gt;Scattered in 1 or 2 regions; not generalized&lt;br&gt;Skin biopsy</td>
</tr>
<tr>
<td><strong>Acne</strong></td>
<td>Pimples – visible lumps on the skin that may be papules, pustules, nodules, or cysts&lt;br&gt;May be old or new scarring&lt;br&gt;With or without active inflammation&lt;br&gt;On face, neck, chest, back, and upper arms&lt;br&gt;Common during adolescence</td>
</tr>
</tbody>
</table>
**Molluscum contagiosum**

This is a common viral infection of the skin.

**Key clinical features**
- pearly-white, umbilicated papular lesions on the face, trunk, and genital area;
- frequently seen among sexually active adults, especially those infected with HIV; 
- extensive molluscum contagiosum has large numbers of lesions (perhaps more than 30) involving more than one body site (such as face and trunk, or trunk and genitalia);
- unusually distributed extragenital sites in adults and genital involvement in children; also if it involves the mucocutaneous junction.

**Treatment**
- removal by enucleation (with forceps); OR
- cautery – pierce the molluscum body with a needle and treat the base with silver nitrate or phenol or any other mild sclerosing agent; OR
- cryotherapy – freeze using liquid nitrogen.

ART should be considered as the primary treatment of extensive and/or unusually distributed molluscum contagiosum in HIV-infected patients. No additional specific treatment is recommended.5  Offer HIV test if status unknown.

**Viral warts**

Warts (verrucae) are caused by the human papillomavirus (HPV) and may regress spontaneously at any time within months or years of their first appearance.

**Key clinical features**
- papules or nodules with a rough (verrucous) surface;
- occur most often on the hands and fingers, but may be found on any area of the body.

Genital warts (Condyloma accuminata) are sexually transmitted infections caused by HPV. The lesions may be seen on any part of the genitalia, including intra-vaginal and intra-anal.

**Treatment**
Alternative treatments include:
- paints or lotions containing salicylic acid;
- podophyllin resin;
- **cryosurgery** – where available, liquid nitrogen applied with a cotton-tipped swab or a spray can be highly effective;
- **electrocautery** can be used when available;
- **trichloroacetic acid** may be another option for treatment of warts.

**Eosinophilic folliculitis**

**Key clinical features**
- extremely pruritic rash seen in patients who are HIV-infected;
- primary lesions are urticarial papules that look like insect bites;
- pustules may be present;
- because of the intense itching, excoriations and post-inflammatory hyperpigmentation are seen;
- lesions are most prominent on the seborrhoeic areas of the skin (scalp, face, chest, upper back).

**Treatment**
- topical steroids – hydrocortisone 1%; OR

---

• betamethasone 0.1% cream;
• symptomatic relief – oral antihistamines such as chlorphenamine.
If the patient is unresponsive to the above, give:
• doxycycline 100 mg twice daily for 8–12 weeks.

**Pityrosporum folliculitis**

**Key clinical features**
• numerous pruritic follicular papules or pustules;
• most commonly seen on the upper trunk and arms.

**Treatment**
• topical steroids – hydrocortisone 1%; OR
• betamethasone 0.1% cream;
• ART if indicated for other reasons (the condition improves with immune recovery);
• symptomatic relief – antihistamines (as above).

**Papular urticaria**

This is an insect-related hypersensitivity reaction (Type IV).

**Key clinical features**
• commonly seen in children in developing countries;
• characterized by crops of pruritic wheals that evolve into serum-filled papules and, less frequently, vesicles;
• lesions seen predominantly on exposed body parts;
• excoriations, due to scratching, lead to secondary bacterial infections;
• spontaneous desensitization usually occurs by the age of 7 years;
• in tropical climates, mosquitoes are the main cause of papular urticaria; flies and bed bugs are the common causes in temperate climates.

In patients who are HIV-infected, there is an exaggerated response to insect bites.

**Treatment**
• topical steroids: hydrocortisone 1% OR betamethasone 0.1% cream;
• symptomatic relief with antihistamines such as chlorphenamine 4 mg twice daily;
• topical antimicrobial (e.g. 2% mupirocin ointment) may be useful to treat secondary bacterial infection;
• use insect repellents, screens, and bed nets;
• disinfect pets if any.

**Drug reactions (see also HIV care guidelines)**
• Drug reactions may be localized to the skin or involve various organ systems.
• The drugs most frequently involved include NNRTIs (NVP and EFV), ABC, sulfa drugs (cotrimoxazole and dapsone), antiepileptics (phenytoin, phenobarbital and carbamazepine), antibiotics (quinolones, penicillins, cephalosporins), and antituberculosis drugs.
• The reaction may present 1–3 weeks after commencing the causative drug. But it may take up to 6 weeks with antituberculosis and antiepileptic medicines.

**Key clinical features**
Drug reactions or eruptions may be mild or severe.

**Mild drug reaction**
• Mild drug reactions typically present as an itchy papular or maculopapular rash with no constitutional symptoms or systemic findings.
• Erythema multiforme is a special morphological type of drug eruption. It presents as a self-limiting symmetrical skin rash with “target lesions” (a pink-red ring around a pale centre). The rash begins abruptly and heals normally in 7–14 days. It is often triggered by HSV infection. It can be a manifestation of drug allergy.
**Severe drug reaction**
- A severe drug reaction may develop macules that rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing.
- Constitutional symptoms and systemic involvement, such as an increase in liver enzymes, may be seen.
- Stevens Johnson Syndrome (SJS) refers to skin changes affecting up to 10% of the body surface area, and involvement of >1 mucosal surface (oral, conjunctival, genital).
- Toxic epidermal necrosis (TEN) refers to skin changes on large areas of the body, sometimes affecting >30% of the body surface area, and presents as sheets of erythema with blistering and skin peeling. Mucosal and systemic involvement may be seen as well.

**Treatment**

**Mild drug reaction**
- Stop the suspect drugs.
- Give antihistamines.
- In some mild drug reactions, it may be possible to continue the drug if it is medically necessary.

**Erythema multiforme**
- If the cause is HSV infection, treat the HSV.
- Discontinue suspected drug if the condition is drug-induced.
- Supportive management includes:
  - oral antihistamines
  - topical calamine lotion.

**Severe drug reaction**
- Stop the suspect drugs (all drugs introduced within one month of the reaction should be considered suspect).
- Hospitalize the patient in an intensive care or burn unit. Supportive care are similar to that for major burns (see Section 3.10) – wound care, fluid and electrolyte management, nutritional support, temperature management, pain control, and monitoring or treatment of superinfections
- Referral to a tertiary dermatologic unit should be considered in toxic epidermal necrosis.
- Give topical antibiotics.
- Maintain hydration and electrolyte balance.
- Give analgesics.
- Use mouth washes and eye ointments.
- Screen and treat empirically for septicaemia.
- Systemic corticosteroids are not recommended in PLHIV\(^6\). Some studies suggest a potential benefit of systemic corticosteroids for SJS but uncertainties remain regarding specific treatment modalities (eg, oral high doses versus intravenous "pulse" bolus doses).

**Patient education**
The health worker should inform the patient about drugs that may have caused the eruption, drugs to avoid, and those drugs that can be used safely. This information should be noted in the patient’s record.

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**Scabies (the seven-year itch)**

Transmission of *Sarcoptes scabei* is through close contact with infested persons and occurs in crowded spaces, conditions involving poor hygiene, and through sexual contact. A more severe form of scabies (Norwegian scabies) can occur if the patient is immunocompromised.

**Key clinical features**

Classical scabies:
- itchy papular lesions;
- itching is typically most severe at night;
- history of a similar problem in the family or close contacts;
- typical lesion of scabies is the burrow of the adult mite, with excoriations from scratching;
- lesions due to secondary bacterial infection are pustules and pustulovesicles;

Typical distribution: finger webs, palms, wrists, elbow, axillae, areola, nipple, umbilicus, external genitalia, and feet.

Scabies is classified into mild (10 lesions or less), moderate (11–49), severe (50 or more) and crusted forms.

Norwegian (crusted) scabies:
- The lesions in crusted scabies are more widespread, crusted with thick, hyperkeratotic scales. There is infestation with a large number of mites. Little itching occurs because of immunocompromise. This form is highly contagious.
- It resembles psoriasis: thick crusts, scales, and dystrophic nails.
- These patches and plaques are commonly seen over elbows, knees, palms, and soles (but they can occur on almost any area of the body). Occasionally, only diffuse redness of skin is apparent.
- Bacterial superinfections are common.

**Investigations**

- Diagnosis is usually clinical.
- The end of a burrow should be unroofed and scraped; examination under a light microscope will reveal a mite, eggs or faecal pellets.

**Treatment**

With one of the following:
- 25% benzyl benzoate emulsion (dilute 1:1 for children; 1:3 for infants); OR
- 5% permethrin cream; OR
- ivermectin 0.2 mg/kg orally as a single dose, repeated in 2 weeks.

If there are crusted scabies, repeat treatments on days 1, 15, and 29, or combine treatment with oral ivermectin and a topical scabicide (benzyl benzoate or permethrin cream).

In addition, a keratolytic, such as 5% salicylic acid, can be used to remove scale bulk.\(^7\)

**Method of application**

- The patient and all close contacts must be treated simultaneously, including the entire household and sexual partners, even if they are asymptomatic.
- Clothing or bed linen used by the patient should be washed and dried out in the sun.
- Do not bathe before applying the treatment (this increases systemic absorption and does not help).
- Apply the cream to the whole skin surface, giving particular attention to the flexures, genitalia, intergluteal cleft, between the fingers and under the fingernails. Include the face, neck and scalp, but avoid areas near the eyes and mouth.

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\(^7\) WHO informal consultation on a framework for scabies control, World Health Organization Regional Office for the Western Pacific, Manila, Philippines, 19–21 February 2019: meeting report

• The cream may irritate the skin a little, especially if there are excoriations.
• Keep the cream on for the treatment period: overnight treatment for three days.
• If any cream is washed off during the treatment period (e.g. hands), reapply immediately.
• Wash the cream off at the end of the treatment period.
• Itching should start to diminish within a few days but may persist for a number of weeks. This does not mean that the treatment has failed. Another cream may help with the itching (calamine lotion).

**Cutaneous tuberculosis**
Cutaneous tuberculosis can present in many forms. Some of the common presentations include:
• warty papules and plaques (tuberculosis verrucosa cutis);
• well-circumscribed, dusky red, soft to firm papules and plaques with or without central scarring (lupus vulgaris);
• multiple sinuses with ulceration at the mouth of the sinus (scrofuloderma);
• chronic ulceration at the mouth or anal region (orificial tuberculosis).
HIV-infected patients are more prone to developing tuberculosis and therefore are at increased risk of presenting with cutaneous hypersensitivity reactions to TB. In HIV-infected patients, these reactions occur with higher CD4 counts, are more florid, and several types may coexist.
• Papulonecrotic tuberculid: papules, pustules, with central necrosis involving acral sites, such as earlobes, elbows, knee, extensors, and buttocks.
• Lichen scrofulosorum: grouped papules on the trunk in association with underlying TB.
• Erythema nodosum: erythematous, tender, evanescent nodules on the legs.

**Investigations**
Diagnose by tissue biopsy and histopathology, and lesion aspirate or tissue culture.

**Treatment**
See WHO TB guidelines.

**Cutaneous histoplasmosis**

**Key clinical features**
• patients are usually ill with systemic involvement – fever, anaemia, respiratory symptoms, lymphadenopathy, hepatosplenomegaly, and skin lesions;
• skin involvement occurs in 5%-10% of patients;
• skin lesions are polymorphous: papules, nodules, plaques, abscesses, and characteristic gingival ulcers;
• this condition may often resemble molluscum contagiosum.

**Investigations**
• Referral for biopsy and culture may be indicated (see Section 7).

**Cutaneous cryptococcosis – see Section 11.8 Cryptococcosis**
This occurs with advanced HIV disease.

**Key clinical features**
• skin involvement occurs in 10% of patients with systemic disease;
• the typical lesions are haemorrhagic, ulcerated nodules and umbilicated papules resembling molluscum contagiosum.

**Investigations**
• A KOH preparation with or without India ink staining will show the characteristic round, thick-walled yeast cells of cryptococcosis.
Acne

Key clinical features
- comedones – whiteheads or blackheads with no redness (blocked hair roots or pores with white or black tips);
- pustules – pus-filled pimples with no redness;
- papules – pimples that appear red due to inflammation;
- nodules – pimples that affect the deeper areas of the skin that can be disfiguring due to inflammation (redness);
- cysts – lesions formed by several nodules coming together;
- scarring, which may or may not be inflamed.

Treatment
- **Severe acne** (nodules, cysts or scarring that is inflamed)
  - Oral antibiotics taken for 3–6 months
    - doxycycline 50 mg daily; OR
    - *tetracycline* 500 mg twice daily; OR
    - erythromycin 500 mg twice daily.
  - Topical applications of: benzoyl peroxide 2.5%–5% or topical tretinoin twice daily until 2 weeks after lesions disappear.
  - Wash face with mild soap twice daily (before topical application).
  - In girls, if taking progesterone-only contraceptive pills or injections, consider changing to combined oral contraceptives.
  - Review in 2 months. If there is no improvement:
    - doxycycline dose can be increased up to 100 mg or 200 mg depending on response.
    - If no improvement in a girl, consult with her about adding combined oral contraceptive pill.
    - Refer for specialist care if very severe acne, if scarring is extensive or worsening, if acne is causing great psychological distress, or is not responding to treatment at six months.
- **Moderate acne** (papules with no nodules, cysts, or inflamed scarring)
  - Apply topical antibiotics twice daily and continue until 2 weeks after lesions disappear.
    - clindamycin 1% gel or lotion; OR
    - erythromycin 2% gel or lotion.
  - Topical applications, face washing, and for girls, contraception change as above.
  - Review in two months. Continue treatment if no improvement. If the condition worsens, give oral antibiotics as for severe acne.
- **Mild acne** (only comedones or pustules):
  - Topical applications as above, face washing, and for girls, contraception change as above.
  - Review in two months. If no improvement, continue treatment. If acne is worse, treat as moderate or severe acne accordingly.

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10.1.4 Vesicular or bullous lesions
Assess the pattern of distribution and whether there is involvement of the mouth.

**DDx: Vesicular or bullous lesions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex     🍊  🍊  🍊</td>
<td>Painful, grouped vesicles with surrounding mild erythema&lt;br&gt;May evolve into a superficial ulcer with crusting&lt;br&gt;Associated with pain or tingling&lt;br&gt;Usually localized to lips or genital area, may involve any site&lt;br&gt;With or without a history of previous episodes&lt;br&gt;Usually heals in 3–5 days&lt;br&gt;Persistent ulcers for &gt;1 month are more common in immunocompromised patients</td>
</tr>
<tr>
<td>Herpes zoster  🍊  🍊  🍊 (see Section 11.39)</td>
<td>Crops of painful vesicles in dermatomal distribution&lt;br&gt;Do not cross midline&lt;br&gt;Intense pain&lt;br&gt;In PLHIV:&lt;br&gt;• recurrent, multidermatomal or disseminated herpes zoster&lt;br&gt;• severe and takes longer to heal</td>
</tr>
<tr>
<td>COVID-19  🍊  🍊  🍊 (see Section 11.6)</td>
<td>Vesicular lesions can appear early in the course of the disease, before other symptoms</td>
</tr>
<tr>
<td>Chicken pox (varicella)  🍊  🍊  🍊 (see Section 11.39)</td>
<td>Fever&lt;br&gt;Discrete (umbilicated) vesicles on an erythematous base&lt;br&gt;Lesions in different stages of development&lt;br&gt;Generalized, but predominantly involving the trunk, cephalocaudal spread&lt;br&gt;Oral lesions&lt;br&gt;In PLHIV, severe disseminated infection including pneumonia 🍊</td>
</tr>
<tr>
<td>Guinea worm disease  🍊  🍊  🍊 (dracunculiasis)</td>
<td>Lower extremity usually&lt;br&gt;Itching, sharp pain and burning sensation of the extremity&lt;br&gt;Blister before ulcer forms when worm emerges&lt;br&gt;Shallow ulcer after the blister bursts&lt;br&gt;Protruding anterior end of the worm through the ulcer&lt;br&gt;Eradicated in Asia</td>
</tr>
<tr>
<td>Anthrax  🍊  🍊  🍊</td>
<td>See 10.1.10 below</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Middle-aged individuals&lt;br&gt;Long history&lt;br&gt;Fragile, flaccid blisters – rupture leaves weeping, denuded skin&lt;br&gt;Blisters extend readily on digital pressure&lt;br&gt;Painful oral ulcers or erosions common&lt;br&gt;Common sites: scalp, trunk, flexures</td>
</tr>
<tr>
<td>Pemphigoid</td>
<td>Elderly age group&lt;br&gt;Tense blisters&lt;br&gt;With or without itching&lt;br&gt;Oral ulcers rare&lt;br&gt;Common sites: trunk, extremities, flexures</td>
</tr>
<tr>
<td>Severe drug reaction – Stevens Johnson syndrome (SJS) and toxic epidermal necrosis (TEN)  🍊  🍊  🍊 (see Section 10.1.3)</td>
<td>History of recently starting a new drug (e.g. sulfas, NVP)&lt;br&gt;Erythematous maculopapular rash with blisters&lt;br&gt;Confluent erythema with sheets of skin peeling and significant oozing&lt;br&gt;Oral, conjunctival, genital mucosal ulceration and crusting&lt;br&gt;Fever&lt;br&gt;Systemic illness</td>
</tr>
<tr>
<td>Monkeypox</td>
<td>Fever, headache, muscle aches, vesicular rash. Can be very ill. Febrile prodrome before rash. Lesions progresses through four stages – macular, papular, vesicular, to pustular – before scabbing over and resolving. (These signs/symptoms can help differentiate from chickenpox which is mostly in children, not very sick, only about 7%–15% have febrile prodrome before rash.) Lymphadenopathy. Low human-to-human transmission. Rarely spread by imported animals or people from sites with outbreaks in West or Central Africa. Similar presentation as smallpox, but with lymphadenopathy. (Smallpox has been eradicated).</td>
</tr>
</tbody>
</table>
## 10.1.5 Nodular lesions

### DDx: Nodular lesions

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema nodosum</strong></td>
<td>Crops of painful, tender, red bumps 1–2 cm in size</td>
</tr>
<tr>
<td></td>
<td>Lesions appear and spontaneously heal, while new lesions appear</td>
</tr>
<tr>
<td></td>
<td>Usually on the legs</td>
</tr>
<tr>
<td></td>
<td>With or without fever</td>
</tr>
<tr>
<td></td>
<td>Associated with tuberculosis, upper respiratory infection, leprosy, drugs,</td>
</tr>
<tr>
<td></td>
<td>rheumatoid arthritis, malignancy</td>
</tr>
<tr>
<td></td>
<td>Do a skin biopsy to confirm</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Single or multiple purple-coloured lesions</td>
</tr>
<tr>
<td></td>
<td>May be papular, nodular, patches, or plaques</td>
</tr>
<tr>
<td></td>
<td>Lesions tend to follow lines of skin cleavage</td>
</tr>
<tr>
<td></td>
<td>Can involve any part of the body including palate</td>
</tr>
<tr>
<td></td>
<td>Lymphoedema may occur if on limbs</td>
</tr>
<tr>
<td></td>
<td>Clinical diagnosis or skin biopsy to confirm</td>
</tr>
<tr>
<td><strong>Bacillary angiomatosis</strong></td>
<td>Single or multiple papules, nodules, and pedunculated lesions</td>
</tr>
<tr>
<td></td>
<td>May appear suddenly and may be tender</td>
</tr>
<tr>
<td></td>
<td>Flesh coloured, purplish, or red lesions</td>
</tr>
<tr>
<td></td>
<td>May be large, friable, polypoid masses</td>
</tr>
<tr>
<td></td>
<td>Signs of systemic illness: fever, lymphadenopathy, splenomegaly, or hepato</td>
</tr>
<tr>
<td></td>
<td>megalay</td>
</tr>
<tr>
<td></td>
<td>Skin biopsy to confirm</td>
</tr>
<tr>
<td><strong>Cutaneous leishmaniasis</strong></td>
<td>Living in an area where disease is previously or currently known, travel to</td>
</tr>
<tr>
<td></td>
<td>endemic area</td>
</tr>
<tr>
<td></td>
<td>Cytopaenia</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Amastigotes seen in samples of tissue or lesion aspirate under the microscope (Giemsa stain)</td>
</tr>
<tr>
<td><strong>Leprosy</strong></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Skin-coloured nodules, papules, and plaques</td>
</tr>
<tr>
<td></td>
<td>Commonly on face and extremities, but can occur at any site</td>
</tr>
<tr>
<td></td>
<td>Other signs of leprosy: sensory loss, peripheral nerve thickening, loss of hair</td>
</tr>
<tr>
<td></td>
<td>Slit skin smear for AFB</td>
</tr>
<tr>
<td><strong>Mycosis fungoides</strong></td>
<td>Pustules, nodules, ulcers, and papules in a patient with systemic symptoms</td>
</tr>
<tr>
<td></td>
<td>Diagnosis by biopsy and histopathology</td>
</tr>
<tr>
<td><strong>Pruritic papular eruption (PPE)</strong></td>
<td>Hyperpigmented papules and nodules</td>
</tr>
<tr>
<td></td>
<td>Occasionally hyperkeratotic</td>
</tr>
<tr>
<td></td>
<td>Symmetrical – affects arms, legs, lower back, and buttocks</td>
</tr>
<tr>
<td></td>
<td>Residual hyperpigmentation after healing</td>
</tr>
<tr>
<td></td>
<td>Resolves with ART</td>
</tr>
<tr>
<td><strong>Cutaneous lymphoma</strong></td>
<td>Long history of nodules, plaques and patches</td>
</tr>
<tr>
<td></td>
<td>Skin coloured or slightly erythematous; annular, doughnut-shaped</td>
</tr>
<tr>
<td></td>
<td>Systemic signs with or without lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly and splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Biopsy to confirm</td>
</tr>
<tr>
<td><strong>Yaws</strong></td>
<td>Papules, or ulcerated nodular lesion with serous discharge</td>
</tr>
<tr>
<td></td>
<td>Primary lesion – extremities</td>
</tr>
<tr>
<td></td>
<td>Secondary lesions – mucocutaneous junctions</td>
</tr>
<tr>
<td></td>
<td>Pain, with or without swelling of small joints</td>
</tr>
<tr>
<td></td>
<td>Heal with scarring</td>
</tr>
<tr>
<td></td>
<td>Hyperkeratosis and fissuring of soles</td>
</tr>
<tr>
<td></td>
<td>Bone deformities</td>
</tr>
<tr>
<td></td>
<td>Residence in endemic area</td>
</tr>
<tr>
<td></td>
<td>Positive syphilis test</td>
</tr>
<tr>
<td></td>
<td>Skin biopsy</td>
</tr>
<tr>
<td><strong>Melioidosis</strong></td>
<td>Nodule, ulcer or skin abscess</td>
</tr>
<tr>
<td></td>
<td>Fever and general muscle aches</td>
</tr>
<tr>
<td></td>
<td>May progress rapidly to bacteremia and septic shock.</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
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<tr>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Key clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>• present as reddish, painful, tender lumps, 1–5 cm in size;</td>
<td></td>
</tr>
<tr>
<td>• commonly located in front of the legs below the knees;</td>
<td></td>
</tr>
<tr>
<td>• usually resolves spontaneously; each of the nodular lesions shrink and then become flat. They leave a bruised appearance and then resolve completely;</td>
<td></td>
</tr>
<tr>
<td>• simultaneously, as some lesions resolve, other lesions may continue to occur elsewhere. This may go on for weeks to months;</td>
<td></td>
</tr>
<tr>
<td>• may occur as an isolated condition or may be triggered by other conditions – sulfa-related drugs, contraceptive pills, estrogens, streptococcal throat infection, fungal diseases, infectious mononucleosis, sarcoidosis, leprosy, and tuberculosis.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diagnosis is mainly clinical. However, a skin biopsy may be needed to confirm.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate for the underlying cause and treat accordingly:</td>
</tr>
<tr>
<td>• NSAID such as ibuprofen,</td>
</tr>
<tr>
<td>• Colchicine 0.5 mg 2 or 3 times daily,</td>
</tr>
<tr>
<td>• Elevate feet and advise the patient to have bed rest.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yaws (frambesia tropica, polypapilloma tropicum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaws is a chronic condition caused by the spirochaete <em>Treponema pertenue</em>, a subspecies of <em>Treponema pallidum</em> that causes syphilis. Yaws affects skin, bone, and cartilage, and leads to disfigurement and disability. Children and adolescents less than 15 years are most commonly affected with peak incidence 6–10 years. Yaws is:</td>
</tr>
<tr>
<td>• not a sexually transmitted infection,</td>
</tr>
<tr>
<td>• transmitted by direct skin contact with an infected person,</td>
</tr>
<tr>
<td>• endemic in certain tropical areas of Africa, Asia, and Latin America,</td>
</tr>
<tr>
<td>• spread in conditions of overcrowding, poor hygiene, and poor sanitation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are 2 stages of Yaws disease, early (infectious) stage and late (non-infectious) stage.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early (infectious) stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Skin</td>
</tr>
<tr>
<td>o Primary lesions:</td>
</tr>
<tr>
<td>◊ small papule or “mother yaw”, contains large numbers of spirochaetes and is usually on the face or leg;</td>
</tr>
<tr>
<td>◊ initial papule may heal, or persist for months as a raspberry-like “framboesia” lesion, or undergo ulceration.</td>
</tr>
<tr>
<td>o Secondary lesions:</td>
</tr>
<tr>
<td>◊ crops of macules or papules anywhere on the body;</td>
</tr>
<tr>
<td>◊ papillomatous or hyperkeratotic lesions on the palms and soles are painful and disabling.</td>
</tr>
<tr>
<td>o Tender regional lymphadenopathy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Periostitis of the long bones (sabre shin) and fingers (dactylitis).</td>
</tr>
<tr>
<td>o Bone pain is usually worse at night.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late (non-infectious) stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Occurs in 10–20% of untreated patients 5 or more years after infection.</td>
</tr>
<tr>
<td>• Necrotic skin lesions and gumma of the bones cause disabling deformities, such as collapse of the nasal bridge (saddle nose).</td>
</tr>
<tr>
<td>• Palmar and plantar hyperkeratosis may persist.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demonstration of the spirochaete by darkfield microscopy of exudate from lesions.</td>
</tr>
</tbody>
</table>
• Serological tests:
  o There are no specific blood tests for yaws.
  o Non-treponemal tests (VDRL, RPR) and treponemal tests (TPHA, FTA) that are used for diagnosing syphilis can also be used for diagnosing yaws. They do not distinguish between yaws and syphilis.

Treatment
• Benzathine penicillin 1.2 million units as a single intramuscular injection is curative; OR
  o Relapse is very rare.
• Azithromycin oral 30 mg/kg (maximum 2000 mg) single dose.

### 10.1.6 Maculopapular rash

**DDx: Maculopapular rash**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| Drug eruption (see Section 10.1.3) | History of recently starting a new drug (e.g. sulfas, NVP)  
Rash generalized or fixed or discrete  
Red, itchy, maculopapular rash  
With or without mucosal involvement |
| Measles (see Section 10.1.3)       | Fever  
Early rash- head and upper trunk; later rash generalized maculopapular rash over whole body  
May have oral lesions – Koplik’s spots  
No documented measles immunization or history measles as child  
Recent exposure to measles case or local measles outbreak  
Most common in young children but may occur in any non-immune adult  
Women infected while pregnant may have severe complications and/or miscarriage or preterm delivery |
| Measles (see Section 10.1.3)       | Fever  
Early rash- head and upper trunk; later rash generalized maculopapular rash over whole body  
May have oral lesions – Koplik’s spots  
No documented measles immunization or history measles as child  
Recent exposure to measles case or local measles outbreak  
Most common in young children but may occur in any non-immune adult  
Women infected while pregnant may have severe complications and/or miscarriage or preterm delivery |
| COVID-19 (see Section 10.1.3)      | Can be accompanied by an erythematous or maculopapular or morbilliform rash (lacy pattern, petechial rash). See below for other skin manifestations observed in COVID-19. |
| Other viral exanthema               | Fever  
Rash is asymptomatic (non-itchy) maculopapular or papular  
Starts on the face, spreads later to the neck, trunk, and limbs  
With or without oral lesions With or without lymphadenopathy  
Resolves spontaneously |
| Erythema migrans (see Section 11.22 Lyme disease) | Occurs in Lyme disease  
Often in or near the axilla, inguinal region, popliteal fossa, or at the belt line.  
Expands slowly over the course of days or weeks, often with central clearing, and may reach >20 cm  
Initially uniformly red  
Often central clearing, bulls-eye appearance  
No vesicles or necrosis in center  
Not painful but may burn or itch  
Warm to touch |
| Viral haemorrhagic fevers (e.g. EVD) (see section 11.11 and 11.40) | Fleeting maculopapular or morbilliform rash on the torso or face may be one early and relatively specific, although insensitive, indicator of infection (rare, EVD)  
More common in fair-skinned persons, also more difficult to see in dark skin |
| Secondary syphilis (see Section 11.32) | Maculopapular lesions are the most common |
| Leprosy (see Section 11.20)         | With or without maculopapular lesions |
| Cutaneous leishmaniasis (see Section 11.19) | Initially a spot lesion, likely at the site of the insect bite, intense itching  
Painless but may enlarge or ulcerate  
Frequently resolves without treatment if immunocompetent |
| Zika                               | Maculopapular rash, itchy  
Appears in 3–12 days from bite of an infected mosquito, often starts on the trunk and spreads to the face, arms, legs, soles, and palms |
Viral exanthema

- Typically present with a prodrome of fever.

Treatment

- Usually asymptomatic and resolves spontaneously.
- Symptom management only: paracetamol for fever.

COVID-19

Skin manifestations that have been observed in patients with COVID-19 (range from 0.2% in Chinese cohort to 20.4% in Italy) at onset and after hospitalization:\textsuperscript{10,11,12}

- erythematous exanthem (lacey pattern, petechial rash)
- livedo reticularis (mottling)
- cutaneous vasculitis
- acute urticaria
- chicken-pox like blisters

"COVID toes": digital infarcts resulting in black crusted lesions on tips of fingers and toes; can be purple, red, pink or blue lesions that resemble pernio (chilblains) or frostbite mainly observed in young adults and children.\textsuperscript{13}

As these cutaneous manifestations are emerging, dermatologists have developed a COVID-19 registry for physicians globally to share dermatological manifestations of COVID-19.\textsuperscript{14}

\textsuperscript{10} Madigan, Micheletti R, and Shinkai K. How dermatologists can learn and contribute at the leading edge of the COVID-19 global pandemic. JAMA Dermatol. 30 April 2020.


\textsuperscript{14} https://www.aad.org/member/practice/coronavirus/registry
### 10.1.7 Plaques

#### DDx: Plaques and patches with itching

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| **Eczema**                         | Inflamed, scaly patches with or without excoriation  
Pruritus and xerosis               |                                                                                                                                 |
|                                    | Oozing, wet rash arms, legs, trunk, face                                                            |                                                                                                                                 |
|                                    | Any site                                                                                           |                                                                                                                                 |
|                                    | Flexures in atopic eczema                                                                           |                                                                                                                                 |
|                                    | Relapses and remissions                                                                            |                                                                                                                                 |
|                                    | Responds to topical corticosteroids and antihistamines                                              |                                                                                                                                 |
| **Dermatophytosis** (ringworm)     | Scaly patches with central clearing (ring pattern)                                                |                                                                                                                                 |
|                                    | Intense itching                                                                                    |                                                                                                                                 |
|                                    | May involve any site – commonly groin and buttocks                                                 |                                                                                                                                 |
|                                    | On scalp produces localized loss of hair                                                           |                                                                                                                                 |
|                                    | With or without nail involvement (thickening of nail plate, white discoloration of nail plate,    |                                                                                                                                 |
|                                    | lifting of nail plate from nail bed)                                                               |                                                                                                                                 |
|                                    | KOH preparation to demonstrate fungal filaments                                                    |                                                                                                                                 |
| **Psoriasis**                      | Plaques with well-demarcated borders                                                                |                                                                                                                                 |
|                                    | Silvery white scales                                                                                |                                                                                                                                 |
|                                    | Commonly involving extensors: elbow, knees, back and scalp, hairline                                |                                                                                                                                 |
|                                    | With or without nail involvement                                                                   |                                                                                                                                 |
|                                    | With or without joint pain or swelling                                                              |                                                                                                                                 |
|                                    | Chronic course                                                                                     |                                                                                                                                 |
|                                    | In patients with HIV – sudden exacerbations and resistant to therapy                                |                                                                                                                                 |
| **Cutaneous leishmaniasis** (Aleppo boil, oriental sore) | Erythematous or pale patches                                                                       |                                                                                                                                 |
|                                    | On extensor surfaces of the extremities                                                            |                                                                                                                                 |
|                                    | Itching not intense                                                                                |                                                                                                                                 |
|                                    | Frequently resolves without treatment in the immunocompetent.                                      |                                                                                                                                 |

#### DDx: Plaques and patches without itching

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pityriasis versicolor</strong></td>
<td>Scaly, hypopigmented and hyperpigmented macules and patches</td>
</tr>
<tr>
<td></td>
<td>Mainly over the upper trunk, stretching skin accentuates lesions</td>
</tr>
<tr>
<td></td>
<td>Fine, bran-like scaling</td>
</tr>
<tr>
<td></td>
<td>KOH to confirm</td>
</tr>
<tr>
<td><strong>Cutaneous lymphoma</strong></td>
<td>Asymptomatic and of long duration</td>
</tr>
<tr>
<td></td>
<td>Nodules, plaques, and patches</td>
</tr>
<tr>
<td></td>
<td>Skin coloured – slightly erythematous</td>
</tr>
<tr>
<td></td>
<td>Systemic involvement – lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly or splenomegaly</td>
</tr>
<tr>
<td><strong>Crusted scabies (Norwegian scabies)</strong></td>
<td>Extensive crusting (psoriasis-like lesions) with thick hyperkeratotic scales on scalp, face, back, feet, and nails</td>
</tr>
<tr>
<td>(see Section 10.2.3)</td>
<td>Commonly in immunocompromised persons</td>
</tr>
<tr>
<td></td>
<td>Less itching</td>
</tr>
<tr>
<td></td>
<td>KOH preparation to demonstrate mite – very high mite burden</td>
</tr>
<tr>
<td><strong>Leprosy (Hansen’s disease)</strong></td>
<td>Single or multiple</td>
</tr>
<tr>
<td>(see Section 11.20)</td>
<td>Hypopigmented or erythematous or coppery-coloured</td>
</tr>
<tr>
<td></td>
<td>Decreased sensation, hair growth, and sweating over patch</td>
</tr>
<tr>
<td></td>
<td>Peripheral nerve thickening</td>
</tr>
<tr>
<td></td>
<td>Slit skin smear for AFB or skin biopsy</td>
</tr>
</tbody>
</table>
Eczema
There are several types of eczema including seborrhoeic dermatitis, contact eczema, and nummular eczema.

Seborrhoeic dermatitis
Key clinical features
- occurs on the sebum-rich areas of the scalp, face, and trunk;
- the scalp is the most common site of involvement and varies from mild, patchy, scaly areas to widespread, thick, adherent crusts;
- forehead, eyebrows, naso-labial folds, posterior part of the neck, and the postauricular skin may also show similar greasy and scaly lesions over red, inflamed skin;
- in HIV-positive patients, seborrhoeic dermatitis tends to be more severe, to relapse frequently, and to improve on ART.

Treatment
- Aqueous cream.
- Use of keratolytic shampoo containing active agents such as salicylic acid, coal tar, zinc pyrithione, and selenium sulphide reduces both the inflammation and scaling.
  To apply: massage into the scalp and leave for 2–3 minutes before rinsing – good foaming action is required.
- Preparations containing combinations of sulphur and salicylic acid can be applied to the scalp and other affected areas. Topical applications of corticosteroids, or azoles, such as ketoconazole, also are effective.

Mild cases:
- 2% ketoconazole shampoo for scalp (lather over hair, scalp);
  OR
- 2% ketoconazole cream for body sites. Leave on for 5 minutes, then wash off. Repeat daily until cleared (usually 2 weeks). After clearance, continue to use once weekly for 2–3 months to prevent recurrence;
  OR
- If there is no response to topical antifungals, use topical steroids: 1% hydrocortisone cream (including face) or 0.1% betamethasone cream (not on face) twice daily (for a maximum of 3–4 weeks). Once lesions clear, continue with topical ketoconazole for 2–3 months.

Refractory cases:
- Oral itraconazole 200 mg daily for a week followed by 200mg once every 2 weeks for several months.
- Whenever apparent seborrhoeic dermatitis does not respond to appropriate therapy, the diagnosis should be reconsidered.

For other eczemas such as contact eczema, nummular eczema
- Find and avoid contact.
- Severe eczema: use very potent corticosteroids for 3–4 weeks (such as clobetasol propionate); also apply emollient.
- Infected eczema: treat with potassium permanganate (1:10 000) compresses and oral antibiotics, followed by a combination of topical corticosteroid and antibiotic as for impetigo or antiseptic ointment.
- Mild eczema: moderately potent topical corticosteroid (such as clobetasol butyrate); also apply emollient.
- Weeping eczema: as for infected eczema, but without oral antibiotics.
Dermatophytosis (ringworm)
This presents as scaly patches or plaques with an active raised edge and central clearing, and nail infections with thickening, scaling, deformity, and discoloration.
- **scalp ringworm (tinea capitis)** typically appears as a patch of scaling alopecia (loss of hair), or a swollen inflammatory area (kerion);
- **ringworm of the trunk (tinea corporis)**;
- **foot ringworm (tinea pedis or athlete’s foot)** – lesions most commonly and frequently first appear in the fourth interdigital web;
- **ringworm of the groin (tinea cruris)** – limited to the groin, inner thighs, and the skin of scrotum in contact with the thigh.

In PLHIV
There is a high incidence of coexisting nail infection, which has to be treated adequately to prevent recurrences of tinea infection of skin.

**Treatment**
**Topical treatment**
- 1% terbinafine hydrochloride; 
- Other creams and powders containing an imidazole, undecyclinic acid, or tolnaftate.

**Systemic treatment when topical treatment has failed:**
- griseofulvin 500 mg – 1 g daily until cure – for extensive and generalized infections. Much longer courses of treatment are required when nails are affected (Note: Beware of interactions with ART. See Section 13.); OR
- fluconazole 150–300 mg/weekly until cure (6–12 months).

Pityriasis versicolor
- Presents as scaly, hypopigmented and hyperpigmented macules and patches, mainly over the upper trunk. Fine, bran-like scaling is seen (more prominent on stretching skin).

**Treatment**
- sodium thiosulfate, 15%: twice daily for 4 weeks should be started;
- selenium sulfide: a thin layer of undiluted 2% detergent-based suspension should be applied at bedtime to the trunk, groin, upper limbs, and axillae, and rinsed off after 5 to 15 minutes – treatment should be repeated after 3 and 6 days;
- ketoconazole, 2%: applied once or twice daily for several weeks;
- fluconazole: a single oral dose of 400 mg fluconazole is reported to be very effective.
- If there is a recurrence: use pulsed monthly fluconazole or itraconazole for three months.

Psoriasis

**Key clinical features**
- commonly present as erythematous plaques with profuse silvery scales.
- occurs on the scalp, extensor surfaces of the limbs and trunk.
- thickening, pitting, and discoloration of the nails are commonly seen.
- inflammatory arthritis may occur in some patients.
- erythrodermic psoriasis involves >90% of the body surface and usually presents as diffuse scaling.

---

15 Both benzoic acid and salicylic acid (Whitfield's ointment) and gentian violet solution are inexpensive fungistatic compounds. Whitfield's ointment has been deleted from the WHO Essential Medicines List because it can have an irritating effect and requires lengthy treatment, but may be considered as an alternative fungistatic agent in resource-limited settings. Gentian violet has been deleted from the WHO Essential Medicines List due to reports of carcinogenicity.
Treatment
Many types of treatment are available. However, none have been shown to prevent relapses. Topical treatment:
- dithranol ointment (0.1% initially, higher strengths later) – for 2–4 weeks;
- crude coal tar ointment, in combination with ultraviolet B therapy can be very effective;
- emollients containing low concentrations (1%–2%) of salicylic acid are a useful adjunct to treatment;
- topical corticosteroids – for short term treatments for face, flexures, hands and feet.

Systemic treatments
- Give oral antibiotics for guttate psoriasis (amoxicillin for 7 days).
- Systemic therapies are used for extensive involvement, and for psoriasis that is not responding to topical therapies. These involve the use of immunosuppressive drugs, which are expensive, have potentially serious side-effects, necessitate close monitoring of patients, and therefore require referral to a dermatology centre.
- Systemic corticosteroids should not be used because of the risk of severe exacerbations on withdrawal.

10.1.8 Pruritus

DDx: Generalized itching without primary cutaneous lesions

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| Xeroderma | Generalized dry skin  
Without or without scaling  
No evidence of systemic causes |
| Scabies (the seven-year itch) (see Section 10.1.3) | Intense pruritus  
Cutaneous lesions may be very few or hardly visible  
History of similar problem in family or other contacts  
Associated with overcrowding, poor hygiene  
May require therapeutic trial with scabicides |
| Pediculosis corporis (body lice, Vagabond’s disease) | Intense pruritus  
With or without excoriations  
With or without red punctae from bites  
Lice on inner seams of clothing, nits (eggs) on threads of clothing |
| Cimicosis (bed bug infestation) | Redness of the skin, intense itching, difficulty in sleeping at night  
Scratch marks may be secondarily infected  
Bite sites may continue to bleed  
Bug excreta is seen as small black or dark brown stains on bed clothing  
Typical unpleasant bug smell  
Shed off nymphal skin |
| Obstructive jaundice (see Section 8.4) | Jaundice – liver failure  
Leukaemia, lymphoma, internal malignancy, iron deficiency, anaemia and thyroid disease are all causes to be excluded |
| Uraemia | Evidence of renal disease  
Elevated urea |
**Xeroderma**

- Xeroderma is generalized dry scaly skin that may be itchy.
- Causes include: malnutrition, chronic diseases, such as chronic renal failure, liver failure, HIV infection, and internal malignancy.

**Treatment**

Rule out the underlying causes.

- Keep the skin moist. Avoid detergents and other degreasing agents, use soap sparingly or replace with aqueous cream or bath oils.
- Avoid hot baths – rather, advise tepid water. In cold climates, use adequate protective clothing.
- Emollients: preparations such as aqueous creams, emulsifying ointments, or urea should be applied to affected skin once or twice daily. Regular and proper application of emollients is the mainstay of therapy.
- Consider treating for scabies if there is persistent itching in an HIV-positive patient, even if there are no typical lesions.
- Use chlorophenamine or other oral antihistamines to reduce itching.
- Use topical steroids for areas of skin that are very itchy due to secondary eczema.

**Pediculosis**

Infection with lice is usually transmitted directly, by contact, or indirectly, via clothing and linens of infested persons.

**Key clinical features**

- Poor hygiene and infrequent bathing tends to increase the chance of body lice infestations (pediculosis corporis).
- The infection may be localized to the scalp (pediculosis capitis) or the pubic region (pediculosis pubis).
- Pediculosis is characterised by intense itching, with excoriations from scratching.
- Close inspection of the skin reveals both the characteristic red punctae from bites and lice.
- Nits are found attached to clothing.
- Exclude secondary bacterial infection.

**Treatment**

Benzyl benzoate can be used for all types of pediculosis. Apply to affected area AND wash off 24 hours later (further applications possibly needed after 7 and 14 days). Other options follow below.

**Pediculosis capitis** (head lice)

- 1% permethrin preparations should be applied to damp hair and left for 10 minutes before rinsing; OR
- 0.5% malathion preparations should be massaged into the scalp and left for at least 12 hours. Do not use malathion more than once a week or for more than three consecutive weeks;
- Treat all household contacts, and soak all combs and brushes in any of the above preparations for at least 2 hours.

**Pediculosis corporis** (body lice)

- Use powdered preparations of permethrin 5%. Dust clothes, and wash in hot water.

**Pediculosis pubis**

- The treatment (the medication and duration of application) is the same as for head lice and should be applied to the pubic area, thighs, axillae, trunk, and head (including eyebrows).
- Sexual partners should be treated simultaneously.
Symptomatic management of itching

Home care:
- If the affected person has dry skin, moisturize with aqueous cream or petroleum jelly mixed with water.
- Use 1 spoon of oil (bath or vegetable) in the bath water when washing.
- Apply diluted chlorhexidine (0.05%) after a bath.
- Rub the itchy skin with local remedies (examples: effective and safe herbs, cucumber, or wet tea bags or leaves put in a clean piece of cloth and soaked in hot water).
- Advice to the patient on care-seeking: seek help from a trained health worker for painful blisters or extensive skin infection.

Outpatient medication or clinical:
- Assess for bacterial, fungal or viral cause – if present, treat (see other sections in this manual).
- Consider that this may be the side-effects of medication.
- Local steroid creams may be useful if inflammation is present in the absence of any infection (bacterial, fungal, or viral).
- Chlorphenamine 4 mg twice daily, up to 4 mg every 4–6 hours (maximum 24 mg daily), or another antihistamine, may be useful for severe itching. If the itching still persists, a short-acting antihistamine and a long-acting antihistamine (from different groups) could be combined for better symptom relief.
- Consider treating for scabies if there is persistent itching in an HIV-positive patient, even if there are no typical lesions.
- If there are multiple skin infections, use a chlorhexidine (0.05%) rinse after bathing.

Specific management options
- Candidiasis – see Section 11.4.
- Eczema or skin allergies will usually respond to topical steroids, e.g. hydrocortisone, betamethasone, or other.

General management options
- Non-specific itch:
  - avoid heat and hot water
  - moisturise and hydrate dry skin
  - apply calamine lotion
  - menthol 1% in aqueous cream.
- Moisturize and hydrate the skin:
  - generous use of aqueous cream as a soap substitute and bland bath oils can restore skin hydration;
  - apply an emollient (liquid paraffin, coconut oil) immediately after a bath.
10.1.9 Urticaria

Key clinical features

- Lesions are intensely pruritic, erythematous, circumscribed plaques (often with central pallour).
- Individual lesions appear over minutes and disappear within a few hours and are often coalescent.
- Sometimes accompanied by angioedema.
- Often triggered by allergens (e.g. food or drug), insect stings or infection.

Evaluate the patient

- Use Quick Check to evaluate emergency signs – make sure patient is breathing normally and that circulation is not compromised.
- Quickly assess the patient, including a medical history and any history of allergies, with an aim to establishing the cause of hypersensitivity.
  - Any recent exposure to something new or unusual?
  - Did the patient swallow medicine bought from a local drug store?
  - Carry out a thorough medication review and stop all medicines that can potentially cause an allergic reaction.

Treatment

For severe urticaria:

- manage as an inpatient;
- ensure the airway is not compromised;
- establish IV access;
- if shock, give epinephrine (see Quick Check page 15) and follow management in Section 3.1.3 Anaphylactic shock.

For all urticaria:

- ensure there is adequate hydration;
- give an antihistamine, such as chlorphenamine;
- if rash is severe, give IV hydrocortisone 100 mg once then repeat every 6–8 hours. Parenteral steroids can be changed to oral steroids once the rash is under control.
## 10.1.10 Skin ulcers

### DDx: Skin ulcers

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic ulcer</strong></td>
<td>Diabetes, poor blood sugar control&lt;br&gt;Ulcers mainly over extremities (predominately feet)&lt;br&gt;May be deep, with greenish yellow slough and foul-smelling discharge&lt;br&gt;Trophic changes: dry, lustreless skin, hair loss, dystrophic nails&lt;br&gt;With or without peripheral pulses&lt;br&gt;With or without pain</td>
</tr>
<tr>
<td><strong>Buruli ulcer (Bairnsdale ulcer, Searle’s ulcer)</strong></td>
<td>Starts as a painless nodule, an area of induration, or a diffuse swelling of the limbs&lt;br&gt;Develops into massive ulcers in persons with generally good body condition&lt;br&gt;Most commonly occurs on the legs&lt;br&gt;Ulcer has raw base with granulation tissue, undermined margins, may be healing at the centre&lt;br&gt;No pain, fever or regional lymphadenopathy&lt;br&gt;Ulcers heal with marked scarring&lt;br&gt;Can be diagnosed clinically or by direct smear examination, culture, or skin biopsy and demonstration acid-fast bacilli; by histological evaluation of tissue biopsy</td>
</tr>
<tr>
<td><strong>Leprosy (trophic ulcers, Hansen's disease)</strong> (see Section 11.20)</td>
<td>Painless ulcers&lt;br&gt;Mainly over extremities&lt;br&gt;Sensory loss over the extremity&lt;br&gt;Peripheral nerve thickening&lt;br&gt;With or without other features of leprosy</td>
</tr>
<tr>
<td><strong>Guinea worm disease (dracunculiasis)</strong></td>
<td>Very painful lower leg ulcer – often the foot&lt;br&gt;Intensely painful oedema, blister then an ulcer caused by emergence of the long worm&lt;br&gt;Accompanied by intense generalized pruritus&lt;br&gt;Fever, nausea, vomiting, diarrhoea, urticaria may accompany or precede vesicle formation&lt;br&gt;Ulcers often develop secondary bacterial infection&lt;br&gt;Eradicated in the SEA Region</td>
</tr>
<tr>
<td><strong>Anthrax (cutaneous form)</strong></td>
<td>Evolve from papular lesions through to vesicular lesions over 1-6 days&lt;br&gt;Can appear as a depressed eschar with accompanied oedema&lt;br&gt;Link to other suspected cases or to contaminated animal products&lt;br&gt;May be associated with other clinical forms – gastrointestinal, pulmonary, or CNS</td>
</tr>
<tr>
<td><strong>Melioidosis</strong> (see Section 11.23)</td>
<td>Nodule, ulcer or skin abscess&lt;br&gt;Fever and general muscle aches&lt;br&gt;May progress rapidly to bacteremia and septic shock</td>
</tr>
<tr>
<td><strong>Chronic venous ulcers</strong></td>
<td>Large irregular ulcers&lt;br&gt;Typically above the malleoli, medial side of leg&lt;br&gt;Surrounding skin hyperpigmented or eczema&lt;br&gt;Varicose veins, oedema of lower limbs&lt;br&gt;With or without pain</td>
</tr>
<tr>
<td><strong>Arterial ulcers</strong></td>
<td>Intensely painful ulcers, pain at rest&lt;br&gt;Mostly on the legs or feet, more on the lateral side&lt;br&gt;The surrounding skin does not show the pigmentation that is usually seen in venous ulcers&lt;br&gt;Clean ulcers, may show areas of necrosis&lt;br&gt;Absent peripheral pulses with claudication pain</td>
</tr>
<tr>
<td><strong>Sickle-cell disease</strong> (see Section 10.14)</td>
<td>Ulcers most common over lateral malleoli&lt;br&gt;Susceptible to secondary infection</td>
</tr>
<tr>
<td><strong>Tropical ulcers (tropical phagedenic ulcer)</strong></td>
<td>Ulcers with raised, slightly undermined border and a yellowish necrotic base&lt;br&gt;Common sites – legs, feet&lt;br&gt;May heal spontaneously&lt;br&gt;May extend, resulting in deep lesions and penetrate into muscle, tendon, bone&lt;br&gt;Heal with much scar tissue</td>
</tr>
<tr>
<td><strong>Bed sores (pressure ulcers)</strong></td>
<td>Patients bedridden, underweight, malnourished, or dehydrated&lt;br&gt;Common sites: bony areas, such as the head, elbows, heels, hips, shoulders, and tailbone.</td>
</tr>
</tbody>
</table>
Diabetic ulcers
Peripheral arterial occlusive disease is common in diabetics.

Assess for risk factors that predispose the skin to ulcer formation and infection.

- Signs or symptoms of claudication: pain occurring in the arch or forefoot at rest or during the night, absent popliteal or posterior tibial pulses, thinned or shiny skin, absence of hair on the lower leg and foot, redness of the affected area when the legs are dependent, and pallor when the foot is elevated.
- Lack of protective sensation (from sensory neuropathy).
- Decreased sweating (from autonomic neuropathy) leading to dry skin and fissure formation.
- Foot deformities due to atrophy of intrinsic musculature are common in diabetic patients, and lead to focal areas of high pressure.
- Poor glucose control leading to impaired wound healing.
- Poor footwear.
- Obesity.

Investigations

- Blood glucose.
- Plain-film X-rays should be obtained to look for soft tissue gas and foreign bodies, and to evaluate the ulcer for bone involvement.
- The involvement of underlying structures and the presence or absence of ischaemia or infection must be determined before an appropriate wound classification can be made and a subsequent treatment plan instituted.

Treatment

- Control blood sugar (follow national guidelines for chronic management of diabetes);
- Protective footwear,
- Send pus for culture and treat with appropriate empirical antibiotics,
- Debride as necessary,
- May require referral for specialist management.

Venous ulcers
These are a common problem causing considerable morbidity due to chronic venous insufficiency and ulceration.

- Usually shallow, less painful, with oedema, eczema, or hyperpigmentation of the surrounding skin.
- Commonly seen just above the medial malleolus.

Treatment

- Control underlying medical and metabolic disorders, e.g. diabetes, hypertension.
- Leg elevation: elevation of the legs as often as possible promotes venous return.
- Compression: apply an elastocrepe bandage from the ankle to the knee, with higher compression applied to the foot, and decreasing compression as the bandage approaches the knee (see figure below). Compression stockings, if available, may be an effective alternative.
- Secondary bacterial infection should be treated empirically (with broad spectrum penicillin or macrolide, or quinolone antibiotics). Treatment for 2 weeks should cover *S. aureus*. If no response, treatment should include MRSA and Gram-negative organisms (see table in Section 10.1.2).
- Topical antibiotics should be avoided due to the risk of increasing bacterial resistance and contact dermatitis.
- Refer for an evaluation of leg veins or ulcer in order to decide on the need for surgical intervention.
Arterial ulcers
These are commonly caused by atherosclerosis of the medium- and large-sized arteries. Other causes include diabetes, thromboangiitis, vasculitis, thalassaemia, and sickle-cell disease.
- These ulcers typically occur over the toes, heels, and bony prominences of the foot. The surrounding skin may exhibit dusky erythema and may be cool to touch, hairless, thin, and brittle, with a shiny texture. The toenails thicken and become opaque and may be lost.
- There may be gangrene of the extremities with decreased or absent pulse in the dorsalis pedis and posterior tibial arteries.
- Pain may be present when the patient is at rest, and may be alleviated by hanging the foot over the side of the bed or sleeping in a chair.

Treatment
- stop smoking;
- control diabetes, hypertension, and hyperlipidaemia, if present;
- patients may find benefits from sleeping in a bed raised at the head end;
- infection can cause rapid deterioration in an arterial ulcer, and treatment with systemic antibiotics should be started;
- patients with rest pain or worsening claudication, or both, and a non-healing ulcer should be referred to a vascular surgeon;
- opioid analgesia may be necessary during the wait for surgery.

Buruli ulcer (Bairnsdale or Searle’s ulcer)
This is caused by environmental mycobacterium – Mycobacterium ulcerans. The disease causes extensive destruction of skin and soft tissue. It can affect any part of the body but most commonly the limbs, and particularly the lower limbs. It is not usually associated with pain, fever, or lymphadenopathy. More than 50% of those infected are children and adolescents under 15 years of age.

Key clinical features
Pre-ulcerative stage:
- history of a prick by thorn or piece of stick
- subcutaneous nodule, papule or plaque on the skin, OR
- oedematous form:

16 Buruli ulcer. WHO. Available at: http://www.who.int/buruli/en/
Skin

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- diffuse, extensive, non-pitting, swelling,
- firm, painless, ill-defined margins,
- involves part or all of a limb or other part of the body (e.g. face),
- may be accompanied by fever.

Ulcerative stage
- ulcer is chronic and painless (can be massive);
- undermined edges, indurated peripherally and necrotic "cotton-wool" base;
- may have multiple ulcers that communicate beneath the skin;
- may involve underlying bone and joints;
- may be painful if secondarily infected;
- spontaneous healing can occur after months or years;
- healing causes scarring that can cause contractures, restricted movement as well as cosmetic disfigurement;
- squamous cell carcinoma can develop in chronically active ulcers

Investigations
Diagnosis is often made clinically by experienced health workers in endemic areas. Laboratory tests used are as follows:

- Direct smear examination
  - On swabs from ulcers or smears from tissue biopsies
  - Can be done at facilities where TB microscopy is done
  - Sensitivity is low 40% because \textit{M. ulcerans} bacilli are not uniformly located within tissue and their numbers decrease over time.

- Culture of \textit{M. ulcerans}
  - On swabs from ulcers or tissue biopsies
  - Takes 6–8 weeks or more
  - Sensitivity is about 20%–60%.

- Polymerase chain reaction (PCR)
  - On swabs of ulcers or tissue biopsies
  - Results within 2 days
  - Sensitivity is about 98%
  - Not widely available. Newer dry-reagent based PCR has been developed for use in the field and may be used in some district hospital laboratories.

- Histopathology
  - On tissue biopsies
  - Sensitivity is about 90%
  - Useful when the results of the above methods are negative
  - Not widely available.

- Radiological imaging
  - Useful when osteomyelitis is suspected.

Treatment
- Antibiotics for all active disease
  - rifampicin 10 mg/kg daily orally for 8 weeks, PLUS streptomycin 15 mg/kg daily IM for 8 weeks (amikacin is an alternative to streptomycin);\footnote{Amikacin is an alternative to streptomycin.} OR
  - rifampicin plus streptomycin for 4 weeks followed by rifampin plus clarithromycin for 4 weeks (alternative regimen); OR
  - rifampicin plus clarithromycin for 8 weeks (alternative regimen). Dose of clarithromycin is 7.5 mg/kg twice daily (not to exceed 500 mg in a day);
  - nodules or uncomplicated cases can be treated without hospitalization.

- Surgical intervention may be needed in addition to antibiotics
  - debridement to remove necrotic tissue;
  - skin grafting to cover skin defects;
  - correction of deformities and contractures;
amputation;
recurrence after surgery alone is 16%–30%.

- Prevention of disability
  - adequate wound care (cleaning, dressing, bandaging);
  - anti-defectomy positioning;
  - control of oedema (compression, elevation);
  - minimize scarring, fibrosis and adhesions (lubricate skin, massage soft tissue, joint stretching exercises);
  - active participation in daily activities.
- Tetanus immunization is necessary

### Pressure sores (bed sores)
Pressure sores are blisters or breaks in the skin caused when the body's weight stops the flow of blood to a certain area. They are often seen in bedridden, underweight, malnourished, and dehydrated patients over bony areas. The head, elbows, heels, hips, shoulders, and tailbone are the most common sites of involvement.

#### Prevention
It is important to note the following:

- Pressure damage occurs more rapidly if the skin is also subject to friction (skin damage) or lateral shearing forces (capillary damage), both of which occur if patients are pulled instead of lifted.
- All carers need to be taught the correct techniques of lifting and turning patients, paying attention to frequent repositioning in immobile patients (every 2 hours is recommended).
- Prevention of pressure sores is better than cure (which is often impossible).
- Specialized dressings (very expensive) promote healing only if pressure is relieved.
- A pressure area will heal if kept clean and relieved of pressure. Adequate pressure-relieving techniques are needed.

#### Symptom management: bedsores

##### Hospital
- Routine irrigation of pressure sores with warm saline helps remove exudates.
- Antiseptics can delay healing.
- If sores are infected or smelly, the exudates can be removed with 10% betadine solution, diluted to 5% with normal saline to avoid damage to new tissue.
- Avoid remedies, e.g. hypochlorites, that damage granulation tissue.
- Pressure-relieving aids:
  - make sure that the patient does not lie on pressure sores,
  - use foam pads or pillows or water beds to take pressure off the sore,
  - use pillows to keep the knees and ankles apart,
  - when the patient is laying on the back, place a pillow under the lower calves to lift the ankles slightly off the bed,
  - change the patient’s position at least every 2 hours. Advise health workers accordingly if the patient is immobile.
- Physical methods of treatment to promote granulation tissue formation:
  - use ice therapy (to reduce oedema in early pressure areas),
  - treat with ultraviolet light,
  - avoid massage – it can increase skin damage,
  - surgical excision of black necrotic tissue can reduce infection and smell,
  - pain in a deep pressure sore is unusual and suggests pus under a necrotic slough.
- Drugs:
  - oral zinc sulfate improves skin healing,
  - vitamin C given daily (especially if nutrition has been poor),
  - broad-spectrum antibiotics with anti-staphylococcal action (if there is cellulitis),
  - anaerobic antibiotics, such as metronidazole, should be included if there is a foul smell or the patient is ill,
barrier creams – applied generously and covered with gauze.

**Outpatient or primary care**
All patients and health workers need advice on good skin care to avoid pressure problems:
- Check for signs of infection. Exclude other skin diseases.

**Home care**
Do the following to soothe the pain of bedsores and quicken healing:
- For small sores, clean gently with salty water and allow to dry.
- If painful, use paracetamol or aspirin.
- For deep or large sores, clean daily with diluted salt water and cover with a clean, light dressing to encourage healing.
  - Advise how to relieve pressure as in hospital care advice.
- Signs of an infected pressure sore include the following (seek help from a health worker):
  - thick yellow or green pus
  - a bad smell from the sore
  - redness or warmth around the sore
  - swelling around the sore
  - tenderness around the sore.

**Advice to the patient on care seeking**
Seek help from a trained health worker for any discoloured skin, or bedsores that are getting worse.

**Tropical ulcers**

**Key clinical features**
- necrotic painful lesions that result from a mixed bacterial infection;
- occur on the lower legs or feet of children and young adults;
- typically, have a raised, slightly undermined border and a yellowish necrotic base;
- can heal spontaneously, or extend into deep lesions that penetrate into muscles, tendons, or bone;
- untreated – can result in much scar tissue and disability.

**Treatment**
- Daily dressing with 0.01% potassium permanganate or 0.005% silver nitrate solution.
- Systemic treatment with procaine benzylpenicillin, 600 000 IU daily (25 000–50 000 IU/kg for children and adolescents under 12 years) for 2–4 weeks.

**Anthrax**^{18}

*Anthrax* is a notifiable, infectious disease, and is transmitted from infected domestic animals or wild game to humans directly or by indirect contact (their products). See Section 9.

**Key clinical features**
- varies from cutaneous, gastrointestinal, or inhalational involving the respiratory tract;
- skin lesions vary from papule to a blister to an ulcer with a black scab;
- blister or ulcer usually surrounded by much oedema.

**Investigations**
- Swabs from vesicular fluid, or from the base of the ulcer.
- Punch biopsy of papule.
- Blood culture prior to antimicrobial treatment.
- Gram stain isolating a Gram-positive rod-shaped *Bacillus anthracis*.

---

Treatment
Treat localized or uncomplicated cutaneous anthrax for 7 to 10 days:
- ciprofloxacin oral 500 mg twice daily (preferred); OR
- doxycycline oral 100 mg twice daily; OR
- if there is known antibiotic sensitivity, amoxicillin 500 mg 3 times daily; OR
  phenoxyemethylenicillin 500 mg 3 times daily are an alternative.
If serious systemic illness or possible inhalation of anthrax, give multidrug IV antibiotic therapy for 10 to 14 days:
- IV ciprofloxacin 400 mg IV twice daily (preferred) OR in ciprofloxacin-intolerant patients, IV
doxycycline 100 mg twice daily; PLUS
- one or additional IV antibiotics active against \textit{B. anthracis} such as rifampicin, macrolides,
aminoglycosides, vancomycin, chloramphenicol, penicillin, ampicillin, clindamycin, or
clarithromycin is recommended. Use at least one antibiotic with good CNS penetration
(rifampicin, vancomycin, penicillin or ampicillin) and consider clindamycin as a third agent
due to its potential inhibition of toxin production.
If in shock, follow septic shock guidelines in Section 3.1.5.

Prevention
- Prolonged antibiotic prophylaxis is recommended only for persons known to have been, or
  are strongly suspected of having been, exposed to substantial doses of aerosolized spores in
  a deliberate release scenario. Report and seek expert advice if suspected bioterrorism.
  Treatment of bioterrorism-related cutaneous anthrax and post-exposure prophylaxis should
  be for 60 days, preferably with ciprofloxacin.
- Restricted availability of vaccines for humans, reserved for persons in at-risk occupations.
- See \textit{Control of communicable diseases manual\textsuperscript{18}} for prevention of naturally-occurring
  anthrax spread from animals, including livestock vaccination, education of persons in risk
  occupations, etc.
Skin

10. Acute and subacute by symptom: SEARO 2021
10.2 Weight loss and malnutrition

Malnutrition occurs when dietary intake is not balanced with nutritional needs. This Section provides guidance on how to assess, classify and treat patients with malnutrition as a consequence of inadequate dietary intake or disease, exhibited by thinness, weight loss, or nutritional oedema.

Micronutrient deficiencies are also a form of malnutrition. Micronutrient deficiencies are a consequence of reduced micronutrient intake or absorption in the body. The most common forms of micronutrient deficiencies are related to iron, vitamin A, and iodine deficiency. See Section 10.18 for treatment of anaemia.

Significant weight loss is defined as the loss of 5% or more of the body weight over a period of 6 months. A body mass index of <18.5 is defined as malnutrition, although the definition of malnutrition varies in different settings.1

Malnutrition can occur as a primary disorder in adolescents and adults in conditions of extreme deprivation and famine. Malnutrition can also be caused by underlying medical and psychiatric conditions, including:

- infectious diseases such as HIV, TB, parasitic infections, other chronic infections
- cancers
- intestinal malabsorption and liver diseases
- endocrine and autoimmune diseases
- psychiatric and behavioural causes leading to anorexia
- alcohol and other substance dependence
- medications and their side-effects
- situations of dependency or insufficient diet, for example the elderly, and people in prisons.

This Section provides guidance on how to approach patients presenting with significant weight loss, as well as how to manage patients presenting with poor nutritional status.

---

## 10.2.1 Clinical approach to a patient with weight loss

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Perform Quick Check to assess life-threatening conditions and treat urgently.</td>
</tr>
<tr>
<td>2.</td>
<td>Assess and classify nutritional status using anthropometric measures, and clinical signs of nutritional oedema.</td>
</tr>
<tr>
<td>3.</td>
<td>Assess for underlying causes of malnutrition, including manifestations of immunosuppression and opportunistic infections (such as chronic diarrhoea, fever, generalized lymphadenopathy, oral lesions, and cough), and tuberculosis.</td>
</tr>
<tr>
<td>4.</td>
<td>Assess HIV status</td>
</tr>
<tr>
<td>5.</td>
<td>Treat symptomatic and underlying causes of malnutrition</td>
</tr>
<tr>
<td>6.</td>
<td>Treat and monitor patients with malnutrition</td>
</tr>
</tbody>
</table>

The approach to patients presenting with malnutrition includes assessing and classifying malnutrition, as well as determining and then treating the underlying cause. It is important to assess, classify and manage malnutrition, no matter what is the underlying cause.

Current nutritional status is an important indicator of treatment outcome in many conditions. For instance, in persons with HIV, baseline malnutrition has a higher mortality even following ART initiation, and nutritional interventions support treatment retention. ART improves nutritional status, but it can also create additional issues with nutritional implications, such as dyslipidaemia and impaired glucose tolerance.

### Assess the patient for life-threatening conditions and treat urgently

Use the Quick Check at the front of this manual to identify and manage emergency conditions. Patients with significant weight loss could present with severe complications of an underlying systemic disease, or severe complications of malnutrition that require urgent interventions.

### Assess and classify nutritional status using anthropometric measures and clinical signs of nutritional oedema

The following anthropometric measures are essential for nutritional assessment and monitoring response to interventions:

- weight in kg
- height in cm
- mid-upper arm circumference (MUAC) in cm.

Then determine:

- extent of unintentional weight loss – compare with prior measurements
- body mass index (BMI)
- extent of malnutrition.

### Unintentional weight loss

Unintentional weight loss is calculated as the percentage of weight lost from the baseline body weight (BBW) using the following formula:

\[
\% \text{ of weight lost} = \left(\frac{\text{BBW} - \text{current body weight}}{\text{BBW}}\right) \times 100
\]

Significant weight loss is defined as the loss of 5% or more of the body weight over a period of six months. However, any unintentional weight loss should carefully be investigated for underlying systemic causes and treated.
Percentage of weight loss is used for WHO clinical staging of HIV disease, but is not recommended for classification of malnutrition.

**Body mass index (BMI)**
BMI is an indicator used to classify underweight, overweight, and obesity in adolescents and adults. It is defined as the weight in kilograms divided by the square of the height in metres.

\[
\text{BMI} = \frac{\text{weight in kilograms}}{(\text{height in metres})^2}
\]

See the table below. For adolescents, it is recommended to calculate the gender-specific BMI for age.2 See the table on the next page.

BMI requires the accurate measurement of both height and weight. Measurement of weight and height require equipment that must be calibrated and maintained. Basic calibration of weighing scales is included in the clinical practice sessions of IMCI, use of WHO Growth Standards and other courses. Quality assurance is required to ensure that reasonable accuracy of the measurements is maintained.

BMI can be inaccurate in several circumstances:
- Oedema complicating malnutrition or other disorders. Note that patients with malnutrition may exhibit nutritional oedema, presenting as bilateral pitting oedema.
- Pregnancy.

Thus, interpretation of these measurements must always be made within a clinical context.

**Table: Classification of nutritional status of adults who are not pregnant or postpartum and are >18 years of age**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16.0</td>
<td>Severe thinness</td>
</tr>
<tr>
<td>16.0 to 17.0</td>
<td>Moderate thinness</td>
</tr>
<tr>
<td>17.0 to 18.5</td>
<td>Mild thinness</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5 to 24.99</td>
<td>Normal</td>
</tr>
<tr>
<td>25–29.9</td>
<td>Overweight – pre-obese</td>
</tr>
<tr>
<td>≥30</td>
<td>Obese</td>
</tr>
</tbody>
</table>

For adolescents, WHO recommends the use of BMI-for-age as the best indicator of malnutrition, the cut-off value being <3rd percentile2. For adolescent patients below 18 years of age, use the BMI-for-age graph at the end of this Section to assess nutritional status.

---

Table: Classification of nutritional status in non-pregnant, non-postpartum adolescents by body mass index-for-age <18 years of age

<table>
<thead>
<tr>
<th>Body mass index</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-3 SD</td>
<td>Severe thinness</td>
</tr>
<tr>
<td>&lt;-2 SD</td>
<td>Thinness</td>
</tr>
<tr>
<td>-2 SD to +1 SD</td>
<td>Normal</td>
</tr>
<tr>
<td>+1 SD to +2 SD</td>
<td>Overweight</td>
</tr>
<tr>
<td>&gt;+2 SD</td>
<td>Obese</td>
</tr>
</tbody>
</table>

 MUAC

MUAC (mid-upper arm circumference) measures the circumference of the left upper arm in centimetres (cm). It is taken at a point midway between the tip of the shoulder and the elbow. MUAC is a proxy measure of nutrient reserves in muscle and fat that are not affected by pregnancy or oedema and are independent of height. MUAC has often been used as an alternative indicator of nutritional status where the collection of height and weight measurements is difficult, such as during emergencies, famine, or refugee crises, or when reliable scales and height boards are not available.

Although there are no normative WHO guidelines for use of MUAC among persons older than 5 years of age, some programmes use MUAC to assess adults and adolescents. However, data are limited on thresholds to classify nutritional status among adults and adolescents based on MUAC. Global MUAC cut-offs for adult malnutrition classification have not yet been established.4 Ethiopia, Namibia, Uganda and Zambia have developed their own cut-offs to screen for programme eligibility. MUAC is included in the South African maternal record and has been suggested for use in detecting malnutrition in adults in public hospitals.5 New evidence for its utility in assessing adults may emerge from ongoing evidence reviews. UNICEF has published specifications for MUAC tapes for use in adults.6

In the IMAI Acute Care guidelines for the health centre level, adolescents and adults can be classified as having severe malnutrition (“severe undernutrition”), and referred to therapeutic feeding if they have a MUAC <160 mm or an MUAC 161–185 mm plus one of the following7:

- pitting oedema up to the knees on both sides; OR
- cannot stand; OR
- sunken eyes.

This has been used to identify patients for admission for therapeutic feeding.

---

4 Tang, AM, Dong K et al. Use of Cutoffs for Mid-Upper Arm Circumference (MUAC) as an Indicator or Predictor of Nutritional and Health-Related Outcomes in Adolescents and Adults: A Systematic Review. Washington, DC: FHI 360/FANTA, 2013.
Measuring MUAC

1. Have the patient bend her/his left arm to a 90 degree angle. Locate the top of the shoulder and the elbow bone.

2. Using a string between the top of the shoulder and elbow, find the mid of the upper arm and mark with a pen.

3. With the patient’s arm relaxed and resting at her or his side, wrap MUAC tape around the arm at the pen mark. There should not be any space between the patient’s skin and the tape, but avoid wrapping the tape too tight.

4. Read the MUAC in mm from middle window exactly where the arrows point inward. Record the MUAC to the nearest 1 mm (0.1 cm).

Assess for underlying causes of weight loss and malnutrition

Look for clinical manifestations of immunosuppression and opportunistic infections (chronic diarrhoea, fever, generalized lymphadenopathy, oral lesions and cough). Assess for TB.

Evaluate the patient by taking a history, a thorough physical examination, and performing laboratory investigations:

- to assess the significance and intentionality of the weight loss
- to look for underlying systemic causes of weight loss

Refer to the DDx tables Loss of weight and Weight loss, while on antiretroviral therapy for the likely differential diagnosis.

History

Use the history to help identify root causes and rate of weight loss.

Ask about:

- weight change and how much, changes in belt notch, changes in the fit of clothing
- fever and night sweats
- diarrhoea
- pain
- cough or shortness of breath
- skin changes
- dietary history:
  - loss of appetite,
  - difficulty eating, dysphasia, sore throat,
  - anorexia,
  - nausea,
  - change in food availability, income, or number and health of persons in household.
- use of alcohol
- medications
- presence of pregnancy or LMP
risk factors for HIV or HIV status, if known
polyuria, polydipsia, polyphagia, nocturia, blurry vision
gynaecological symptoms (vaginal bleeding, discharge, pelvic pain)
water supply, sanitation, and hygiene.

**Physical examination**

**Look for:**
- general appearance: weak, hunched over, slowed movements, wasted appearance, distribution of fat (lipodystrophy or lipoatrophy);
- vital signs: hypotension, tachycardia, fever or hypothermia, tachypnoea;
- skin: pallour, jaundice, hyperpigmentation, turgor, non-healing sores, hair loss, lanugo;
- mouth: dry mucous membranes, thrush, ulcers;
- neck: lymphadenopathy, thyromegaly;
- musculoskeletal and extremities:
  - muscle wasting or contraction;
  - oedema of extremities: examine ankles and lower legs for pitting oedema. If symmetrical, oedema is present and its cause must be determined. In adults, nutrition-associated oedema frequently presents as bilateral pitting oedema, facial oedema, and ascites. In addition to malnutrition, causes of oedema include pre-eclampsia (in pregnant women), severe proteinuria (nephrotic syndrome), nephritis, acute filariasis (the limb is hot and painful), heart failure, and wet beriberi. Non-nutritional causes of oedema can readily be identified by the history, physical examination, and urinalysis. See Section 10.4.
- cardiac, pulmonary, abdominal exam;
- rectal and vaginal examination;
- neurological and psychiatric assessment.

**Investigations**

**Essential**
- HIV testing and CD4 count, if positive
- stool examination (for occult blood, ova, or parasites)
- haemoglobin
- full blood count (FBC)
- sputum AFBs, or other additional investigation, if smear-negative, or pulmonary or extrapulmonary, TB is suspected (see Section 15)
- check glucose – blood or urine to exclude diabetes mellitus
- urine dipstick – protein, blood, or glucose.

**Additional**
- blood tests as necessary – check renal, liver, thyroid functions
- ultrasound
- cancer screening (for example, VIA for cervical cancer, feel for masses or abnormal lymph nodes).

A detailed nutrition and diet history, as well as an assessment of symptoms associated with weight loss, helps in identifying any underlying diseases. The availability of adequate food and household food security should also be assessed.
10.2.2 Consider the likely cause of loss of weight

Use the first differential diagnosis table for all patients to identify a diagnosis or underlying cause of weight loss. In PLHIV on ARV therapy, there are additional causes for weight loss that should be considered; these appear in the second DDx table below. If the patient is a known HIV-positive individual or is taking antiretroviral treatment, also see HIV guidelines for the management of weight loss in people with HIV after using this Section.

### DDx: Loss of weight

<table>
<thead>
<tr>
<th>Consider as diagnosis or underlying cause</th>
<th>If patient has</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly controlled diabetes</td>
<td>Polyuria and polydipsia</td>
</tr>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
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<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Raised blood glucose</td>
</tr>
<tr>
<td>Other chronic diseases: CHF, COPD, other</td>
<td></td>
</tr>
<tr>
<td>chronic lung disease</td>
<td></td>
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<tr>
<td>Peptic ulcer disease, gastritis</td>
<td>Chronic vomiting</td>
</tr>
<tr>
<td>Hyperemesis in pregnancy</td>
<td>Pregnancy, especially first trimester</td>
</tr>
<tr>
<td>Substance use</td>
<td></td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Thyroid enlargement and proptosis</td>
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<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Palpitations and tachycardia</td>
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<tr>
<td></td>
<td>Heat intolerance, excessive sweating, tremor</td>
</tr>
<tr>
<td></td>
<td>Nervousness</td>
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<tr>
<td></td>
<td>Brisk reflexes</td>
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<tr>
<td></td>
<td>Low TSH</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Fever</td>
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<tr>
<td></td>
<td>Night sweats</td>
</tr>
<tr>
<td></td>
<td>Cough (especially chronic or persistent)</td>
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<tr>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Sputum or FNA AFB positive</td>
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<tr>
<td></td>
<td>Exudative ascites or pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray – suggestive changes</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – abdominal lymphadenopathy</td>
</tr>
<tr>
<td>HIV wasting syndrome</td>
<td>Loss of weight &gt;10% from baseline (WHO clinical stage 3)</td>
</tr>
<tr>
<td></td>
<td>Chronic diarrhoea or fever longer than 1 month with unexplained cause (WHO</td>
</tr>
<tr>
<td></td>
<td>clinical stage 3)</td>
</tr>
<tr>
<td></td>
<td>Known HIV-positive</td>
</tr>
<tr>
<td>Chronic diarrhoea, e.g. cryptosporidiosis,</td>
<td>Diarrhoea &gt;1 month</td>
</tr>
<tr>
<td>isosporiasis, HIV enteropathy</td>
<td>Not responsive to empirical therapy</td>
</tr>
<tr>
<td>(see Section 8.3 and HIV guidelines)</td>
<td>Known HIV-positive</td>
</tr>
<tr>
<td></td>
<td>Low CD4 count</td>
</tr>
<tr>
<td></td>
<td>Other WHO clinical stage 4 defining condition</td>
</tr>
<tr>
<td>Other neglected tropical diseases (NTD)</td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium avium</em> complex (MAC)</td>
<td>Fever</td>
</tr>
<tr>
<td>(see Section 11.25)</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Known HIV-positive</td>
</tr>
<tr>
<td></td>
<td>Low CD4 count</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>(see Sections 10.5b Painful or difficult</td>
<td>Odynophagia, dysphagia, and retrosternal chest pain</td>
</tr>
<tr>
<td>swallowing and 11.4 Candida)</td>
<td>Responsive to fluconazole</td>
</tr>
<tr>
<td>Malabsorption syndromes, e.g. celiac</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td>disease, sprue</td>
<td>Distended abdomen with bloating</td>
</tr>
<tr>
<td></td>
<td>Loose fatty stools (steatorrhoea)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Symptoms vary according to site of malignancy, e.g. cervical, Kaposi sarcoma,</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>Evidence of primary tumour, evidence of metastases</td>
</tr>
<tr>
<td>Starvation</td>
<td>Poverty and lack of availability of food</td>
</tr>
</tbody>
</table>
| Depression  | Sad or low mood  
|-------------|-----------------|
|             | Fatigue or loss of energy  
|             | Loss of appetite  
|             | Sleep disturbances  
|             | Previous history of depression  

| Eating disorders, e.g. anorexia nervosa, bulimia  | Abnormal focus on eating behaviour, body shape, and weight  
|--------------------------------------------------|--------------------------------------------------|
|                                                   | Avoidance of food  
|                                                   | Adequate food available, no organic cause found  

| Other psychiatric disorders, e.g. psychosis  | Delusions about food  
| (see Section 10.10)                         |                     

| Dementia with poor care  | Forgetfulness  
| (see Section 10.10)      | Misplacing things  
|                         | Difficulty in carrying out daily routines  
|                         | Lack of caretaker or support system.  

**DDx: Weight loss while on antiretroviral therapy – consider all of the above, plus:**

<table>
<thead>
<tr>
<th>Diagnosis or underlying cause</th>
<th>In favour</th>
</tr>
</thead>
</table>
| IRIS (Immune reconstitution inflammatory syndrome) | Usually starts within 2–3 weeks of initiating ART  
| (see HIV guidelines) | Fever, sweats  
|                     | Possibly enlarging lymph nodes  
|                     | Cough  
|                     | Evidence of pathogen or disease, e.g. chest X-ray changes  

| Opportunistic infection, e.g. tuberculosis | Symptoms of specific OI, e.g. fever, night sweats, cough, lymphadenopathy, diarrhoea  
| (See HIV guidelines) | Low CD4 count  

| Symptomatic hyperlactataemia or lactic acidosis | Many months on ART, good adherence  
| (See HIV guidelines) | On AZT or d4T-containing regimen (or ddI)  
| | Nausea and vomiting  
| | Abdominal pain  
| | Dyspnoea (late stage) with deep breathing  
| | Dehydration  
| | No evidence of new OIs  
| | Low bicarbonate, high anion gap  
| | High lactate  
| | High CD4 count  
| | Undetectable viral load  

| Lipoatrophy (as part of lipodystrophy) | Months to years of successful ARV therapy  
| (See HIV guidelines) | d4T-containing ARV regimen  
| | Fat wasting, particularly of face, arms, and legs  
| | No constitutional symptoms  
| | Normal chemistries  
| | High CD4 count  
| | Viral load undetectable  

| Treatment failure and HIV disease progression | On antiretroviral drugs >6 months  
| (See HIV guidelines) | Features of HIV – new Stage 2, 3, 4 events  
| | Decreasing CD4 – see ART failure section  
| | High viral load (failing ARV regimen)  

| Lymphoma | Non-tender, enlarging nodes  
|          | Systemic symptoms: fever, weight loss, night sweats, malaise, itch  
|          | Evidence of spread to skin, CNS, gut, lung, bone marrow  
|          | Low CD4 count  
|          | Histology – B or T cell proliferation  

| Inadequate food security | Good adherence, no evidence of OIs, insufficient food or no stable livelihood.  
|-------------------------|-------------------------------------------------|
10.2.3 Treat weight loss and malnutrition and its underlying causes

Having used the differential diagnosis tables to determine the diagnosis or underlying cause contributing to the weight loss or malnutrition, treat both the immediate symptomatic as well as the underlying causes at all levels. For example, in the case of oral or oesophageal candidiasis, symptomatic treatment for mouth pain and odynophagia should be offered, as should treatment with antifungal agents. Stage HIV disease using clinical (WHO clinical stage 3 and 4) or immunological (CD4 count ≤350 cells/mm³) criteria, and initiate ART if eligible. See HIV guidelines.

Refer to various Sections of this manual based on likely diagnoses.

Treat and monitor patients with poor nutritional status

Treat moderate malnutrition in outpatient care

Moderately thin adolescents and adults require an additional 20%–30% calorific intake that should be provided, in addition to their normal intake, in the form of frequent smaller amounts of locally available nutrient-rich food. Recommend diet considering those needs.

If available, enrol the person in a programme where nutritional assessment, counselling, and support including supplementary feeding are available.

Undernutrition is a major problem among older adults, affecting up to 22% of them. Age-related physiological changes increase the risk of undernutrition and subsequent physical and cognitive impairments. Undernutrition in the elderly leads to reduced bone and muscle mass, increased frailty, diminished cognitive function and ability to care for oneself, and thus a higher risk of becoming dependent on care.

- In older adults with undernutrition (BMI <18.5 kg/m²), give oral supplemental nutrition with dietary advice. Evidence indicates that oral supplemental nutrition can significantly reduce mortality and improve weight gain.
- Assess muscle mass and muscle strength as part of the assessment of nutritional status.
- Give dietary counselling, to ensure a healthy diet with adequate energy, protein and micronutrients for all older people, including those who are at risk of or affected by undernutrition. Protein absorption decreases with age, and thus standard protein intakes may not be sufficient for older adults. 9

For all patients with active tuberculosis and moderate undernutrition, Nutritional assessment, counselling, and management for persons with active tuberculosis and moderate undernutrition.

Determine and treat the underlying cause of malnutrition. Offer nutritional counselling and information for weight gain. Encourage small and frequent meals. Treat nausea, thrush, and diarrhoea when indicated. Link or refer to community or home-based nutritional interventions or food security initiatives, if possible. Ensure follow-up visits and assessment.

Treat severe malnutrition

Adolescents and adults with severe malnutrition may be managed as outpatients in a food-by-prescription programme, providing that they are ambulatory (good Karnovsky score) and do not

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8 The WHO Department of Nutrition for Health and Development (NHD) is developing evidence-based guidelines for nutritional interventions and has established the Nutrition Guidance Expert Advisory Group (NUGAG) to conduct evidence reviews and recommendations. A training course in nutritional care and support for people living with HIV is available at http://www.who.int/nutrition/publications/hivaid/9789241591898/en/index.html

9 Essential nutrition actions: mainstreaming nutrition through the life-course. WHO Geneva 2019
have a medical condition that requires hospital admission. Those with severe malnutrition should be treated as inpatients if an outpatient therapeutic feeding programme does not exist.

**Hospital care of malnutrition**

**Initial treatment (stabilization):**
If able to consume food, patients with severe malnutrition require ready-to-use therapeutic foods. Therapeutic foods should not be combined with additional vitamins and minerals, since they are already fortified at levels considerably higher than the RDA, to correct deficiencies and allow rebuilding of lost tissues.

The initial goal of treatment is to prevent further tissue loss. The amount of food given per kg of body weight is much less for adults than for children, and decreases with increasing age reflecting the lower energy requirements of adults. Recommended amounts for different ages are given in the table on the next page. These amounts will meet all nutrient requirements of adolescents and adults. Nasogastric tube feeding should only be used when there is no alternative.

Adolescent and adult patients who have severe malnutrition can be given any or all of the following: ready-to-use food, fortified blended flours, formula milks (F75, F100), as available.

**Table: Dietary requirements for initial treatment of severely malnourished adolescents and adults**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Daily energy requirements</th>
<th>Volume of diet required (ml/kg per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Kcal/kg)</td>
<td>(KJ/kg)</td>
</tr>
<tr>
<td>7–10</td>
<td>75</td>
<td>315</td>
</tr>
<tr>
<td>11–14</td>
<td>60</td>
<td>250</td>
</tr>
<tr>
<td>15–18</td>
<td>50</td>
<td>210</td>
</tr>
<tr>
<td>19–75</td>
<td>40</td>
<td>170</td>
</tr>
<tr>
<td>&gt;75</td>
<td>35</td>
<td>150</td>
</tr>
</tbody>
</table>

* Individual needs may vary up to 30% from these figures depending on sex, activity level, infections and other factors. 
* F-75 and F-100 are therapeutic milk products designed to treat severe malnutrition. Ingredients include concentrated milk powder, food oil, and dextrin vitamin complexes. The designations mean that the product contains respectively 75 and 100 kcsals per 100 ml.

Severely malnourished adults and adolescents are also susceptible to hypothermia, hypoglycaemia, and dehydration. Treat and prevent hypothermia, hypoglycaemia (see Quick Check page 28), and dehydration (see Section 8.3).

Adolescent and adult patients who have severe malnutrition should be assessed for co-existing medical conditions and provided with appropriate treatment.

Ready-to-use food has been shown to be very effective for children with severe acute malnutrition. It has recently been used for PLHIV. Ready-to-use food has potential in this area as it is energy- and nutrient-dense, can be made with an appropriate balance of nutrients, and does not require cooking. Its high energy density means that sufficient calories can be delivered without the patient being expected to digest large bulky meals. Adaptations and alternative formulations for adults and specific patient groups are underway. These are relatively expensive, and cost-effectiveness is a consideration.

Care should be taken when administering intravenous feeds and fluids to patients with unknown cardiac status and albumin levels, as severe oedema (including pulmonary oedema) may result.

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In patients with HIV, antiretroviral medication should not be stopped during re-feeding, unless there are other reasons to stop the medications. For a patient who is not yet receiving ARVs, ART should not be initiated during the initial management of severe acute malnutrition (stabilization phase) but should start during or after the rehabilitation phase. The rehabilitation phase after which ART should be initiated is short (several days up to 2 weeks). When possible, find out what may be causing the loss of weight and manage accordingly. Use the above differential diagnosis tables of Loss of weight and Weight loss in the previous section while on antiretroviral therapy.

**Rehabilitation**

An improving appetite indicates the beginning of rehabilitation. During rehabilitation, it is usual for adolescents and adults to become very hungry, sometimes refusing the specialized foods and requesting enormous amounts of other foods. When this happens, a diet should be given that is based on traditional foods, but with added oil, mineral mix, and vitamin mix. Provide a wide variety of nutrient-dense foods, and allow the patient to eat as much as she or he desires. In the rehabilitation phase, adolescent and adult patients recovering from severe malnutrition should continue to receive therapeutic foods plus traditional foods with added oil, vitamins and minerals, as tolerated.

If possible, continue to give the formula feed with the vitamin and mineral mixes between meals and at night. If necessary, present the formula feed as a medicine.

**Criteria for discharge**

Severely malnourished adolescents and adults can be discharged when:
- they are eating well and gaining weight
- they have a reliable source of nutritious food outside the hospital
- any other health problems have been diagnosed and treatment has begun.

Adults should continue to receive a supplemented diet as outpatients until their BMI is >18.5; for adolescents, their diets should be supplemented until their BMI-for-age is >5th percentile of the median NCHS/WHO reference values.²

**Failure to respond to treatment**

Failure to respond to treatment in adults and adolescents is usually due to an unrecognized underlying illness, a nutrient deficiency, or refusal to follow the treatment regimen.

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**10.2.4 Prevent malnutrition/undernutrition**

**10.2.4.1 Prevent malnutrition during illness**

Encourage the sick person to eat, but do not use force as the body may not be able to accept it, and the patient may vomit.
- Offer smaller, attractive meals of what the sick person likes more frequently.
- Let the sick person choose the foods she or he desires to eat from what is available.
- Encourage the patient to eat nutrient-dense foods that are locally available.

Monitor weight and address causes of weight loss before the patient develops malnutrition.

Special nutrition prevention for certain diseases, for example:
- For all persons with active tuberculosis, nutritional assessment and counselling
- Feeding protocols for adults and children older than six months with viral haemorrhagic fever (including Ebola, Marburg and Crimean-Congo haemorrhagic fever).¹¹

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¹¹ Essential nutrition actions: mainstreaming nutrition through the life-course. WHO Geneva 2019
Advice to patient on care-seeking: Seek help from a trained health worker if you notice rapid weight loss or if the sick person consistently refuses to eat any food or is not able to swallow.

Community nutrition delivery mechanisms have been shown to be effective in many programmes. Community-based feeding programmes and home-based care share many common components, including emphases on physical care, a continuum of care, health education, local capacity-building, ensured access, sustainable support, and community-based case-finding strategies.

If available, enrol the person in a programme where nutritional assessment, counselling, and support, including supplementary feeding, are available. Determine and treat underlying causes of malnutrition. Offer nutritional counselling and information for weight gain. Encourage small and frequent meals. Treat nausea, thrush and diarrhoea when indicated. Link or refer to community- or home-based nutritional interventions or food security initiatives, if available.

To prevent malnutrition in PLHIV, where feasible, recommend home care for adolescents and adults living with HIV.12

10.2.4.2 Prevent malnutrition/undernutrition by supplementation, preventive treatment or nutrition counselling13

- In settings where the baseline prevalence of any soil-transmitted infection is 20% or more, deworm non-pregnant and pregnant women.
- In settings where the prevalence of infection with soil-transmitted helminths (hookworm and/or *T. trichiura*) among pregnant women is 20% or more and where anaemia is a severe public health problem (40% or higher among pregnant women), deworm pregnant woman after the first trimester.
- In settings where the prevalence of anaemia in non-pregnant women is 40% or higher:
  - give daily iron supplementation for menstruating non-pregnant adolescent girls,
  - give daily iron supplementation for non-pregnant women (15–49 years).
- In settings where the prevalence of anaemia in non-pregnant women is 20% or higher, give intermittent iron and folic acid supplementation for non-pregnant women (15–49 years)
- In settings where the prevalence of anaemia in non-pregnant women is 40% or higher,
- Give dietary counselling, to ensure a healthy diet with adequate energy, protein and micronutrients for all older people, including those who are at risk of or affected by undernutrition. Protein absorption decreases with age, and thus standard protein intakes may not be sufficient for older adults.

See IMPAC or other pregnancy guidelines for interventions for pregnant women.

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13 Essential nutrition actions: mainstreaming nutrition through the life-course. WHO Geneva 2019
10. Acute and subacute by symptom: SEARO 2021

Weight loss and malnutrition

BMI-for-age GIRLS
5 to 19 years (z-scores)

BMI (kg/m²)

Obesity
Overweight
Normal
Thinness
Severe thinness

Age (completed months and years)

Months
Years
10 3 6 9 5 6 9 2

2007 WHO Reference
Weight loss and malnutrition

10. Acute and subacute by symptom: SEARO 2021

BMI-for-age BOYS

5 to 19 years (z-scores)

2007 WHO Reference
10.3 Swelling of the limbs

Swelling of the limbs may be:
- **bilateral**, usually due to:
  - oedema (defined below)
- **unilateral**, due to:
  - infections (e.g. cellulitis)
  - blocked veins (e.g. by blood clot or compression)
  - blocked lymphatic duct (e.g. by tumour or infections)
  - trauma and bleeding.

The swelling may be subtle and only found on examination, or the patient may complain of:
- swollen limbs
- unexplained weight gain
- tightness of rings or shoes
- other symptoms associated with the primary cause.

If the swelling involves the whole body the patient may complain of:
- facial swelling or puffiness.

**Oedema** is fluid collecting in the interstitial spaces and is found in dependant areas, e.g. the legs (in ambulant patients) or the sacrum (in bed-bound patients).

**Anasarca** is when the oedema and swelling is generalized and affects the whole body and not just the legs.

### 10.3.1 Clinical approach to swelling of the limbs

<table>
<thead>
<tr>
<th>Step 1:</th>
<th>Perform Quick Check. In women, consider pre-eclampsia (pregnancy with raised blood pressure). Ask about a possible snake or other animal bite, as this may require urgent attention.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2:</td>
<td>Take a history and examine the patient. Determine the extent and duration of the swelling.</td>
</tr>
<tr>
<td>Step 3:</td>
<td>Assess HIV status</td>
</tr>
<tr>
<td>Step 4:</td>
<td>Classify using DDx tables and consider likely differential diagnoses</td>
</tr>
<tr>
<td>Step 5:</td>
<td>Perform investigations that may confirm your diagnosis</td>
</tr>
<tr>
<td>Step 6:</td>
<td>Initiate treatment and monitor response</td>
</tr>
</tbody>
</table>

**History**

**General**

Is the limb swelling unilateral or bilateral?
- **Is the onset:**
  - acute (within the previous day)
  - subacute (over the past week)
  - chronic and long-standing?
Swelling of the limbs

- Is there associated pain or tenderness?
- Is there associated lymphadenopathy?
- Does the patient have fever?
- Ask about the possibility of pregnancy.

For generalized oedema, ask about symptoms that may indicate an underlying cause.

- **cardiac:**
  - dyspnoea on exertion
  - orthopnoea (difficulty lying flat)
  - paroxysmal nocturnal dyspnoea (PND) (shortness of breath at night)
  - known cardiac disease.

- **liver:**
  - history of liver disease or jaundice.

- **renal disease**

- **low-protein states:**
  - malnutrition
  - chronic diarrhoea.

### Examination

#### General

- Assess the extent of the swelling:
  - Is it bilateral or unilateral?
  - Does it involve only the upper or lower limbs or the whole body?

- **Is the swelling pitting?**
  - Pitting can be demonstrated by applying firm pressure to the swollen area with the thumb (preferably over a bone, e.g. the anterior tibia). Pressure is applied for a few seconds, and if an indentation persists after the release of the pressure, it is referred to as pitting oedema.

### Look for an underlying cause

- **Blood pressure** – particularly if pregnant.

- **Look for local causes:**
  - tumours or nodules on the skin – e.g. Kaposi sarcoma
  - any infection or inflammation of the limb
  - enlarged lymph nodes draining the site.

- **Look for other causes:**
  - evidence of congestive cardiac failure, particularly elevated JVP
  - evidence of liver disease – assess the size and consistency of the liver, look for signs of chronic liver disease (see Sections 8.4 Jaundice and 10.8 Ascites).

- **Assess other systems:**
  - pulmonary oedema or pleural effusion
  - ascites (see Section 10.6 Ascites)
  - evidence of Kaposi sarcoma elsewhere.

### Assess HIV status
## 10.3.2 Differential diagnosis of oedema

Classify the swelling according to the:

1. **extent** – unilateral (confined to a single limb) **or** bilateral or generalized and
2. **duration** – acute or subacute in onset or long-standing.

### DDx: Unilateral limb swelling

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute onset</strong></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>Low grade fever &lt;38.5°C</td>
</tr>
<tr>
<td></td>
<td>Risk factors – immobilization or trauma to pelvis, limb, long haul bus or plane</td>
</tr>
<tr>
<td></td>
<td>travel, pregnancy, malignancy</td>
</tr>
<tr>
<td></td>
<td>Calf pain and tenderness</td>
</tr>
<tr>
<td></td>
<td>Swelling of leg with pitting oedema, erythema</td>
</tr>
<tr>
<td>Cellulitis (see Section 10.1)</td>
<td>Systemically ill – fever and tachycardia</td>
</tr>
<tr>
<td></td>
<td>Redness and inflammation of the skin and subcutaneous tissue</td>
</tr>
<tr>
<td></td>
<td>Old bite or sore</td>
</tr>
<tr>
<td></td>
<td>Laboratory – high WCC</td>
</tr>
<tr>
<td>Local injury</td>
<td>History of trauma or sprain</td>
</tr>
<tr>
<td></td>
<td>Bruising</td>
</tr>
<tr>
<td></td>
<td>Pain with movement or weight-bearing</td>
</tr>
<tr>
<td>Snake-bite (see Section 3.9)</td>
<td>History of bite</td>
</tr>
<tr>
<td></td>
<td>Rapidly progressive swelling</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td><strong>Subacute or chronic</strong></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>HIV-positive</td>
</tr>
<tr>
<td></td>
<td>Purple plaques and nodules</td>
</tr>
<tr>
<td>Lymphatic obstruction</td>
<td>History of malignancy (e.g. Kaposi sarcoma, breast, pelvic), surgery or radiation to the area</td>
</tr>
<tr>
<td></td>
<td>Non-pitting oedema</td>
</tr>
<tr>
<td></td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td>Enlarged lymph nodes</td>
</tr>
<tr>
<td>Lymphatic filariasis (see 11.14)</td>
<td>Insidious onset</td>
</tr>
<tr>
<td></td>
<td>Non-tender</td>
</tr>
<tr>
<td></td>
<td>Endemic area</td>
</tr>
<tr>
<td>Venous insufficiency (e.g. post DVT)</td>
<td>Prior history of DVT</td>
</tr>
<tr>
<td></td>
<td>Distended veins.</td>
</tr>
</tbody>
</table>

---

10. Acute and subacute by symptom: SEARO 2021

Swelling of the limbs 10.3 – 55
DDx: Bilateral limb swelling or generalized swelling

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute onset</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Cardiac failure** | History of heart disease  
Dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea  
Pitting oedema of legs  
Hepatomegaly  
Crackles in chest, S3 gallop  
Elevated JVP |
| **Renal disease – acute nephritic syndrome**  
see Section 5.3 | Hypertension, oliguria  
Urine dipstick: macroscopic haematuria, red cell casts, dysmorphic RBCs, leukocytes and some proteinuria |
| **Subacute or chronic** | |
| **Renal disease – nephrotic syndrome**  
see Section 5.3 | Pitting oedema  
Anasarca with periorbital oedema  
Urine dipstick: proteinuria  
Abnormal renal function tests |
| **Severe malnutrition**  
see Section 10.2 | Wasted  
Hair loss  
Hyperpigmentation  
Facial oedema  
Ascites may be present  
Low serum albumin |
| **Chronic liver disease, cirrhosis** | Jaundice, palmar erythema, spider angioma, caput medusae  
Splenomegaly, ascites  
Fetor hepaticus  
Gynaeacomastia  
Duputren's contracture  
Elevated LFTs: elevated AST, ALT, alkaline phosphatase  
*Low serum albumin level*  
*Prolonged INR* |
| **Pretibial myxoedema – hyperthyroidism** | Heat intolerance, sweating, tremor, tachycardia  
Weight loss  
Constipation  
Fatigue  
Irregular menstrual flow  
Non-pitting oedema – nodular appearance above the malleoli |
| **Portal vein obstruction** | Known history  
Abdominal distension  
Splenomegaly  
Normal LFTs. |

Perform investigations
- urine dipstick – protein, glucose
- blood glucose
- serum albumin, protein
- renal function test (serum creatinine, BUN)
- liver function tests
- ultrasound of the abdomen or pelvis
- *doppler ultrasound* of the limbs – if DVT suspected.
10.3.3 Treatment of limb swelling with pitting oedema

- It is important to identify the underlying cause in order to give specific treatment:
  - For bilateral pitting oedema due to interstitial fluid (such as cardiac, renal, or liver failure), give diuretics.
  - Do not give diuretics for lymphatic obstruction or other causes of non-pitting oedema (lymphoedema).

- furosemide 40–80 mg:
  - diuresis should occur within 1 hour and lasts 6 hours; preferred treatment in most cases of oedema.
    - hypotension can occur
    - hypokalaemia can occur (see Section 5.2)
    - avoid at night (sleep disturbance)
    - high doses needed in renal failure (see Section 11.28).
  - Infuse furosemide slowly (not more than 4 mg/minute).

- amiloride 5–10 mg daily
  - potassium-sparing diuretic
  - given with furosemide to prevent hypokalaemia
  - do not give if hyperkalaemia or renal failure.

- spironolactone 100–200 mg daily (can give up to 400 mg), given with furosemide:
  - preferred combination in cirrhosis and end-stage heart failure
  - potassium sparing diuretic
  - causes nausea, gynaecomastia
  - contraindicated in hyperkalaemia and hyponatraemia.

- hydrochlorothiazide 25 mg daily
  - use in combination with furosemide for resistant generalized oedema but not in cirrhosis
  - avoid if the patient also has gout
  - hypokalaemia can occur.

10.3.4 Symptom management of pitting oedema

In addition to treatment of infection or diuretic treatment for pitting oedema, several interventions can reduce morbidity.

- Exercise
  - flex the ankles
  - walking reduces ankle oedema

- Elevation of the legs
  - legs should be above horizontal
  - support the whole limb

- Compression stockings

- Compression pump
  - shifts soft oedema very rapidly
  - beware of precipitating heart failure by sudden shift of fluid
  - keep pressure below 60 mm Hg
  - follow up with a support stocking

- Skin care
  - use bland non-scented products for daily cleansing and moisturizing
  - compression and good skin care can reduce the occurrence of leakage, lymphocele, papilloma
  - non-adherent dressings can reduce leakage
  - try support stockings (above the knee). Stop if uncomfortable
  - provide good skin care to prevent cellulitis and infection (see Sections 10.1).
10.3.5 Manage lymphoedema (non-pitting oedema)

- **Treatment**
  - diuretics not indicated, and not effective
  - elevation
  - exercise
  - bandages
  - compression garments
  - massage (manual lymph drainage)
  - compression pump
  - antibiotics if cellulitis develops – see Section 10.1.

- **Prevention**
  - Careful skin hygiene to prevent infection – encourage the use of moisturizers and topical antibiotics after even small breaks in the skin.
  - Elevate affected extremities as much as possible, even while asleep.
  - Avoid tight-fitting clothes.
  - Avoid medical procedures (except IV lines or blood draws) on affected extremities.
10.4 Lymphadenopathy and lumps

This Section provides an approach to the patient with a swelling or lump that may be an abnormal enlargement of lymph nodes.

### 10.4.1 Clinical approach to lymphadenopathy and lumps

<table>
<thead>
<tr>
<th>Step 1:</th>
<th>Use Quick Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure that there are no serious or life-threatening conditions. Be aware that lymph nodes can cause compression of the upper airway and difficulty breathing. Suppurating lymph nodes may be infective – separate these patients at triage.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2:</th>
<th>Take a history and examine the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm that it is lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Look for underlying cause and associated conditions.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3:</th>
<th>Assess HIV status</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Step 4:</th>
<th>Classify the lymphadenopathy and consider the likely differential diagnosis using the DDx table(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDx localized or regional lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>DDx generalized lymphadenopathy.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 5:</th>
<th>Perform investigations</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Step 6:</th>
<th>Initiate treatment and monitor the patient’s response. Always consider TB</th>
</tr>
</thead>
</table>

**History**

- How long has it been there, and is it changing in size?
- Is it painful?
- Is it draining pus or fluid?
- Prior TB or contact with TB?
- Travel or occupational exposure?
- Constitutional symptoms?

**Examination**

**Confirm lymphadenopathy**

- Exclude other possible causes for a mass such as:
  - hernia
  - aneurysm
  - lipoma
  - abscess
  - foreign body
  - cyst
  - neoplasm
  - neurofibroma.
- Position: see figure for sites.
Remember that each group of lymph nodes drains a specific area and local pathology will occur in the drainage area.

- quality – assess lymph nodes for:
  - size: (remember that the lymph nodes grow progressively until the age of late childhood, and then undergo progressive atrophy during puberty. It is, therefore, normal to have palpable anterior cervical, inguinal, and axillary nodes in children)

Check for:
- erythema
- tenderness
- warmth
- consistency (Are they firm? Are they fluctuant?)
- mobility (Are the lymph nodes matted together? Are they fixed to the adjacent structures?)
- pulsatile?
- bowel sounds.

Classify the lymphadenopathy as localized or regional, or generalized.

- **Localized or regional lymphadenopathy** – nodes are localized to a single site. The cause is often apparent if the area is thoroughly examined. Look for evidence of local pathology such as:
  - dental, or ear, nose, or throat disease
  - STIs
  - skin problems – infections, bites, dermatitis, phlebitis
  - malignancy
  - breast pathology.

- **Generalized lymphadenopathy** is the enlargement of lymph nodes at two or more sites. Look for evidence of underlying systemic disease.
  - Perform general examination looking particularly for pallour, wasting, fever, petechiae or other rash.
  - Examine the liver, spleen and other organ systems.
  - Feel for bone tenderness.

Nodes may be enlarged within the chest and abdomen. These may be seen on a chest X-ray or an abdominal ultrasound.

**Assess HIV status**

**Investigations**

- **Full blood count:**
  - look for evidence of infection, disseminated disease or malignancy.
- **Perform sputum examination for TB.**
- **Chest X-ray (see Section 8.2):**
  - lymphadenopathy is often apparent as hilar shadows
  - look for evidence of TB.
- **Ultrasound:**
  - abdominal lymphadenopathy, organomegaly or free fluid in the abdomen.
• Fine needle aspiration (FNA) of lymph node (see Section 7.2.5). Pay special attention to the choice of lymph node on which to perform FNA.
  o send sample for AFB smear.
• Additional tests may include:
  o cytology – look for presence of malignant cells (use fixative on the slide)
  o culture – identify specific organisms (if enough fluid or pus is aspirated).

**DO NOT DO** an FNA if the mass is pulsatile or has bowel sounds. It could be an aneurysm or hernia.

• Lymph node biopsy (see Section 7.2.6 Procedures):
  o microscopy – identification of organisms (specific stains may be required for certain organisms)
  o culture – specific organisms may be isolated
  o histology – characteristics of tissue architecture
  o cytology – evidence of malignancy and severity of dysplasia.

Consider locally common diseases that may require specific investigations. See DDx tables below.

**Treatment**

For focal infection:

• Start broad-spectrum antibiotics that include coverage for *Staphylococcus aureus* and *Streptococcus pyogenes*.
• Expect an improvement within 48 hours and a response to treatment within a week.
• If there is poor response to treatment, consider TB or malignancy. A biopsy may be indicated.

For management of conditions requiring specific treatment, see Section links in the differential diagnosis tables.
10.4.2 Classify the lymphadenopathy and consider the differential diagnosis

Assess whether the lymphadenopathy is localized or regional, or generalized, and consult the relevant DDx table below to consider the likely differential diagnosis.

**DDx: Localized or regional lymphadenopathy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB lymphadenitis</strong></td>
<td>Unilateral – in neck</td>
</tr>
<tr>
<td></td>
<td>May be fluctuant or discharging</td>
</tr>
<tr>
<td></td>
<td>Single or multiple nodes – not red, painful, or inflamed; may be matted</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms – night sweats, loss of weight, fever</td>
</tr>
<tr>
<td></td>
<td>Evidence of TB elsewhere (e.g. typical chest X-ray, sputum AFB)</td>
</tr>
<tr>
<td></td>
<td>FNA – AFB positive</td>
</tr>
<tr>
<td><strong>Focal infection</strong></td>
<td>Acute onset</td>
</tr>
<tr>
<td></td>
<td>Painful, red, inflamed</td>
</tr>
<tr>
<td></td>
<td>Local source of infection</td>
</tr>
<tr>
<td><strong>Sexually transmitted infection</strong></td>
<td>Tender inguinal lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Coalescence of nodes – may be fluctuant or discharging</td>
</tr>
<tr>
<td></td>
<td>History of genital ulcers</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Dark purple, painless lesions or nodules</td>
</tr>
<tr>
<td></td>
<td>Associated lymphoedema</td>
</tr>
<tr>
<td><strong>Lymphoma</strong></td>
<td>Non-tender, enlarging nodes</td>
</tr>
<tr>
<td></td>
<td>Systemic symptoms – fever, weight loss, night sweats, malaise, itch</td>
</tr>
<tr>
<td></td>
<td>Evidence of spread to skin, CNS, gut, lung, bone marrow</td>
</tr>
<tr>
<td></td>
<td>Low CD4 count</td>
</tr>
<tr>
<td></td>
<td>Histology – B or T cell proliferation</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td>Non-tender, hard, irregular node</td>
</tr>
<tr>
<td></td>
<td>Node fixed to surrounding tissue</td>
</tr>
<tr>
<td></td>
<td>Evidence of primary malignancy in the area drained by the lymph node</td>
</tr>
<tr>
<td><strong>Leukaemia</strong></td>
<td>Petechiae</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Sweating</td>
</tr>
<tr>
<td></td>
<td>Extreme fatigue</td>
</tr>
<tr>
<td></td>
<td>FBC-anaemia, thrombocytopenia, neutropaenia, lymphocytosis</td>
</tr>
<tr>
<td></td>
<td>Blast cells in peripheral blood, bone marrow, or tissue biopsy</td>
</tr>
<tr>
<td><strong>Immune reconstitution inflammatory syndrome (IRIS)</strong></td>
<td>Recent initiation of ART with very low CD4 count</td>
</tr>
<tr>
<td></td>
<td>Painful, enlarging lymph nodes – neck or axilla</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td><strong>Lymphatic filariasis</strong> (endemic areas) (see Section 11.14)</td>
<td>Acute: recurrent episodes of fever, tender localized lymphadenopathy, and epididymitis</td>
</tr>
<tr>
<td></td>
<td><strong>Chronic:</strong> lymphoedema of associated limb</td>
</tr>
<tr>
<td><strong>Plague – bubonic</strong></td>
<td>Unwell patient with fever, extreme tiredness</td>
</tr>
<tr>
<td></td>
<td>Large, painful, very tender lymph gland – bubo</td>
</tr>
<tr>
<td></td>
<td>History of exposure to possibly infected rodents or fleas.</td>
</tr>
</tbody>
</table>
## DDx: Generalized lymphadenopathy

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral infections</strong></td>
<td>Prodrome of malaise, fever, upper respiratory tract symptoms, body or joint pain. Generalized rash and lymphadenopathy. Possible causes – measles, rubella, EBV, CMV or this may be an HIV seroconversion illness.</td>
</tr>
<tr>
<td><strong>Miliary TB</strong></td>
<td>Night sweats, loss of weight, fever. Evidence of TB elsewhere (e.g. chest X-ray, sputum or FNA – AFB positive). May have associated hepatosplenomegaly.</td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex (MAC)</strong> see Section 11.25</td>
<td>Unwell patient. Persistent fever and night sweats, diarrhoea, with or without pulmonary symptoms. May have hepatomegaly and anaemia. Lymph node FNA – AFB positive (culture needed to distinguish from TB). Advanced HIV infection: CD4 &lt;100.</td>
</tr>
<tr>
<td><strong>Persistent generalized lymphadenopathy</strong> see below</td>
<td>Symmetrical nodes &gt;3 months. Early HIV disease and often asymptomatic, but can coexist with more advanced manifestations. Occipital and epitrochlear lymph nodes enlarged.</td>
</tr>
<tr>
<td><strong>Nocardiosis</strong></td>
<td>Multiple abscesses in skin and lungs. Recurrent fever. Immunocompromised patient CD4 &lt;100.</td>
</tr>
<tr>
<td><strong>Fungal infections</strong> e.g. penicilliosis, histoplasmosis, cryptococcosis</td>
<td>Unwell patient – fever, malaise, skin lesions with or without lung involvement. Immunocompromised patient: CD4 &lt;100.</td>
</tr>
<tr>
<td><strong>Secondary syphilis</strong> see Section 11.32</td>
<td>Firm, discrete, and mildly tender nodes. Fever. Maculo-papular rash – involving palms and soles. History of previous chancre or residual genital chancre (25%). Syphilis test positive.</td>
</tr>
</tbody>
</table>

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### Bubonic plague¹

**Treatment:**
- streptomycin 1 gram every 12 hours IV (preferred); OR
- gentamicin 5 mg/kg/day in 3 equal doses every 8 hours or 5 mg/kg once daily (alternative); OR
- doxycycline 200 mg loading dose then 100 mg oral or IV twice daily (alternative); OR
- chloramphenicol 50 mg/kg/day in 4 equal doses (preferred for plague meningitis). Treatment is for 7–10 days.
  Consider post-exposure prophylaxis for close contacts (e.g. household, care providers), especially contacts of pneumonic plague:
  - doxycycline 100 mg oral twice daily for 7 days (preferred); OR
  - ciprofloxacin 500 mg twice daily for 7 days (alternative).

Note: Notify all cases of suspected plague within 24 hours. See Section 9.

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10.4.3 Approach to lymphadenopathy in PLHIV

Lymphadenopathy in PLHIV is an important finding at any stage. For all patients with HIV all sites should be examined regularly for the presence of nodes and any change in node size or consistency. If significant lymphadenopathy is present, every effort should be made to find a cause, as this may be due to opportunistic infections, IRIS, or persistent generalized lymphadenopathy.

**Opportunistic infections**
- Look for infections and treat before commencing ART to reduce the risk of IRIS.
- Tuberculosis is very common.

**Persistent generalized lymphadenopathy (PGL)**
- WHO Stage 1 condition – PGL is a clinical diagnosis after exclusion of opportunistic infections.
  - defined as non-tender, enlarged lymph nodes of >1 cm in 2 or more non-contiguous sites (excluding inguinal) and persisting for ≥3 months,
  - lymphadenopathy is symmetrical and often involves the posterior cervical, axillary, occipital, and epitrochlear nodes,
  - no specific treatment is required.
- Generalized lymphadenopathy in advanced HIV disease is often due to an underlying opportunistic infection.

**Immune reconstitution inflammatory syndrome (IRIS)**
IRIS commonly presents with lymphadenopathy. It may be necessary to aspirate or biopsy the lymph node for a definitive diagnosis.

Common IRIS conditions include:
- TB
- MAC
- cryptococcosis
- Kaposi sarcoma
- lymphoma.

Treat the underlying condition and continue ART. See HIV guidelines for more details.

10.4.4 Symptom management of lymphadenopathy

- Provide adequate analgesia.
- If the swelling is severe steroid therapy may be required, but only when specific treatment for the cause is also provided.
- Ensure discharging lymph nodes are covered.
10.5 Abdominal complaints

Each symptom is dealt with in its own subsection. Patients may present with several combinations of the symptoms discussed below, e.g. abdominal pain plus diarrhoea. Therefore, it is important to determine each major symptom, work through the differential diagnosis tables for each, and develop a coherent treatment plan.

Section 10.5 includes:
- 10.5a Abdominal pain
- 10.5b Painful or difficult swallowing
- 10.5c Nausea and vomiting
- 10.5d Constipation

Diarrhoea is covered in Section 8.3.

10.5a Abdominal pain

| 10.5a.1 | Clinical approach to abdominal pain |
| 10.5a.2 | Differential diagnosis of abdominal pain and management of specific conditions |
| 10.5a.3 | Approach to abdominal pain in PLHIV |

- Dyspepsia, gastritis, peptic ulcer disease
- Pancreatitis
- Cholecystitis and cholangitis
- Peritonitis
- Ascariasis

This Section provides an approach to the diagnosis and management of a patient with abdominal pain, either upper or epigastric, or generalized pain. Lower abdominal pain is also addressed in other guidelines on female genitourinary problems.

10.5a.1 Clinical approach to abdominal pain

**Step 1:** Use Quick Check
Ensure that there are no serious or life-threatening conditions. Be aware that a patient with abdominal pain could have a surgical abdomen (see below) or a gynaecological emergency that requires surgery. The patient **should not eat** until this diagnosis has been ruled out.

**Step 2:** Take a history and examine the patient

**Step 3:** Assess HIV status

**Step 4:** Classify the abdominal pain and use the DDx tables to work through a differential diagnosis
- DDx: Generalized abdominal pain
- DDx: Upper abdominal or epigastric pain

**Step 5:** Perform investigations

**Step 6:** Initiate treatment and monitor the patient’s response

**Emergency treatments**
Always consider the possibility of an acute surgical abdomen or gynaecological emergency, e.g. an ectopic pregnancy. Patients should not eat or drink before this is ruled out.

A “surgical abdomen” is any abdominal condition which would result in a rapidly worsening prognosis in the absence of surgical intervention. A high level of suspicion should be maintained.
in immunocompromised patients when typical signs of peritoneal inflammation may be reduced or absent.

- **General signs and symptoms of a surgical abdomen:**
  - a very ill patient with or without fever and shock
  - little pain relief from analgesics
  - localized, generalized, or rebound tenderness on palpation
  - distended abdomen
  - diminished or absent bowel sounds
  - no flatus or bowel movements.

- **X-ray findings suggestive of a surgical abdomen include:**
  - hollow organ perforation: free intra-peritoneal air, or air under the diaphragm on upright chest or abdominal X-ray (note that this finding, although uncommon, is specific for a surgical abdomen and should prompt immediate surgical consultation);
  - hyper-inflated bowel – consider peritonitis.

- **Use ultrasound to exclude other causes of an acute surgical abdomen.**

If a surgical abdomen is strongly suspected, refer to the Quick Check for urgent interventions and the WHO manual *Surgical care at the district hospital*\(^1\) for definitive care.

**History**

The history of the presenting complaint should include:
- nature of the pain – onset, duration, location, quality, and radiation;
- exacerbating or relieving factors (e.g. food, antacids, exertion, defecation);
- associated symptoms (e.g. fevers, chills, weight loss or gain, nausea, vomiting, diarrhoea, constipation, blood in the stool, change in the colour of urine or stool, yellow discoloration of the eyes).
- **Medical history**
  - previous history of similar abdominal pain
  - history of peptic ulcer
  - symptoms suggestive of systemic disease (e.g. cough, fever, night sweats)
  - substance use including alcohol
  - immune status.
- **Medication history**
  - ART (duration of therapy is important)
  - over-the-counter medications (e.g. paracetamol, aspirin, NSAIDs)
  - traditional remedies
  - antibiotic therapy.
- **Menstrual and pregnancy history**
- **Geographical location for diseases specific to certain regions (notably, prevalence of schistosomiasis and soil-transmitted helminths)**
  - If the patient is from a schistosomiasis endemic area, treat empirically with praziquantel (see Section 11.31).

**Examination**

- **Targeted general examination:**
  - vital signs
  - jaundice, pallour, lymphadenopathy

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signs of chronic liver disease (e.g. scratch marks, palmar erythema, ascites, spider naevi, caput medusa, bruising, oedema).

- Abdominal examination:
  - look for abdominal distension
  - palpate for masses, tenderness, peritoneal signs (rebound tenderness and guarding)
  - listen for bowel sounds
  - percuss for ascites – shifting dullness
  - do rectal examination and also look for blood in stool
  - examine the groin and the scrota for inguinal masses and hernias.

- Pelvic examination
  - in women with lower abdominal pain.

- Other organs
  - look for pneumonia or heart failure – may cause abdominal pain
  - shingles can cause localized abdominal pain.

### Classify abdominal pain and use the differential diagnosis tables

Classify the pain based on the clinical presentation.

Refer to the respective DDx tables below to help work through a differential diagnosis.

- Generalized abdominal pain (DDx table) (see also lower abdominal pain in guidelines for management of women’s genitourinary problems).
- Upper abdominal or epigastric pain (DDx table).

### Perform investigations

- **Laboratory investigations**: The following are recommended investigations for all patients:
  - urine analysis (dipstick and microscopy – for haematuria and S. haematobium ova)
  - pregnancy test
  - U&F, FBC, glucose.

- Investigations based on clinical findings include:
  - liver functions
  - amylase
  - serum lactate if the patient is taking ART.

Stool for macroscopic and microscopic examination – look for occult blood and various helminth infections, including Schistosoma ova. This may require repeated examinations or concentration procedures.

- Imaging:
  - abdominal X-ray
  - chest X-ray
  - abdominal ultrasound is useful to identify:
    - abdominal lymph nodes
    - liver and spleen pathology
    - appendix mass
    - gall stones, cholecystitis
    - renal stones or hydronephrosis
    - pelvic inflammatory disease with collections or a mass
    - ectopic pregnancy.

### Initiate treatment and monitor response

For management of specific conditions associated with abdominal pain, see the text after the DDx tables.
# 10.5a.2 Differential diagnosis of abdominal pain and management of specific conditions

The differential diagnosis differs for generalized abdominal pain and for upper abdominal or epigastric pain. Use the appropriate table below. In women with lower abdominal pain, see also guidelines for management of women’s genitourinary problems.

## DDx: Generalized abdominal pain

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical abdomen</strong>*</td>
<td>Rebound tenderness, guarding</td>
</tr>
<tr>
<td></td>
<td>Pain not responding to analgesics</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Decrease in flatus or stool</td>
</tr>
<tr>
<td></td>
<td>Abdominal X-ray – dilated loops of bowel, air fluid levels</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray – free air under the diaphragm</td>
</tr>
<tr>
<td></td>
<td>*Consider bowel obstruction or perforation, appendicitis, peritonitis, mesenteric infarct, ruptured ectopic pregnancy. Manage according to Quick Check page 10. See also guidelines for management of women’s genitourinary problems and the WHO Manual Surgical Care at the District Hospital.</td>
</tr>
<tr>
<td><strong>Ectopic pregnancy</strong></td>
<td>Positive pregnancy test (or may be negative)</td>
</tr>
<tr>
<td></td>
<td>Pain usually in lower abdomen</td>
</tr>
<tr>
<td></td>
<td>Abnormal vaginal bleeding</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Cervical motion tenderness on pelvic exam</td>
</tr>
<tr>
<td></td>
<td>Shock (if ruptured)</td>
</tr>
<tr>
<td></td>
<td>History of previous ectopic pregnancy</td>
</tr>
<tr>
<td><strong>Appendicitis</strong></td>
<td>Low grade fever</td>
</tr>
<tr>
<td></td>
<td>Early – peri-umbilical pain</td>
</tr>
<tr>
<td></td>
<td>Later – pain localized to right lower quadrant</td>
</tr>
<tr>
<td></td>
<td>FBC – high WCC</td>
</tr>
<tr>
<td><strong>Bowel obstruction</strong></td>
<td>Colicky abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>No stool or flatus</td>
</tr>
<tr>
<td></td>
<td>Bowel sounds – none, or if partial obstruction, high-pitched tinkling with rushes</td>
</tr>
<tr>
<td></td>
<td>Hernia detected</td>
</tr>
<tr>
<td><strong>Abdominal TB</strong></td>
<td>Pain usually non-specific and chronic</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms – fever, weight loss, night sweats</td>
</tr>
<tr>
<td></td>
<td>Abdominal swelling, mass, or ascites</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray – evidence of pulmonary TB</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – para-aortic lymph nodes or ascites</td>
</tr>
<tr>
<td></td>
<td>Biochemistry – low SAAG ascites (see Section 10.8)</td>
</tr>
<tr>
<td><strong>Typhoid</strong></td>
<td>Seriously ill without other apparent cause</td>
</tr>
<tr>
<td>(see Section 8.1)</td>
<td>Prolonged high fever</td>
</tr>
<tr>
<td></td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td></td>
<td>Relative bradycardia compared with fever</td>
</tr>
<tr>
<td></td>
<td>Geographic area</td>
</tr>
<tr>
<td></td>
<td>FBC – decreased WCC</td>
</tr>
<tr>
<td><strong>COVID-19</strong></td>
<td>One third of patients may have GI symptoms (case observations have ranged from 5%–40%)(^2)(^3)</td>
</tr>
<tr>
<td>(see Section 11.6)</td>
<td>Loss of appetite, nausea, vomiting, diarrhoea, abdominal pain can occur</td>
</tr>
<tr>
<td></td>
<td>GI symptoms may occur before respiratory symptoms of COVID-19</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>Elevated ALT, AST; direct viral injury to liver has been suggested Patient taking ARVs for &gt;6 months Patient taking an NRTI, e.g. d4T, ddl, or AZT Female, overweight Loss of weight, fatigue, malaise Nausea or vomiting Serum lactate &gt;5 mmol/l Arterial pH &lt;7.3, widened anion gap &gt;13 Elevated ALT/AST, LDH, and amylase</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>Most common cause of severe gastroenteritis in the young, the elderly, and people who have suppressed immune systems Abdominal pain, diarrhoea, nausea, vomiting Chills, clammy skin, excessive sweating, fever, joint stiffness Leakage (incontinence) of stool Muscle pain Poor feeding, vomiting blood (very rare), weight loss</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Abdominal pain in the left lower quadrant Fever Nausea Change in bowel habits Peritoneal signs – guarding and rebound</td>
</tr>
<tr>
<td>Helminthic infections – ascaris</td>
<td>High worm burdens may cause abdominal pain and intestinal obstruction Eggs on stool exam by direct wet mount or after concentration</td>
</tr>
<tr>
<td>Protozoan infections</td>
<td>Chronic watery diarrhoea Wasting and malnutrition Geographical area Other symptoms of advanced HIV</td>
</tr>
<tr>
<td>Strongyloidiasis (see Section 11.31)</td>
<td>Diarrhoea – may have blood Cough Serpiginous (snake-like) skin lesions Visible parasites on stool or sputum examination</td>
</tr>
<tr>
<td>Irritable bowel syndrome (IBS)</td>
<td>Abdominal cramping, bloating, and a change in bowel habits between constipation and diarrhoea More often in women than men No known cause of IBS</td>
</tr>
<tr>
<td>Inflammatory bowel disease (ulcerative colitis and Crohn’s disease)</td>
<td>Peak incidence in young adults (15–25 years old) Ranges from mild disease (insidious onset, non-bloody diarrhoea, poor weight gain) to severe (fulminant presentation, severe abdominal pain, bloody diarrhoea, tenesmus, and fever) Abdominal tenderness Perianal involvement (fistulae, anal tag, or fissure) Extraintestinal manifestation: eye involvement (e.g., uveitis), skin involvement (e.g., rash, erythema nodosum, pyoderma gangrenosum), peripheral arthritis (involving large joints and ankylosing spondylitis), sclerosing cholangitis, thromboembolism, lung disease, renal stones, anaemia, and digital clubbing Palpable abdominal mass (suggestive of a fistula) and oral ulcerations can occur in Crohn’s disease Diagnosis based on characteristic history and endoscopy</td>
</tr>
<tr>
<td>Urinary tract infection, cystitis (see Section 11.38)</td>
<td>Offensive smelling urine Painful urination Frequency of urination Urgency of urination Cloudy urine Urine dipstick – leucocytes, nitrites, blood Urine microscopy – leucocytes, RBCs, bacteria</td>
</tr>
<tr>
<td>Acute pyelonephritis (see Section 11.38)</td>
<td>Fever Rigours Flank pain Painful urination</td>
</tr>
</tbody>
</table>
| Renal stones | Acute attacks of severe colicky back or flank pain, radiating to groin (loin to groin radiation)  
History of previous attacks  
Taking indinavir or sulphadiazine  
Urine dipstick – blood  
Urine microscopy – red cells and crystals  
Abdominal X-ray – stones may be visible in renal tract  
Ultrasound – urethral dilatation, hydronephrosis, stones |
| Mycobacterium avium complex (MAC)  
(see Section 11.25) | Persistent fever  
Diarrhoea  
Hepatomegaly  
Wasting  
FBC – severe anaemia and neutropaenia  
Elevated ALP and GGT  
CD4 <50 |
| Drug induced | History of medications known to cause abdominal side-effects |
| Dissecting abdominal aortic aneurysm | Sudden onset severe pain  
Shock  
Abdominal pain radiating to the back  
Pulsatile abdominal mass with peritonism  
Ultrasound – aortic dilatation, intimal flap dissection |

**DDx: Upper abdominal or epigastric pain**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| Gastritis, peptic ulcer disease | Burning epigastric pain and tenderness  
Relieved by food and antacids (more likely gastric ulcer)  
History of alcohol or NSAID use  
Complications – signs of upper GI bleed or perforation |
| Oesophagitis  
CMV see 11.10  
(Candida see Section 11.4) | Upper epigastric and retrosternal pain  
Worse on eating and swallowing  
See Section 10.5.b |
| Gastroparesis | Delayed gastric emptying, commonly occurring in diabetes  
Heartburn or pain in the upper abdomen with spasms in the stomach area  
Nausea or vomiting of undigested food – sometimes several hours after a meal  
Early feeling of fullness after only a small amount of food  
Weight loss due to poor absorption of nutrients or low calorie intake  
Abdominal bloating  
Fluctuating blood glucose levels – high and low  
Lack of appetite  
Gastro-oesophageal reflux |
| Viral hepatitis  
(see Section 11.16) | Jaundice  
Malaise  
Loss of appetite  
Exposure to hepatotoxic drugs – TB medications, NVP, EFV  
History of heavy alcohol intake  
Right upper quadrant pain  
High ALT, AST, bilirubin |
| Cholecystitis  
(inflammation of the gall bladder) | Nausea, vomiting, loss of appetite  
Pain is steady and severe – patient is often reluctant to move  
Pain worse after eating  
Right upper quadrant pain radiating to right shoulder or back  
Guarding  
Jaundice if duct obstruction  
Tender hepatomegaly or tenderness over site of gallbladder |
10. Acute and subacute by symptom: SEARO 2021

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade fever or chills</td>
<td>High WBC, ALP, AST/ALT, amylase, bilirubin</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – gall stones or sludge, thickened gall bladder wall, dilated common bile duct if obstruction, pericholecystic fluid, sonographic Murphy’s sign (pain when gallbladder is pushed by transducer)</td>
</tr>
<tr>
<td></td>
<td>Abdominal X-rays usually normal</td>
</tr>
<tr>
<td></td>
<td>HIV patients – acalculous cholecystitis (no stones seen)</td>
</tr>
<tr>
<td><strong>Cholangitis</strong> (inflammation of the bile ducts)</td>
<td>Similar to above, but with:</td>
</tr>
<tr>
<td></td>
<td>• high-grade fever</td>
</tr>
<tr>
<td></td>
<td>• jaundice</td>
</tr>
<tr>
<td></td>
<td>• rigours</td>
</tr>
<tr>
<td></td>
<td>• shock</td>
</tr>
<tr>
<td><strong>Choledocholithiasis</strong></td>
<td>Abdominal pain, fever, loss of appetite, nausea, vomiting, jaundice</td>
</tr>
<tr>
<td></td>
<td>Risk factors – previous history of gallstones (can occur if gall bladder has been removed)</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Pain radiating to the back</td>
</tr>
<tr>
<td></td>
<td>Pain is exacerbated by eating and when lying down and relieved by sitting up or leaning forward</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>Fever, tachycardia</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>May be severely ill with shock</td>
</tr>
<tr>
<td></td>
<td>History of excessive alcohol intake</td>
</tr>
<tr>
<td></td>
<td>Exposure to NRTIs – d4T, ddl, 3TC, ritonavir</td>
</tr>
<tr>
<td></td>
<td>Purple hue on the skin around the flanks may signify retroperitoneal bleeding from haemorrhagic pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Amylase &gt;3 times normal, increased lipase, increased TG, high AST, high ALT, high ALP, increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – gallstones, pancreatic oedema, abdominal fluid</td>
</tr>
<tr>
<td><strong>Lactic acidosis</strong></td>
<td>Patient taking ARVs for &gt;6 months</td>
</tr>
<tr>
<td></td>
<td>Patient taking an NRTI, e.g. d4T, ddl, or AZT</td>
</tr>
<tr>
<td></td>
<td>Female, overweight</td>
</tr>
<tr>
<td></td>
<td>Loss of weight, fatigue, malaise</td>
</tr>
<tr>
<td></td>
<td>Nausea or vomiting</td>
</tr>
<tr>
<td></td>
<td>Serum lactate &gt;5 mmol/l</td>
</tr>
<tr>
<td></td>
<td><em>Arterial pH &lt;7.3, widened anion gap &gt;13</em></td>
</tr>
<tr>
<td></td>
<td>Elevated ALT/AST, LDH, and amylase</td>
</tr>
<tr>
<td><strong>Splenic abscess</strong></td>
<td>Left upper quadrant pain</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Pain referred to left shoulder</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – splenic abscesses</td>
</tr>
<tr>
<td></td>
<td>Associated signs of TB</td>
</tr>
<tr>
<td><strong>Pneumonia</strong> (see Section 8.2)</td>
<td>May present as right or left upper quadrant pain</td>
</tr>
<tr>
<td></td>
<td>Chest examination reveals consolidation of the lung adjacent to site of abdominal pain.</td>
</tr>
</tbody>
</table>

**Management of specific conditions causing abdominal pain**

**Dyspepsia, gastritis, and peptic ulcer disease**

**Treatment**

- Empirical therapy before investigations is acceptable (gastroscopic or barium studies).
- Advise the patient to discontinue NSAIDS, alcohol, caffeine, cigarettes.
- Treat with proton pump inhibitors:
  - omeprazole 20 mg once daily for 4–8 weeks.
- In refractory cases: consider diagnosis of *Helicobacter pylori*. It is better to confirm the diagnosis of *H. pylori* before treating. Test according to national guidelines with available tests. These may include rapid tests on blood, breath, or stool, or may require endoscopy to...
obtain a biopsy sample. Have a high index of suspicion for malignancy, which will require a gastroscopy and biopsy to exclude.

- If test is positive, give triple therapy:

  amoxicillin 1 g twice daily:
  + clarithromycin 500 mg twice daily
  + omeprazole 20 mg twice daily

  then

  omeprazole 20 mg once daily for 4–6 weeks.

  - For patients with allergy to amoxicillin, use metronidazole 400 mg twice daily.
  - If clarithromycin is unavailable, use amoxicillin 1 g twice daily and metronidazole 400 mg twice daily.
  - For second-line therapy, replace clarithromycin with doxycycline 100 mg twice daily.

- Patients who do not respond should be referred for further investigations, e.g. endoscopy.

### Pancreatitis

#### Common causes

- alcohol
- gall stones
- high triglyceride levels (more than 1000 mg/dl) – protease inhibitors may cause elevated lipid levels
- toxins, such as scorpion bite or organophosphate insecticides
- in patients with HIV infection:
  - medications
    - ART – ddl or d4T, especially if used in combination
    - for OIs – cotrimoxazole, pentamidine, sulfonamides
  - patients with CMV or MAC infection
- other medications – valproic acid, furosemide, tetracycline, ACE inhibitors, sulfur drugs.

Pancreatitis usually presents as an acute process, but can lead to chronic pancreatitis if the insult recurs.

#### Ranson's criteria

At admission:

- age in years >55 years
- white blood cell count >16 000 cells/mm³
- blood glucose >10 mmol/l (more than 200 mg/dl)
- serum AST >250 IU/l
- serum LDH >350 IU/l

If the Ranson score is ≥3, severe pancreatitis is indicated, and rapid intervention is necessary. It indicates poor prognosis.

If the score is <3, the pancreatitis is less severe and could resolve with symptomatic management.

Re-evaluate after 48 hours.

---

Treatment

**Mild acute pancreatitis**
- Nothing by mouth.
- Aggressive IV hydration, especially in the first 24–48 hours, to replace the large amount of fluid lost to the third space.
- Analgesia – an opioid such as morphine is usually required.
- Stop toxic medications.
- Re-assess regularly and re-evaluate Ranson's criteria after 48 hours.
- Close clinical monitoring to recognize complications early:
  - monitor intake and output (urine output of 0.5 ml/kg/hour is desirable)
  - monitor pain control
  - monitor for signs of septic shock (low BP, tachycardia, poor perfusion)
  - monitor for early signs of respiratory failure (tachypnoea, acidotic breathing).

**Severe acute pancreatitis**
- Supportive treatment as above and referral to a higher level for surgical consultation and nutritional support.

**Complications of pancreatitis**
- Prolonged pancreatitis with haemodynamic instability, fever, and poor response to medical therapy should be referred for surgical opinion and management at an intensive care unit.
- A deterioration in clinical condition may indicate complications.
  - Early complications (within days of onset)
    - pancreatic necrosis
    - acute lung injury or acute respiratory distress syndrome with hypoxaemia (see Section 3.2.3)
    - septic shock – hypotension, tachycardia, low urine sodium concentration (see Section 3.1.5)
    - haemorrhage.
  - Late complications (within four weeks, seen on a contrast-enhanced CT scan)
    - pancreatic pseudocyst
    - abscess.

**Cholecystitis and cholangitis**

**Treatment**
- Check for emergency signs using Quick Check.
- Administer IV fluids.
- Insert a nasogastric tube for drainage, or suction if vomiting.
- No oral intake (except for medication).
- Treat with antibiotics and expectant (conservative) management and then, once stabilized, arrange and refer for surgical assessment.
- Empirical antibiotic therapy according to local patterns of resistance, availability, and severity of illness. For cholangitis, for 10–14 days:
  - ampicillin 2 g IV every 4 hours PLUS gentamicin IV 1.5 mg/kg every 8 hours PLUS metronidazole 500 mg IV or orally 3 times daily; OR
  - ceftriaxone 1 g IV once daily PLUS metronidazole (1 g rectally or 500 mg orally 3–4 times daily or 500 mg IV 3 times daily); OR
  - ciprofloxacin 400 mg IV (or 500 mg orally) twice daily plus metronidazole as above.
- For cholecystitis – no jaundice or rigours and able to take oral medication:
  - amoxicillin-clavulanic acid 1 g orally 3 times daily (1 g orally 4 times daily if more severe); OR
  - ciprofloxacin 500 mg orally twice daily plus metronidazole 500 mg orally 3–4 times daily.

**Note** Early surgical assessment or referral should be done for those with complications or those not responding to treatment.
Complications of cholecystitis and cholangitis

- Gangrene or perforation of the gallbladder requiring surgical intervention to remove the gall bladder.

Peritonitis

Peritonitis is an acute, life-threatening condition caused by bacterial contamination of the peritoneal cavity. The major causes of peritonitis include:

- appendicitis
- perforated peptic ulcer
- anastomotic leak following surgery
- strangulated bowel
- pancreatitis
- cholecystitis
- intra-abdominal abscess
- haematogenous spread of infective agents such as typhoid or TB
- typhoid perforation
- ascending infection, for example, in salpingitis and postpartum infection.

Key clinical features

- sharp pain that is worse on movement or coughing
- fever
- abdominal distension, tenderness, and guarding
- diminished or absent bowel sounds
- shoulder pain (referred from diaphragm)
- tenderness on rectal or vaginal examination (suggests pelvic peritonitis).

These features may be minimal in elderly patients or those who are immunosuppressed. Therefore for these patients it is important to maintain a high index of suspicion for the condition.

Treatment

The treatment of peritonitis is the treatment of the underlying cause.

- Administer IV fluids.
- Insert a nasogastric tube for drainage.
- Give IV antibiotics, providing aerobic, Gram negative and anaerobic coverage, e.g. ampicillin 2 g IV every 6 hours, PLUS gentamicin 1.5 mg/kg IV every 8 hours, PLUS metronidazole 500 mg IV every 8 hours.
- Record fluid balance and vital signs on the bedside chart every 6 hours.

Assess or refer for surgical intervention as appropriate. The nature of the intervention will depend on the cause of the peritonitis, e.g. appendectomy for appendicitis, repair of a perforated viscus, or drainage of an abscess.

Ascariasis

Treatment

- albendazole 400 mg oral once; OR
- mebendazole 500 mg oral once or 100 mg twice daily for 3 days.

---

Ascariasis can uncommonly cause intestinal and biliary obstruction that may require surgical intervention.

### 10.5a.3 Approach to abdominal pain in PLHIV

The approach to patients with abdominal pain is similar in HIV-infected and uninfected patients (see flow chart below), except that HIV-infected patients may present atypically due to underlying immune suppression.

The common causes of abdominal pain listed above occur also in PLHIV, and these should remain high on the differential diagnosis list. However, there are some additional conditions to consider including:

- MAC, CMV, fungal and protozoal infections causing diarrhoea and associated intermittent, dull abdominal pain;
- drug side-effects (e.g. pancreatitis, lactic acidosis) – take a full drug history;
- HIV-related lymphomas, which can cause abdominal pain with intestinal obstruction.

**Figure: Approach to HIV-infected patient with abdominal pain**

<table>
<thead>
<tr>
<th>Abdominal pain</th>
<th>Check for danger signs: guarding, distension, loss of bowel sounds, high temperature, shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient on ART?</td>
<td>See Quick Check page 10</td>
</tr>
<tr>
<td>Look for associated symptoms and location of pain</td>
<td>See HIV guidelines on ARV toxicities</td>
</tr>
<tr>
<td>Epigastric or upper abdominal pain, +/- nausea and vomiting</td>
<td>Check for: gastritis, PUD, gallbladder stones, hepatitis, cholecystitis, malignancies</td>
</tr>
<tr>
<td>Generalized +/- fever, vomiting, or nausea</td>
<td>Check for: malaria, TB, liver or spleen abscess, UTI, typhoid fever, other OIs (CMV, crypto, MAC)</td>
</tr>
<tr>
<td>Generalized +/- diarrhoea</td>
<td>See Section 8.3 Diarrhoea</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>Check for: UTI, appendicitis, PID, pelvic abscess. In females check gyn history and complications</td>
</tr>
</tbody>
</table>
10.5b Painful or difficult swallowing

Painful or difficult swallowing may occur with liquids or solids, and patients may complain of problems at the onset of swallowing or a sensation of food getting “stuck” in their throats.

10.5b.1 Clinical approach to painful or difficult swallowing

<table>
<thead>
<tr>
<th>Step 1: Use Quick Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure that there are no serious or life-threatening conditions. Be aware that a patient with difficulty swallowing may present with dehydration and electrolyte imbalances as a result of poor oral intake. Refer to Quick Check for management of these patients.</td>
</tr>
</tbody>
</table>

| Step 2: Take a history and examine the patient |
| Step 3: Assess the patient’s HIV status |
| Step 4: Consider likely differential diagnosis using the DDx table(s) |
| Step 5: Perform investigations as required |
| Step 6: Initiate treatment and monitor the patient’s response |

**History**
- Is it painful to swallow, or is there difficulty in swallowing?
- Is it associated with liquids or solids?
- What is the duration of symptoms?
- Are there any associated symptoms – cough, fever, heartburn, weight loss, nausea, vomiting, vomiting blood, breathing problems, or other?

**Examination**
- Check the patient’s weight and temperature.
- Check the oral cavity for white plaques or ulcers.
- Assess hydration and nutritional status.

**Assess the patient’s HIV status**
HIV infection will change the possible differential diagnoses for painful or difficult swallowing, as a number of opportunistic infections can cause these symptoms, such as CMV and *Candida* oesophagitis. An HIV test and CD4 count are helpful in determining the underlying cause. See Figure below for approach to painful or difficult swallowing in patients with HIV.

**Investigations**
- FBC, urea, and electrolytes.
### 10.5b.2 Differential diagnosis and treatment of painful or difficult swallowing

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candida oesophagitis</strong></td>
<td>Painful swallowing&lt;br&gt;Oral thrush (<em>Candida</em>)&lt;br&gt;Pain in chest behind the sternum&lt;br&gt;Responds to fluconazole</td>
</tr>
<tr>
<td>(see Section 11.4)</td>
<td></td>
</tr>
<tr>
<td><strong>CMV or HSV oesophagitis</strong></td>
<td>Fever&lt;br&gt;Severe pain on swallowing&lt;br&gt;Pain in chest behind the sternum&lt;br&gt;Painful oral ulcers&lt;br&gt;Associated visual loss or CMV retinitis on fundoscopy&lt;br&gt;CD4 &lt;50</td>
</tr>
<tr>
<td>(see Section 11.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Foreign body in throat</strong></td>
<td>History of object lodging in throat&lt;br&gt;Vomiting or increased salivation (complete salivation)&lt;br&gt;Choking (see Quick Check)</td>
</tr>
<tr>
<td><strong>Gastric reflux</strong></td>
<td>Pain or burning sensation in chest (heartburn)&lt;br&gt;Bitter or sour taste in back of mouth&lt;br&gt;Worse after eating or at night&lt;br&gt;Chronic reflux can lead to strictures and difficulty in swallowing (initially solids, then liquids)</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Purple lesions on the palate or gums&lt;br&gt;Lesions can be painful or ulcerate&lt;br&gt;Lesions may become infected&lt;br&gt;Associated painless purple nodules on skin</td>
</tr>
<tr>
<td>(see Section 10.13)</td>
<td></td>
</tr>
<tr>
<td><strong>Mouth or throat infection</strong></td>
<td>Pain on swallowing&lt;br&gt;Ulcer or abscess may be seen&lt;br&gt;Enlarged or inflamed tonsils&lt;br&gt;Fever&lt;br&gt;Enlarged lymph nodes in the neck</td>
</tr>
<tr>
<td>(see Section 10.13)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral cancer</strong></td>
<td>Painful or difficult swallowing&lt;br&gt;Ulcers or masses that do not heal&lt;br&gt;Dental changes&lt;br&gt;Weight loss&lt;br&gt;Bleeding</td>
</tr>
<tr>
<td><strong>Oesophageal cancer</strong></td>
<td>Loss of appetite&lt;br&gt;Weight loss&lt;br&gt;Progressive difficulty in swallowing (initially solids, then liquids)&lt;br&gt;Painful swallowing&lt;br&gt;Anaemia</td>
</tr>
<tr>
<td><strong>Oesophageal stricture or web, or diverticula</strong></td>
<td>Difficulty swallowing&lt;br&gt;Discomfort with swallowing&lt;br&gt;A feeling that food gets stuck in the oesophagus&lt;br&gt;Regurgitation of food&lt;br&gt;Weight loss&lt;br&gt;Risk factors – gastro-oesophageal reflux disease (GERD)&lt;br&gt;Prolonged use of a nasogastric tube&lt;br&gt;Ingestion of corrosive substances&lt;br&gt;Viral or bacterial infections&lt;br&gt;Injuries caused by endoscopes</td>
</tr>
<tr>
<td><strong>Achalasia</strong></td>
<td>Difficulty in swallowing solids and liquids&lt;br&gt;Weight loss&lt;br&gt;Chronic cough&lt;br&gt;Hiccups&lt;br&gt;Heartburn&lt;br&gt;Regurgitation.</td>
</tr>
</tbody>
</table>
Initiate treatment and monitor the patient’s response

- Initial empirical treatment is recommended for symptoms suggestive of gastro-oesophageal reflux (give a trial of omeprazole) or of Candida oesophagitis (give fluconazole – see Section 11.4) until symptoms resolve.
- For treatment of specific conditions, see text and referenced Sections below.

10.5b.3 Approach to oesophagitis in PLHIV

Key clinical features

- Common causes of oesophagitis in patients with HIV include: Candida, CMV, aphthous ulcers, HSV (see next figure).
- Oral Candida associated with painful or difficult swallowing is highly suggestive of Candida oesophagitis. However, its absence does not exclude the diagnosis – especially in patients who have been using topical antifungals.
- Gastro-oesophageal reflux disease (GERD) may present like oesophagitis, and should be considered in the differential diagnosis.

Treatment

- Empirical management as above with fluconazole for patients with recent onset of symptoms:
  - if symptoms suggest reflux disease, give trial of antacid therapy
  - if empirical Candida therapy fails, consider treating for CMV, HSV, or reflux disease
  - if still failing to respond, referral for gastroscopy plus biopsy can be considered.

Pain management

- Pain medication may be required according to analgesic ladder (see Section 12).
- Crush and disperse aspirin 600 mg in a small amount of water and rinse the mouth; gargle if throat is painful.

Diet

- Introduce soft diet to decrease discomfort.
- Avoid extremely hot, cold or spicy foods.
- Increase fluid intake when swallowing pills.
10. Acute and subacute by symptom: SEARO 2021

**Figure: Approach to painful or difficult swallowing in PLHIV**

- **Odynophagia or dysphagia**
  - Treat presumptively for oesophageal candidiasis
  - Improved after 7 days
    - No* → Treat presumptively for HSV
    - Improved after 7 days
      - Continue aciclovir for 14 days
      - Recurrence is likely unless ART is commenced
      - Consider prophylaxis with aciclovir 400 mg twice daily

* Consider treating for reflux disease, if no improvement, refer for oesophagoscopy for diagnosis

* At any point, if symptoms are suggestive of GERD, consider treatment with acid blockers.
* Consider CMV disease especially if findings are suggestive of CMV in other sites (i.e. retinitis) (see Section 11.10).
* Kaposi sarcoma, lymphoma, and oesophageal carcinoma can cause painful and difficult swallowing. Further investigations including barium studies, endoscopy and biopsy may be required for a definitive diagnosis.
10.5c Nausea and vomiting

This Section discusses an approach to the diagnosis and management of nausea, with or without vomiting. There are many causes for nausea and vomiting such as:

- gastric causes (e.g. peptic ulcer, infection, gastro-oesophageal reflux);
- central causes (e.g. headache, motion sickness, inner ear problems, raised intracranial pressure, offensive smells);
- pregnancy (hormone changes, pressure on stomach by the uterus);
- drugs and toxins;
- other illnesses (e.g. hepatitis, myocardial infarction).

10.5c.1 Clinical approach to nausea and vomiting

<table>
<thead>
<tr>
<th>Step 1:</th>
<th>Use Quick Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure that there are no serious or life-threatening conditions.</td>
<td></td>
</tr>
</tbody>
</table>

| Step 2: | Take a history and examine the patient |

| Step 3: | Assess the patient’s HIV status |

| Step 4: | Consider likely differential diagnosis using the DDx table(s) |

| Step 6: | Perform investigations |

| Step 6: | Initiate treatment and monitor the patient’s response |

History

- History of presenting complaint:
  - number and timing of episodes (after food, in the morning, after certain medications)
  - contents of vomitus (food, blood, bile, or coffee grounds)
  - association with changes in position or motion
  - associated symptoms (abdominal pain diarrhoea, fever, headache, visual changes, heartburn).
- Exposure to toxins:
  - food history (others who ate the same food are sick)
  - medications and treatments (such as chemotherapy)
  - drug or alcohol use.
- travel history
- menstruation, contraception, pregnancy.

Examination

- Targeted general exam:
  - signs of dehydration (increased thirst, dry lips or mouth, decreased skin turgor)
  - concentrated or reduced urine
  - jaundice
  - weight loss
  - rashes, spider naevi.
- CNS exam:
  - level of consciousness
Assess the patient's HIV status
HIV infection changes the possible differential diagnoses for nausea and vomiting, and should be considered in all patients presenting with these symptoms.

Investigations
- FBC – low Hb or low WBC
- electrolytes (Na, K, Cl)
- urea and creatinine
- stool for macro or microscopic examination and occult blood
- pregnancy test in women
- liver profile – AST, ALT, bilirubin
- abdominal X-ray
- ultrasound (for hepatomegaly, gallstones, thickened gallbladder wall, dilated common bile duct).

10.5c.2 Differential diagnosis and treatment of nausea or vomiting
Use the DDx table below to work through a differential diagnosis based on findings.

Initiate treatment and monitor the patient’s response
Treatment will depend on the differential diagnosis. For symptom management of nausea and vomiting, see 10.5.c.2 below. For management of specific conditions, see referenced Sections or other guidelines.

DDx: Nausea or vomiting

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal causes</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Associated diarrhoea&lt;br&gt;Acute onset&lt;br&gt;Fever&lt;br&gt;Cramping abdominal pain</td>
</tr>
<tr>
<td>Gastritis or peptic ulcer disease</td>
<td>Blood in vomitus – see Quick Check&lt;br&gt;Epigastric pain, discomfort, or tenderness&lt;br&gt;Nausea&lt;br&gt;Loss of appetite&lt;br&gt;History of alcohol or NSAID use</td>
</tr>
<tr>
<td>Gastroparesis</td>
<td>Delayed gastric emptying, commonly occurring in diabetes&lt;br&gt;Heartburn or pain in the upper abdomen with spasms in the stomach area&lt;br&gt;Nausea or vomiting of undigested food – sometimes several hours after a meal&lt;br&gt;Early feeling of fullness after only a small amount of food&lt;br&gt;Weight loss due to poor absorption of nutrients or low calorie intake&lt;br&gt;Abdominal bloating&lt;br&gt;Fluctuating blood glucose levels – high and low&lt;br&gt;Lack of appetite&lt;br&gt;Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Condition</td>
<td>Symptoms and Signs</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Oesophagitis</strong></td>
<td>Painful or difficult swallowing</td>
</tr>
<tr>
<td>(see Section 10.5b)</td>
<td>Pain or burning sensation in the chest (heartburn)</td>
</tr>
<tr>
<td></td>
<td>Bitter or sour taste in back of mouth</td>
</tr>
<tr>
<td></td>
<td>Worse at night, after eating or when lying down. <em>Candida</em> in the mouth (may suggest <em>Candida</em> oesophagitis)</td>
</tr>
<tr>
<td><strong>Cholecystitis</strong></td>
<td>Associated right upper quadrant abdominal pain with radiation to right shoulder or back</td>
</tr>
<tr>
<td>(see Section 10.5a)</td>
<td>Pain often severe – patient reluctant to move</td>
</tr>
<tr>
<td></td>
<td>Pain worse after eating</td>
</tr>
<tr>
<td></td>
<td>Tender hepatomegaly or tenderness over site of gallbladder</td>
</tr>
<tr>
<td></td>
<td>Low grade fever or chills</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>FBC – leukocytosis</td>
</tr>
<tr>
<td></td>
<td>Laboratory results – high ALP, high AST/ALT, increased amylase, increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – hepatomegaly with or without abscesses, gall stones, thickened gall bladder wall, dilated common bile duct</td>
</tr>
<tr>
<td></td>
<td>Abdominal X-rays usually normal</td>
</tr>
<tr>
<td></td>
<td>In HIV patients, acalculous cholecystitis (without stones) occurs</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Pain – radiates to the back, worse after eating and when lying down</td>
</tr>
<tr>
<td></td>
<td>Fever, tachycardia, dehydration</td>
</tr>
<tr>
<td></td>
<td>Vomiting after eating</td>
</tr>
<tr>
<td></td>
<td>History of excessive alcohol intake</td>
</tr>
<tr>
<td></td>
<td>May be severely ill with shock – see Quick Check</td>
</tr>
<tr>
<td></td>
<td>Exposure to NRTIs – d4T, ddl, 3TC, RTV</td>
</tr>
<tr>
<td></td>
<td>Purple hue overlying skin</td>
</tr>
<tr>
<td></td>
<td>Laboratory results – amylase more than 3 times normal, increased lipase</td>
</tr>
<tr>
<td></td>
<td>Ultrasound – gallstones</td>
</tr>
<tr>
<td><strong>Ileus</strong></td>
<td>Diffuse abdominal discomfort</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td></td>
<td>Abdominal X-ray: air fluid levels</td>
</tr>
<tr>
<td></td>
<td>Diminished bowel sounds</td>
</tr>
<tr>
<td><strong>Acute hepatitis</strong></td>
<td>Mild fever</td>
</tr>
<tr>
<td>(viral, alcohol, drugs, toxins)</td>
<td>(see Sections 8.4 and 11.16)</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td></td>
<td>Malaise, loss of appetite</td>
</tr>
<tr>
<td></td>
<td>Exposure to drugs (TB medications, NVP, RTV, EFV, ABC), alcohol, toxins</td>
</tr>
<tr>
<td></td>
<td>Right upper quadrant pain</td>
</tr>
<tr>
<td></td>
<td>Laboratory results – high ALT, AST, bilirubin</td>
</tr>
<tr>
<td><strong>Anthrax</strong></td>
<td>Gastrointestinal – initially non-specific nausea, vomiting, anorexia, mild diarrhoea, and abdominal pain. May progress to severe abdominal pain, haematemesis, bloody diarrhoea, massive ascites, and signs suggestive of acute abdomen</td>
</tr>
<tr>
<td>(gastrointestinal)</td>
<td>Fainting spells, asthenia</td>
</tr>
<tr>
<td></td>
<td>Fever and headache</td>
</tr>
<tr>
<td><strong>Intestinal obstruction or constipation</strong></td>
<td>Crampy abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Not able to pass flatus or stool</td>
</tr>
<tr>
<td></td>
<td>History of previous abdominal surgery</td>
</tr>
<tr>
<td></td>
<td>Bowel sounds – high-pitched, can be decreased</td>
</tr>
<tr>
<td><strong>Non-gastrointestinal causes</strong></td>
<td>Endemic area</td>
</tr>
<tr>
<td>Association with general febrile illness (e.g. malaria)</td>
<td>Fever, chills</td>
</tr>
<tr>
<td></td>
<td>Sweats</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Malaise, myalgia</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly, hepatomegaly, jaundice</td>
</tr>
</tbody>
</table>
| **Meningitis**  (see Section 10.8) | Headache, stiff neck  
Fever  
Confusion  
Petechial rash (if meningococcal) |
|-------------------------------|------------------------------------------------|
| **Migraine**  (see Section 10.8  
Headache) | History of previous episode  
Preceding aura  
Moderate to severe headache, photophobia, nausea |
| **Raised intracranial pressure**  (see Section 10.8  
Headache) | Headache and visual disturbances  
Hypertension  
Unequal pupils  
Focal neurologic deficit  
Fundoscopic examination – loss of retinal vein pulsation, papilloedema |
| **Inner ear problems**  (motion sickness, labirintitis) | History of being in a boat, plane or car  
Associated dizziness, vertigo, nystagmus  
Pain, discomfort, or blocked ear |
| **Hypercalcaemia**  (see Section 5.2) | Fatigue, confusion  
Loss of appetite, constipation  
Muscle weakness  
Evidence of associated malignancy  
Plasma calcium >2.6 mmol/l |
| **Uraemia**  (see Section 5.3) | Known renal disease  
Hiccups, confusion and loss of appetite  
Convulsions  
Uraemic frost on skin  
High urea and creatinine in laboratory results |
| **Symptomatic hyperlactataemia or lactic acidosis** | On ART >6 months  
On NRTI, e.g. d4T, ddI, or AZT  
Female, >40, high BMI  
Loss of weight, fatigue, malaise  
Abdominal pain  
Fast, deep breathing  
Serum lactate >5 mmol/l  
*Low pH (<7.3), low bicarbonate, high anion gap (>13)*  
Elevated ALT/AST, LDH, and amylase |
| **Pregnancy-related vomiting and hyperemesis gravidarum** | First 16–18 weeks of pregnancy  
Worse in the mornings  
Loss of weight  
Dehydration, ketoacidosis |
| **Opioids**  (see Section 3.4) | History of using morphine  
Nausea, drowsiness, constipation  
Constricted pupils (miosis) |
| **Other drugs** | AZT, ABC (hypersensitivity), protease inhibitors; rifampicin; NSAIDs |
| **Myocardial infarction** | Severe, crushing, retrosternal chest pain or discomfort  
Radiation of pain to left shoulder, arm, jaw  
Associated sweating, anxiety, nausea  
History of smoking, hypertension, cholesterol, diabetes  
Previous episodes of angina |
| **Heat-related (heat stroke or exhaustion)**  (see Section 8.1.4) | Exposure to heat and lack of adequate hydration  
Hot, flushed, dry skin with reduced sweating, rapid pulse, rapidly rising temperature to over 40.5 ºC (heat stroke)  
Pale, cold, clammy skin, weak pulse, low BP, high temperature (heat exhaustion)  
Confusion, convulsions |
| **Psychogenic**  (see Section 10.10) | Related to specific sights, smells or sounds  
Related to emotional states – anxiety, fear. |
10.5c.3 Symptom management for nausea or vomiting

- **Home care**
  For vomiting of less than 24 hours with no associated danger signs (e.g. blood in vomit, dehydration, headache or stiff neck, severe abdominal pain):
  - drink plenty of fluids
  - eat favourite, available foods that cause less nausea
  - eat frequent, small portions of food
  - use effective and safe local remedies, e.g. licking ash from wood.
  Advise the patient to seek help at a health facility if:
  - they have been vomiting for more than 24 hours; OR
  - if they have a dry tongue; OR
  - are passing little urine; OR
  - have abdominal pain.

- **Medications**
  - **Antiemetics:**
    - metoclopramide 10 mg IV/orally 3 times daily; OR
    - chlorpromazine 25–50 mg IM/orally four times daily; OR
    - ondansetron 4–8 mg IV twice daily or orally (for 24–48 hours) for moderate or severe vomiting, vomiting related to chemotherapy, or in hyperemesis gravidarum.

Metoclopramide should not be used in bowel obstruction or severe constipation.

Haloperidol 1.5 mg at bedtime is also an effective antiemetic if other agents are not available.
10.5d Constipation

Constipation is common in adults with complaints of less frequent stools or stools that are more painful to pass. Definitions include a stool frequency of <3 per week. Patients may complain of difficulty passing stools or decreased stool volume.

It is important to exclude intestinal obstruction or any symptoms that may suggest colon cancer.

**History**

- History of constipation:
  - Stool frequency
  - Straining at stool?
  - Painful defecation?
  - Onset and duration
  - Any abdominal pain?
  - Does constipation alternate with diarrhoea? (See irritable bowel syndrome, Section 10.5a)
  - Recent weight loss?
  - Family history of colon cancer or inflammatory bowel disease?

- What medicines used?
  - Opioid induced constipation is common in those suffering from chronic or cancer-related pain

- Ask about daily physical activity.

**Examination**

- If patient complains of abdominal pain, check for abdominal distention and listen to bowel sounds (high-pitched or decreased?).
- Perform a rectal examination to decide whether impacted.

**Treatment**

- Stop offending medicine if feasible.
- Give frequent oral fluids.
- Encourage high-fibre foods, such as fruits with the skin, vegetables, nuts and grains (aim at 20 to 25 grams/day).
- Encourage ambulation, if possible.
- If necessary, give laxative, e.g. senna (initially 15 mg at night; increase if necessary to 30 mg at night).
- If impacted (a solid, immobile bulk of stool in the rectum):
  - gently apply petroleum jelly or insert soapy solution into the rectum by enema.
  - manual disimpaction – start with manual fragmentation if necessary. After this is accomplished, an enema with mineral oil will help to soften the stool and provide lubrication.
10.6 Ascites

Ascites is the abnormal accumulation of fluid within the peritoneal cavity, presenting with:
- abdominal discomfort
- increase in belt or clothing size
- shortness of breath (cardiac failure, pleural effusion)
- peripheral oedema.

It may be secondary to:
- local causes in the peritoneum or other systemic diseases
- increase in the portal venous pressure observed in cirrhosis and heart failure
- direct peritoneal involvement by an infectious or neoplastic process
- a low serum albumin state with decreased oncotic pressure (nephrotic syndrome and kwashiorkor);
- less frequently, end-stage renal disease or other medical conditions.

10.6.1 Clinical approach to a patient with ascites

Step 1: Perform Quick Check
Use the Quick Check to assess the patient for serious and life-threatening conditions.
Patients with ascites may present with:
- shortness of breath or respiratory failure from pulmonary oedema secondary to CHF or a huge abdomen that interferes with normal breathing;
- shock or hypotension caused by circulatory failure; or
- severe subacute bacterial peritonitis leading to sepsis; or
- bleeding disorders in patients with chronic liver disease (cirrhosis).

Step 2: Take a history and perform a physical examination

Step 3: Assess HIV status

Step 4: Perform investigations

Step 5: Consider the likely differential diagnosis using the DDx tables

Step 6: Initiate treatment and monitor the patient’s response

History
Specific
Ask about:
- abdominal discomfort and a stretching sensation of the flanks and groin
- increase in belt or clothing size
- early satiety (fullness)
- shortness of breath – in cardiac failure, or pleural effusion
- swelling of the legs
- facial or upper extremity swelling, or generalized swelling – in case of nephrotic syndrome or end-stage renal disease
- lower back pain
• abdominal pain in hepatosplenic conditions, or irritation of the parietal peritoneum by infection or cancer.

General
• co-morbid diseases – chronic hypertension with chronic heart failure, chronic liver disease (cirrhosis, cancer, hepatitis, schistosomiasis, malignancies)
• alcohol use
• TB, HIV
• food security or dietary history
• protein-losing enteropathies – bowel disorders
• chronic renal diseases – proteinuric state.

Examination
General
• Confirm the ascites by the presence of:
  o shifting dullness to differentiate ascites from other causes of abdominal swelling
  o fluid thrill.
• Look for evidence of chronic liver disease or decompensation
  o signs suggestive of cirrhosis
  o jaundice
  o spider naevi
  o palmar erythema
  o overt encephalopathy or flapping tremors.
• The presence of heart failure:
  o distended jugular veins
  o heart gallop rhythm
  o pulmonary crackles (pulmonary oedema).
• Generalized oedema (anasarca):
  o involving both upper and lower extremities
  o most commonly associated with nephrotic syndrome and end-stage renal disease
  o can be seen in severe heart failure.
• Cachexia (wasting) and diffuse lymphadenopathy (tuberculosis or a neoplastic disease).

Specific
Inspection:
• distended abdomen
• stretched skin marks
• bulging flanks, and occasionally an umbilical hernia
• visible abdominal venous pattern (caput medusa) with the direction of flow away from the umbilicus (portal hypertension).
Palpation:
• splenomegaly (in marked portal hypertension, tuberculosis, lymphoma)
• liver – small and firm or non-palpable in cirrhosis
• enlarged in schistosomiasis (pre-sinusoidal portal hypertension) and Budd-Chiari syndrome (post-hepatic portal hypertension)
• hard nodular in primary liver cancer or metastatic disease – suggesting that direct peritoneal seeding is the cause of ascites
• pelvic and rectal examination to look for genitourinary and gastrointestinal malignancies.

Perform investigations
• See Section 7.4.3 for instructions on diagnostic paracentesis (abdominal tap).
  o Observe gross appearance.
10. Acute and subacute by symptom: SEARO 202

10.6 Ascites

- Send ascitic fluid for:
  - protein (albumin level)
  - cell count (WBC, RBC)
  - Gram stain, AFB, and culture
  - cytology (if malignancy suspected).

- LFTs – AST, ALP; bilirubin; albumin
- FBC
- INR (PT) and PTT or crude clotting time (Section 7.2.18) if not available
- stool microscopy
- urine dipstick or 24-hour urine albumin (an albumin level <2.5 g/dl and 24-hour proteinuria >3 g are diagnostic of nephrotic syndrome)
- ESR
- abdominal ultrasound (detects small amounts of ascites and defines abnormalities present in the liver parenchyma and portal circulation)
- doppler ultrasound – to look for venous obstruction.

10.6.2 Classify ascites and consider the likely differential diagnosis

Classify the fluid as a transudate or exudate, and calculate the SAAG

Classify according to protein measurement of the fluid.
- transudate: protein <30 g/litre in peritoneal fluid
- exudate: protein >30 g/litre in peritoneal fluid

Calculate the SAAG (serum-to-ascites albumin gradient)

\[ \text{SAAG} = (\text{serum albumin}) - (\text{ascitic fluid albumin}) \]

- A SAAG >1.1 g/dl (11 g/litre) indicates that the patient has portal hypertension:
  - cirrhosis
  - heart failure
  - Budd-Chiari syndrome and schistosomiasis.
- A SAAG <1.1 g/dl (less than 11 g/litre) rules out portal hypertension:
  - ascites caused by infectious or neoplastic peritoneal disease
  - severe acute pancreatitis
  - a low albumin state (nephrotic syndrome and kwashiorkor).

Consult the relevant differential diagnosis table.

**DDx: Ascites with SAAG >1.1 (portal hypertension) – transudate**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Known risk factor – alcoholism, history of jaundice, chronic HBV or HCV (see Section 11.14)</td>
</tr>
<tr>
<td></td>
<td>Small nodular liver, jaundice</td>
</tr>
<tr>
<td></td>
<td>Signs of chronic liver disease – gynaecomastia, caput medusae, palmar erythema, spider naevi, flapping tremor</td>
</tr>
<tr>
<td></td>
<td>Upper gastrointestinal bleeds from varices</td>
</tr>
<tr>
<td></td>
<td>Peritoneal fluid analysis (straw coloured, WBC &lt;250 predominantly mesothelial, RBC &lt;10 000, protein &lt;2.5 g/dl)</td>
</tr>
<tr>
<td></td>
<td>High bilirubin and INR</td>
</tr>
<tr>
<td></td>
<td>Low serum albumin</td>
</tr>
<tr>
<td>Condition</td>
<td>In favour</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>Distended jugular veins, heart gallop, pulmonary crackles (pulmonary oedema), hepatomegaly, oedema of lower limbs Peritoneal fluid analysis – straw coloured, protein &gt;2.5 g/dl, WBC &lt;250 Abdominal ultrasound – hepatomegaly, distended IVC with minimal respiratory cycle change</td>
</tr>
<tr>
<td><strong>Budd-Chiari syndrome</strong></td>
<td>Risk factors for thrombosis (haematological and other malignancies, contraceptives containing estrogen) Consistent features on ultrasound – see below</td>
</tr>
<tr>
<td><strong>Schistosomiasis</strong></td>
<td>Upper Gl bleeding from varices Stool positive for ova Ultrasound – periportal fibrosis, splenomegaly, enlarged veins, collateral vessels. (see Section 11.34)</td>
</tr>
</tbody>
</table>

**DDx: Ascites with SAAG <1.1 (no portal hypertension)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial peritonitis</strong></td>
<td>Acute abdomen – see Section 10.7a Abdominal pain Systemically ill Peritoneal fluid analysis – turbid or purulent; protein &gt;2.5 g/dl; WBC often &gt;1000 and predominantly PMN; RBC &lt;10 000; positive Gram stain and culture Abdominal X-ray – free air under diaphragm. If perforation of hollow organ suspected, titrate bile and amylase from sample</td>
</tr>
<tr>
<td><strong>SBP in cirrhosis</strong></td>
<td>Fever, abdominal pain, encephalopathy Peritoneal fluid analysis – turbid or purulent WBC &gt;250 Positive Gram stain and culture</td>
</tr>
<tr>
<td><strong>Tuberculous peritonitis</strong></td>
<td>Constitutional symptoms – low grade fever, weight loss, night sweats, generalized lymphadenopathy, hepatosplenomegaly More common in HIV with evidence of immunosuppression Peritoneal fluid analysis – clear, haemorrhagic or chylous; protein &gt;2.5 g/dl; WBC often &gt;500 predominantly lymphocytes; RBC occasionally &gt;10 000 Positive AFB or culture (not always), high ESR Ultrasound – hepatosplenomegaly, peritoneal thickening, abdominal lymphadenopathy, micro-abscess in spleen or liver</td>
</tr>
<tr>
<td><strong>Neoplasms</strong></td>
<td>Systemic symptoms – weight loss, night sweats Peritoneal fluid analysis – straw-coloured, haemorrhagic, mucinous or chylous; protein &gt;2.5; WBC often &gt;500 with variable cell types; RBC occasionally &gt;10 000; positive cytology, high ESR Ultrasound – liver mass, abdominal mass or peritoneal thickening</td>
</tr>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>History of heavy alcohol intake Epigastric or central abdominal pain Peritoneal fluid analysis – turbid, haemorrhagic, chylous; protein &gt;2.5 g/dl; variable WBC and RBC counts High serum and ascites amylase levels Ultrasound – oedematous pancreas, may be normal</td>
</tr>
<tr>
<td><strong>Nephrotic syndrome</strong></td>
<td>Peritoneal fluid analysis – straw coloured, protein &lt;2.5 g/dl, WBC &lt;250, RBC &lt;10 000 Serum albumin &lt;2.5 g/dl Urine dipsticks, proteinuria, and 24-hour proteinuria &gt;3.5 g Ultrasound may show enlarged kidneys</td>
</tr>
<tr>
<td><strong>Malnutrition</strong></td>
<td>Rarely causes clinical ascites in adults Peripheral oedema is common Peritoneal fluid analysis – straw coloured, protein &lt;2.5 g/dl, WBC &lt;250, RBC &lt;10 000 Serum albumin &lt;2.5 g/dl Urine dipstick – no protein</td>
</tr>
<tr>
<td><strong>Visceral leishmaniasis</strong></td>
<td>Slow progression of fever, malaise, and weight loss Marked cachexia, splenomegaly, hepatomegaly, jaundice Low platelets or pancytopaenia Demonstration of parasite by smear or culture in bone marrow or spleen. (see Section 11.19)</td>
</tr>
</tbody>
</table>
10.6.3 Manage ascites according to cause

It is important to establish the underlying cause of the ascites since the management differs in relation to different causes.

Manage ascites with SAAG >1.1 (portal hypertension) – transudate

General management

- Salt restriction <2 grams (less than half a teaspoon) per day.
- Combined oral diuretics – keep the ratio between the two drugs constant:
  - spironolactone 100 mg increased up to a maximum dose of 400 mg/day PLUS furosemide 40 mg to a maximum of 160 mg/day
  - Caution in rapid diuresis
  - Monitor daily weights and urine output
  - Therapeutic peritoneal tap if indicated – assess for ascites and see box below
  - Intractable ascites need to be referred for further investigations
  - Refer patients who are not responding for shunt operations or possible liver transplantation.

Therapeutic paracentesis in portal hypertension (see Section 7.4.3)

The amount of fluid taken out daily by paracentesis should be 2–3 litres.

Exception: occasionally, patients with massive ascites will develop abdominal discomfort and severe shortness of breath and will require a large volume therapeutic paracentesis (4–5 litres) for control of the symptoms.

Diuresis

Patients with peripheral oedema tolerate mobilization of a high fluid volume (2 litres/day) without developing intravascular depletion and azotaemia.

Patients with ascites but without oedema can develop hypovolaemia and acute renal failure if the rate of fluid removal exceeds 500 ml/day.

Diuretic-resistant ascites is defined by a lack of response to maximum doses of spironolactone and furosemide in a patient on a low sodium diet. These patients often need serial large volume therapeutic paracenteses, not exceeding 4–5 litres to avoid intravascular volume depletion and acute renal failure.

Manage cirrhosis

Prevent complications from cirrhosis:

- Look for a cause – serology for hepatitis B, C (see Section 11.16).
- Advise the patient to avoid alcohol.
- Determine the severity of cirrhosis using the modified Child-Turcotte-Pugh classification (use Table below).
- If available, refer for endoscopy to look for oesophageal varices. If varices present, use a low-dose non-selective beta blocker (e.g. propranolol titrated to achieve a 25% reduction in the heart rate), as primary prevention for upper gastrointestinal bleeding secondary to documented oesophageal varices.
- Consider whether patient has hepatic encephalopathy (see Section 3.4.1).
- Consider long-term lactulose, titrated to achieve 2–4 bowel movements per day, if signs of hepatic encephalopathy.
- Be careful about fluid management and avoid nephrotoxic drugs (e.g. NSAIDs and aminoglycosides) to prevent hepatorenal syndrome.
- Refer patients with severe cirrhosis, hepatic encephalopathy and metabolic complications to a specialist for management of complications and for evaluation for other therapies.

Scoring to determine the severity of cirrhosis

- The score uses 5 markers of liver disease. Each measure is scored 1–3; with 3 indicating the most severe derangement.
### Table: Child-Turcotte-Pugh classification

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (total)</td>
<td>&lt;34 μmol/l (&lt;2 mg/dl)</td>
<td>34–50 μmol/l (2–3 mg/dl)</td>
<td>&gt;50 μmol/l (&gt;3 mg/dl)</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&gt;35 g/l</td>
<td>28–35 g/l</td>
<td>&lt;28 g/l</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.71–2.20</td>
<td>&gt;2.20</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Suppressed with medication</td>
<td>Refractory</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Grade I–II (or suppressed with medication)</td>
<td>Grade III–IV (or refractory)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total points</td>
<td>5–6</td>
<td>7–9</td>
<td>10–15</td>
</tr>
</tbody>
</table>

#### Manage ascites SAAG <1.1 (no portal hypertension) – transudate

Ascites caused by neoplastic or infectious processes and secondary to acute pancreatitis and a low albumin state should be managed differently.

- Treat the primary disease. See Section 10.5a if peritonitis is suspected.
- Avoid sodium restriction and diuresis as this can be harmful and lead to unwanted intravascular volume depletion and acute renal failure.
- May require large volume therapeutic paracentesis (4–5 litres) to manage or alleviate symptoms of discomfort.

#### Spontaneous bacterial peritonitis

- Suspect in patients with cirrhosis and ascites presenting with:
  - fever
  - abdominal pain
  - altered mental status
  - hepatorenal syndrome.

**Investigations**

- Paracentesis (see Section 7.4.3) – WBC count ≥500, neutrophils ≥250 cells/mm³.

**Treatment**

- Give ceftriaxone 2 grams daily for 5–10 days.
- If available, albumin 25% IV 1.5 g/kg on Day 1 and 1 g/kg on Day 3.

**Prevention**

- Antibiotic prophylaxis – for all patients with:
  - a history of SBP
  - a current upper gastrointestinal bleeding episode
  - ascitic fluid albumin level less than 1 g/dl.
- cotrimoxazole (1 double-strength tablet daily); OR
- ciprofloxacin 250–500 mg daily; OR
- norfloxacin 400 mg daily.

#### Schistosomiasis (see Section 11.29)

Schistosomiasis leads to granulomatous inflammation and the obstruction of the blood flow to the liver.

- Referral is usually needed if a shunt operation for portal hypertension is available upon referral.
10.7 Neurological problems including deficits

10.7.1 Introduction to managing neurological problems

A patient presenting with headache, meningeal signs, change in mental status, seizures, or neurological deficit could require urgent management. You will need to use different parts of this Section and of the manual to work through a differential diagnosis for the problem.

Use Sections 7, 8 and 9

- 10.7 Neurological deficit without meningeal signs (no headache, stiff neck, vomiting – if present, also see Section 10.8)
  - patient with a stroke-like syndrome
  - patient with spinal cord problem (myelopathy)
  - patient with peripheral motor or sensory nervous system problem
  - patient with a cranial nerve abnormality.

- 10.8 Headache
  - headache with no abnormal physical findings
  - headache with abnormal physical findings (including meningeal signs, fever, neurological deficit, seizures).

- 10.9 Seizures or convulsions
  - seizures due to a systemic illness
  - seizures due to intracranial infection or lesion
  - chronic recurrent seizures.

Use Section 2 – Quick Check

- for emergency management of a convulsing or comatose patient
- for patients with a history of head trauma.

Use Section 3 – Approach to the severely ill patient

- for a patient with a decreased level of consciousness, confusion, intoxication, or agitation (Section 3.4)
- for a patient who is convulsing or in status epilepticus (Section 3.5).

Use Section 10.11 – Eye problems

- for acute visual loss.

It is possible to clinically recognize and treat common neurological problems without the use of complex diagnostic tests.
10.7.2 Clinical approach to management of patient with a neurological deficit without meningeal signs

This Section addresses the management of a patient who presents with a neurological deficit and without meningeal signs. Use this Section for a patient presenting with the following symptoms:

- motor deficit (weakness, paralysis, loss of balance, difficulty speaking)
- sensory deficit (tingling, numbness, pain)
- cranial nerve deficits (facial weakness, vertigo, double vision).

### Step 1: Use Quick Check
Ensure that there are no serious or life-threatening conditions. Use the Quick Check for management of life-threatening conditions, such as coma and convulsions.

### Step 2: Take a history and examine the patient
If the patient has difficulty speaking or is confused, obtain a good history from the family.

### Step 3: Assess the patient’s HIV status

### Step 4: Classify the deficit using the table Classification of motor and sensory neurological deficit

### Step 5: Use the DDx tables to work through a differential diagnosis:
- DDx: Stroke-like syndrome
- DDx: Spinal cord problem (myelopathy)
- DDx: Peripheral motor or sensory nervous system problem
- DDx: Peripheral neuropathy (distal – DSPN)
- DDx: Cranial nerve abnormalities.

### Step 5: Perform investigations
Perform investigations according to the differential diagnosis and availability of tests. It is possible to diagnose and manage neurological problems without the use of complex diagnostic tests.

### Step 7: Initiate treatment and monitor response

**Quick Check**
Ensure that there are no serious or life-threatening conditions. Use the Quick Check for patients with coma and convulsions. Ask specifically about any history of head injury.

**History**
- History of the following presenting complaints, including onset (sudden or insidious) and duration:
  - motor changes (e.g. difficulty combing hair, writing, squatting, climbing stairs)
  - sensory changes
  - vision, hearing, or speech problems
  - difficulty with balance or walking
  - meningeal signs – headache, stiff neck
  - associated fever, constitutional symptoms
  - associated nausea, vomiting, dizziness
  - associated seizures
  - change in consciousness, behaviour, mood
  - change in memory or cognition
  - bowel and bladder disturbances.
- Medical history:
  - risk factors for stroke (hypertension, diabetes, heart disease, obesity, bleeding disorders, clotting, pregnancy)
  - HIV infection (CD4 count, ART)
  - TB infection (current TB symptoms, previous TB, or TB contact)
malignancy
syphilis
history of head injuries
medications (e.g. aspirin, anticoagulants, oral contraceptive pill).
Other infections such as COVID-19. Patients with COVID-19 may have neurological symptoms without respiratory symptoms.\(^1\) As demonstrated in SARS-CoV and Mers-CoV, the neuroinvasive and neurotropic potential of SARS-CoV-2 has been observed and may be through the direct invasion of neural tissues, inflammatory response, or immune dysregulation.\(^2\)

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### Examination

#### General signs
- vital signs
- signs of immune compromise
- level of consciousness
- neck stiffness, meningeal signs (if present, also see Section 10.8).

#### Examine the fundi
- Perform fundoscopy (see Section 10.11)
- Look for loss of spontaneous venous pulsations, blurred optic disc margins, and elevated optic head as evidence of papilloedema.

#### Assess higher functions
- orientation to person, place, or time
- memory
- speech
  - difficulty articulating words (dysarthria)
  - difficulty understanding or expressing words (aphasia)
- gait, ability to walk
- assess for cognitive deficits (see Sections 3.4 and 10.10)
  - In PLHIV, assess for possible HIV-associated cognitive disorders.

#### Examine cranial nerves
- see Table: Common cranial nerve palsies and their differentials.

#### Examine motor system
- power, tone, reflexes.

#### Examine the sensory system
- examine for touch, pain, temperature, and position sense
- screen for peripheral neuropathy
  - In PLHIV, assess for HIV-associated distal sensory polyneuropathy.

#### Examine cerebellar function
- assess for intention tremor, hypotonia, nystagmus, broad-based gait, and incoordination.

---


Assess HIV status
There are a number of neurological conditions associated with immune suppression from HIV infection. The HIV status of a patient will impact on the differential diagnosis and management.

10.7.3 Classify the neurological deficit and consider the likely differential diagnosis
Neurological deficit can result from a number of different conditions that cause injury to the brain, spinal cord, or peripheral nerves. Classifying the deficit will help you to work through a differential diagnosis and determine the most likely cause.

Table: Classification of motor and sensory neurological deficit

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features in favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke-like syndrome</strong></td>
<td>Onset acute (stroke) or subacute</td>
</tr>
<tr>
<td>(due to injury to the brain – results in</td>
<td>Unilateral</td>
</tr>
<tr>
<td>upper motor neuron deficit)</td>
<td>Weakness or numbness in face, arm, or leg</td>
</tr>
<tr>
<td></td>
<td>Difficulty speaking, swallowing</td>
</tr>
<tr>
<td></td>
<td>Dizziness, blurred vision, loss of balance</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Cerebellar signs</td>
</tr>
<tr>
<td><strong>Spinal cord problem (myelopathy)</strong></td>
<td>Slow, subacute onset, or acute trauma to the spinal cord. May present abruptly or gradually.</td>
</tr>
<tr>
<td>(due to injury to the spinal cord)</td>
<td>Bilateral or unilateral</td>
</tr>
<tr>
<td></td>
<td>Paraparesis or quadriplegia</td>
</tr>
<tr>
<td></td>
<td>Loss of motor function and sensation (touch, temperature)</td>
</tr>
<tr>
<td></td>
<td>Loss of bladder or bowel control</td>
</tr>
<tr>
<td><strong>Peripheral motor or sensory nervous system problem (neuropathy)</strong></td>
<td>Acute or subacute onset</td>
</tr>
<tr>
<td>(due to injury to the peripheral nerves)</td>
<td>Motor – weakness, cramps, spasms</td>
</tr>
<tr>
<td></td>
<td>Sensory – tingling, numbness, pain</td>
</tr>
<tr>
<td></td>
<td>Autonomic – BP instability, reduced sweating, incontinence, sexual problems</td>
</tr>
<tr>
<td></td>
<td>HIV positive, alcohol use, malnutrition</td>
</tr>
<tr>
<td><strong>Cranial nerve problems</strong></td>
<td>Isolated or multiple cranial nerve palsies</td>
</tr>
<tr>
<td></td>
<td>Eye and vision changes</td>
</tr>
<tr>
<td></td>
<td>Difficulties with balance or hearing</td>
</tr>
</tbody>
</table>

Once you have classified the deficit, use the DDx tables below to find a likely cause.
- DDx: Stroke-like syndrome
- DDx: Spinal cord problem (myelopathy)
- DDx: Peripheral motor or sensory nervous system problem
- DDx: Peripheral neuropathy (distal sensory peripheral neuropathy)
- DDx: Cranial nerve abnormalities.

Perform investigations
Perform investigations according to the likely differential diagnosis.
- Lumbar puncture to examine the CSF (see Section 7.4 for the procedure and Section 10.8 for further work-up):
  - perform fundoscopy to exclude papilloedema;
  - this is especially important if HIV infection;
  - important if you suspect meningitis or subarachnoid bleed;
10. Acute and subacute by symptom: SEARO 2021

- may be considered in the presence of focal signs if no signs of impending herniation (see Section 10.10.b);
- may be considered for headache, for more information see Section 10.8;
- CSF for opening pressure, appearance, microscopy for cells and other microorganisms, chemistry, cryptococcal antigen, rapid syphilis test, TB.

- **Bloods:**
  - FBC
  - cryptococcal Ag
  - toxoplasma IgG
  - rapid syphilis test.
- **Spinal X-rays:**
  - for neurological deficit with a spinal level.
- **CT scan (if indicated and available).**

**Initiate treatment and monitor response**

Management of patients with a neurological deficit and no meningeal signs will depend on the availability of CT scanning. As a rule of thumb, 80%–90% of patients can be managed at district level without CT scan. Very few district hospitals have CT scanners, but CT scanning may be available at a referral hospital for specific patients.

If there is no access to CT scanning and LP is contraindicated (see Section 10.8 Headache), then empirical therapy should be started for TB and toxoplasmosis or any other diagnosed conditions, especially in the case of HIV-infected patients.

**10.7.4 Stroke-like syndrome**

Problems affecting the brain or central nervous system can cause stroke-like syndromes due to damage to the upper motor neurons. The differential for a patient presenting with a stroke-like syndrome is broad. In settings of high HIV prevalence, certain conditions occur more commonly.

Use the DDx table below to work through a differential diagnosis for a patient presenting with a stroke-like syndrome.

**DDx: Stroke-like syndrome**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular accident</td>
<td></td>
</tr>
</tbody>
</table>
| Ischaemic or haemorrhagic stroke | Sudden onset  
Hypertensive, diabetic, history of smoking  
Unilateral weakness or numbness in face, arm, or leg  
Difficulty speaking or swallowing  
Dizziness or blurred vision  
Difficulty walking or problem with balance  
Confusion  
No progression of deficit (may have some improvement over time) |
| Intracranial masses        |                                                                           |
| Cerebral toxoplasmosis     | Subacute onset over days to weeks  
Headache  
With or without fever  
Focal signs  
Dull affect, impaired level of consciousness  
Seizures  
CT scan – multiple ring enhancing lesions  
HIV infection – CD4 <100 |
| Cryptococcoma              | Subacute onset over days to weeks  
Fever, malaise, headache |

**Neurological deficit**

10.7 – 97
<table>
<thead>
<tr>
<th><strong>Neurological deficit</strong></th>
<th><strong>10. Acute and subacute by symptom: SEARO 2021</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin lesions resembling <em>molluscum contagiosum</em></strong>&lt;br&gt;LP – high opening pressure&lt;br&gt;HIV infection – CD4 &lt;50&lt;br&gt;CSF: increased lymphocytes, low glucose, high protein, + India ink, + CRAG&lt;br&gt;N.B.: CSF may be normal.</td>
<td><strong>10.7 – 98</strong> <strong>Neurological deficit</strong>&lt;br&gt;<strong>10. Acute and subacute by symptom: SEARO 2021</strong></td>
</tr>
<tr>
<td><strong>Tuberculoma</strong>&lt;br&gt;Gradual onset over days to weeks&lt;br&gt;Focal neurological deficit&lt;br&gt;Evidence of TB elsewhere&lt;br&gt;CSF – increased lymphocytes, low glucose, high protein</td>
<td><strong>Schistosomiasis can also cause disorders with neurological manifestations (see Section 11.29).</strong>&lt;br&gt;<strong>3 Mao L, Jin H, Wang M et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020; 77(6): 683-690.</strong></td>
</tr>
<tr>
<td><strong>Bacterial brain abscess</strong>&lt;br&gt;May result from contiguous spread or bacteraemia&lt;br&gt;Gradual onset over weeks&lt;br&gt;Headache, neck stiffness, altered mental status, signs of increased ICP&lt;br&gt;Focal deficits beginning days after headache, seizures&lt;br&gt;LP should be avoided</td>
<td><strong>Other infections</strong></td>
</tr>
<tr>
<td><strong>Tumours (benign tumour, lymphoma, metastases)</strong>&lt;br&gt;Insidious onset&lt;br&gt;Cranial nerve palsies, mental status change&lt;br&gt;Focal neurology</td>
<td><strong>Progressive multifocal leucoencephalopathy (PML)</strong>&lt;br&gt;Clumsiness&lt;br&gt;Visual changes, hemiparesis, dysarthria, aphasia; seizures&lt;br&gt;Progression over 1–9 months&lt;br&gt;HIV infection – CD4 &lt; 100</td>
</tr>
<tr>
<td><strong>Neurocysticercosis</strong>&lt;br&gt;(see Section 11.9)&lt;br&gt;Seizures&lt;br&gt;Headache, nausea, vomiting, altered mental status&lt;br&gt;Endemic area&lt;br&gt;CSF – high WBC, eosinophils&lt;br&gt;Skull X-ray – multiple calcified cysts&lt;br&gt;CT – multiple calcified cysts and active fluid-filled cysts</td>
<td><strong>Neurosyphilis</strong>&lt;br&gt;(see Section 11.32)&lt;br&gt;Subacute onset of headache, dizziness, personality changes followed by stroke-like syndrome&lt;br&gt;CSF – normal glucose high protein, high WBC + CSF VDRL (not RPR or FTA)&lt;br&gt;VDRL or RPR</td>
</tr>
<tr>
<td><strong>Viral encephalitis</strong>&lt;br&gt;(herpes, CMV)&lt;br&gt;(see Sections 11.10)&lt;br&gt;Acute or subacute onset&lt;br&gt;Prodrome of high fever, headache, nausea, lethargy, myalgia&lt;br&gt;Frontal or temporal lobe focal signs&lt;br&gt;Seizures, confusion, altered level of consciousness, bizarre behaviour&lt;br&gt;CSF – increased lymphocytes, normal glucose, mildly elevated protein</td>
<td><strong>COVID-19</strong>*&lt;br&gt;(see Section 11.6)&lt;br&gt;Some studies have reported up to 36% of COVID-19 patients have neurological symptoms.(^3)&lt;br&gt;More common with severe infection.&lt;br&gt;Early symptoms include taste and smell impairment, headache, dizziness. Other neurological symptoms: altered consciousness (may be secondary to hypoxiaemia), delirium/encephalopathy, agitation,, coma, ischaemic stroke, hypoxic ischaemic brain injury, haemorrhagic strokes, seizures, meningo-encephalitis, myopathy, nerve pain, Guillain-Barré syndrome, peripheral neuropathy, and optic neuritis. Guillain-Barré syndrome, acute disseminated encephalomyelitis, and acute haemorrhagic leukoencephalitis-like presentations may occur weeks after the acute stage of infection.(^1)</td>
</tr>
</tbody>
</table>

\(^*\) Schistosomiasis can also cause disorders with neurological manifestations (see Section 11.29).
Approach to HIV-infected patients with stroke-like syndrome

Assess patient for clinical signs and symptoms of disseminated infections such as TB, syphilis, cryptococcal infection.

- Investigate according to findings:
  - CD4 count
  - toxoplasma serology
  - cryptococcal serology (serum or CSF)
  - RT PCR SARS-CoV-2
  - syphilis serology
  - platelet count/coagulation studies
  - investigations for TB if suggestive – CXR, sputum AFB, lymph node FNA.

- CD4 count and degree of immunosuppression help guide diagnosis.

- Toxoplasmosis or TB are common causes:
  - TB is more likely if there are signs of TB elsewhere.
  - Toxoplasmosis is unlikely if CD4 >200.

**Commence empirical treatment without delay**

- If a CT scan is immediately available:
  - interpret CT findings.
  - if a lumbar puncture is safe (see Section 10.8), do CSF investigations.
  - based on CT or CSF findings, treat for the most likely cause (if uncertain, always cover for toxoplasmosis).
  - if no response to treatment – review diagnosis.

- If a CT scan is not immediately available:
  - weigh the risks of a lumbar puncture versus empirical therapy.
  - initiate empirical treatment for toxoplasmosis and TB (if evidence of TB infection elsewhere in body);
  - review patient and revise diagnosis depending on CD4 count, results of other investigations, subsequent CT scan, and response to treatment.
  - consider referral for CT if available and patient not responding to empirical treatment.

**Table: Neurological conditions according to immune status**

<table>
<thead>
<tr>
<th>HIV-negative or CD4 &gt;500 (but all can also occur with lower CD4 count)</th>
<th>CD4 &lt;200</th>
</tr>
</thead>
<tbody>
<tr>
<td>• benign and malignant brain tumours</td>
<td>• toxoplasmosis (usually CD4 &lt;100)</td>
</tr>
<tr>
<td>• CVA</td>
<td>• tuberculoma or TB meningitis</td>
</tr>
<tr>
<td>• neurosyphilis</td>
<td>• primary CNS lymphoma (usually CD4 &lt;50)</td>
</tr>
<tr>
<td>• tuberculoma or TB meningitis</td>
<td>• CVA – intracerebral haemorrhage related to thrombocytopenia</td>
</tr>
<tr>
<td>• neurocysticercosis</td>
<td>• progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>• secondary malignancy or brain metastases</td>
<td>• bacterial causes/abscesses</td>
</tr>
<tr>
<td><strong>CD4 200–500</strong></td>
<td>• cryptococcal meningoencephalitis</td>
</tr>
<tr>
<td>• HIV-associated neurocognitive disorders (HAND)</td>
<td>• neurocysticercosis</td>
</tr>
<tr>
<td></td>
<td>• HIV-associated neurocognitive disorders (HAND)</td>
</tr>
</tbody>
</table>
## 10.7.5 Spinal cord problem (myelopathy)

Problems affecting the spinal cord cause damage to the lower motor neurons and sensory nerves. The differential for myelopathy is broad; however, in settings of high HIV prevalence, certain conditions occur more commonly than others.

### DDx: Spinal cord problem (myelopathy)

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compressive</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Spinal cord compression (herniated disc, tumour – benign, malignant, or metastatic – abscess) | Slow onset  
Back pain  
Numbness or tingling in toes, fingers, or buttocks  
Weakness, unsteadiness, difficulty walking  
Urine or faecal retention or incontinence  
Evidence of primary cancer (breast, lung, prostate, lymphoma) |
| Spondylosis (osteoarthritis of the spine) | Slow onset  
Pain or stiffness in neck, thoracic, or lumbar spine – radiation down arm or leg, worse in the morning, worse with movement  
Numbness or tingling in the arms, legs, hands, or feet  
Weakness, unsteadiness, difficulty walking  
Loss of bladder or bowel control |
| **Infectious/inflammatory** | | |
| Tuberculosis of the spine | Onset over months  
Back pain (lasting weeks to months), muscle spasm  
Fever  
Weight loss  
Night sweats  
Spinal deformity (kyphosis) |
| HIV-associated myelopathy | Slow onset  
Progressive weakness or stiffness in the legs (sometimes arms)  
Sensory loss, sphincter dysfunction, incontinence  
Increased reflexes, up-going plantar response (Babinski)  
Erectile dysfunction in men  
Difficulty walking  
Advanced HIV disease  
Associated HIV dementia or peripheral neuropathy |
| Transverse myelitis (herpes, varicella, CMV, HIV, TB, polio, rabies, measles, syphilis, hepatitis, schistosomiasis, bartonella, mycoplasma, multiple sclerosis, paraneoplastic, AV malformation) (see Section 11 for more on specific communicable diseases) | Acute onset  
Back pain  
Sensation of a tight band around the trunk  
Numbness or tingling below a certain spinal level  
Weakness in legs (arms involved less often)  
Muscle spasms  
Bowel and bladder dysfunction  
Associated headache, fever, loss of appetite  
Other symptoms depending on the cause |
| Tertiary syphilis (see Section 11.32) | Slow onset  
Numbness or tingling in the hands or feet  
Weakness of limbs, unsteadiness, wide-based walk  
Loss of reflexes, incontinence  
Memory loss, psychiatric problems, visual loss |
| **Metabolic** | | |
| Vitamin B12 deficiency | Subacute onset  
Megaloblastic anaemia  
Numbness or tingling in the hands or feet  
Weakness in legs, ataxia, wide-based walk  
Absent ankle reflexes  
Poor joint position and vibration sense  
Peripheral neuropathy  
Dementia, depression. |
10.7.6 Peripheral motor or sensory nervous system problem

Problems affecting the peripheral nervous system can cause motor or sensory disturbances, and occur as a result of damage to the peripheral nerves and nerve roots. The differential for a patient presenting with weakness, numbness, tingling and pain is broad. However, in settings of high HIV prevalence, certain conditions occur more commonly due to the effect of HIV on the nerves, as well as the effect of opportunistic infections, neoplasms, and medications.

The most common conditions are mononeuropathies (focal disorders affecting a single nerve or nerve group) and radiculopathies (disorders of the nerve roots).

Different disorders can be roughly distinguished by whether or not they are focal or multifocal, symmetrical or asymmetrical, and whether they are primarily sensory or have a motor or autonomic component.

**On taking the patient’s history, the following information is important:**

- onset and progression of symptoms
- symmetrical or asymmetrical, distal or proximal, focal or multifocal
- bladder control problems
- sweating, temperature or pulse instability (autonomic involvement)
- HIV infection (if positive, CD4 count)
- exposure to drugs (INH, d4T, ddI) or toxins (alcohol, lead).

**On examination, pay particular attention to the following:**

- sensory function (pain, light touch, vibration, proprioception)
- motor function (power, tone, reflexes)
- spinal examination
- sphincter function
- cranial nerves abnormalities.

**Investigations**

- CSF analysis may be helpful for distinguishing between various conditions that have involvement at the spinal cord level (see differential diagnosis table).
- In the absence of sophisticated nerve conduction tests, diagnosis is commonly based on clinical context and pattern recognition.
- Specific investigations according to the clinical suspicion of underlying problems.

**DDx: Peripheral motor or sensory nervous system problem**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal or asymmetrical deficits</td>
<td></td>
</tr>
<tr>
<td>Compression of nerve or nerve root</td>
<td>Weakness and sensory disturbance in the distribution of affected nerve and</td>
</tr>
<tr>
<td>(lymphoma, TB, carpal tunnel syndrome, bleed)</td>
<td>indicative of the level of the lesion</td>
</tr>
<tr>
<td>Mononeuritis multiplex (hepatitis B, hepatitis C, HIV, CMV, varicella zoster, leprosy)</td>
<td>Pain, weakness, and paraesthesias in the distribution of affected nerve or nerves</td>
</tr>
<tr>
<td></td>
<td>Pain over area</td>
</tr>
<tr>
<td></td>
<td>Weakness of related muscles</td>
</tr>
<tr>
<td></td>
<td>If CD4 &lt;50, can have severe form affecting multiple nerves of the shoulder girdle</td>
</tr>
<tr>
<td>Category</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Polyradiculopathy</td>
<td>Commonly CMV, also varicella zoster, lymphoma, syphilis</td>
</tr>
<tr>
<td>Symmetrical neuropathy (motor or sensory)</td>
<td></td>
</tr>
<tr>
<td>Distal symmetrical sensory polyneuropathy (DSPN)</td>
<td>HIV, medication, nutritional deficiencies, alcohol, diabetes</td>
</tr>
<tr>
<td>Toxic neuropathy</td>
<td>Toxins, solvents, insecticides, alcohol, drugs including heroin and amphetamines</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td></td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy (AIDP)</td>
<td>e.g. Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Tetanus</td>
<td></td>
</tr>
<tr>
<td>Botulism</td>
<td></td>
</tr>
<tr>
<td>Symmetrical neuropathy (motor or sensory)</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>(see Section 11.27)</td>
</tr>
</tbody>
</table>
10. Acute and subacute by symptom: SEARO 2021

**Acute poliomyelitis***
- Muscle weakness, headache, stiff neck, fever
- Spinal poliomyelitis: paralysis of shoulder girdle often precedes intercostal and diaphragmatic paralysis
- Bulbar poliomyelitis: facial weakness, dysphagia, dyspnoea, nasal voice, inability to swallow saliva, weak sternocleidomastoid and trapezius muscles. Can progress to respiratory paralysis

**Systemic causes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypokalaemia</td>
<td>Generalized motor weakness, atrial or ventricular arrhythmias</td>
</tr>
<tr>
<td>(see Section 5.2)</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td></td>
<td>ECG changes – ST depression, flattened (or absent) T waves, U waves</td>
</tr>
<tr>
<td></td>
<td>(positive deflection after the T wave), prolonged P–R interval</td>
</tr>
<tr>
<td></td>
<td>Laboratory: very low potassium</td>
</tr>
<tr>
<td></td>
<td>Chronic diarrhoea.</td>
</tr>
</tbody>
</table>

* Acute flaccid paralysis in persons <15 years or acute paralytic illness at an age where polio is suspected should be reported immediately and investigated (see Section 9).

**10.7.7 Peripheral neuropathy**

(See also HIV guidelines for peripheral neuropathy as an ART toxicity.)

Peripheral neuropathy is a term used to describe dysfunction in one or more of the peripheral nerves. In this section, the term "peripheral neuropathy" (PN) is used specifically to refer to distal symmetrical sensory polyneuropathy (DSPN) – a condition that starts at the base of the feet and progresses upwards causing numbness, paraesthesias, and pain.

There are a number of different causes of PN including: nerve compression, autoimmune or inflammatory conditions, toxin- or drug-induced damage, and inherited conditions. It is important to look for the cause as early detection and treatment will stop and may even reverse the progression of symptoms. Pain due to PN may become irreversible if left for too long.

In settings with a high HIV and TB prevalence, PN is a common problem that can be irreversible and debilitating for patients who are affected by it. Peripheral neuropathy is the most frequent neurological complication of HIV infection. This could be either primarily due to HIV infection (after all other comorbid causes have been excluded) or secondary to ART.

**DDx: Peripheral neuropathy**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Symmetrical, glove-stocking distribution:</td>
</tr>
<tr>
<td></td>
<td>• starts in toes and balls of feet</td>
</tr>
<tr>
<td></td>
<td>• spreads to rest of foot, ankle, and up the legs</td>
</tr>
<tr>
<td></td>
<td>• in severe cases fingers or hands involved</td>
</tr>
<tr>
<td></td>
<td>Sensory changes (often worse at night):</td>
</tr>
<tr>
<td></td>
<td>• numbness or increased sensitivity to touch</td>
</tr>
<tr>
<td></td>
<td>• progresses to tingling, burning, or pain</td>
</tr>
<tr>
<td></td>
<td>• impaired vibration sensation and temperature perception</td>
</tr>
<tr>
<td></td>
<td>• in severe cases: super-sensitivity to touch (unable to wear shoes or lie under bed sheets)</td>
</tr>
<tr>
<td></td>
<td>Motor function usually preserved:</td>
</tr>
<tr>
<td></td>
<td>• weakness uncommon</td>
</tr>
<tr>
<td></td>
<td>• reduced or absent ankle jerk reflexes</td>
</tr>
<tr>
<td></td>
<td>• walking and balance may appear abnormal due to pain</td>
</tr>
<tr>
<td></td>
<td>• if rapidly progressive weakness and high lactate, consider HIV-associated neuromuscular weakness syndrome associated with lactic acidosis</td>
</tr>
</tbody>
</table>
### Medicines, substance use

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient taking one or more offending medicine:</td>
<td></td>
</tr>
<tr>
<td>- most common: INH, d4T, or ddI</td>
<td></td>
</tr>
<tr>
<td>- other medicines: ethambutol, ethionamide, dapsone, vincristine, thalidomide, lithium carbonate, metronidazole, high-dose vitamin B6, cisplatin</td>
<td></td>
</tr>
</tbody>
</table>

### Heroin or amphetamine use

#### Symptoms:
- similar to peripheral neuropathy caused by HIV (see above)
- reports of deep aching pain across the top of the foot

### High lactate
- associated with NRTI-mediated neuropathy

### Diabetes

#### Glove-stocking distribution:
- starts in toes or soles
- spreads to ankles and calf

#### Poor glycaemic (blood sugar) control

#### Evidence of other diabetic complications:
- peripheral vasculopathy, nephropathy, retinopathy

#### Sensory changes:
- numbness or pain

### Nutritional deficiency

#### Low serum vitamin B12

#### Clinically malnourished

### Alcohol

#### History of alcohol overuse

#### Other evidence of chronic alcohol abuse

### Other infections:

#### (varicella zoster, CMV, hepatitis C, syphilis, *Cryptococcus*, leprosy)

#### Other evidence of the infection that is causing the neuropathy
(see Section 11 for more on specific diseases).

### Diagnosis

- The brief peripheral neuropathy screen (BPNS) should be used to assess for HIV-associated distal sensory polyneuropathy (DSPN).
  - subjective – ask for symptoms of pain, burning, pins and needles, or numbness in the hands or feet
  - objective – assess sensation of the hands and feet, vibration sense, and ankle tendon reflexes.

### Treatment

- Treat or remove the cause.
- Give thiamine if known history of alcohol use.
- If the patient is on TB treatment or on ART – refer to TB and HIV guidelines respectively for management and drug substitution.
- After discontinuation of the offending drug, it may take a few weeks for the pain to decrease, and in that time the pain may even worsen.
- Peripheral neuropathy primarily due to HIV infection may improve once the patient is put on effective ART:
  - also give one pyridoxine 50 to 75 mg daily.
- Pain control by anticonvulsants and tricyclics for neuropathic pain:
  - amitriptyline is widely used for peripheral neuropathy; dose: start at 25–75 mg at night (increase as needed if side-effects are tolerated) to a maximum dose of 300 mg daily; OR
  - carbamazepine – start at 100 mg twice daily and increase to a total of up to 1600 mg daily.
  - If HIV-positive and on ART with poor response to amitriptyline, then the use of gabapentin is recommended:
    - Dose: day 1, an initial dose of 300 mg daily; day 2, 300 mg twice daily; day 3, 300 mg 3 times daily. Dose can then be titrated 100 mg increments every 3 days as needed,
Acute and subacute by symptom:

- Analgesics including opiates may provide some relief – see Section 12 for a stepwise approach to controlling pain.
  - Low-dose opioids may be required for relief of neuropathic pain, following trial with tricylic antidepressant agents.

Prevention

- It is desirable to give pyridoxine (vitamin B6) 10 mg daily to patients taking INH as prophylaxis or as part of TB treatment.
- Avoid the use of stavudine, see HIV guidelines.
- Educate and monitor patients taking stavudine and substitute if any toxicity.
- Control diabetes and hypertension.

### 10.7.8 Common cranial nerve palsies and their differentials

Problems affecting the cranial nerves can occur as a result of central or peripheral nervous system conditions. See the table below for likely signs and symptoms.

<table>
<thead>
<tr>
<th>Cranial nerve palsies</th>
<th>Presentation</th>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second nerve palsy (optic nerve)</td>
<td>Acute visual loss</td>
<td>See Section 10.12 Eye problems</td>
</tr>
<tr>
<td>Third nerve palsy (oculomotor nerve)</td>
<td>Fixed, dilated pupil, Ptosis, Eye looks downwards and outwards, Double vision</td>
<td>Ruptured aneurysm, Subarachnoid haemorrhage, HIV vasculopathy, Diabetes mellitus, Syphilis</td>
</tr>
<tr>
<td>Fourth nerve palsy (trochlear nerve)</td>
<td>Double vision, Restricted eye movement up in adduction, Concurrent third and sixth nerve palsy, Recent head injury</td>
<td>Often idiopathic, Head injury, Aneurysms, Tumours, Multiple sclerosis</td>
</tr>
<tr>
<td>Fifth nerve palsy (trigeminal nerve)</td>
<td>Pain or paraesthesias in face, Weak jaw clenching, Wasting of temporalis and masseter muscles</td>
<td>Trigeminal neuralgia, Herpes zoster</td>
</tr>
<tr>
<td>Sixth nerve palsy (abducens nerve)</td>
<td>Double vision, Unilateral paresis of eye abduction</td>
<td>Raised intracranial pressure, Tumours or masses, Meningitis, Early disseminated Lyme disease (see Section 11.22)</td>
</tr>
<tr>
<td>Seventh nerve palsy (facial nerve)</td>
<td>Facial muscle weakness, Lower motor neuron (LMN) = forehead paralysed, Upper motor neuron (UMN) = forehead is spared, Ramsay Hunt = facial weakness + vertigo + loss of taste</td>
<td>LMN: Bell's palsy – idiopathic, Ramsay Hunt – varicella zoster (treat with steroid + aciclovir), Early disseminated Lyme disease can cause unilateral or bilateral cranial nerve palsies (especially of the facial nerve) (see Section 11.22), UMN: Stroke, Tumour</td>
</tr>
<tr>
<td>Eighth nerve palsy (vestibulo-cochlear nerve)</td>
<td>Onset acute, chronic or recurrent, Sensorineural hearing loss, Vertigo (hallucination of movement), Associated nausea, vomiting, tinnitus, Nystagmus</td>
<td>Brainstem stroke, Menieres disease, Aminoglycoside antibiotics, Labyrinthitis (acute onset), Benign paroxysmal positional vertigo (recurrent)</td>
</tr>
</tbody>
</table>
10. Acute and subacute by symptom: SEARO 2021
This Section provides an approach to the patient with headache, with or without meningeal signs or fever. Headache is a common complaint in clinical practice, and it is important to distinguish benign headaches from those due to a serious condition. If the patient reports the headache as severe or the “first or worst” of its kind, then it is more likely to be due to a serious cause.

Headaches are most thoroughly classified by the International Headache Society’s International Classification of Headache Disorders (ICHD) 2004. This classification is accepted by WHO.

1. Primary headaches
   - migraine
   - tension-type headache
   - cluster headache and other trigeminal autonomic headaches
   - other primary headaches (e.g. primary cough headache, exertion headache, headache associated with sexual activity).

2. Secondary headaches
   - head or neck trauma
   - cranial or cervical vascular disorder
   - non-vascular intracranial disorder
   - substance use or its withdrawal
   - infection
   - homeostasis
   - facial pain attributed to a disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
   - psychiatric disorders.

3. Cranial neuralgias, central and primary facial pain, and other headaches

Secondary headaches may be further sub-divided, as in the differential diagnosis tables below, into:
   - headache with meningeal signs, with or without fever
   - headache with no meningeal signs, with or without fever
   - headache with no meningeal signs and no fever
   - extracranial causes of headache.
10.8.1 Clinical approach to a patient with headache

<table>
<thead>
<tr>
<th>Step 1:</th>
<th>Perform Quick Check</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use the Quick Check and ensure that there are no serious or life-threatening conditions, such as altered consciousness or convulsions.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2:</th>
<th>Take a history and examine the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine whether the onset is acute or chronic. Look for meningeal signs, fever, rash, and agitation or confusion.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3:</th>
<th>Assess the patient’s HIV status</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Step 4:</th>
<th>Perform investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>If in doubt, do a lumbar puncture (LP). If the patient is HIV-positive, do an LP. There are few contraindications to an LP, and the diagnostic benefit is significant. Ask whether a CT scan will change management and whether it is available through referral.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 5:</th>
<th>Work through the differential diagnosis using the DDx tables</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DDx: Headache with no abnormal physical findings</td>
<td></td>
</tr>
<tr>
<td>• DDx: Headache with abnormal physical findings.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 6:</th>
<th>Initiate management and monitor the patient’s response</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Flow chart 1: Approach to headache in a patient with HIV infection or unknown HIV status and suspected CN infection.</td>
<td></td>
</tr>
<tr>
<td>• Flow chart 2: Approach to headache in HIV-negative patient with suspected CN infection.</td>
<td></td>
</tr>
</tbody>
</table>

Take a history and examine the patient
A good history and examination will help determine the cause of the headache. Headache syndromes show a typical pattern in the history and an absence of unexplained physical signs. As noted, a headache that is the first of its kind or the worst of its kind is more likely to be from a serious cause.

History
- History of presenting complaint:
  - onset (sudden or gradual)
  - duration (hours, days, weeks, months)
  - stiff neck
  - associated dizziness, nausea, or vomiting
  - motor or sensory abnormalities
  - vision, hearing, or speech problems
  - trouble with balance or walking
  - associated seizures, change in level of consciousness
  - change in behaviour, mood, memory, or cognition
  - constitutional symptoms (fever, weight loss, night sweats).
- Medical history:
  - risk factors for stroke (hypertension, diabetes, heart disease, obesity, bleeding disorders, clotting, pregnancy)
  - TB, HIV (if positive, CD4 count and ART history)
  - malignancy
  - syphilis
  - history of head injury
  - current medications.
- Exposure to infectious diseases:
  - COVID-19 (or living in area where there is community transmission)
  - TB contact
  - Living in or travelled to endemic area (malaria, dengue, rickettsia).
Examinations

General signs
- vital signs
- level of consciousness, using AVPU or Glasgow Coma Scale
- rash:
  - look for petechiae or purpura. It may look like bruises and can be difficult to see on dark skin. Check paler areas such as palms, soles, torso, conjunctiva, palate.
  - look for signs of viral infection, sinusitis, toothache, or ear infection.

Meningeal signs
- neck stiffness
- Kernig’s sign (resistance to straightening of the leg while hip is flexed)
- Brudzinski’s sign (flexing the neck causes flexion of the hip or knee).

Fundoscopy for papilloedema
See Section 10.11.

Higher functions
- orientation to person, place, or time
- speech, cranial nerves, motor and sensory system, cerebellar function (as indicated). See Section 10.7 Neurological deficit.
- ability to walk.

Assess the patient’s HIV status 🏺
HIV infection influences the likely differential diagnosis for headache, as there are a number of opportunistic infections that can present with headache. Whenever possible, an HIV test should be done, and the CD4 count should be checked if a patient is HIV-positive.

Perform investigations

Bloods
- full blood count with white cell differential count to look for infection
- malaria smear if endemic area (coinfection with malaria and meningitis is common)
- ESR if temporal arteritis suspected.

Lumbar puncture (LP)
For more on how to perform an LP, see Section 7.4 Procedures.

LP in patients with HIV infection
Lumbar puncture carries no excessive risk in patients with TB meningitis or cryptococcal meningitis, even in the presence of papilloedema, vomiting, or an altered mental state. In advanced HIV these infections are very common, and you should have a low threshold for performing an LP in these patients. See flow diagram below for management approach.

LP is recommended in the following situations:
- If blood or pus is suspected in subarachnoid space:
  - sudden onset severe headache and suspected subarachnoid bleed
  - recent onset headache with fever or neck stiffness or pain and meningitis is suspected.
- If a headache is the first of its kind or the worst of its kind, it will need investigation after considering a migraine.
- If the patient is HIV-positive with signs and symptoms of meningitis.

DO NOT perform an LP if there is:
- local skin or soft tissue infection at LP site
- known or suspected bleeding disorder (risk of spinal haematoma)
- any sign of impending brain shift (herniation) is present
  - rapidly deteriorating level of consciousness
- recent seizure (within 30 minutes) or status epilepticus
- brainstem signs
  ◊ unequal pupils
  ◊ abnormal posturing
  ◊ irregular respirations.
- If signs of impending brain shift are present, do the following:
  ◊ refer to Quick Check for emergency management
  ◊ commence empirical antibiotics if you suspect CNS infection
  ◊ do a CT scan to look for evidence of brain shift before doing an LP.

Cerebrospinal fluid (CSF) analysis
See the table below for characteristic CSF findings for various diagnoses.

- **Opening pressure**
  - measure routinely. This can be done with an intravenous infusion set and is useful for the diagnosis and management of cryptococcal meningitis
  - assess the macroscopic appearance (to the naked eye). Is it clear, cloudy, purulent, straw-coloured, blood-stained?

- **Microscopy**
  - Routine:
    ◊ cell count
    ◊ glucose (compare with blood glucose for CSF: plasma glucose ratio)
    ◊ protein
    ◊ Gram stain.
  - If the patient is HIV-infected or of unknown HIV status, perform the following:
    ◊ India ink
    ◊ cryptococcal latex agglutination test (CrAg)
    ◊ if clinical signs of syphilis are present or if diagnosis uncertain:
      - perform CSF rapid syphilis test (RPR/VDRL) – low sensitivity but high specificity.
        A positive test confirms the diagnosis of neurosyphilis.
  - Mycobacterial microscopy is not recommended due to low sensitivity.

- **Culture**
  - Bacterial culture:
    ◊ if limited resources, use selectively, in cases of poor response to treatment, suspected drug resistance, very ill patient with inconclusive CSF findings.
    ◊ if readily available, use if Gram stain is positive.
  - Mycobacterial culture:
    ◊ usefulness is limited during initial diagnosis (time delay for results).
    ◊ consider using if there is suspected drug-resistant TB, previous TB, unsure of diagnosis (MAC versus TB).
  - Fungal culture:
    ◊ useful for previously treated cryptococcal meningitis in HIV-infected patients on ART to distinguish reinfection from immune reconstitution inflammatory syndrome (IRIS).

- **Cytology**
  - if CNS malignancy is suspected.

**CT scan**
If a CT scan is available, do it before an LP in the following circumstances:

- clinical findings suggest a space-occupying lesion
- signs of brain shift (herniation)
- coma of unknown cause.

Start empirical antibiotics while waiting for CT in all cases of suspected meningitis.
### Table: Characteristic CSF findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset</th>
<th>White cell count (cells/mm³)</th>
<th>CSF glucose: blood glucose ratio</th>
<th>Protein</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial meningitis</td>
<td>Hours to days</td>
<td>Usually &gt;100 PMNs</td>
<td>Low (&lt;50%)</td>
<td>High</td>
<td>Cloudy or purulent CSF, Organisms on Gram stain, Positive culture</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Days to weeks</td>
<td>Usually &gt;50¹ lymphocytes</td>
<td>Low (&lt;50%)</td>
<td>Normal or high</td>
<td>India ink, CrAg positive, High opening pressure</td>
</tr>
<tr>
<td>Cryptococcal IRIS meningitis</td>
<td>Days (recent initiation of ART)</td>
<td>Usually &gt;100 lymphocytes</td>
<td>Low (&lt;50%)</td>
<td>High</td>
<td>CrAg positive, India ink may be negative, Cryptococcal culture negative</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Days to weeks</td>
<td>Usually &gt;100 lymphocytes</td>
<td>Low to very low (&lt;30%)</td>
<td>High</td>
<td>Cloudy CSF, Evidence of TB elsewhere</td>
</tr>
<tr>
<td>Tuberculoma (cerebral)</td>
<td>Days to weeks</td>
<td>Raised lymphocytes</td>
<td>Low (&lt;50%)</td>
<td>Very high</td>
<td>Focal neurology, Evidence of TB elsewhere</td>
</tr>
<tr>
<td>Syphilitic meningitis</td>
<td>Days to weeks</td>
<td>Variable lymphocytes</td>
<td>Normal (60%)</td>
<td>Slightly elevated</td>
<td>VDRL positive (FTA not used in CSF)</td>
</tr>
<tr>
<td>Neurosyphilis latent</td>
<td>Months to years (decades)</td>
<td>&gt;5 cells</td>
<td>Normal (60%)</td>
<td>Slightly elevated</td>
<td>VDRL or RPR positive</td>
</tr>
<tr>
<td>Aseptic or viral meningitis²</td>
<td>Hours to days</td>
<td>Variable lymphocytes</td>
<td>Normal (60%)</td>
<td>Slightly elevated</td>
<td>Gram stain and culture negative (consider acute HIV infection)</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>New onset seizures</td>
<td>High eosinophils</td>
<td>Normal (60%)</td>
<td>Normal</td>
<td>Active fluid-filled cysts on CT</td>
</tr>
<tr>
<td>Bacterial brain abscess</td>
<td>Days</td>
<td>Slightly high WBC</td>
<td>Normal (60%)</td>
<td>Normal</td>
<td>Evidence of sinusitis, otitis, or abscess in other organs</td>
</tr>
<tr>
<td>Lymphomatous meningitis</td>
<td>Days to weeks</td>
<td>Variable; lymphocytes</td>
<td>Normal to low</td>
<td>Elevated</td>
<td>Cytology, Other evidence of systemic lymphoma</td>
</tr>
<tr>
<td>Viral encephalitis (herpes, CMV, PML)</td>
<td>Hours to days</td>
<td>High lymphocytes</td>
<td>Normal (60%)</td>
<td>Slightly elevated</td>
<td>Focal neurology (frontal or temporal), Seizures</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>Sudden onset severe headache</td>
<td>Increased red blood cells</td>
<td>Normal (60%)</td>
<td>Elevated</td>
<td>Normal or severe neurological deficit with or without meningeal signs</td>
</tr>
</tbody>
</table>

¹ Unless IRIS, in which case typically >50.
² Studies in patients with COVID-19 and neurological complications indicate that detection of SARS-CoV-2 in CSF sees to be rare with no or variable white count.1,2,3

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10. Acute and subacute by symptom: SEARO 2021
10.8.2 Consider the likely differential diagnosis

Use the differential diagnosis tables to work through a likely differential diagnosis.

DDx: Primary headache

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension headache</td>
<td>Mild to moderate dull, aching head pain</td>
</tr>
<tr>
<td></td>
<td>Pressure or tightness band around the head</td>
</tr>
<tr>
<td></td>
<td>Tenderness of the scalp, neck, shoulders</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Can last up to a week</td>
</tr>
<tr>
<td>Migraine</td>
<td>Intense throbbing, unilateral pain</td>
</tr>
<tr>
<td></td>
<td>History of previous attacks</td>
</tr>
<tr>
<td></td>
<td>Pain preceded by aura or prodrome</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td></td>
<td>May have visual defects</td>
</tr>
<tr>
<td></td>
<td>Sensitivity to light and sound</td>
</tr>
<tr>
<td></td>
<td>Lasts hours; can last days</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>Acute onset – within minutes – usually at the same time each day</td>
</tr>
<tr>
<td></td>
<td>History of previous attacks</td>
</tr>
<tr>
<td></td>
<td>Excruciating, deep, piercing pain</td>
</tr>
<tr>
<td></td>
<td>Unilateral, pain around the eye</td>
</tr>
<tr>
<td></td>
<td>Excessive tearing</td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection on the side of the pain</td>
</tr>
<tr>
<td></td>
<td>Blocked or runny nose on the side of the pain</td>
</tr>
<tr>
<td></td>
<td>Horner’s syndrome (droopy eyelid, constricted pupil, reduced sweating).</td>
</tr>
</tbody>
</table>

DDx: Secondary headache

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache with meningeal signs (with or without fever)</td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>Acute onset: hours to days</td>
</tr>
<tr>
<td>(see Management, below)</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Meningeal signs</td>
</tr>
<tr>
<td></td>
<td>Purpuric rash (if meningococcal)</td>
</tr>
<tr>
<td></td>
<td>CSF – high PMNs, very low glucose, very high protein; Gram stain may be</td>
</tr>
<tr>
<td></td>
<td>positive</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>Subacute onset: days to weeks</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Meningeal signs</td>
</tr>
<tr>
<td></td>
<td>Focal neurological deficit</td>
</tr>
<tr>
<td></td>
<td>Evidence of TB elsewhere</td>
</tr>
<tr>
<td></td>
<td>CSF – high lymphocytes, low glucose, higher protein</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>Subacute onset: days to weeks</td>
</tr>
<tr>
<td>(see Section 11.8)</td>
<td>HIV infection, signs of weak immune system</td>
</tr>
<tr>
<td></td>
<td>Meningeal signs (may be absent), fever (may be absent), malaise</td>
</tr>
<tr>
<td></td>
<td>Skin lesions resembling molluscum contagiosum</td>
</tr>
<tr>
<td></td>
<td>LP – high opening pressure</td>
</tr>
<tr>
<td></td>
<td>CSF – high lymphocytes, low glucose, high protein, positive India ink, positive CrAg (CSF may be normal in severe immunocompromise – AIDS)</td>
</tr>
<tr>
<td>Aseptic or viral meningitis</td>
<td>Acute onset: hours to days</td>
</tr>
<tr>
<td></td>
<td>Can be part of acute HIV infection; uncommon-COVID-19</td>
</tr>
<tr>
<td></td>
<td>Meningeal signs</td>
</tr>
<tr>
<td></td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Usually self-limiting</td>
</tr>
<tr>
<td></td>
<td>CSF – high lymphocytes, normal glucose, mildly elevated protein</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Condition</th>
<th>Onset</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| **HIV meningitis**                            | Acute onset: hours to days  
Acute HIV infection  
Rash, pharyngitis  
Meningeal signs  
CSF – increased lymphocytes, normal glucose, mildly elevated protein |
| **Viral encephalitis (herpes, CMV, PML)**     | Acute or subacute onset  
Prodrome of high fever, headache, nausea, lethargy, myalgia  
Frontal or temporal lobe focal signs  
Seizures, confusion, altered level of consciousness  
CSF – increased lymphocytes, normal glucose, mildly elevated protein |
| **Headache with no meningeal signs (with or without fever)** |       |                                                                                               |
| **Cerebral toxoplasmosis**                    | Subacute onset: days to weeks  
Dull affect, altered level of consciousness  
Focal signs  
Seizures  
Fever  
CT scan – single or multiple ring-enhancing lesions  
HIV-infected or signs of immune compromise  
CD4 <100/mm³ |
| **Subarachnoid haemorrhage**                 | Very acute onset  
Severe headache, "worst ever"  
Neurological deficit  
Meningeal signs (may be absent)  
No fever  
CSF – very high RBCs, high protein |
| **Neurosyphilis – syphilitic meningitis**     | Subacute onset: days to weeks  
Meningeal signs (may be absent)  
CSF – high WBC, normal glucose, high protein, positive VDRL or RPR |
| **Bacterial brain abscess**                  | In HIV-negative patients may result from contiguous spread or bacteraemia.  
Gradual onset: weeks  
Headache, neck stiffness, altered mental status, signs of increased ICP  
Focal deficits beginning days after headache, seizures  
LP should be avoided. |
| **Cerebral tuberculoma**                     | Subacute onset: days to weeks  
Focal neurological deficit  
No meningeal signs  
Constitutional symptoms (including fever, weight loss, night sweats)  
Evidence of TB elsewhere  
CSF – high lymphocytes, low glucose, higher protein |
| **Anthrax**                                   | Haemorrhagic leptomenigitis  
Neck pain with or without flexion  
Headache, changes in mental state  
Vomiting and high-grade fever  
Markedly elevated CSF pressure and the appearance of blood in the CSF are followed rapidly by disorientation, loss of consciousness, and death. |
| **Tetanus**                                   | Acute onset (after injury or exposure)  
Muscle rigidity (jaw, neck, shoulders, back)  
Neck stiffness  
With or without fever  
Autonomic dysfunction (hypertension, tachycardia, sweating)  
Increased deep tendon reflexes  
Alert mental state |
### Headache with no meningeal signs and no fever

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke (CVA)</strong></td>
<td>Sudden onset, focal signs – hemiparesis, aphasia, unilateral facial weakness</td>
</tr>
<tr>
<td>(see Section 10.7)</td>
<td>Raised BP, normal CSF</td>
</tr>
<tr>
<td><strong>Neurocysticercosis</strong></td>
<td>New onset seizures, cognitive deficits, personality changes, CSF – high WBC, eosinophils, CT – multiple fluid-filled active cysts</td>
</tr>
<tr>
<td>(see Section 11.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Neurosyphilis – syphilitic meningitis</strong></td>
<td>Onset over days to weeks, CSF – high protein, high WBC, RPR or VDRL positive on CSF</td>
</tr>
<tr>
<td>(see Section 11.32)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary CNS lymphoma</strong></td>
<td>Insidious onset, seizures, neurologic deficit – cranial nerve palsies, mental status change, immunocompromised, CD4 &lt;50/mm³</td>
</tr>
<tr>
<td><strong>Brain metastases</strong></td>
<td>Headache – worse at night, vomiting, low-grade fever, focal signs, seizures, deterioration in mental status, evidence of the primary tumour, e.g. breast</td>
</tr>
<tr>
<td><strong>Severe hypertension</strong></td>
<td>BP &gt;180/110 mmHg, confusion, fundoscopy – sclerosis, exudates, haemorrhages, papilloedema, with or without abnormal renal function (if severe), with or without raised cholesterol</td>
</tr>
<tr>
<td><strong>Severe pre-eclampsia or eclampsia</strong></td>
<td>Pregnant 2nd or 3rd trimester, BP &gt;140/90, oedema or anasarca, visual disturbances, confusion, urine – proteinuria, increased uric acid, increased urea, increased creatinine, high ALT/AST, low platelets (HELLP syndrome)</td>
</tr>
<tr>
<td>(see Quick Check page 37 and SEARO Pocket Book for the Care of Mothers)</td>
<td></td>
</tr>
<tr>
<td><strong>Extra-cranial causes of headache</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Malaria</strong></td>
<td>Acute onset, fever, positive malarial RDT or microscopy, FBC – anaemia</td>
</tr>
<tr>
<td>(see Section 8.1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Dengue fever</strong></td>
<td>Pain behind the eyes, fever, joint pains, myalgia, petechiae, travel to or living in endemic area, positive dengue IgM or IgG</td>
</tr>
<tr>
<td>(see Section 8.1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Sinusitis</strong></td>
<td>Tender sinuses, pain or pressure in the face, nasal discharge, blocked nose or post-nasal drip, fever, history of previous episodes, laboratories – all normal</td>
</tr>
<tr>
<td>(see Section 11.30)</td>
<td></td>
</tr>
</tbody>
</table>
| **Rickettsial diseases**  
*(see Section 8.1)* | **Headache severe**  
Fever  
Rash – often involves palms and soles  
Eschar (dark scab) at the site of the bite or history of contact with tick or flea  
High ALT/AST |
|---|---|
| **Toothache**  
*(see Section 10.13)* | **Pain starts in the mouth**  
**Pain on chewing**  
**Dental caries**  
**Fever**  
**Increased WCC (high PMN) in blood** |
| **Tonsillitis**  
*(see Section 10.13)* | **Pain starts in the mouth**  
**Pain on swallowing**  
**Fever**  
**If severe – difficulty breathing, meningism, headache**  
**Increased WCC (high PMN) on blood** |
| **Trigeminal neuralgia** | **Sudden, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial (trigeminal) nerve**  
**Usually unilateral**  
**Facial muscle spasms with severe pain**  
**Triggers include touching affected area, chewing, talking, brushing teeth, cold air, smiling or grimacing.** |

**Initiate management and monitor response**
For primary headache not due to a treatable cause, refer for definitive diagnosis and management.

**Secondary headache**

**Empirical treatment:**
- **Empirical treatment differs depending on the patient’s immune status:**
  - If HIV-infected, do a CD4 count as soon as possible to guide the differential diagnosis. Use flow chart 1, below, for management.
  - If HIV status unknown, manage initially as HIV-infected and perform HIV test as soon as possible. Use flow chart 1, below, for management.
  - If HIV-negative, use flow chart 2, below, for management.
Flow chart 1: Approach to headache in a patient with HIV infection or unknown HIV status and suspected central nervous system infection

**HIV-positive**

- No LP performed
  - Focal neurological or brainstem signs present?
    - No
      - Treat: bacterial meningitis toxoplasmosis
      - Start investigation for TB
      - Take serum CrAg
    - Yes
      - India ink or CrAg positive
      - Improve by 48 hours?
        - Yes
          - Continue treatment
          - Do LP when safe
        - No
          - Reconsider LP
            - Add treatment for:
              - TB meningitis (if other evidence of TB)
              - cryptococcal meningitis (if serum CrAg positive)
            - Refer DDx table
      - Gram positive or CSF findings consistent with bacterial meningitis
      - Treat: cryptococcal meningitis (see below)
      - Treat: bacterial meningitis (see below)
      - CSF findings consistent with TB meningitis
      - Treat: TB meningitis and bacterial meningitis (see below)
  - LP performed
    - CSF analysis: cell count, glucose, protein Gram stain, India ink, CrAg
    - India ink or CrAg positive
    - Improve by 48 hours?
      - Yes
        - Continue treatment
      - No
        - Repeat LP
          - Consider wrong or dual diagnosis
          - Refer DDx table
    - Gram positive or CSF findings consistent with bacterial meningitis
      - Treat: bacterial meningitis (see below)
      - Treat: TB meningitis and bacterial meningitis (see below)
    - CSF findings consistent with TB meningitis
      - Treat: TB meningitis and bacterial meningitis (see below)

**References**

- **10.8 – 116 Headache**
- **10. Acute and subacute by symptom: SEARO 2021**
Flow chart 2: Approach to headache in HIV-negative patient with suspected central nervous system infection

Assess risk of herniation – consider LP

- No LP performed
  - Focal neurological or brainstem signs present?
    - No
      - Treat: bacterial meningitis
        - Add steroids
        - Improvement by 48 hours?
          - Yes
            - Continue treatment
              - Do LP when safe
            - No
              - Reconsider LP
                - Look for TB elsewhere
                - If found, treat TB meningitis
                - Refer DDx table
          - No
            - Refer to focal neurological deficit section

    - Yes
      - Refer to focal neurological deficit section

- LP performed
  - CSF analysis: cell count, glucose, protein Gram stain
    - Gram positive or CSF findings consistent with bacterial meningitis
      - Treat: bacterial meningitis (see below)
      - Improvement by 48 hours?
        - Yes
          - Refer DDx table
        - No
          - Repeat LP
            - Refer DDx table
  - CSF findings consistent with TB meningitis
    - Clinical evidence of TB elsewhere in body?
      - Yes
        - Treat: TB meningitis
        - Repeat LP at 1 week
          - If no resolution
            - Consider TB Rx
            - Refer DDx tables
      - No
        - Reconsider LP
          - Look for TB meningitis
          - If found, treat TB meningitis
          - Refer DDx table
  - Other
    - Refer DDx tables
10.8.3 Treatment of specific conditions

Acute bacterial meningitis
Acute bacterial meningitis is the most common cause of meningitis with an acute onset. It is a medical emergency. If it is clinically suspected, start treatment immediately while waiting for results to confirm the diagnosis.

On taking the patient's history, look for:
- prodrome of non-specific symptoms
- classic triad of
  - fever
  - headache
  - neck stiffness
- photophobia, vomiting
- confusion, seizures.

On examination look for:
- very unwell or rapidly deteriorating patient
- meningeal signs
  - neck stiffness
  - positive Kernig's or Brudzinski's sign
- rash – petechial or purpuric (non-blanching) – meningococcal meningitis
- focal neurological deficit (may develop in later stages).

If CSF findings are consistent with bacterial meningitis, refer to the table Characteristic CSF findings, above.

Treatment
If acute bacterial meningitis is suspected, begin empirical therapy immediately without waiting for the laboratory confirmation. Refer to national guidelines and epidemiology of local resistance patterns for individual cases and meningitis epidemics.

Empirical therapy
- ceftriaxone 2 g IV or IM twice daily (preferred):
  - 5–7 days for Neisseria meningitidis and Haemophilus influenzae
  - 10–14 days for Streptococcus pneumoniae or unknown organism.
- empirical therapy if ceftriaxone is unavailable:
  - ampicillin 2 g IV every 4 hours AND cotrimoxazole 10–20 mg per kg (based on the trimethoprim component) IV per day divided into 2–4 doses (alternative).
- modifications to empirical therapy
  - If there is a high prevalence of pneumococcal resistance to penicillin, add vancomycin 1 g IV twice daily, if available.
  - If risk factors are present for L. monocytogenes (see below), add ampicillin 2 g IV every 4 hours.
  - If patient has anaphylactic allergy to penicillin, give chloramphenicol 1 g IV every 6 hours PLUS cotrimoxazole 10 to 20 mg per kg (based on the trimethoprim component) IV per day divided into 2–4 doses.
  - oily chloramphenicol 100 mg/kg IM (maximum dose 3 g) single dose (repeat after 24–48 hours if necessary), only in meningococcal epidemics. An alternative to oily chloramphenicol is ceftriaxone 2 grams.4

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In adults with suspected bacterial meningitis, consider giving dexamethasone 10 mg IV every 6 hours for 4 days immediately prior to antibiotics. The administration of steroids should not delay the administration of antibiotics. If antibiotics are started first, do not administer dexamethasone.

**Therapy for confirmed infections**

Treatment should be guided by local microbial epidemiology, resistance patterns, and results of CSF cultures, if available.

- *Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae*:
  - ceftriaxone: see above (can be used for patients with a non-anaphylactic allergy to penicillin);
  - ampicillin (dose above) may be used for sensitive *H. influenzae* isolates;
  - benzylpenicillin (4 million units [2.4 g] IV every 4 hours) may be used for sensitive *S. pneumoniae* and *N. meningitidis* isolates;
  - If anaphylaxis to penicillin, give chloramphenicol and cotrimoxazole (see doses above).

- *Listeria monocytogenes* (more common in the elderly, pregnant women, and those with impaired immunity, including HIV): ampicillin 2 g IV every 4 hours for at least 21 days PLUS gentamicin 5 mg per kg per day divided into three doses until patient improves (at least one week).
  - In patients with anaphylactic allergy to penicillin, alternative is cotrimoxazole 10 to 20 mg per kg (based on the trimethoprim component) IV per day divided into 2–4 doses.

**Protection of contacts of confirmed cases of bacterial meningitis (not in outbreak situation)**

- *N. meningitidis*: Prophylaxis is recommended for close contacts (household members, roommates, intimate contacts, individuals at a child-care centre, young adults in dormitories, military recruits in training centers, and sitting next to an index patient for more than 8 hours on an airplane; individuals who have been exposed to oral secretions (for example, by kissing, mouth-to-mouth resuscitation, endotracheal intubation or endotracheal tube management). If a close contact develops fever, prompt evaluation is recommended. Recommended prophylaxis:
  - ciprofloxacin 500 mg orally as a single dose; OR
  - ceftriaxone 250 mg IM as a single dose; OR
  - rifampicin 600 mg orally 2 times daily for 2 days.

- *H. influenzae*: Prophylaxis of all household contacts (including adults) is recommended only when the index case has *H. influenzae* serotype b (Hib) AND the household has at least one child under the age of one year (excluding the index case) or has a child 1–3 years old who is not adequately immunized. Recommended prophylaxis:
  - ciprofloxacin 500 mg orally as a single dose; OR
  - ceftriaxone 250 mg IM as a single dose; OR
  - rifampicin 400 mg orally once daily for 4 days.

- *S. pneumoniae*: Prophylaxis of household contacts is not recommended.

**Cryptococcal meningitis and IRIS** (see Section 11.8)

Cryptococcus is the most common cause of meningitis in patients with advanced HIV infection.

Note: Without the results of a lumbar puncture, other concomitant infections cannot be excluded and should be covered with empirical therapy.

**Tuberculosis meningitis**

TB meningitis occurs more commonly in HIV-infected patients, but it may also occur in HIV-negative patients. The meningeal inflammation is due to the spread of the TB to the meninges.

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via the blood or rupture of a tuberculoma in the brain. TB is usually found in another part of the body, e.g. pulmonary TB.

On history, look for:
- night sweats, loss of weight
- gradual onset headache
- low-grade fever
- neck stiffness
- symptoms of TB in other systems, i.e. cough
- TB contact.

On examination, look for:
- meningism
- cranial nerve palsies
- decreased conscious state
- focal neurological deficit
- evidence of TB elsewhere (lymphadenopathy, chest signs).

Investigations
For the CSF analysis, refer to table Characteristic CSF findings, above.
- may appear cloudy
- high protein (40–100 mg/dl)
- low glucose (<20 mg/dl)
- cell count 500/mm³ – lymphocytes.

The CSF findings can often be ambiguous. If the findings are unclear, look for evidence of TB elsewhere in the body.

Treatment
- For treatment guidelines refer to Tuberculosis guidelines.

### 10.8.4 Symptom management of headache

**In-hospital management**
- Work through differential diagnosis for headache as outlined above in this chapter.
- Treat pain using the WHO pain ladder: begin with analgesics such as paracetamol or NSAIDS and change to analgesic-opioid combinations and ultimately to strong opioids if the patient has continued pain.
- If there is raised intracranial pressure:
  - If due to inflammation or intracranial masses, give a high dose of corticosteroids, e.g. dexamethasone 16 mg IV daily for about 5 days.
  - If due to intracranial haemorrhage, do not give corticosteroids.

**Outpatient or primary care management**
- Ask the patient about the nature of the headache and whether he or she has had a seizure.
- Give paracetamol or ibuprofen.
- Give nasal decongestants if paranasal sinus congestion is suspected.
- Refer to the hospital if the patient fails to respond.
- In patients with ongoing symptoms after acute COVID-19 illness, headache is one of the most common. Regular follow-up and coordinated support may be needed.⁶

**Home care**

- The patient should rest.
- The patient should try self-steaming, using a basin with hot water (but warn them to be careful of being burned by the water).
- The patient should take an over-the-counter pain medicine, e.g. paracetamol.
- Advise patients to seek medical help if the headache is not responding to treatment.
10. Acute and subacute by symptom: SEARO 2021
10.9 Neurological problems: seizures (without meningism or fever)\(^1\)

Seizures result from a number of different causes and are associated with a variety of conditions. Taking a good history is essential for all patients presenting with seizures, as it helps determine a possible cause and guides your management approach. An eyewitness account is essential for determining whether the episode was in fact a seizure.

Injury to the brain, such as trauma, infection, toxin damage, drug withdrawal, severe hypertension, and mass lesions with pressure effect can all result in seizures.

Epilepsy is defined as two or more seizures in a patient without a reversible condition. Epilepsy may be due to a structural brain abnormality or previous brain damage. However, in many cases, the cause is unknown (idiopathic). Acute causes of seizures must be excluded before a diagnosis of epilepsy is made.

### 10.9.1 Clinical approach to a patient with seizures

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1:</td>
<td><strong>Perform Quick Check</strong>&lt;br&gt;Ensure that there are no serious or life-threatening conditions. Use Quick Check for the emergency management of convulsions remembering to protect the airway and keep the patient away from danger. DO NOT put anything into the mouth. Remember to check glucose and consider pregnancy in women.</td>
</tr>
<tr>
<td>Step 2:</td>
<td><strong>Take a history and examine the patient</strong>&lt;br&gt;An eyewitness account helps establish whether the patient has had a seizure. Determine the type of seizure, and whether this is the first episode. Examine the patient for a possible cause. If you suspect meningitis (fever, neck stiffness), proceed to Section 10.10b Headache.</td>
</tr>
<tr>
<td>Step 3:</td>
<td><strong>Assess HIV status</strong>&lt;br&gt;HIV infection alters the differential diagnosis of seizures.</td>
</tr>
<tr>
<td>Step 4:</td>
<td><strong>Consider a differential diagnosis using the DDx table.</strong>&lt;br&gt;(^*) See DDx: Seizures without meningism or fever, on next page.</td>
</tr>
<tr>
<td>Step 5:</td>
<td><strong>Perform investigations</strong>&lt;br&gt;Bloods, lumbar puncture, and CT scanning are useful in helping to find a cause for the seizure. Always ask yourself whether a LP or CT scan will aid diagnosis and management.</td>
</tr>
<tr>
<td>Step 6:</td>
<td><strong>Initiate treatment and monitor the patient’s response</strong>&lt;br&gt;After initial emergency management of the convulsing patient, further management of seizures will depend on the differential diagnosis and the likely cause. See the management approach below.</td>
</tr>
</tbody>
</table>

### History

- Determine if the patient had a seizure:
  - ask an eyewitness if someone else was present at the time of the episode.
- Obtain a description of the event:
  - the type of seizure (parts of body involved, generalized or focal)

• whether there was loss of consciousness
• loss of bladder or bowel control.

• Take a medical history to determine:
  o associated headache, fever, neck stiffness
  o history of previous seizures and possible precipitating factors and events
  o other illnesses – HIV infection, renal dysfunction, hypertension
  o medications including antiepileptics, antidiabetic agents, antiretrovirals
  o toxin exposure
  o alcohol or drug use or withdrawal
  o prescription drug overdoses
  o use of traditional remedies or medicines
  o other toxins (organophosphates, cleaning liquids)
  o current pregnancy.

Examination
• Look for evidence that a seizure occurred (bitten tongue, soiled clothes, postictal mental state).
• Conduct a focused neurological exam to look for possible cause.
• Assess the following:
  o altered conscious state (use AVPU or GCS)
  o localizing signs
  o papilloedema
  o meningeal signs (see Section 10.8 Headache for details).

Assess the patient's HIV status
HIV infection influences the likely differential for seizures. There are a number of opportunistic infections that can present with seizures, and it is important to consider HIV infection when investigating a patient with new onset seizures.

10.9.2 Consider the likely differential diagnosis
Assess whether the seizure is related to a systemic illness or condition, to an intracranial lesion or infection, or is part of an ongoing chronic seizure pattern. Consult with the relevant section of the DDx table below.

DDx: Seizures without meningism or fever*

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures as part of a systemic illness or condition</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Cerebral malaria (see Section 8.1.6) | Fever  
Positive smear or rapid malaria test  
Hypoglycaemia  
Living in or travelled to an endemic area |
| Hypoglycaemia (see Quick Check page 28 and Section 3.4) | Sudden onset repeated seizures  
Use of diabetic medication  
Unresponsive or confused  
Responds to administration of glucose |
| Hypertensive encephalopathy | BP >180/110 mmHg  
Confusion  
Fundoscopy – sclerosis, exudates, haemorrhages, papilloedema |
| Eclampsia (see Quick Check page 8) | Pregnant 2nd or 3rd trimester  
BP >140/90  
Oedema or anasarca  
Visual disturbances, confusion  
Urine – proteinuria  
Laboratory – increased uric acid, increased urea, increased Cr, high ALT/AST, low |
<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic disturbances (see Section 5.2)</td>
<td>Recent illness, e.g. diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Electrolyte disturbances, e.g. hypoNa+, hypoMg++, hypoCa++, and uraemia</td>
</tr>
<tr>
<td>Overdose (drug or prescription) (see Section 3.6)</td>
<td>Known history of substance abuse</td>
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<tr>
<td></td>
<td>History of cocaine, amphetamine, ecstasy, or other</td>
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<tr>
<td></td>
<td>Track marks at injection sites</td>
</tr>
<tr>
<td></td>
<td>Pinpoint or dilated pupils</td>
</tr>
<tr>
<td></td>
<td>On tricyclic antidepressants (TCA)</td>
</tr>
<tr>
<td>Alcohol withdrawal (see Section 3.7)</td>
<td>History of alcohol use</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Other evidence of chronic liver disease</td>
</tr>
<tr>
<td>Seizures due to intracranial infection or lesion</td>
<td></td>
</tr>
<tr>
<td>Brain abscess (see Section 10.7)</td>
<td>Fever, headache</td>
</tr>
<tr>
<td></td>
<td>Local spread: from sinuses, ear, teeth – discharging ear, tender mastoid, tender bridge of nose, dental caries, haematogenous spread. e.g. from lungs, heart, skin, abdomen</td>
</tr>
<tr>
<td>Meningitis (see Section 10.8)</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Neck stiffness</td>
</tr>
<tr>
<td>Viral encephalitis, e.g. herpes simplex</td>
<td>Lethargy and altered mental status</td>
</tr>
<tr>
<td></td>
<td>Focal neurological deficit</td>
</tr>
<tr>
<td></td>
<td>Papilloedema</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td>Toxoplasma encephalitis (see Section 11.38)</td>
<td>Onset over days to weeks</td>
</tr>
<tr>
<td></td>
<td>Focal signs</td>
</tr>
<tr>
<td></td>
<td>Impaired level of consciousness</td>
</tr>
<tr>
<td></td>
<td>CD4 less than 100</td>
</tr>
<tr>
<td></td>
<td>CT scan – single or multiple ring enhancing lesions</td>
</tr>
<tr>
<td>Masses (lymphoma, tuberculoma, tumours)</td>
<td>Insidious onset</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve palsies, mental status change</td>
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<tr>
<td></td>
<td>Focal neurology</td>
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<tr>
<td>Trauma</td>
<td>History of trauma or whiplash injury</td>
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<tr>
<td></td>
<td>Contusions or lacerations on head or face</td>
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<tr>
<td></td>
<td>X-ray or CT scan evidence of trauma</td>
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<tr>
<td>Chronic, recurrent seizures</td>
<td></td>
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<tr>
<td>Neurocysticercosis (see Section 11.9)</td>
<td>Cognitive deficits</td>
</tr>
<tr>
<td></td>
<td>Personality changes</td>
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<tr>
<td></td>
<td>CSF – high WBC, eosinophils</td>
</tr>
<tr>
<td></td>
<td>CT – multiple calcified cysts active fluid filled cysts</td>
</tr>
<tr>
<td>Epilepsy (see below)</td>
<td>Known history of epilepsy</td>
</tr>
<tr>
<td></td>
<td>Previous history of seizures</td>
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<tr>
<td></td>
<td>Family history of epilepsy</td>
</tr>
<tr>
<td></td>
<td>No reversible causes found.</td>
</tr>
</tbody>
</table>

* Consider other causes of seizures: schistosomiasis, bartonellosis (cat scratch disease), African human trypanosomiasis. See Section 11 Multisystem diseases list for details on these diseases.

**Perform investigations**

For all convulsing patients, measure:
- glucose
  - give IV glucose D50, 25–50 ml if unable to test. See Quick Check page 28.
Do investigations according to the differential diagnosis:
• malaria microscopy (if not immediately available, RDT can be performed while waiting for the result of the blood smear);
• electrolytes:
  o electrolyte disturbances can cause seizures (see Section 5.2.2). Measure electrolytes if available.
• CSF analysis (see Section 10.8 Headache):
  o if you suspect blood or pus (i.e. subarachnoid bleed or meningitis).

Note: Do not delay antibiotic therapy if meningitis is suspected and you are unable to do a CSF analysis.

Often CT scans are not widely available. If CT is available at a referral centre, refer the patient for a CT in the following circumstances:
• unexplained neurological findings
• intractable or worsening epilepsy (in a patient who is compliant)
• onset of seizures late in life (where a cause is unclear).

Treatment
Acute seizure control – see Quick Check page 28 and Section 3.5 for the management of a convulsing patient.
• Identify and treat reversible causes (blood glucose, electrolytes, blood pressure, infection, drug overdoses).

After acute seizure control, a decision needs to be made regarding ongoing management.

Management of seizures with no apparent cause depends on the history and number of episodes
A patient presents having had 1 or 2 seizure episodes but now looks completely well. What should be done?
• Do not treat a first episode seizure:
  o the risk of second seizure is less than 50%
  o are you sure that the patient really had a seizure?
  o wait to see if another or others occur.

A patient presents having had at least 2 convulsions in the last year (recurrent):
• Investigate if there are unexplained neurological or physical findings.
• Treat any underlying cause.
• Start antiepileptics.

Monotherapy with any of the standard antiepileptic drugs:
• phenobarbital: start 60 mg daily, maintenance at 60–180 mg daily
• phenytoin: start at 150–200 mg daily, maintenance at 200–400 mg daily
• valproic acid: start at 400 mg, maintenance 400–2000 mg daily (should be considered in children and adults with convulsive epilepsy)
• carbamazepine: start 100–200 mg once daily, maintenance at 400–1400 mg daily).

However, given costs, phenobarbital is often considered as a first option. In some settings its availability is constrained by regulatory issues. Carbamazepine may be considered with partial onset seizures.

Certain newer anti-epileptic medications (lamotrigine, levetiracetam and topiramate) can be offered as add-on therapy in patients with medication-resistant convulsive...
epilepsy. The essential anti-epileptic medications (carbamazepine, phenobarbital, phenytoin, and valproic acid) may be of benefit as add-on therapy in patients with medication-resistant convulsive epilepsy.²

Phenobarbital is a good antiepileptic but interacts with antiretrovirals (NNRTI, PIs) to lower drug levels via the cytochrome P450 system in the liver.

Valproic acid is a good alternative as it does not interact with antiretrovirals. However, it is expensive. It should be used in patients who are already on ART and are to be started on antiepileptics.

Valproic acid and the use of multiple drugs to control seizures should be avoided in pregnant women.

A patient with a history of seizures in the past presents after 2 years of being seizure-free.

- In this circumstance, the decision to withdraw or continue antiepileptic drugs (AEDs) should be made after consideration of several clinical, social, and personal factors, and with the involvement of the patient and the family.
- Among clinical factors, those discouraging treatment withdrawal include:
  - presence of an underlying neurological condition;
  - epilepsy syndrome with high potential for seizure relapse (e.g. myoclonic epilepsy or any symptomatic epilepsy);
  - history of high seizure frequency or status epilepticus.
- Social and personal factors play a role in the final decision:
  - patient preference;
  - extremely infrequent seizures;
  - occupational stigma and psychological effects of continued AED use.

Additional intervention details

- Psychological treatments such as relaxation therapy, treatments based on CBT principles, psycho-educational programmes, and family counselling may be considered as additional treatments for epilepsy.
- People with epilepsy can lead normal lives. They can marry and have children.
- People with epilepsy can work in most jobs. However, they should avoid certain jobs, such as working with or near heavy machinery.
- People with epilepsy should avoid cooking on open fires and swimming alone.
- People with epilepsy should avoid excessive alcohol and any recreational substances, sleeping much less than usual, or going to places where there are flashing lights.
- National laws related to the issue of driving and epilepsy need to be observed.

10.10 Approach to patients with mental health problems

- Clinical approach to mental health problems
  - History and physical examination
  - Approach to good clinical practice and balanced care
  - Special considerations in adolescents

- Suicide and deliberate self-harm assessment and management
  - Suicide risk assessment
  - Management of the suicidal patient
  - Pharmacotherapy in patients with suicide risk

- Abnormal behaviour or thinking (with DDx table)
  - Assessment of abnormal behaviour
  - Delirium
  - Intellectual disability in adolescents and adults
  - Dementia

- Psychosis
  - Definitions of brief and persistent psychotic disorders
  - Clinical management of psychosis not accompanied by mania or severe depression
  - Use of antipsychotic medications: some basic principles and cautions
  - Considerations for long-term antipsychotic therapy

- Bipolar disorder
  - Psychosocial interventions in bipolar disorders
  - Pharmacologic management of bipolar disorders

10.10.6 Sad or low mood including depression (with DDx table)
  - Assessment of patients with sad or low mood or depression
  - Depressive symptoms due to medical conditions
  - Depressive symptoms due to adverse life events
  - Acute management of depression
  - Use of non-pharmacological interventions
  - Use of antidepressant medications: some basic principles and cautions
  - Use of antidepressant medication in the management of a depressive episode (moderate to severe)
  - Management of severe depression with psychotic symptoms

- Anxiety
  - Assessment and diagnosis of anxiety
  - Management of anxiety
  - Psychotropic therapy for anxiety
  - Making a specific anxiety disorder diagnosis (with DDx table)
  - Management of specific anxiety disorders

Note: if you are using the mhGAP intervention guide for primary care of mental health conditions – this Section, aimed at district hospital care by a district clinician, has been updated to reflect the new recommendations from the evidence review¹ and to maintain compatibility with the mhGAP intervention guide, now in its second version.²

This Section integrates consideration of medical conditions and mental disorders, through the use of differential diagnosis tables and Appendix A, Medical conditions to consider before starting treatment for mental disorders, and when patients do not respond to initial psychiatric therapy.

¹ Update of the Mental Health Gap Action Programme (mhGAP); guidelines for mental, neurological and substance use disorders, WHO 2015
10.10.1 Clinical approach to mental health problems

Symptoms that alert the clinician to the possibility of a mental disorder
Any of the following signs or symptoms can indicate the presence of a mental disorder.
- A notable change in mental status.
- The development or new onset of unusual or bizarre behaviour.
- A diminished level of functioning or symptoms in one or more of the following areas:
  - self-care, such as bathing, dressing, eating
  - family relations – spouse, children, relatives
  - attendance or performance at work or school
  - doing housework or household tasks
  - social activities, seeing friends
  - remembering things
  - subjective distress (sadness, fear, anxiety, irritability)
  - agitation, outbursts of anger, potential for violence, homicidal thoughts
  - suicidal thoughts or recurrent thoughts of death
  - disturbed sleep and appetite
  - diminished concentration, impairment in complex thinking, difficulty in learning new tasks
  - emotional numbing or lack of a full range of emotions
  - delusions and hallucinations
  - confusion.

As outlined in the steps below, the clinical approach to assessing these symptoms begins by ensuring the patient’s safety and then excluding any life-threatening or significant medical conditions.

Clinical approach to all patients

<table>
<thead>
<tr>
<th>Step 1: Ensure the patient’s safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>See Section 10.10.2 and note the guidelines for managing suicidal, violent, or agitated patients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2: Ensure that the patient does not have any life-threatening medical conditions, especially delirium, or any other significant medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use Section 3.4 – the approach to the severely ill patient, and follow the guidelines for decreased level of consciousness or confusion or intoxication or agitation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3: Take a present history from the patient and family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess symptoms of abnormal behaviour and sad or anxious states of mind.</td>
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<tr>
<td>Assess the impact on function.</td>
</tr>
<tr>
<td>Assess stressful life events and recent losses.</td>
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<tr>
<td>Ask about drug and alcohol use.</td>
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<tr>
<td>Ask for treatments received for the presenting problem and the response to it.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4: Take a past history from the patient and family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the person had similar symptoms in the past?</td>
</tr>
<tr>
<td>Is there a history of psychiatric hospitalizations?</td>
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<tr>
<td>Is there a history of past use of psychotropic medication?</td>
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<tr>
<td>What was the response to treatment and mental health interventions?</td>
</tr>
<tr>
<td>Is there a history of suicide attempts or violence toward others?</td>
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<tr>
<td>Is there a history of exposure to traumatic events?</td>
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<tr>
<td>Is there a history of alcohol or substance use?</td>
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<tr>
<td>Is there a childhood history of learning or developmental disabilities?</td>
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<table>
<thead>
<tr>
<th>Step 5: Perform a mental status evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess:</td>
</tr>
<tr>
<td>appearance and behaviour</td>
</tr>
<tr>
<td>orientation</td>
</tr>
<tr>
<td>speech</td>
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<tr>
<td>mood quality, range and appropriateness of emotions</td>
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<tr>
<td>thinking processes and clarity of content</td>
</tr>
</tbody>
</table>
10. Acute and subacute by symptom: SEARO 2021

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- perceptual abnormalities
- suicidal ideation, intent, or plans
- violent or homicidal ideation, intent, or plan
- cognitive functioning
- awareness of illness and need for its treatment.

**Step 6:** Conduct or review baseline investigations

Ask yourself:
- Have I considered underlying medical conditions and side-effects of medication or home remedies?
- What is the person’s HIV status? 🏺
- Have I considered alcohol or substance use or withdrawal?
- Have I reconsidered delirium? If you think the patient may have delirium, use Section 3.4.

**Step 7:** Determine whether the patient is experiencing abnormal behaviour or a sad or anxious state of mind

- If both abnormal behaviour and a sad or anxious state of mind are present, assess abnormal behaviour first.

**Step 8:** Based on your assessment and classification, institute appropriate treatment

- Based on steps 1 and 2, consider whether hospitalization or other urgent mental health intervention is needed.
- Provide the patient and family with counselling and psycho-education (see Appendix 1).
- Enlist psychosocial support (family, friends, peers).
- Institute psychotherapies as available and appropriate (see Appendix 1).
- Give medication as available and appropriate.
- Assess for long-term care referral as available and appropriate.

**Step 9:** If the patient does not respond to the initial course of psychiatric treatment, then reconsider assessment for medical conditions (see Appendix 2)

**Step 10:** If the patient continues to have a poor response to treatment at a second-level care facility, refer to specialty care for:
- clarification of the diagnosis
- the development of an optimal treatment regimen
- stabilization of the patient.

Back-referral from specialty care with suggestions for further management is often the most efficient and affordable means for continuing the patient’s treatment.

### History and physical examination

**Start by taking a good history**

Enquire about the symptoms that are common to many mental disorders, and that may alert the provider to the presence of a mental health concern.

Whenever possible, and after obtaining consent to do so from capable patients, include family members and friends when obtaining this history.

**Important elements of a history**

- The time of onset of the current episode.
- Type and severity of the symptoms.
- Current medical problems or diagnoses.
- Decrease in the level of functioning, including social isolation and decreased productivity.
- Precipitating stressful life events.
- Past or recent exposure to traumatic events.
- Occurrence of gender-based or domestic violence.
- Current medications or home remedies, particularly those that have been initiated recently.
- Personal history of drug or alcohol abuse.
- Family history of drug or alcohol abuse.
- Personal history of prior mental disorder and treatment.
- Family history of mental disorder and treatment.
- Available social and family support.
Co-morbidity of mental disorders with each other
- Co-morbidity is common because the presence of one mental disorder increases the risk for other mental disorders.
- Co-morbid alcohol or substance use disorders increase the complexity of treating other mental health symptoms and disorders. Treatment for both disorders is required.
- Many patients do not fit neatly into diagnostic categories. In those cases, treatment is often targeted to symptoms.
- Use the following hierarchy when symptoms of multiple disorders are present.
  - if patient is actively using alcohol or substances, reassess symptoms after patient is no longer intoxicated
  - if the patient is withdrawing from alcohol or other substances, provide medical care for withdrawal, and reassess symptoms
  - if the patient has abnormal behaviour and a sad or anxious state of mind, treat abnormal behaviour as the primary condition and then address the sad or low mood.
  - if the patient has a sad or low mood and an anxious state of mind, treat the sad and low mood as the primary condition.

Co-morbidity of mental disorders with medical conditions
- Co-morbidity is common between mental disorders and medical conditions, and each increases the risk for the other.
- When compared with the general population, people with mental health disorders have increased morbidity and mortality from medical conditions.
- As people age or acquire medical conditions, mental and medical disorders commonly are found to coexist.

Approach to good clinical practice and balanced care
Management of patients with mental health disorders involves the provision of a supportive, safe and healing environment and a trusting and therapeutic working relationship.

The way in which this environment is created will vary across settings depending on resources and local approaches to mental health care.

Non-specialist health-care providers should acquire appropriate knowledge and skills for, and follow good clinical practices in, their interactions with people with mental, neurological, and substance use disorders and their families. These should include the following:
- attentive or active listening;
- effective and cultural, language, or gender-sensitive communication, including communication with behaviourally disturbed, anxious, and withdrawn patients;
- obtaining important psychosocial information (including family, living, financial and social circumstances) from the patient and family;
- assessing psychosocial stress;
- being non-judgemental towards patients and families;
- providing adequate privacy in interactions with patients and families;
- planning treatment in consultation with the patient and family, keeping in mind their preferences;
- providing appropriately detailed information and advice in a supportive manner;
- communicating a realistic hope for better functioning and recovery;
- responding sensitively to the disclosure of private and emotional events (such as sexual violence or suicide attempts, especially where illegal);
- providing information on the patient's health status and diagnosis in a clear, accurate, empathetic, and culturally appropriate way, keeping in mind the patient's preferences, and in consultation with the family;
- monitoring progress and encouraging self-monitoring of symptoms;
- monitoring adverse effects of any treatment;
- facilitating necessary follow-up and treatment continuation;
- facilitating necessary specialist referral;
- facilitating necessary linkages with community-based supports.

Non-specialist health-care providers should ensure the protection of and respect the rights of people with mental, neurological and substance use disorders and their families. This should include the following:
- respecting the rights of patients and families within the health-care facilities,
- obtaining full and informed consent for all diagnostic and treatment interventions,
- observing the confidentiality of patients and promoting their participation in all aspects of their treatment.

Psychosocial support and psycho-education are helpful interventions in all mental health disorders. Psychotherapies are often effective in treating specific mental health symptoms and disorders. Depending on the resources and expertise that exist, psychotherapy may be delivered in individual or group settings.
Psychotropic medications, alone or combined with psychotherapies, have been shown to be effective in treating many mental health disorders.

Many mental health disorders have a chronic and recurring course and require longer-term approaches to care, including psychosocial rehabilitation, to minimize disability.

General principles in prescribing psychotropic medications
- Weigh the effectiveness of the medication in reducing symptoms against the impact of adverse side-effects.
- Keep in mind that the metabolism of psychotropic medications can vary by race and ethnicity and, within any given group, the metabolism of psychotropic medications can vary widely among individuals.
- The elderly and medically ill often require lower doses than younger, physically healthy adults.
- Ensure that medication management adheres to local principles of informed consent, including a determination of the patient’s capacity to make treatment decisions.
- Assess the patient’s acceptance of the treatment and anticipate the possibility of non-adherence.
- Manage non-adherence with a non-judgemental approach.
- It is best when a family member or friend can help a patient with medication management. However, it is essential that a capable patient consents to communication with those family members or friends.
- Explain the following to patients and, as appropriate, family members or friends:
  - the symptoms may not immediately respond to the medication;
  - medication side-effects often diminish or disappear over time;
  - adherence to psychotropic medications over time is required to maintain a therapeutic response;
  - medications that have been used for more than several weeks should be tapered rather than abruptly stopped, to reduce discontinuation symptoms and relapse risk.

The categorization of mental health symptoms can be confusing and overwhelming to the busy clinician. In this Section, a simplified approach is presented based on the differential diagnosis of two main categories, abnormal behaviour (which is characteristic of possible delirium, dementia, intellectual disability, or psychosis) and sad or anxious states of mind (which may indicate a mood or an anxiety disorder). It is anticipated that this will enable more efficient assessment and diagnosis of major mental disorders by non-specialist clinicians.
The following algorithm illustrates where specific symptoms are addressed in these guidelines.

**Special considerations in adolescents**

**Adolescent mental health**

Adolescence is a time of rapid physical, psychological, and social changes that can be accompanied by anxious, sad, and angry thoughts and feelings. But if symptoms persist, become strange or abnormal, or prevent a teen from being able to carry out their usual activities, including school work or healthy socialization, this may be an indication of a mental health disorder.

**Points to consider regarding adolescent mental health**

- Adolescence is both a common time of developmental stress and a common time of onset of mental disorders. Differentiating between the two can be challenging. Adolescents can experience any of the conditions mentioned in this Section; however, their presentation may vary from the adult presentation.
- Educating adolescents and their families about the normal development of teens and the signs of mental health problems is critical for preventing, identifying and treating mental disorders.
- Adolescents are often reluctant to discuss substance use, sexual activity, suicidal ideation, or conduct

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problems with parents and adults. Health-care workers can best overcome this barrier by creating youth-friendly, trusting, and confidential relationships with teens. Share information with family members and others only with the adolescent’s permission.

- Finding an individual identity and separating from family can cause turmoil and the rejection of parental advice. But difficult behaviours may also reflect mental health problems that can put young people at higher risk for abuse and neglect, suicide, substance abuse, school failure, violence and impulsive behaviours that jeopardize health.

- Teens who have experienced sexual and physical abuse are at increased risk for the onset and persistence of suicidal behaviour and mental health problems. Social isolation and academic failure, bullying, and harsh or humiliating punishments may also be tied to adolescent depression and anxiety.

- Alcohol and drug use can occur in adolescents. Concurrent substance misuse can worsen mental health problems and render standard mental health interventions less effective. Concurrent treatment of both substance use and other mental disorders is the ideal way to offer care.

**10.10.2 Suicide and deliberate self-harm assessment and management**

- Suicide is the act of deliberately killing oneself.
- Self-harm is the intentional injury or poisoning of oneself, which may or may not have a fatal outcome. This is generally a sign of serious underlying mental disorder even when the intent is not suicide. For poisoning see Section 3.8.

Regardless of the diagnosis, an assessment for risk of suicide should always be performed. Asking about self-harm does NOT provoke acts of self-harm. It often decreases anxiety associated with thoughts or acts of self-harm and helps the person feel understood.

Attempt to establish a therapeutic working relationship with the patient and then directly ask about suicide and self-harm behaviours.

- Do you feel that you would be better off dead?
- Do you have thoughts of hurting yourself?
- Have you ever attempted suicide?
- Why did you want to hurt yourself?

**Suicide risk assessment**

It is a difficult task to accurately predict an individual patient’s suicide risk. Factors that suggest increased risk include:

- Psychiatric disorders (generally depression, alcoholism, and personality disorders).
- Physical illness (terminal, painful or debilitating illness, AIDS).
- Previous suicide attempts.
- Family history of suicide, alcoholism, or other psychiatric disorders.
- Divorced, widowed or single status.
- Living alone (socially isolated).
- Unemployed or retired.
- Bereavement in childhood.
- If the patient is under psychiatric treatment, the risk is higher in:
  - those who have recently been discharged from hospital
  - those who have made previous suicide attempts.
- In addition, recent life stressors associated with increased risk of suicide include:
  - marital separation
  - bereavement
  - family disturbances
  - change in occupational or financial status
  - rejection by a significant person

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4 Update of the Mental Health Gap Action Programme (mhGAP) guidelines for mental, neurological and substance use disorders, WHO 2015
The suicide assessment should include the assessment of:
- current suicidal thoughts and plans
- characteristics of any attempt, past or present
- the presence of a severe mental disorder
- the presence of substance intoxication or disorder
- risk factors for suicide as noted above
- available family and psychosocial supports and the patient’s capacity to cope with difficulty.

Assessing suicide risk through questions and observations

1. Assess whether the person has current suicidal thoughts
   - Questions
     o Do you feel unhappy and hopeless?
     o Do you feel unable to face each day?
     o Do you feel life is a burden?
     o Do you feel life is not worth living?
     o Do you feel like committing suicide?
   - Further questions
     o Have you made any plans to end your life?
     o How are you planning to do it?
     o Do you have the means in your possession to carry out suicide (pills, guns, poisonings, or other methods)?
     o Have you considered when to do it?
   - Ask the patient or accompanying friends or family about self-harm.

2. Assess the characteristics of any attempt that was made
   - Was the attempt planned or was it impulsive?
   - Did the person let anyone know or leave a suicide note?
   - Were steps taken to avoid discovery?
   - Did the person attend the hospital or clinic of their own volition?
   - What method was used?
   - How does the patient feel now about the attempt?
   - Look for signs of poisoning or intoxication or signs of self-injury.
   - Medically treat as necessary.
     o Ensure that the person is closely monitored to prevent further self-harm.
     o Do not leave the patient alone or unsupervised.

3. Assess whether there is an imminent risk of self-harm or suicide
   - Ask the patient and carer about current thoughts or plans to commit suicide or self-harm.
   - Ask about history of thoughts or plans of self-harm in the past month or acts of self-harm in the past year.
   - Ask about access to means for following through on those thoughts or plans.
   - Assess for current mental disorder, suicidal ideation, and intent.
   - Look for signs of emotional distress, hopelessness, agitation, uncommunicative behaviour, social isolation.

4. Assess coping resources and activate psychosocial support
   - What coping mechanisms does the person have?
   - What are the family and social supports?
   - What is the service support?
Management of the suicidal patient

- If a suicide attempt has been made, observe for signs of self-injury and urgently treat associated medical complications.
- Remove means of self-harm.
- If a suicide attempt has been made or a plan or threat exists for imminent suicide:
  - do not leave patient alone;
  - talk gently with the patient;
  - keep the patient in a secure and supportive environment in the facility – if possible, offer a separate quiet room while waiting;
  - assign a named staff member or family member for continued monitoring to ensure patient safety;
  - attend to the patient’s mental state and emotional distress.
- Management of the medical consequences of an act of self-harm may require admission to a general (non-psychiatric) hospital. In these cases, when admission for medical management is done, close monitoring is necessary to prevent subsequent self-harm in the hospital.
- Assess for underlying mental disorders and start appropriate treatment.
- In situations where there is imminent risk of serious self-harm, urgent referral to a mental health service is recommended. However, if such a service is not available, activate psychosocial support. Family, friends, concerned individuals, and other available resources should be mobilized to ensure close monitoring of the individual as long as the imminent risk persists.
- Consult a mental health specialist if available. Admit to a psychiatric hospital or mental health service (if possible) if needed to treat an underlying severe mental health disorder.
- Assess for and begin treatment of co-morbid problems:
  - physical (including chronic pain, epilepsy)
  - mental disorders and substance use – follow this Section as well as guidance on substance use in mhGAP
  - emotional problems.
- When the patient is well enough for conversation, follow good clinical practice – spend enough time, listen effectively, offer emotional support, and be sensitive to the patient’s distress.
- Use counselling, psycho-education and psychotherapies.
- Involve carer or family support as needed and as appropriate for the patient:
  - provide psycho-education and support for carers and family.
  - as caring for a suicidal patient can be extremely stressful, provide support to the carers and family. Emphasize that they should avoid hostility or aggression, even if frustrated.
- Work to understand and lessen suicidal feelings; explore reasons to stay alive.
- Focus on positive strengths and build on coping resources.
- A structured problem-solving approach should be considered as a treatment for persons with a history of acts of self-harm.
- Provide information about community-based services and patient support or self-help groups and facilitate access to these services.
- Ensure careful follow-up, including the involvement of carers and community health services. Regular contact with a non-specialized health worker is recommended. The contact should be more frequent initially and less frequent as the patient improves.
- Continue to assess suicide risk until the patient is stable.
- The individual, family, and relevant others should be advised to restrict access to the means for self-harm (e.g. pesticides and other toxic substances, medication, firearms) as long as the individual has thoughts or plans of self-harm. Advise the family and others relevant that
asking about suicide will often lessen the anxiety of the patient and they may feel better understood.

- Follow up patient over time with regular contact and ensure continuity of care.

### Pharmacotherapy in patients with suicide risk

- Treat underlying mental disorders and substance use disorders.
- Special considerations in patients with suicide risk include the following:
  - Medication may give access to a means of suicide or cause side-effects, such as restlessness, that may increase the risk of suicide.
  - Choose drugs with fewer side-effects to ensure compliance.
- Choose medications that are less dangerous in overdose (e.g. selective serotonin re-uptake inhibitors instead of tricyclic antidepressants).
- Dispense small quantities of medicines (e.g. not more than one week’s medicine while the patient is still suicidal).
- As appropriate, involve relatives in the care and dispensing of medications.
- Maintain close follow-up and monitoring of the patient.

### 10.10.3 Abnormal behaviour or thinking

Use this Section if the presenting symptoms include:

- agitation, frightening or unusually impulsive behaviour;
- unkempt appearance and odd ways of relating to others, or odd mannerisms;
- disorganized or strange speech, thoughts, or behaviour;
- distortions of thinking and perceptions;
- reporting or responding to hallucinations (e.g. reacting to false or imagined perceptions, such as talking to imaginary people as a result of hearing voices);
- reporting or responding to delusions (e.g. fixed false beliefs, such as hiding from imaginary persecutors);
- severe self-neglect; inability or disinterest in caring for self;
- inappropriate or narrowed range of emotions;
- impairment in cognition, memory, and attention.

### Assessment of abnormal behaviour

Accurate differentiation among the possible causes of abnormal behaviour, such as delirium, dementia, intellectual disability, or developmental disorders and psychosis is essential. Although these disorders can present with similar signs and symptoms, the management is different. Delirium is a period of acute confusion that is attributable to a medical condition, and treatment involves diagnosis and management of the underlying medical condition. Dementia is a chronic degenerative disease of the brain that typically worsens over time. Progression of some causes of dementia may be partially reversed with treatment (e.g. antiretroviral treatment may halt the progression of, or partially reverse, HIV dementia).

Intellectual disability or developmental disorders have a childhood onset and will benefit from the provision of family psycho-education and community-based rehabilitation. Psychosis is a sign of a severe mental disorder in which contact with reality is lost or highly distorted, and may be found in schizophrenia, bipolar disorder, or brief reactive psychosis.

Patients presenting with abnormal behaviour and fever likely have an underlying medical condition that must be identified and treated. In these patients, refer to Section 8.1.

Some patients displaying these behaviours may be difficult to assess. It may be necessary to get corroborative information from family, friends or other informants.
The table that follows presents a differential diagnosis of disorders in which patients display abnormal behaviours. See also Appendix 2.

**DDx: Behaviour that is strange, bizarre, agitated, or atypically impulsive: key symptoms and screening questions or observations**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Key differentiating symptoms</th>
<th>Screening questions and observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>Onset over hours to days</td>
<td>Patient appears confused, inattentive, incoherent</td>
</tr>
<tr>
<td></td>
<td>Fluctuating level of consciousness within the day (e.g. confused one minute, clear-minded the next, occurring throughout the day and often worsening at night)</td>
<td>Patient appears to be agitated or withdrawn. Ask: Where are you? What day is this? Where possible, a complete screening mental status examination should be administered</td>
</tr>
<tr>
<td></td>
<td>Prominent difficulties in focusing, shifting, or maintaining attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulty orienting to place, time, and sometimes person</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of underlying cause based on physical examination or abnormal laboratory investigations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever may be present</td>
<td></td>
</tr>
<tr>
<td>Delirium due to alcohol or sedative withdrawal</td>
<td>Symptoms of delirium (as above)</td>
<td>See delirium screening questions and observations above</td>
</tr>
<tr>
<td></td>
<td>Chronic use with sudden discontinuation of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• alcohol, substances, or medications with addiction potential (e.g. diazepam)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremulousness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unstable vital signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visual hallucinations</td>
<td></td>
</tr>
<tr>
<td>Intoxication from alcohol or other substance</td>
<td>Acute onset</td>
<td>Ask: What did you drink or take today? Consider informant interview about substance use history</td>
</tr>
<tr>
<td></td>
<td>History of alcohol or substance use</td>
<td></td>
</tr>
<tr>
<td>Intellectual disability (may also be called developmental disability, learning disability, or mental retardation)</td>
<td>Childhood onset</td>
<td>Interview informants</td>
</tr>
<tr>
<td></td>
<td>Failure to achieve usual childhood milestones</td>
<td>In moderate or severe disabilities, patients often look or behave atypically. This may include:</td>
</tr>
<tr>
<td></td>
<td>Problems developing normal social interactions</td>
<td>• unusual physical features, expressions, or gestures</td>
</tr>
<tr>
<td></td>
<td>Problems learning in school</td>
<td>• unusual social behaviours</td>
</tr>
<tr>
<td></td>
<td>May be associated with abnormal faces, sensory disabilities, and physical or motor disorders</td>
<td>• obvious cognitive impairments</td>
</tr>
<tr>
<td>Dementia</td>
<td>Gradual onset</td>
<td>Patient may be agitated, confused, or withdrawn</td>
</tr>
<tr>
<td></td>
<td>Deficits in intellectual domains, in the absence of an alteration in consciousness, with impairment of mental functioning including:</td>
<td>Level of consciousness does not show rapid fluctuations</td>
</tr>
<tr>
<td></td>
<td>• forgetfulness</td>
<td>Forgetfulness is a prominent feature</td>
</tr>
<tr>
<td></td>
<td>• misplacing things</td>
<td>Ask:</td>
</tr>
<tr>
<td></td>
<td>• difficulty in performing automatic tasks (such as carrying out daily routines)</td>
<td>Where are you?</td>
</tr>
<tr>
<td></td>
<td>• impaired speech or word-finding difficulty</td>
<td>What day is it?</td>
</tr>
<tr>
<td></td>
<td>• change in personality or behaviour</td>
<td>What year is it?</td>
</tr>
<tr>
<td></td>
<td>• presence of neurological symptoms</td>
<td>Mention 3 objects – e.g. shoe, dog, chair</td>
</tr>
<tr>
<td></td>
<td>• unsteady gait, loss of balance</td>
<td>Ask patient to repeat immediately and in five minutes</td>
</tr>
<tr>
<td></td>
<td>• impaired hand–eye coordination</td>
<td>If possible, use a cognitive screening tool</td>
</tr>
<tr>
<td></td>
<td>• slowed response time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• leg weakness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• dropping things</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• tremors, poor handwriting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• decline in motor skills</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• incontinence</td>
<td></td>
</tr>
<tr>
<td>Dementia due to HIV infection (HIV-associated)</td>
<td>Symptoms of dementia noted above</td>
<td>If HIV status is unknown, test for HIV infection in accordance with local law. Look for signs of HIV-related medical illnesses</td>
</tr>
<tr>
<td></td>
<td>Psychomotor slowing is often present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dementia onset at younger age than normally expected</td>
<td></td>
</tr>
<tr>
<td>Mental health problems</td>
<td>HIV-positive</td>
<td>Dementia is more common with advanced HIV disease</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>HSV encephalitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(see Sections 10.8)</td>
<td>Fever</td>
<td>May have excessive animation and inflated self-esteem, diminished comprehension, and hypersexuality</td>
</tr>
<tr>
<td></td>
<td>Focal neurological deficits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Altered thinking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personality changes – hypomania, loss of emotional control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased comprehension and memory</td>
<td></td>
</tr>
<tr>
<td><strong>Schizophrenia and other psychotic conditions not otherwise noted in this table</strong></td>
<td>Hallucinations, most commonly auditory (hearing voices of people who are not there)</td>
<td>Patient may be agitated, suspicious, frightened or withdrawn</td>
</tr>
<tr>
<td></td>
<td>Delusions: false fixed beliefs that may be elaborate or bizarre</td>
<td>Conversation with patient often elicits implausible information. Ask for elaboration in a matter-of-fact manner</td>
</tr>
<tr>
<td></td>
<td>Disorganized thinking or speech</td>
<td>Ask: Do you hear voices when there is no one present or speaking to you?</td>
</tr>
<tr>
<td></td>
<td>Disorganized behaviour, occasionally to the point of inability to care for self</td>
<td>Ask: have you been troubled by unusual experiences lately? Have you felt threatened by events or people recently? Do you believe that people are trying to harm you? Tell me more?</td>
</tr>
<tr>
<td></td>
<td>No fluctuation of consciousness</td>
<td>Mood is often restricted or out of keeping with content of conversation</td>
</tr>
<tr>
<td></td>
<td>Physical examination and laboratory results do not suggest an underlying medical explanation of the symptoms</td>
<td>Interview informants</td>
</tr>
<tr>
<td></td>
<td>History of previous episode or psychiatric hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor social and occupational functioning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often long-standing history, usually at least 6 months for schizophrenia</td>
<td></td>
</tr>
<tr>
<td><strong>Bipolar disorder:</strong></td>
<td>Distinct period ≥1 week characterized by:</td>
<td>Patient is often irritable, loud, or excited</td>
</tr>
<tr>
<td><strong>Manic phase</strong></td>
<td>• abnormally elevated or irritable mood</td>
<td>Patient may be speaking very rapidly</td>
</tr>
<tr>
<td><strong>Manic episode</strong></td>
<td>• decreased need for sleep</td>
<td>Patient may make grandiose statements, such as having supernatural powers or being extremely successful and wealthy when this is not the case</td>
</tr>
<tr>
<td></td>
<td>• elevated energy</td>
<td>Patient may have slept few hours yet appear alert and energetic</td>
</tr>
<tr>
<td></td>
<td>• racing thoughts</td>
<td>Ask: Do you feel you are unusually happy or excessively irritable? Is your energy unusually high? Do you feel that you do not need any sleep? Do you feel your thoughts are racing?</td>
</tr>
<tr>
<td></td>
<td>• rapid pressured speech</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• increased sense of self-importance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• excessive pursuit of risk-taking behaviours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• history of previous manic episode or psychiatric hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• history of depression or currently taking antidepressant medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• family history of bipolar disorder</td>
<td></td>
</tr>
</tbody>
</table>

If the patient screens positive for a particular disorder, then proceed with assessment as appropriate for that specific disorder.

In all cases, non-specialist health-care providers should ensure the protection of, and the respect for, the rights of people with mental, neurological, and substance use disorders and their families. This includes the following:

- respecting the rights of patients and families within health-care facilities;
- obtaining full and informed consent for all diagnostic and treatment interventions;
- following local mental health regulations pertaining to the assessment and management of mental health conditions;
- observing the confidentiality of users and promoting their participation in all aspects of their treatment.

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Delirium

Delayed diagnosis and management of delirium can be fatal because it often occurs as a manifestation of an underlying severe medical condition. Risk factors and causes include:

- high fever from any cause (refer to Section 10.1 Fever);
- advanced stages of immunosuppression due to HIV, including associated infections and malignancies of the CNS;
- other severe medical conditions, including hypoxia and metabolic abnormalities (see Appendix 2);
- substance use or withdrawal;
- intoxication from any cause, including substances of misuse and ingestion of toxins (see Section 3.8 Poisoning);
- drug overdose (accidental or deliberate);
- head or brain injuries;
- previous episodes of delirium;
- dementia, including HIV dementia;
- drug interactions in patients taking multiple medications (e.g. for HIV or tuberculosis).

Diagnosis of delirium

- The disturbance of consciousness with reduced ability to focus, and sustain or shift attention.
- A change in cognition or the development of a perceptual disturbance.
- The disturbance is developed over hours to days and fluctuates during the course of the day, and the disturbance is caused by the consequences of a general medical condition (including alcohol or drugs, medication, or acute head injury).
- Often accompanied by alterations in sleep patterns, alterations in the level of activity, including underactivity or hyperactivity with arousal and agitation, emotional instability, and poor judgement.

If delirium is suspected, refer to Section 3.4.2 Delirium.

Delirium is frequently overlooked

Common misdiagnoses include the following:

- When patients appear hypoactive, depression is a frequent misdiagnosis for delirium.
- When patients appear agitated or restless, a primary psychotic disorder is a frequent misdiagnosis for delirium.
- When patients have a history of dementia, acute changes in mental status due to delirium is often overlooked.

Intellectual disability in adolescents and adults

Diagnosis of intellectual disability

Intellectual disability is a lifelong condition characterized by limitations in mental functioning. A person with an intellectual disability may learn and develop more slowly and may require support to assist with full functioning. Some persons with intellectual disabilities may develop mental health problems, which further compounds their functional limitations. Typically, this presents with the onset of new behaviours that the family or community cannot manage.

WHO classifies intellectual disability into 4 levels on the basis of functioning: mild, moderate, severe and profound.

Common signs indicating a history of delayed development beginning in childhood include:

- failure to achieve usual childhood developmental milestones
- problems in learning self-care
- problems in learning in school and developing occupational skills;
- inappropriate social or sexual behaviour.
Coexisting conditions and differential diagnoses include:
- physical disabilities and motor disorders (e.g. cerebral palsy)
- epilepsy
- hypothyroidism
- incontinence
- depression
- sensory disabilities, such as impaired vision and hearing
- attention deficit or hyperactivity disorder
- autism spectrum disorders
- other psychiatric and behavioural disorders
- nutritional deficiencies.

Management of intellectual disability
When an adolescent or adult with intellectual disability presents with a marked change in function or a significant alteration in behaviour, consider the possibility of a new onset mental health disorder and treat as indicated. Among adolescents, also consider developmental issues. In particular, growing physical strength and the increasing sexual drive that comes with the onset of puberty often present new challenges to caregivers.
- Discuss prior management strategies and rehabilitation efforts.
- Advise the family about handling the presenting problem, including enlisting additional support.
- Assess and treat any comorbid medical and mental disorders.
- Avoid any unnecessary psychotropic medication. If medication is required, use caution as people with developmental disorders are often more sensitive to side-effects.
- Refer to educational and rehabilitation services that are age-appropriate. When possible, look for work opportunities that match the person’s strengths.
- Avoid institutionalization.
- Rewarding effort, not results, is the best overall approach to help the patient and family adapt to the patient's functional limitations.

Dementia – a decline in cognitive functions including memory, thinking and new learning
Dementia is a disorder of the brain causing a decline in cognitive function that is usually progressive and chronic. It may be classified based on symptom severity and impact of impairment on functioning, as follows:
- mild – independent living is possible
- moderate – some assistance is needed for activities of daily living
- severe – close supervision is necessary.

The symptoms associated with dementia can be wide-ranging. In the degenerative forms of dementia, forgetfulness, declining mental function, and apathy (lack of emotion) are the most prominent features. As the disorder progresses, patients can lose their capacity to independently manage many activities of daily living. Clinicians should be aware that dementia can be distressing to patients and families.

⚠️ Patients with HIV are at risk for HIV-associated dementia. This underscores the importance of determining HIV status of patients when they present with signs and symptoms suggestive of dementia. At a population level, the rates of severe HIV dementia have fallen considerably with the early introduction of ART that results in full viral load suppression. Among HIV-positive individuals, the likelihood of HIV dementia increases with the progression of systemic HIV disease and immunological decline.
Diagnosis of dementia
The 3 most common causes of dementia are:
1. Alzheimer disease
2. Vascular dementia (formerly known as multi-infarct dementia)
3. HIV dementia.

HIV dementia can occur at any age, whereas Alzheimer disease and vascular dementia occur primarily in the elderly.

If there is a history of progressive cognitive impairment over a six-month period that impairs function, a diagnosis of dementia is likely. Abrupt onset of acute cognitive impairment suggests a diagnosis of delirium or a delirium superimposed on a dementia rather than dementia alone. In all cases of cognitive impairment, it is essential to correct any ongoing medical problems that may be contributing to the impaired cognitive status. Common co-morbidities include hypothyroidism, cardiovascular disease, sexually transmitted infections, anaemia, poor dietary intake, malnutrition, and medication side-effects.

Non-specialist health-care providers should seek to identify possible cases of dementia in the primary health-care setting and in the community. Patient examination, key informant interview, and cognitive tests should be used to assist in confirming these cases. For a formal dementia diagnosis, a more detailed history, medical review, and mental state examination should be carried out to exclude other common causes of cognitive impairment and decline.

Non-pharmacological management of dementia
Convey the results of the assessment with sensitivity, and help the patient and family access support that will promote independence, mobility and function.

Always attend to the safety of the patient first.
- Ensure the patient’s safety with appropriate environment and level of supervision.
- Ensure that the patient is taking medications as prescribed.
- Protect wandering patients, and supervise any cigarette smoking that occurs.
- Use strategies to prevent falls (e.g. reduce clutter on floors, re-evaluate medications that lead to orthostatic hypotension, encourage tailored physical activity to maintain mobility).

Consider cognitive interventions applying principles of reality orientation, cognitive stimulation, or reminiscence therapy for the care of people with dementia. Health-care providers should be trained to deliver these interventions and family members should be involved in their delivery. Examples include:
- reorienting the patient;
- encouraging the presence of familiar objects and people;
- emphasizing routines;
- providing lighting that corresponds with day and night;
- providing a clock and calendar in the room to help keep patients oriented to time and to the day of the week;
- using memory aids;
- offering activities that keep the patient's mind alert;
- ensuring that individuals who require eyeglasses or hearing aids wear these to help lessen confusion and disorientation.

Interventions for health-care workers should be provided as a part of the overall management of people with dementia.
- Educate family members about the nature of dementia and methods for helping patients to maintain the activities of daily living. Inform about key adaptations in the home that may foster independence and functioning.
Information should be provided to people with dementia as well as to family members and other informal carers, keeping in mind the preferences of the patients and their families.

Training of health-care workers involving active carer participation (e.g. role playing of behavioural problem management) may be indicated later in the course of the illness for carers who are coping with behavioural symptoms.

The psychological strain of health-care workers should be addressed with support, counselling, or cognitive-behaviour interventions.

Depression in health-care workers should be managed according to the recommendations for depression.

Where feasible, home-based respite care may be encouraged for carers of people with dementia.

Consider referral for psychiatric care when:
- uncertainty remains about the diagnosis;
- there is accompanying depression, psychosis, mania, or substance abuse;
- there are behavioural disturbances;
- a need exists for consultation regarding psychotropic medications, particularly when multiple psychotropic medications may be necessary, increasing the risk of drug–drug interactions and toxicity;
- complex psychosocial strategies need to be implemented.

**Pharmacological management of dementia**

- All individuals with dementia should receive regular medical review (at least every 3–6 months) and appropriate care.

- In persons with dementia presenting with behavioural symptoms, a complete physical assessment and medication review should be performed to identify any possible underlying precipitants for these symptoms. Appropriate management of these precipitants should be offered before considering the use of psychotropic medicines and non-pharmacological interventions.

- When dementia is complicated by behavioural or psychological disturbances and non-pharmacological interventions are not effective in the management of these symptoms, antipsychotic medications may be useful in treating agitation, delusions and hallucinations.

- If behavioural symptoms persist or there is a clear and imminent risk of harm to the patient with severe and distressing symptoms, the short-term use of haloperidol or atypical antipsychotic medications can be considered, preferably with specialist inputs. To the extent possible, informed consent and agreement should be obtained from the patient or carer with regard to the balance of risk and benefit.

- Antipsychotics have been associated with increased risk of stroke; therefore, as much as possible, they should be avoided.

- When using antipsychotic medication in patients with dementia, use the lowest possible dose and increase slowly as needed. For example, haloperidol should be initiated at 0.5 mg and titrated slowly with frequent review of impact and side-effects, particularly extrapyramidal side-effects. Thioridazine and chlorpromazine should not be used due to high potential for orthostatic hypotension and anticholinergic side-effects.

- Patients with dementia are often sensitive to medication side-effects and at a population level, antipsychotic medications appear to increase the risk of death in elderly patients with dementia.

- In people with dementia with symptoms or signs suggestive of moderate or severe depression, the use of fluoxetine may be considered.

- Benzodiazepines have been shown to increase confusion and decrease concentration. As such, it is recommended that diazepam be avoided.
In the case of HIV-associated dementia, neurocognitive impairment may be partially reversible through the use of effective ART that fully suppresses viral replication. Fully suppressive ART is the treatment of choice for the prevention and treatment of HIV dementia.

10.10.4 Psychosis

Psychosis is a state in which a person's grasp of reality (or reality-testing) is diminished. This may be manifested by:
- hallucinations (most often auditory);
- delusions;
- disorganized or strange speech;
- bizarre behaviour or disorganized behaviour to the point that self-care is impaired;
- lack of insight (e.g. patients may not see themselves as ill or in need of treatment, family or friends may bring them);
- inappropriate or narrowed range of emotions;
- social withdrawal.

<table>
<thead>
<tr>
<th>Definitions of brief and persistent psychotic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic disorders that are not attributable to an underlying medical condition can be divided into 2 categories.</td>
</tr>
<tr>
<td>1. Brief (acute) and transient psychotic disorders</td>
</tr>
<tr>
<td>Disorders characterized by the acute onset of psychotic symptoms and severe disruption of ordinary behaviour. The onset of symptoms is acute, often related to a significant stressor. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed two weeks. Usually, there is full recovery, and no evidence of an organic cause.</td>
</tr>
<tr>
<td>2. Persistent or recurrent psychotic disorders</td>
</tr>
<tr>
<td>Persistent or recurrent psychotic disorders can be further broken down based on whether or not a predominant mood or affective symptoms accompany the psychosis. Schizophrenia is the most common and severe non-affective chronic psychotic illness. These disorders often begin with non-specific symptoms, such as social withdrawal, loss of interest in usual activities, apathy, and diminished functioning. They generally have their onset in late adolescence and young adult life. The most common examples of recurrent or persistent psychotic disorders with prominent mood symptoms include mania with psychotic features (as one phase of bipolar mood disorder) and a severe depressive episode with psychotic features.</td>
</tr>
</tbody>
</table>

Diagnosis of psychosis

The diagnosis of a psychotic disorder is made by the identification of the abnormal behaviour suggestive of psychotic symptoms described above.

Important risk factors for the development of psychosis include:
- prior psychiatric illness
- family history of psychotic illness
- substance misuse, including intoxication, abuse, dependence, and withdrawal
- exposure to severe stressors or traumatic events.

In addition, psychotic symptoms may be associated with a general medical condition or medications. Examples include patients with late-stage HIV disease who may develop psychosis more commonly than people in the general population. Examples of medications that may be associated with the development of psychotic symptoms include EFV and (anabolic) steroids.
Differential diagnosis

The differential diagnosis of a patient presenting with psychotic symptoms includes the following.

- Delirium and dementia (see Section 10.10.3 above).
- Other medical causes:
  - even after excluding delirium and dementia, psychotic symptoms may be caused by an underlying medical condition, such as the conditions described in Appendix 2.
  - although a past history of a chronic or recurrent psychotic disorder strongly suggests an exacerbation or a relapse of that disorder, a relapse can also be precipitated by a serious medical problem, underscoring the importance of evaluation for an underlying or coexisting medical aetiology.
- Primary psychotic disorders, including schizophrenia, mania, and depression with psychotic features.
  - see the description for schizophrenia and other psychotic disorders in the table above.
  - DDx: Behaviour that is strange, bizarre, agitated, or atypically impulsive: key symptoms and screening questions or observations.
- Auditory hallucinations are the most common hallucinations in primary psychotic disorders. Other types of hallucinations should increase the index of suspicion that there is an underlying medical problem.
- Schizophrenia may present with “negative” symptoms, such as lack of emotion, lack of motivation, and paucity of thought. These symptoms may, however, be confused with the side-effects of antipsychotic medications.
- Patients with chronic psychotic disorders have decreased cognitive performance and may struggle with memory, concentration, complex thinking, and learning new tasks but not to the degree seen in dementia.
- People with severe and persistent mental disorders are often at higher risk of being infected with HIV and other sexually transmitted infections due to elevated rates of unsafe sexual activities, including sexual victimization, and co-morbid substance use. Even if an individual has a confirmed primary psychotic disorder, consideration should be given to HIV status.
- Certain symptoms not typically classified as psychotic can nonetheless be bizarre or involve a loss of reality testing, such as the repeated rituals seen in obsessive compulsive disorder and the flashbacks associated with post-traumatic stress disorder.

Investigations

A parallel history from family members should be taken whenever possible. Psychotic patients may have poor insight into their symptoms and may fail to report them or, in some instances, they may conceal them.

Clinical management of psychosis not accompanied by mania or severe depression

- Assessment for the safety of the patient and others should be performed as soon as possible.
- Patients should be provided with the opportunity to seek support in making decisions about their treatment when they require it. Consult local mental health laws and guidelines.
- Initial hospitalization often is required for acute stabilization, especially for patients who are at imminent risk of violence or self-harm. Also, hospitalization may be needed for those with new-onset psychosis.
- Assessment for an underlying medical etiology and the initiation of appropriate medical treatment are essential.
- Provide psycho-education that supports the patient's recovery. Instil realistic hope and emphasize the importance of continuing regular activities.
- Support the family and provide guidance in their interactions with the patient.
- Antipsychotic medication is the mainstay of the acute management of psychotic symptoms. Emphasize the importance of medication adherence to reduce symptoms and suffering.
• Encourage regular follow-up care, including the management of concurrent medical conditions. Patients with chronic psychotic disorders are at increased risk of co-occurring conditions, including substance use, HIV/AIDS, diabetes, heart disease, and smoking-related illnesses. These patients require a comprehensive approach to assessment and care over and above the management of psychotic symptoms.

• Negative health-care worker attitudes have been documented as interfering with the delivery of medical care. It is important that health-care facilities develop training resources for health-care workers to help overcome fear and stigma associated with working with patients with psychosis.

• Facilitate rehabilitation in the community. Long-term treatment of chronic psychotic disorders such as schizophrenia often require interventions based on principles of psychosocial rehabilitation, including cognitive behavioural therapy (CBT), skills-building, and family interventions. These interventions should be continued as long as needed by the user and their family, and therefore should be planned and developed in a sustainable way.

Use of antipsychotic medications: some basic principles and cautions

• Haloperidol or chlorpromazine should be routinely considered in individuals with psychotic disorders (see also mhGAP).

• The minimal effective dose of antipsychotics should be used, paying attention to minimizing adverse effects.

• Continue trial medication at optimum dose for 4–6 weeks before considering it ineffective. Always check for treatment adherence.

• Patients on long-term antipsychotic treatment should be given adequate information and encouraged to make a choice between oral and depot preparations, especially with the view to improve adherence. Depot antipsychotics should not be used for prompt control of acute psychotic symptoms.

• Patients on antipsychotic medicines (oral and depot preparations) should be monitored regularly for symptom relief, functioning, and any adverse effects.

• Women with psychotic disorders (including schizophrenia) who are planning a pregnancy, or are pregnant or breastfeeding and require antipsychotic treatment to manage symptoms, should be treated with low-dose oral haloperidol or chlorpromazine.

• Depot antipsychotics should not be routinely prescribed to women with psychotic disorders (including schizophrenia) who are planning a pregnancy or who are pregnant or breastfeeding, because there is relatively little information on their safety.

General principles for using antipsychotic medications: haloperidol, chlorpromazine, long-acting injectable fluphenazine

Contraindications and cautions: Do not use for alcohol withdrawal. Antipsychotic medications are associated with increased risk of death in elderly patients with dementia, and associated with increased risk for seizures and blood disorders.

Serious acute side-effects:
• acute dystonic reaction or severe muscle spasm (give biperiden)
• neuroleptic malignant syndrome, a potentially life-threatening disorder characterized by muscular rigidity, elevated temperature, and high blood pressure.

Serious long-term side-effects:
• involuntary muscular movements that may not be reversible (tardive dyskinesia).

Educate the patient and family:
• Review medication facts as relevant
• Medications are not addictive
• Warn against the use of alcohol.
**Haloperidol as antipsychotic**

**In healthy adults:**
- initiate treatment with 1.5–3 mg once daily,
- depending on symptom severity, symptom response, and tolerability, can be titrated up to 20 mg daily,
- typical effective dose: 3–20 mg daily,
- use lowest effective dose.

**In elderly or medically ill patients:** (including those with HIV stage 3 or 4 – these patients are very sensitive to the side-effects of haloperidol.)
- initiate treatment with 0.5–1 mg once daily,
- depending on symptom severity, symptom response, and tolerability, can be titrated up to 5 mg daily,
- higher doses may be needed, but there is a significant risk of toxicity,
- use the lowest effective dose.

**Chlorpromazine as antipsychotic**

**In healthy adults:**
- initiate treatment with 75 mg at night,
- depending on symptom severity, symptom response, and tolerability, can be titrated up to 300 mg daily,
- typical effective dose is 75–300 mg daily, but up to 1000 mg may be necessary in severe cases,
- use the lowest effective dose.

**In elderly or medically ill patients** (including those with HIV stage 3 or 4)
- haloperidol is preferred because even low doses of chlorpromazine may cause severe hypotension resulting in falls.

**Fluphenazine as antipsychotic** – long-acting, injectable for long-term management

Other contraindications and cautions: Neuromuscular side-effects can take a long time to clear after drug discontinuation. Avoid for acute treatment because it is difficult to titrate the dose in accordance with symptom response and tolerability.

**In healthy adults**
- start with 12.5 mg deep intramuscular injection in the gluteal region,
- typical effective dose is 12.5–100 mg IM every 2 to 5 weeks,
- repeat IM injections every 2 to 5 weeks as follows:
  - if the initial dose was well-tolerated and effective, continue to use that dose;
  - if the initial dose was tolerated but did not control the symptoms, the dose may be increased in increments of 12.5 mg.

**In elderly or medically ill patients** (including those with HIV stage 3 or 4):
- oral haloperidol is preferred because severe extrapyramidal side-effects may take a long time to clear after medication discontinuation,
- if using injectable fluphenazine, start with 6.25 mg deep intramuscular injection,
- typical effective dose is 6.25–50 mg every 2 to 5 weeks,
- repeat the IM injections every 2 to 5 weeks as follows:
  - if the initial dose was well-tolerated and effective, continue to use that dose;
  - if the initial dose was tolerated but did not control the symptoms, the dose may be increased in increments of 6.25 mg IM; a maximum dose of 100 mg IM may be given although such a dose is rarely required.

**In all adults:**
- the length of time between injections depends on how long the medication lasts in controlling symptoms and how well the patient tolerates the medication,
- use the lowest effective dose,
- long-acting medication is particularly useful in patients who have difficulty complying with treatment,
- if severe side-effects occur, discontinue the injections, wait until the side-effects clear, and begin an oral antipsychotic.

**Second-generation antipsychotics** (with the exception of clozapine which is indicated for treatment-resistant psychosis) can be offered for the treatment of psychotic disorders (including schizophrenia). There is no clinically relevant advantage of one second-generation antipsychotic over others, and the choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication.

In adolescents with psychotic disorders (including schizophrenia and bipolar disorder),
certain second-generation antipsychotic medications (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) can be offered as a treatment option under the supervision of a specialist. If treatment with one of the above agents is not feasible, first-generation antipsychotics (haloperidol, chlorpromazine, perphenazine, molindone) may be used under the supervision of a specialist.6

**Considerations for long-term antipsychotic treatment**

In patients with full and sustained remission following a first psychotic episode, continue antipsychotic treatment for at least 12 months after the beginning of remission.

Any further continuation of antipsychotic treatment should be based on a clinical review, preferably by a mental health specialist, and taking into account the preferences of the patient, and in consultation with the family.

In patients with long-term or recurrent psychotic disorders (including schizophrenia) who are stable for several years on anti-psychotics, treatment withdrawal may be considered, keeping in mind the increased risk of relapse, the possible adverse effects of medicines, and patient preferences in consultation with the family. Preferably, this decision should be made in consultation with a mental health professional. If medicines are withdrawn, patients and family members need to be educated to detect early symptoms of relapse, and close clinical monitoring should be done.

**10.10.5 Bipolar disorder**

Bipolar disorder is characterized by recurrent episodes of mood instability throughout a patient’s adult life, usually accompanied by significant changes in activity and behaviour. The course of the disorder is characterized by three phases: (i) acute mania, involving elevations of mood; (ii) depressive phases, involving periods of low mood; and (iii) maintenance phase, where recovery and wellness is generally preserved. Pharmacological interventions are specific to each phase.

Patients with bipolar disorder can present with marked changes in behaviour and it is important to consider the diagnosis of bipolar disorder in patients presenting with abnormal behaviour as well as in patients presenting with disturbance of mood.

Clinical management involves psychosocial and pharmacological interventions.

**Psychosocial interventions in bipolar disorders**

- Ensure patient safety and manage concurrent medical conditions.
- Provide psycho-education. Patients and families need to understand the phases of mood disturbance and how to self-monitor for extreme moods in order to best prevent severe relapses.
- Encourage a regular sleep cycle.
- Encourage patient to avoid alcohol and psychoactive substances.
- Help patients reactivate social networks and to seek support from family and community-based resources.
- Provide regular follow-up.

**Pharmacological management of bipolar disorder**

(i) **Acute mania (with or without psychosis) in a patient with bipolar disorder**

The management of acute mania requires mood stabilizer medications and often also requires anti-psychotics. Psychiatric hospitalization is often required.

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6 WHO Mental Health GAP Action Programme Guideline Update 2015
If the patient is on an antidepressant, it should quickly be tapered down and discontinued, balancing the risks of withdrawal syndrome against the impact of the antidepressant worsening the mania.

The onset of effectiveness of haloperidol is more rapid than mood stabilizers and should be considered first in individuals with severe symptoms of acute mania, for the management of agitation.

Lithium\(^7\) or sodium valproate should be considered in individuals with acute mania for mood stabilization. Carbamazepine may also be helpful in the treatment of acute mania.

\(\text{\textbullet\ }\) Carbamazepine may negatively interact with antiretroviral medications and is best avoided for PLHIV taking ART.

In women planning a pregnancy, or who are pregnant or breastfeeding, lithium and sodium valproate should be avoided. In this group, low-dose haloperidol should be considered with caution.

In the elderly patient, start with lower doses of medications and increase slowly. Anticipate increased risk of drug interactions.

(ii) **Acute depression (with or without psychosis) in a patient with bipolar disorder**

Treatment of the depressive phase of bipolar disorder is particularly challenging as antidepressant medication may precipitate a manic or hypomanic phase if the patient is not first adequately treated with mood stabilizing medications.

Consider the diagnosis of bipolar depression if the patient presenting with a depressive episode has a known or suspected history of mania (see Table: Mood stabilizers below).

- The treatment of choice for bipolar depression is a mood stabilizer agent (sodium valproate, lithium\(^7\)).
- Once the patient is adequately treated with a mood stabilizer, an antidepressant agent can be added to help further alleviate depressive symptoms. Patients should be informed of the risk of switching to mania before starting antidepressant medication.
- Antidepressant treatment should begin at a low dose and be increased gradually if necessary. Fluoxetine should be preferred to tricyclics. Patients should be monitored carefully for early symptoms or signs of mania. Antidepressant medication should be stopped soon after remission of depressive symptoms, while the mood stabilizer continued.
- Behavioural activation, lifestyle modification and cognitive behaviour therapy should be used to help alleviate depressive symptoms. Use of these interventions in combination with a mood stabilizer may help the patient avoid the use of an antidepressant medication.

**Table: Mood stabilizers**

For lithium see mhGAP

<table>
<thead>
<tr>
<th>Valproic acid (sodium valproate) for mood stabilization in bipolar disorder and acute mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindications and cautions: Do not use for alcohol withdrawal.</td>
</tr>
<tr>
<td>Serious side-effects include:</td>
</tr>
<tr>
<td>• hepatotoxicity (can be fatal)</td>
</tr>
<tr>
<td>• pancreatitis</td>
</tr>
<tr>
<td>• hyponatraemia from drinking excess fluid</td>
</tr>
<tr>
<td>• blood dyscrasias</td>
</tr>
</tbody>
</table>

\(^7\) Instructions on using lithium could be added from mhGAP guidelines if lithium laboratory monitoring is available.
severe allergic reaction.

Educate the patient and the family:
• Review cautions and side-effects.
• Mood stabilizers are not addictive.
• Warn against use of alcohol.

In healthy adults:
• initiate treatment with 500 mg at night,
• depending on symptom severity, response, and tolerability, increase the dose by 200 mg every 7 days,
• typical effective dose is 1000–2000 mg daily.

In elderly or medically ill patients (including those with HIV stage 3 or 4):
• initiate treatment with 200 mg in the morning and 200 mg at night,
• increase the dose by 200 mg every 7 days until there is a clinical response or the therapeutic blood level is reached,
• the maximum dose can vary; assess tolerability and the clinical response.

**Carbamazepine – for mood stabilization in bipolar disorder, acute mania**

Contraindications and cautions: Avoid in pregnancy. Induces the metabolism of many other medications.

Serious but uncommon side-effects include:
• severe hypersensitivity or allergic reactions of skin or organs
• arrhythmias, AV block, heart failure
• blood dyscrasias
• hepatitis or hepatic failure or pancreatitis
• hyponatraemia from drinking excess fluid.

Educate the patient and the family:
• Review cautions and side-effects.
• Mood stabilizers are not addictive.
• Warn against use of alcohol.

In healthy adults:
• initiate treatment with 200 mg at night,
• increase the dose by 200 mg every 3–4 days until there is a clinical response,
• give in divided doses to reduce toxicity,
• typical effective dose is 400–600 mg daily, but in severe cases may need 1000 mg.

In elderly or medically ill patients (including those with HIV stage 3 to 4):
• initiate treatment with 100 mg at night,
• increase the dose by 100 mg every 3–4 days until there is a clinical response,
• give in divided doses to reduce toxicity,
• the maximum dose can vary; assess tolerability and the clinical response,
• be alert to possible virologic failure in patients taking antiretroviral medications for HIV.

(iii) Maintenance treatment of bipolar disorder

Treatment with a mood stabilizer, in combination with psychosocial interventions, is important to maintain wellness and avoid relapses of mania and depression in a patient with bipolar disorder.

Lithium or sodium valproate should be considered in the maintenance treatment of bipolar disorder. Lithium can only be used when laboratory monitoring of blood levels is available.

Carbamazepine can also be used but may negatively interact with antiretroviral medications and is best avoided in PLHIV taking ART.

Certain second-generation antipsychotics (aripiprazole, olanzapine, paliperidone extended release, quetiapine, and risperidone long-acting injection release) can be offered for the maintenance treatment of bipolar disorder. If treatment with one of these agents is not feasible,
first-generation antipsychotics or carbamazepine may be used. Maintenance treatment should be offered in primary health care settings under the supervision of a specialist.\(^8\)

In women planning a pregnancy, or pregnant or breastfeeding, lithium and sodium valproate should be avoided. These patients should be referred to specialist mental health care, when possible.

Maintenance treatment should continue for at least two years after the last episode of bipolar disorder. The decision to continue maintenance treatment after two years should preferably be done by a mental health specialist.

If a patient has frequent relapses of mania or depression while on mood stabilizer therapy, consider switching or adding agents. These patients should be referred to specialist mental health care, when possible.

Refer to specialty care guidelines for further information about the treatment of bipolar depression.

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\(^8\) WHO Mental Health GAP Action Programme (mhGAP) Guideline Update 2015
Sadness and anxiety can be very common feelings in everyday life. The causes of sad or low mood, anxiety, nervousness, or excessive worry often can be attributed to mood disorders or anxiety disorders. Clinical assessment seeks to correctly identify those patients who are experiencing a depressive episode or an anxiety disorder, so that adequate treatment may be instituted. However, several other physical and psychiatric disorders may manifest with symptoms of sad or low mood, and must be considered by the clinician in the differential diagnosis. These disorders can include:

- delirium with low mood (see Section 10.10.3)
- intellectual disabilities (see Section 10.10.3)
- dementia (see Section 10.10.3)
- psychosis (see Section 10.10.4)
- substance use disorders
- depression secondary to medical illnesses and medications.

In this Section, a depressive episode refers to patients whose sadness is severe or persistent, who have a range of emotional and physical symptoms that characterize major depression, whose symptoms deviate from normal expected reactions to life stressors, traumas and challenges, and who experience a significant impairment in function or life quality due to the depressive episode.

Sad or low mood and anxious states of mind often occur together. If there is prominent low mood, treat the depression first. However, temporary relief from anxiety symptoms may be needed, particularly at the outset of treatment.

At the start of treatment, always consider the possibility that medical causes may be contributing to depressive disorders. When patients do not respond to treatment for sad or anxious states of mind, see medical causes listed in Appendix 2.

The lifetime risk of developing a depressive disorder is 10%–20% in women and somewhat less in men. It is estimated that 20% of patients presenting to general medical clinics have depressive episodes. Depression often presents concomitantly with physical health problems, and patients with chronic disease complicated by severe depression have significantly worse health outcomes than patients with chronic disease without severe depression. Severe depression occurs more frequently in patients with HIV than in the general population, and can greatly affect their ability to adhere to antiretroviral treatment.

**Assessment of patients with sad or low mood or depression**

Depressive disorders may present with both psychological and physical symptoms. Many patients with depression do not volunteer emotional complaints, presenting instead with somatic complaints, which typically include:

- fatigue, which can be severe
- insomnia and, less commonly, hypersomnia
- somatic complaints, including changes in appetite and weight
- bodily complaints, such as burning sensations in the head, unexplained aches, and pains.

Psychological or emotional complaints are often elicited on inquiry. The symptoms cause significant distress and may markedly impair function and quality of life. The table below, DDx: Sad or low mood or depression, lists the defining characteristics of disorders associated with sad or low mood or depression.
Common presenting symptoms that should alert the clinician to a possible depressive disorder and should trigger the use of this Section include the following:

- sad or low mood
- fatigue or loss of energy or tiredness
- loss of interest or pleasure
- guilt or loss of self confidence
- hopelessness and feelings of worthlessness
- suicidal thoughts or acts or thoughts of death (Section 10.10.2 Suicide risk)
- disturbed sleep
- loss of libido
- disturbed appetite (weight loss or gain)
- feeling tense, anxious, excessively worried, or frightened
- unexplained somatic symptoms:
  - tingling, numbness
  - shortness of breath
  - gastrointestinal distress
  - palpitations
  - aches and pains
- reliving past traumas in thoughts, images, dreams or acts
- persistent preoccupation with stressful life events or stressors.

Patients presenting with these states of mind should receive an assessment for risk of suicide, self-harm, or the potential for violence or harm to others (see Section 10.10.2 Suicide risk).

**Investigations**

- Evaluation of the patient, including mental health history, review of medications, medical history, and mental status examination.
- Consider medical conditions and laboratory investigations as appropriate.
- History from family or friends if available and if the patient consents to these discussions.
- Use the DDx tables below to identify the most suitable diagnoses to account for the patient’s symptoms, and to guide treatment initiation.
- Consider the role of the following risk factors for depressive disorders in the patient’s presentation.
  - past history of depressive episodes or family history of depressive episodes
  - female gender
  - major stressful life events including family conflict, loss, or separation
  - chronic medical illness, including HIV infection
  - absence of positive social support
  - adverse social environment (poverty, homelessness, isolation, stigma, discrimination)
  - indications of the progression of HIV infection (notification of positive test, progression of symptoms, drop in CD4 count)
  - substance misuse
  - side-effects of prescribed medications
  - present or past exposure to physical and sexual abuse.
### Depressive episode

- Symptoms persist for at least two weeks and occur on most days for most of the day.
- Distinct period with defined onset characterized by:
  - sad or low mood
  - fatigue or loss of energy or tiredness
  - loss of interest or pleasure
  - guilt or loss of self-confidence
  - hopelessness and feelings of worthlessness
  - changes in appetite and sleep
  - loss of libido
  - suicidal thoughts or acts or thoughts of death

Antidepressants usually are helpful.

### Dysthymia

- A more persistent and chronic (>2 years) period of sadness and low mood; fewer and less severe symptoms than in severe depression but associated with significant impairment of quality of life and function.
- Antidepressant medication and psychotherapy often are indicated, but response to treatment may be more limited than seen with depressive episode.

### Bipolar disorder – depressive episode or depressive phase

- Current symptoms of depressive episode.
- Lifetime history of both depressive episode and mania or, its milder form, hypomania.
- Antidepressant medications can induce or precipitate manic episodes in patients with personal or family histories of bipolar disorder.
- Mood stabilizers are the treatment of choice for bipolar disorder. In the depressive phase, treat first with mood stabilizer such as lithium. Consider adding antidepressants only if mood stabilizer is insufficient to alleviate depressive symptoms. Use antidepressants to treat the depressive episode for the shortest possible period.

### Depressive episode with psychotic features

- Current symptoms of depressive episode.
- In addition to the symptoms of depression, the patient develops psychotic symptoms, e.g., delusions or hallucinations.
- Treatment necessitates the use of antipsychotic and antidepressant medications.

### Depressive symptoms due to general medical condition

- Medical illness or medications used to treat medical conditions may contribute to depressive symptoms.
- Symptoms may be due to a depressive disorder, the general medical condition, or both.
- Treatment may involve addressing the underlying medical disorder or instituting antidepressant medication treatment.

### Depressive symptoms due to dementia

- While memory loss is the hallmark symptom of dementia, many dementias, including HIV dementia, may present with symptoms of low mood, depression, and a slowing down or blunting of emotional responses.
- It is important to remember that many patients with dementia may also have a depressive episode. Both conditions will require targeted intervention.

### Uncomplicated bereavement

- A period of sadness following the death of a close friend or relative; the passage of time and the support of friends and family are usually sufficient to help people through a period of bereavement. If bereavement began in the prior 2 months, do not consider antidepressants as first-line therapy. Use culturally appropriate mourning and support to facilitate adjustment.
- Although bereavement is not a mental disorder, some people may be at risk of developing the full constellation of persistent symptoms that meet the criteria of a major depressive episode and may require consideration of targeted antidepressant therapy.

### Adjustment disorder (especially with depressive features)

- Time-limited mood symptoms may develop in response to a major stressful event without the full constellation of psychological and physical symptoms that are characteristic of severe depression.
- Treatment should focus on helping the patient to manage the adversity, by providing hope and reassurance, problem-solving, and facilitating connection with natural support systems.
- Physical activity should be encouraged and psychotherapies considered where available.
- Should the symptoms persist and their severity worsen, an adjustment disorder may develop into a depressive episode requiring antidepressant therapies.

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### DDx: Sad or low mood or depression

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Symptom constellation and treatment considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive episode</strong></td>
<td>Symptoms persist for at least two weeks and occur on most days for most of the day. Distinct period with defined onset characterized by: sad or low mood, fatigue or loss of energy or tiredness, loss of interest or pleasure, guilt or loss of self-confidence, hopelessness and feelings of worthlessness, changes in appetite and sleep, loss of libido, suicidal thoughts or acts or thoughts of death. Antidepressants usually are helpful.</td>
</tr>
<tr>
<td><strong>Dysthymia</strong></td>
<td>A more persistent and chronic (&gt;2 years) period of sadness and low mood; fewer and less severe symptoms than in severe depression but associated with significant impairment of quality of life and function. Antidepressant medication and psychotherapy often are indicated, but response to treatment may be more limited than seen with depressive episode.</td>
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<tr>
<td><strong>Bipolar disorder – depressive episode or depressive phase</strong></td>
<td>Current symptoms of depressive episode. Lifetime history of both depressive episode and mania or, its milder form, hypomania. Antidepressant medications can induce or precipitate manic episodes in patients with personal or family histories of bipolar disorder. Mood stabilizers are the treatment of choice for bipolar disorder. In the depressive phase, treat first with mood stabilizer such as lithium. Consider adding antidepressants only if mood stabilizer is insufficient to alleviate depressive symptoms. Use antidepressants to treat the depressive episode for the shortest possible period.</td>
</tr>
<tr>
<td><strong>Depressive episode with psychotic features</strong></td>
<td>Current symptoms of depressive episode. In addition to the symptoms of depression, the patient develops psychotic symptoms, e.g., delusions or hallucinations. Treatment necessitates the use of antipsychotic and antidepressant medications.</td>
</tr>
<tr>
<td><strong>Depressive symptoms due to general medical condition</strong></td>
<td>Medical illness or medications used to treat medical conditions may contribute to depressive symptoms. Symptoms may be due to a depressive disorder, the general medical condition, or both. Treatment may involve addressing the underlying medical disorder or instituting antidepressant medication treatment.</td>
</tr>
<tr>
<td><strong>Depressive symptoms due to dementia</strong></td>
<td>While memory loss is the hallmark symptom of dementia, many dementias, including HIV dementia, may present with symptoms of low mood, depression, and a slowing down or blunting of emotional responses. It is important to remember that many patients with dementia may also have a depressive episode. Both conditions will require targeted intervention.</td>
</tr>
<tr>
<td><strong>Uncomplicated bereavement</strong></td>
<td>A period of sadness following the death of a close friend or relative; the passage of time and the support of friends and family are usually sufficient to help people through a period of bereavement. If bereavement began in the prior 2 months, do not consider antidepressants as first-line therapy. Use culturally appropriate mourning and support to facilitate adjustment. Although bereavement is not a mental disorder, some people may be at risk of developing the full constellation of persistent symptoms that meet the criteria of a major depressive episode and may require consideration of targeted antidepressant therapy.</td>
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<tr>
<td><strong>Adjustment disorder (especially with depressive features)</strong></td>
<td>Time-limited mood symptoms may develop in response to a major stressful event without the full constellation of psychological and physical symptoms that are characteristic of severe depression. Treatment should focus on helping the patient to manage the adversity, by providing hope and reassurance, problem-solving, and facilitating connection with natural support systems. Physical activity should be encouraged and psychotherapies considered where available. Should the symptoms persist and their severity worsen, an adjustment disorder may develop into a depressive episode requiring antidepressant therapies.</td>
</tr>
</tbody>
</table>
The figure illustrates common mood syndromes. A patient with bipolar disorder will have distinct episodes of low mood and euphoria or high mood. A patient with depressive episodes will have episodes of low mood with a return to wellness, but episodes may be recurrent, and mild symptoms may persist between episodes. Some patients have persistently low mood; if this persists for at least 2 years without returning to wellness, they are considered to have dysthyemic disorder. Severe depression and dysthymia may occur together, resulting in a baseline state of depression with periodic exacerbations.

**Depressive symptoms due to medical conditions**

Physical or somatic symptoms associated with depression, such as fatigue, weight loss, and insomnia, may be caused by physical illness alone or the medications used to treat physical illnesses. However, it is not uncommon for physical illness and depression to coexist. In these cases, there is a risk of diagnosing only one condition. When both disorders exist, it is important to identify and treat both, as each can contribute to worsening of the patient’s health status.

- Physical illnesses may present with sad or low mood as a key symptom. The low mood is often accompanied by fatigue, lethargy, and loss of motivation.
- Medications used to treat physical syndromes may cause low mood, loss of interest, and fatigue. Some medications used to treat HIV (e.g. EFV) have been associated with low-mood symptoms.

Medical conditions and medications that can present with depression can be found in Appendix 2.

**Depressive symptoms related to adverse life events**

Adverse life events can contribute to sad or low mood, but a depressive episode is not an expected outcome of such events. Depressive episodes often develop following an adverse or stressful life event but are distinguished from the conditions described in the table above, DDx: Sad or low mood or depression, by the symptom severity, the persistence, and pervasiveness of the mood symptoms and the functional impact. The DDx table also outlines other conditions to consider when making the differential diagnosis of sad or low mood. These conditions may be thought of as existing on a continuum of reactions to adverse life events.

In general, with the help of natural support systems and the passage of time, most people will recover from the distress of adverse life events and circumstances. More targeted interventions, including antidepressant medications and psychotherapies, will be needed when symptom burden is greater and functional impact is more severe.

**Acute management of depression**

When symptoms of a depressive episode are pervasive, persistent, and of moderate to severe intensity, medication treatment is usually necessary to reduce the symptoms. When symptoms are mild, psychotherapy and counselling without medications may be sufficient to treat the episode.
Physical activity and behavioural activation should be encouraged in all patients experiencing depressive episodes. However, in moderate and severe depression, this intervention should only be used as adjunct to antidepressants or brief structured psychological treatments.

All patients should receive comprehensive clinical care including psycho-education, counselling and support, activation of social networks, structured physical activity programming, medication management, and regular follow up. Where human resources permit, referral for psychotherapy and additional psychiatric and mental health services should be considered.

Health-care workers should perform the following for patients presenting with severe depression:
- assess for suicide risk (see Section 10.10.2) and ensure safety,
- initiate medication treatment,
- provide counselling,
- initiate management of any co-morbid conditions (e.g. treat substance use disorders, medical conditions, and pain).

**Non-pharmaceutical management of depression**
- Counselling and psychotherapy often are sufficient for the treatment of a depressive episode of mild intensity. Antidepressant medications should not be offered for the initial treatment of a mild depressive episode.
- Assess for and try to reduce stressors.9
- Reactivate the person’s previous social network. Identify prior social activities that, if started again, may potentially provide direct or indirect psychosocial support, e.g. family gatherings, visiting neighbours, and community activities.9
- Even if it is difficult, encourage the person to try to do as many of the following as possible and explain to person (and carer) that these activities can help improve mood:9
  - Try to start again (or continue) activities that were previously pleasurable.
  - Try to maintain regular sleeping and waking times.
  - Try to be as physically active as possible.
  - Try to eat regularly despite changes in appetite.
  - Try to spend time with trusted friends and family.
  - Try to participate in community and other social activities as much as possible.
- WHO (as well as other agencies) has developed manuals describing the use of several brief psychological treatments for depression:
  - *Problem Management Plus*10 describes the use of behavioural activation, relaxation training, problem solving treatment and strengthening social supports.
  - *Group Interpersonal Therapy (IPT) for Depression*11 describes group treatment of depression.
  - *Thinking Healthy*12 describes the use of cognitive-behavioural therapy for perinatal depression.

See also Appendix A which describes psychotherapy and mental health counselling and cognitive behaviour therapy (CBT).

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9 WHO Mental Health GAP Action Programme (mhGAP) Guideline Update 2015


11 [http://www.who.int/mental_health/mhgap/interpersonal_therapy/en](http://www.who.int/mental_health/mhgap/interpersonal_therapy/en)

Use of antidepressant medications: some basic principles and cautions

- Antidepressant medications are the most effective treatment for a depressive episode of moderate to severe symptom intensity.
- Fluoxetine\(^{13}\) or tricyclic antidepressants (TCAs) should be considered as treatment in individuals with moderate to severe depressive disorder.
- If fluoxetine is available, it may be better tolerated and equally effective as TCAs and may be initiated instead of a TCA.
- If drug treatment is required in older people, fluoxetine is preferable to tricyclics, which should be avoided due to side-effects.
- In adolescents with depressive episodes, do not consider antidepressant medication as first-line treatment. Psychosocial treatments, including psychotherapy, are preferable. If no response to psychosocial treatments, consider using the lowest effective dose of fluoxetine (but not other SSRIs or TCAs). Adolescents on fluoxetine should be monitored closely for suicidal ideations or behaviour. For all adolescents on fluoxetine, support and supervision from a mental health specialist should be obtained.
- Antidepressants should not be considered in the treatment of children younger than 12 years of age.
- If drug treatment is required in women with a depressive episode or disorder who are planning a pregnancy, pregnant, or breastfeeding, avoid antidepressants as much as possible. Psychosocial treatments, including psychotherapy, are preferable. If no response to psychosocial treatments, consider using the lowest effective dose of antidepressant medication.
- If antidepressant medication is required in patients with cardiovascular disease, SSRIs are the first choice. Do not prescribe TCAs to people at risk of serious cardiac arrhythmias or recent myocardial infarction.
- Antidepressant medications can precipitate mania in patients with a personal or family history of mania or bipolar disorder.
- With both SSRIs and TCAs, the early phase of acute antidepressant treatment may be a time of heightened risk for agitation, and harm to self or others.
- When starting antidepressants, monitor patient for risk of harm to self or others at every contact.
- All TCAs are highly lethal in overdose. To minimize the harm if overdose occurs, patients should have access to only a small supply at the initiation of treatment or at any points when suicide risk is high.
- If severe anxiety is present or if marked and akathisia or agitation develops on SSRIs, consider short-term use of low-dose diazepam, i.e. 5–10 mg daily for 1 week. Diazepam does not treat depression and carries a risk of dependence.
- Dosage adjustment of medication should be based on symptom response and tolerability. The treatment goal is full remission of symptoms and a full return to the level of function.
- At each visit, assess medication tolerability and check adherence.
- If the patient has a poor symptom response by week 12 despite good adherence to the maximum tolerated dose of a medication, switch to another antidepressant.
- In adult individuals with depressive disorders who have benefited from initial antidepressant treatment, do not consider ending the antidepressant treatment before 9–12 months after recovery. Treatment should be regularly monitored, with special attention to treatment adherence. Frequency of contact should be determined by the adherence, the severity of symptoms, and by local feasibility issues.
- When terminating antidepressant medication treatment, remind the patient about the possibility of withdrawal symptoms. Counsel to taper the dose slowly and avoid abrupt discontinuation.
- Advise patients to self-monitor for early signs of symptom relapse.

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13 Other SSRIs are available.
Antidepressant medication in comparison with psychological treatment for moderate-severe depressive disorder

As first-line therapy, health-care providers may select psychological treatments such as:

- behavioural activation [BA],
- cognitive behavioural therapy [CBT], or
- interpersonal psychotherapy [IPT]) or
- antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]).

They should keep in mind the possible adverse effects associated with antidepressant medications, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences.

Health-care providers can offer different treatment formats of WHO’s recommended, structured psychological interventions for adults and older adolescents with depressive disorder. These include behavioural activation, cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT), problem-solving treatment as an adjunct treatment (e.g. in combination with antidepressants). Different treatment formats for consideration include (a) individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists, as well as (b) self-help psychological treatment.

While face-to-face psychological treatment or guided self-help psychological treatment are likely to have better outcomes than unguided self-help, the latter may be suitable for those people who either (a) do not have access to face-to-face psychological treatment or guided self-help psychological treatment, or (b) are not willing to access such treatments.14

Use of antidepressant medication in the management of a depressive episode (moderate to severe)

The two antidepressants available in the WHO formulary are fluoxetine and amitriptyline. Doses and titration are noted below.

### Fluoxetine for depression

Contraindications and cautions: Watch for increased risk for agitation and suicidal ideation and behaviour (see Section 10.10.2). If there is a history of mania or bipolar disorder, use a mood stabilizer first (see Section 10.10.5 on bipolar disorder for further details).

Educate the patient and family:
- about side-effects
- that the medication is not addictive
- to avoid the use of alcohol
- that it usually takes several weeks to get a response – do not be discouraged
- that the patient may feel worse initially due to side-effects; most side-effects gradually diminish.

In healthy adults:
- Initiate treatment with 20 mg of fluoxetine daily.
- May start at 10 mg daily to reduce the risk of side-effects that undermine adherence, and then increase to 20 mg as tolerated.
- If 10 mg dosing is not available, give 20 mg every other day (fluoxetine has a very long half-life)
- If the patient has severe insomnia (caused by the psychiatric illness or fluoxetine), consider adding diazepam 5 mg at bedtime. Gradually taper and discontinue diazepam as psychiatric symptoms improve.
- If no response in 4–6 weeks or partial response at 6 weeks, the fluoxetine dose may be increased to 40 mg.

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14 WHO mhGAP action programme guidelines update 2015.
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In elderly or medically ill patients or patients who cannot initially tolerate a 20 mg daily dose (including those with HIV stage 3 or 4):
- Initiate treatment with 10 mg daily for three weeks.
- If 10 mg doses are not available, give 20 mg every day (fluoxetine has a very long half-life).
- Bear in mind that fluoxetine dosing can be increased as gradually as needed to manage uncomfortable side-effects. Patients usually become accustomed to the side-effects in time.
- If the patient has severe insomnia (caused by psychiatric illness or fluoxetine), consider adding diazepam 2–5 mg at bedtime. Avoid diazepam in cognitively-impaired patients. Gradually taper and discontinue diazepam as psychiatric symptoms improve.
- After three weeks, the dose can be raised to 20 mg daily, or raised more gradually, according to patient tolerability and symptom response.
- The fluoxetine dose may be gradually increased up to 60 mg as necessary and tolerable to achieve optimal response.
- When switching from fluoxetine to amitriptyline, note concerns mentioned above and start with lower doses of amitriptyline.

Amitriptyline for depression

Contraindications and cautions: In depressed patients, watch for increased risk for agitation and suicidal ideation and behaviour (see Section 10.10.2). If there is a history of mania or bipolar disorder, give only in combination with a mood stabilizer (see Section 10.10.5 Bipolar disorder for further details). Do not give if there is a history of arrhythmia or recent heart attack. If suicide risk is a concern, give only 1 week’s supply at a time, or have the caregiver dispense the drug. It may impair the ability to perform skilled tasks such as driving – take precautions until the patient is accustomed to the drug.

Educate the patient and family:
- about side-effects
- that the medication is not addictive
- to avoid the use of alcohol
- that it usually takes several weeks to get a response in depression – do not be discouraged
- that the effect on sleep or pain may be seen within 2–3 days
- that the patient may feel worse initially due to the side-effects; most side-effects gradually diminish.

In healthy adults:
- Initiate treatment with 50 mg of amitriptyline at bedtime.
- Increase by 25–50 mg every 1–2 weeks, aiming for 100–150 mg by 4–6 weeks, depending on response and tolerability.
- If no response in 4–6 weeks or partial response at 6 weeks, may increase to a maximum dose of 200 mg given in divided doses or a single dose at night.

In elderly or medically ill patients (including those with HIV stage 3 or 4):
- Initiate with 25 mg at bedtime.
- Increase by 25 mg weekly, aiming for a target dose of 50–75 mg by 4–6 weeks.
- If no response at 6–12 weeks or partial response at 12 weeks, may increase gradually to 100 mg in divided doses.
- Monitor carefully for orthostatic hypotension.

Management of a severe depressive episode with psychotic symptoms

- Patients with both severe depression and psychosis are at an increased risk of suicide compared with patients with severe depression alone (see Section 10.10.2).
- Begin treatment with both an antipsychotic and an antidepressant, following dosages as described in the medication boxes above. Monitor carefully for side-effects, which are more common when 2 medications are given together.
Once stabilization has been achieved, the antipsychotic medication can be slowly tapered. The antidepressant should be continued for 9–12 months after symptom remission, as described below in the treatment of depressive episodes.

- If psychosis re-emerges, restore the antipsychotic treatment.
- If specialty care is available, referral for stabilization and management is desirable.

## 10.10.7 Anxiety

Anxiety often presents as apprehensiveness, fearfulness, nervousness, or excessive worry, accompanied by physical symptoms. Anxiety can be normal in stressful life situations. However, symptoms out of proportion to the severity of the stressful situation that persist after the stressor has gone, and that interfere with a person’s daily life, indicate an anxiety disorder. An anxiety disorder also can occur in the absence of any external stressor. Anxiety disorders are very common, often have a recurrent or chronic course, and may last for decades in the absence of effective treatment.

### Assessment and diagnosis of anxiety

In addition to assessment for suicide risk (see Section 10.10.2), patients who present with anxiety should be screened as follows.

- Check for the following symptoms of anxiety:
  - feeling tense, anxious, apprehensive or frightened
  - being excessively worried.
- Physical symptoms of anxiety:
  - palpitations
  - suffocation sensations
  - dizziness
  - trembling
  - shaking
  - pins and needles sensations.
- Patients who complain of sadness frequently experience feelings of anxiety.
- Check for the following symptoms of depression:
  - low mood or sadness
  - loss of interest or pleasure
  - hopelessness
  - decreased energy or increased fatigue.
- If the diagnosis is positive for depression, see Section 10.10.6.
- If negative for depression, follow the guidelines below for anxiety disorders.

### Diagnosis of anxiety

A diagnosis of anxiety disorder should be made when the patient presents with the symptoms above, especially if the symptoms are severe and the patient’s daily functioning is impaired.

### Differential diagnosis for anxiety

- If symptoms of abnormal behaviour are present, assess and treat for abnormal behaviour conditions.
- If symptoms of sad or low mood are prominent, treat for depressive disorder.
- If the patient does not respond to treatment for anxiety, see Appendix 2 for medical conditions associated with anxiety.

### Management of anxiety

Severe anxiety disorders should be treated. Patients with milder symptoms may benefit from support, counselling, and relaxation training. Among people with milder symptoms and recent
onset; first provide support, address social issues, and continue to monitor the symptoms. Treatment for severe symptoms often involves medication and counselling.

- Address underlying medical conditions that could cause the anxiety symptoms, including possible modification of prescribed medication (see Appendix 2).
- Discuss health behaviours that may reduce anxiety, including eliminating caffeine, regulating sleep hygiene, and decreasing the use of alcohol and substances.
- Benzodiazepines can be used for the short-term treatment of an acute episode of severe anxiety caused by a stressful life event. Longer-term treatment (beyond 2 weeks) with benzodiazepines is not indicated as it carries a risk of dependence and the potential for addiction and abuse.
- SSRI medications are useful for the longer-term treatment of most anxiety disorders.
- Amitriptyline and clomipramine can be useful for selected anxiety disorders. Before using these medications, see below, Making a specific anxiety disorder diagnosis.
- Pharmacological interventions should not be offered to adolescents with anxiety disorders in non-specialist settings.

In non-specialized care, relaxation training should be considered as treatment for anxiety symptoms of at least 2 weeks duration (in the absence of depressive disorder), for patients who are in distress or have some degree of impaired functioning.

Cognitive behaviour therapy (CBT) is an excellent treatment for anxiety disorders.

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**Psychotropic therapy for anxiety**

**Diazepam – for short-term treatment only for acute anxiety**

Contraindications and cautions: Diazepam can be abused. Long-term treatment with diazepam can cause substance dependence. If a patient becomes dependent on diazepam, sudden discontinuation can cause withdrawal syndrome (this has similarities to alcohol withdrawal). It should not be given to patients using alcohol. Benzodiazepine use in patients with post-traumatic stress disorder may have a very high rate of development of dependence and should be used sparingly and with extreme caution.

Educate the patient and family:

- Review side-effects.
- Be cautious about the addictive potential.
- Warn against use of alcohol.

**In healthy adults**

- Initiate treatment with 2 mg of diazepam 1 to 3 times daily.
- May increase gradually if needed to 5–10 mg twice daily.
- Maximum dose is 20 mg during a 24-hour period.

**In elderly or medically ill patients** (including those with HIV stage 3 or 4)

- Initiate treatment of 2 mg of diazepam once daily (may repeat another dose in a day).
- May increase gradually to 10–20 mg daily if necessary and tolerated. However, the preferred maximum dose in elderly patients is 10 mg daily after a gradual increase.

**In all adults**

- Taper medication slowly after symptoms have been controlled.
- Wherever possible, do not exceed a 2-week duration of treatment.
- If the symptoms return, consider SSRI treatment.

**Fluoxetine for chronic anxiety disorders** – same dosing as for depression (see Section 10.10.6 for cautions and dosing)

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**Making a specific anxiety disorder diagnosis**

When there is a range of available treatments, it may be desirable to make a specific diagnosis of an anxiety disorder. There are several types of anxiety disorders with different symptoms, but the symptoms cluster around excessive, irrational fear and dread. The table on the next page,
DDx: Specific anxiety disorders with screening questions and treatments, provides key features and specific screening questions related to each type of anxiety disorder: generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, and phobias (including social phobia). This Table also lists treatments with known effectiveness for each disorder.

<table>
<thead>
<tr>
<th>Anxiety disorder</th>
<th>In favour</th>
<th>Screening questions</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized anxiety disorder (GAD)</strong></td>
<td>Prominent worry</td>
<td>Have you been worrying a lot about many different things (for quite some time)?</td>
<td>Counselling, support, relaxation training</td>
</tr>
<tr>
<td></td>
<td>Feeling tense or nervous</td>
<td>Have you been experiencing (tension-related symptoms) headache, pounding heart, complaint of &quot;stress&quot;, or insomnia?</td>
<td>Fluoxetine</td>
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<td>Sense of foreboding</td>
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<td></td>
<td>Poor concentration</td>
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<td></td>
<td>Dizziness</td>
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<td></td>
<td>Sweating</td>
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<td></td>
<td>Fast or pounding heart</td>
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<td></td>
<td>Chest pain or constriction</td>
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<td></td>
<td>Dry mouth</td>
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<td></td>
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<tr>
<td></td>
<td>Stomach pains</td>
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<td></td>
<td>Restlessness, inability to relax</td>
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<td></td>
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<tr>
<td></td>
<td>Headaches</td>
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<td></td>
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<tr>
<td><strong>Post-traumatic stress disorder (PTSD)</strong></td>
<td>History of traumatic event</td>
<td>Do you often think or dream about something terrible that happened to you in the past?</td>
<td>Access to psychological first aid support for acute trauma exposure</td>
</tr>
<tr>
<td></td>
<td>Re-experiencing symptoms, e.g. flashbacks, nightmares. Avoidance symptoms, e.g. avoids stimuli associated with the trauma, has sense of detachment and numbness. Hyper-arousal symptoms, e.g. insomnia, irritability, difficulty in concentrating, hyper-vigilance, exaggerated startle response</td>
<td>Can these thoughts or dreams be linked to a particular traumatic event?</td>
<td>CBT including graded self-exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do you avoid things that remind you of this event?</td>
<td>Fluoxetine</td>
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<td></td>
<td></td>
<td></td>
<td>Amitriptyline</td>
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<tr>
<td><strong>Obsessive-compulsive disorder (OCD)</strong></td>
<td>Obsessions: Recurrent and persistent thoughts, impulses, or images causing marked anxiety or distress The patient may consider them &quot;silly&quot; but cannot escape them Recognizes and attempts to ignore or suppress such thoughts, impulses or images or to neutralize them with some other thought or action Compulsions: Repetitive and excessive behaviour or unrealistic mental acts that the person feels driven to perform in order to reduce anxiety from obsessions. These commonly include repetitive checking, washing or cleaning, rearranging and ordering objects to prevent or reduce distress or prevent some dreaded event or situation Patients often have both obsessions and compulsive rituals</td>
<td>Do you have thoughts that disturb you but feel out of your control?</td>
<td>CBT (exposure and response prevention)</td>
</tr>
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<td></td>
<td></td>
<td>Are there certain things that you must do over and over in order to feel better?</td>
<td>Fluoxetine, often required in high doses</td>
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<td></td>
<td></td>
<td></td>
<td>Clomipramine</td>
</tr>
<tr>
<td><strong>Panic disorder</strong></td>
<td>Recurrent and unexpected panic attacks (spontaneous episodes of severe anxiety that start suddenly, rise rapidly, and last from a few minutes to an hour) Physical sensations, such as palpitations, chest pain, sense of choking, churning stomach, dizziness, feelings of unreality, feelings of</td>
<td>Do you ever have periods of intense fear or anxiety with chest pain, pounding heart, shortness of breath, and sweating that occur out of the blue?</td>
<td>CBT</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Fluoxetine</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Amitriptyline</td>
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</tbody>
</table>
impending disaster (losing control, going mad, sudden death, heart attack). Worry about the implications of the attack or its consequences and about having more attacks. A significant change in behaviour related to the attacks (e.g. avoiding places where they have occurred).

| Phobias               | Unreasonably strong fear or avoidance of people, places, or events such as:  
|                       | leaving home  
|                       | being alone at home  
|                       | crowds or public places  
|                       | open spaces  
|                       | performing in public  
|                       | social events  
|                       | animals, darkness, heights, blood, or others  
|                       | Person recognizes that the fear is excessive or unreasonable. |
|                       | Do you avoid certain places or situations or objects because they frighten you or make you feel anxious?  
|                       | Is there anything you tend to avoid or fear more than most people do? |
|                       | CBT  
|                       | Fluoxetine improves social phobia (severe anxiety around people) but not specific phobias (e.g. animals, heights). |

Management of specific anxiety disorders

When a specific anxiety diagnosis has been made, CBT is particularly effective for panic disorder, obsessive-compulsive disorder (OCD) and social phobia.

Exposure to traumatic life events is common and may be associated with the development of PTSD. Some important principles related to psychosocial therapies for PTSD and exposure to traumatic events.

- Single session psychological debriefing should not be used for people exposed recently to a traumatic event as an intervention to reduce the risk of post-traumatic stress, anxiety or depressive symptoms.
- Providing access to support, based on the principles of psychological first aid, should be considered for people in acute distress exposed recently to a traumatic event.
- If it is possible to continue to follow-up on the patient, graded self-exposure based on the principles of CBT should be considered in patients with PTSD symptoms.
- Psychotherapy for PTSD may be very effective, but it is essential that it is delivered by a therapist who is able to be attentive about establishing a sense of safety for the patient, who is able to guide the patient in reducing the intensity of overwhelming emotions, and who is able, over time, to help the patient to integrate the traumatic event psychologically.

In addition to CBT, medication therapies are helpful for specific anxiety disorders. OCD usually requires higher doses of fluoxetine, up to 80 mg, to achieve a therapeutic response in comparison with other anxiety disorders. OCD can also be treated with clomipramine.

Clomipramine for treatment of obsessive compulsive disorder, depression, and anxiety.

This is a tricyclic antidepressant, like amitriptyline. See 10.10.6 for side-effects, contraindications, cautions, and patient and family education.

In healthy adults:
- Initiate a dose of 10–25 mg daily at bedtime.
- Increase in divided doses by 25 mg every 4–7 days to a therapeutic dose of 150–200 mg in divided doses or a single dose at night.
- When switching or discontinuing, taper the dose gradually to discontinue.

In elderly or medically ill patients (including those with HIV stage 3 or 4):
- Initiate a dose of 10 mg daily at bedtime.
- Increase in divided doses by 10 mg every 4–7 days to 50–75 mg.
- May continue to increase the dose as needed and tolerated up to the maximum dose for healthy adults.
When switching medication or discontinuing treatment, taper the dose gradually to discontinue.

Monitor carefully for hypotension.

**Somatoform disorder**

- Although not classified as an anxiety disorder, somatoform disorder can confer excessive worry, anxiety and low mood. Patients with somatoform disorder present with multiple physical complaints that cannot be explained by either a known medical disorder after appropriate clinical investigations or by another mental disorder, such as depression or an anxiety disorder. Complaints can include, among other symptoms:
  - persistent headache
  - dizziness
  - chronic fatigue or tiredness
  - nausea
  - chronic pain
  - urinary or gynaecological complaints
  - gastrointestinal complaints (e.g. flatulence).

Treatment based on CBT principles (e.g. re-attribution, graded activities) should be considered in repeat adult patients with medically unexplained somatic complaints who are in substantial distress, and who do not meet the criteria for a depressive disorder.

Where a depressive or anxiety disorder coexists, specific treatment interventions should be initiated.
Appendix 1. Psychotherapy and mental health counselling

(i) Supportive psychotherapy and mental health counselling
Psychosocial support and psycho-education are helpful interventions in mental health disorders.

- An effective counsellor can provide tremendous help to a patient with mental health concerns, or a person facing adverse life events, by being empathetic, respectful, patient, compassionate, honest, and trustworthy.
- An effective counsellor uses supportive psychotherapy and counselling skills to support a patient’s functioning through:
  - the promotion of coping skills;
  - the use of problem-solving techniques;
  - helping patients with the containment and management of feelings and distress;
  - the provision of support and the instillation of hope;
  - reassurance and positive reinforcement;
  - decreasing isolation;
  - fostering connections with the patient’s natural support systems;
  - focusing on short-term activities for pleasure and aiming to restore self confidence;
  - countering misconceptions, stigma, and discrimination;
  - providing psycho-education about the nature of mental health disorders and their treatments;
  - highlighting the patient’s efforts to cope, fostering hope, and recognizing that the patient is doing the best that they can.

(ii) Cognitive behaviour therapy
Cognitive behaviour therapy (CBT) is based on the idea that feelings are affected by thinking and behaviour.

- CBT aims to improve a patient’s sense of well-being by identifying key patterns of thinking that are dysfunctional or distorted. These thoughts may contribute to unrealistic and overly negative appraisals of self and others, and may contribute to the patient’s mental health symptoms.
- CBT has been shown to be helpful in managing a range of mood and anxiety disorders.

Therapy approaches may include keeping a record of thought patterns and feelings related to specific events, examining automatic thoughts and assumptions, evaluating unhelpful or unrealistic belief systems that pertain to one’s view of self, others, or the world, graded exposure to settings or activities that may have been avoided, and trying out new ways of interacting with others.

(iii) Interpersonal psychotherapy
Interpersonal psychotherapy is an effective treatment for depression, including bipolar depression.

- Therapy aims to improve a patient’s sense of well-being by identifying key areas involving interpersonal functioning, i.e. the interactions that one has with others and how depression may impact on and be impacted by these interactions.

Common areas of focus in interpersonal psychotherapy include:
- exploration of grief and loss
- life changes and social role changes
- social isolation and lack of meaningful relationships
- disputes and disagreements with others.

Interpersonal therapy may be delivered in individual or group settings, and has been shown to be effective when delivered in many situations including low-resource settings.
(iv) Psycho-education

- Review symptoms and give essential information:
  - summarize the patient’s symptoms and explain the diagnosis or illness
  - explain the benefits and risks of treatment
  - establish the patient’s coping practices and encourage their use
  - counter misconceptions, stigma and discrimination
  - empathize with the patient’s distress.

- Explore ways to reduce stress with patients and family:
  - provide supportive counselling (appropriate to circumstances)
  - emphasize a problem-solving approach to help work towards solutions that will bring a greater sense of well-being
  - foster connections with the patient’s natural support systems, helping the patient to utilize family, friends, and community supports
  - explore activities that will enhance functioning and self-confidence and give pleasure.

- Help the patient and family to maintain hope:
  - highlight the patient’s efforts to cope and recognize that she or he is doing the best that she or he can.

- Remain an effective support:
  - an effective counsellor can provide tremendous help to a patient by being empathic and respectful, patient and compassionate, and honest and trustworthy.
Appendix 2. Medical conditions to consider before starting treatment for mental disorders and when patients do not respond to initial psychiatric therapy

Many patients with mental health disorders have concurrent medical conditions that require treatment. Additionally, many medical conditions may present with mental health symptoms.

<table>
<thead>
<tr>
<th>Medical conditions that may present with mental health symptoms</th>
<th>Confusion, severe agitation, or bizarre behaviour</th>
<th>Sad or low mood</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosyphilis</td>
<td>x</td>
<td>x</td>
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<td>HIV infection</td>
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<td>x</td>
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<td>Systemic infections</td>
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<tr>
<td>Liver failure</td>
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<tr>
<td>Dehydration</td>
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<td>Fluid and electrolyte disturbance</td>
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<td>Renal failure</td>
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<tr>
<td>Hypoglycaemia</td>
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<td>x</td>
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<tr>
<td>Diabetic ketoacidosis</td>
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<tr>
<td>Hypoxia</td>
<td>x</td>
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<tr>
<td>Prescribed medication side-effects, as well as drug-drug interactions and overlapping toxicities</td>
<td>x</td>
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<tr>
<td>Withdrawal from alcohol and substances</td>
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<tr>
<td>Endocrinopathy: hypothyroidism</td>
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<tr>
<td>Endocrinopathy: hyperthyroidism</td>
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<tr>
<td>Cushing’s syndrome</td>
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<td>Addison’s disease</td>
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<td>Pheochromocytoma</td>
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<td>Neurological disorders:</td>
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<tr>
<td>Epilepsy</td>
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<td>Head trauma and intracranial lesion</td>
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<tr>
<td>Parkinson’s</td>
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<td>Stroke</td>
<td>x</td>
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<td>Encephalitis</td>
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<td>Vitamin deficiencies (e.g. endemic neuritis)</td>
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<tr>
<td>vitamin B12</td>
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<td>vitamin B1</td>
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<td>Undernutrition</td>
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<td>Anaemia</td>
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<td>Cardiovascular conditions:</td>
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<td>Congestive heart failure</td>
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<td>Myocardial infarction</td>
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<td>Arrhythmias</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Poisoning:</td>
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<tr>
<td>Ingested poisons, such as pesticides and plants</td>
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<tr>
<td>Accidental and intentional overdose</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
10.11 Eye problems

10.11.1 Clinical approach to a patient with eye problems

Step 1: Perform Quick Check
Exclude any serious or life-threatening conditions that might present with eye symptoms. Consider malignant hypertension and imminent eclampsia. Assess for sight-threatening conditions that require urgent intervention or an appropriate referral.

Step 2: Take a history and examine the patient
Examine the eye and classify the eye problem.

Step 3: Assess the patient’s HIV status

Step 4: Work through the appropriate differential diagnosis tables

Step 5: Perform investigations as necessary

Step 6: Treat and monitor the patient’s response to treatment, or refer as necessary

History

Specific questions
- What are the symptoms?
  - pain
  - light discomfort or photophobia
  - red eye
  - watering of the eyes
  - discharge
  - itching
  - dryness
  - sensation of foreign body.

1 For colour illustrations of some of these eye problems, see poster available at http://www.who.int/blindness/sop_en.pdf
• Is there a history of trauma?
• What are the visual symptoms?
  o loss of or decreased vision
  o diplopia (double vision)
  o halos around lights
  o floaters (black or grey specks in the field of vision)
  o flashes of light.
• What is the duration of symptoms?
• What is the progression of symptoms?
• Look at the patient’s past history of similar symptoms.
• Are there any locally endemic conditions in the community (e.g. trachoma, onchocerciasis, conjunctivitis)?

**General questions**
• Systemic diseases – hypertension, diabetes mellitus, connective tissue disorders?
• Comorbidities – HIV, malignancies?

**Examination**

**Do a general physical examination**

**Do a specific eye examination**
A basic ophthalmic examination may require the following:
• a torch for gross examination of the eye structure and pupil response
• blue light filter
• Snellen chart or “E” chart for illiterate patients (or a LogMar chart)
• fluorescein drops or impregnated paper strips
• short-acting mydriatic drops (e.g. 1% tropicamide) to dilate pupils – remember to assess visual acuity and pupil response first
• direct ophthalmoscope
• topical anaesthetic drops (e.g. lidocaine)
• cotton buds to remove foreign body
• handheld applanation tonometer (Schiotz or Puff tonometer), if available.
10. Acute and subacute by symptom: SEARO 202

**Assess visual acuity**
- Use a Snellen chart to measure distance acuity – this can be at any distance (e.g. 3 or 6 metres) as long as it is documented.
  - Make sure the room is well lit.
  - Have patient occlude one eye with palm (make sure patient is not peeking and is not applying pressure on the occluded eye).
  - Ask patient to read aloud each letter in the first row, or indicate with the hand what direction the E is pointing. Then proceed to the next smaller line until not able to distinguish all the letters on that line.
  - Record the last line read accurately after the distance from the chart, for example 6/24, if the patient was 6 metres from the chart and the last line read was 24.
  - If the patient is not able to read the top line, move forward a metre and retest up to 3 metres. If still not able to read top line, test whether the patient can count fingers and record this. If not able to count fingers, test whether the patient can detect hand motion. If not, test for light perception with a bright torch.
  - Then test the other eye and record.
  - Then test with glasses on.
  - If acuity is less that 6/18 then assess again using pinhole and see if it improves; if yes, then a refractive error is likely.
- Assess near vision using specific near vision acuity chart, or assess ability to read newsprint or very crudely the ability to count fingers or detect motion.
- Assess colour vision using Ishihara plates or test for red desaturation (a good indicator of optic nerve dysfunction).

**Assess visual fields**
- Use confrontation testing to detect gross defects (e.g. homonymous hemianopia – loss of half the visual field). Confrontation testing compares the examiner’s visual field with the patient’s, and may yield vital information that is often missed.
- Assessment of more discrete visual field loss (e.g. from glaucoma) requires formal perimetry.

**Examine the adnexa (attachments or structural components of the eye)**
- Examine the eyebrows and eyelids. Look for ptosis (drooping), infection, congestion, hordeolum, warts, Molluscum contagiosum.
  - Evert the eyelid to detect all foreign bodies.

**Examine the conjunctiva**
- Look for discharge, swelling, or congestion.

**Examine the cornea**
- Look for haziness, ulcers (herpetic or bacterial), and inflammation.
  - Test for sensory loss with a wisp of cotton wool.
  - The naked eye may not detect corneal defects due to ulcerations or abrasions. If there is trauma or a foreign body sensation in the eye, do fluorescein staining as follows:
    ◊ moisten a fluorescein-impregnated strip with a drop of saline or artificial tears.
    ◊ touch the strip to the inside of the lower lid.
    ◊ illuminate the cornea with an ophthalmoscope with a blue filter if available (if not available, a strong white light may also reveal defects).
    ◊ look for epithelial defects that stain bright green.

**Examine both pupils**
- Are they equal in size?
  - Examine their reactivity to light. Shine a light alternately from one eye to the other.
    ◊ A normal response is equal constriction of both pupils, regardless of which eye the light is directed at. This indicates an intact direct and consensual pupillary light reflex.
An abnormal response, or relative afferent pupillary defect (RAPD), will show that light directed in the affected eye will cause only mild constriction of both pupils (due to decreased response to light from the afferent defect), while light in the unaffected eye will cause a normal constriction of both pupils due to an intact afferent path and an intact consensual pupillary reflex. Thus, light shone in the affected eye will produce less pupillary constriction than light shone in the unaffected eye.

- **Examine the lens**
  - Look for any opacity (mature cataracts may be visible with torch examination.

- **Perform fundoscopy to visualize the fundus, optic disc and vessels**
  - Fundoscopy is an examination of the posterior segment of the eye and is done using a direct ophthalmoscope.
  - It should take place in a suitably darkened room.
  - The patient's right eye should be examined with the examiner's right eye, and vice versa.
  - The patient is asked to focus on an object in the distance, and the examiner's head is kept vertical to permit this.
  - This approach with the patient fixing on a distant straight-ahead target allows you to visualize the optic disc very easily.
  - Turn to the +10DS lens in the lens wheel and observe the eye from 10 cm. Slowly move closer to the patient and at the same time gradually reduce the power of the lens in the wheel and focus on the crystalline lens, the vitreous, and finally the fundus. The power of lens necessary to focus on the fundus will depend on any uncorrected refractive error in the patient or in the observer.
  - Once a blood vessel on the fundus has been located, move along it and locate the optic disc. While examining the disc, you will need to consider its colour, its margins, and the cup if there is one. Also, note the presence of optic atrophy and papilloedema.
  - Retinal blood vessels should be examined in each quadrant after locating the disc. The veins are relatively large and dark red, while the arteries are relatively thin and brilliant red.
  - Next, examine the retinal background, which is the normal retina between the blood vessels and other identifiable structures.
  - To examine the macula and the fovea, instruct the patient to look into the ophthalmoscope light:
    - this step will cause the pupil to constrict, dazzle the patient, and you will notice some troublesome corneal reflections;
    - these factors make the macula a difficult area to visualize. It may be useful to use a smaller aperture beam and slightly reduce the light intensity;
    - the normal macula is the area between the superior and inferior temporal blood vessel arcades, and its centre is the fovea.

- **Assess ocular movements**
  - Ask the patient follow your finger with their eyes without moving the head; test the six cardinal points of gaze in an H pattern.
  - Look for failure of movement and for nystagmus (pause to check it during upward and lateral gaze).

- **Assess ocular pressure**
  - If suspect glaucoma, press lightly on the globe with the fingers. Does the eye feel hard?
  - If handheld tonometer is available, measure intraocular pressure.

- Additional examination usually performed by specialized eye-care professionals.
  - Slit lamp examination.

Classify the problem as red eye (with or without pain) or visual loss and consult the relevant DDx table below. For HIV-infected patients, see also these specific sections.
10.11.2 Approach to red eye

Red eye is commonly a sign of treatable conditions such as conjunctivitis. It is important to exclude more serious underlying conditions such as acute congestive glaucoma or iridocyclitis. Problems relating to the posterior chamber almost never present with a red eye.

Ask whether there is pain with the red eye.

### DDx: Red eye

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red eye with no pain</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious conjunctivitis</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>bacterial</strong></td>
<td>Mucopurulent discharge with matting of eyelids</td>
</tr>
<tr>
<td>• <strong>viral</strong></td>
<td>Conjunction congestion</td>
</tr>
<tr>
<td></td>
<td>Lid oedema if viral</td>
</tr>
<tr>
<td></td>
<td>Itchy, burning with gritty feeling</td>
</tr>
<tr>
<td></td>
<td>Local outbreaks in the community</td>
</tr>
<tr>
<td><strong>COVID-19</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Leptospirosis</strong></td>
<td>History of conjunctival exposure to water contaminated with urine of infected animals</td>
</tr>
<tr>
<td><em>(see Section 8.1)</em></td>
<td>Red eyes (conjunctival suffusion) without purulent discharge involving both eyes – early phase of illness</td>
</tr>
<tr>
<td></td>
<td>Fever and myalgias</td>
</tr>
<tr>
<td><strong>Allergic conjunctivitis</strong></td>
<td>Bilateral</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
</tr>
<tr>
<td></td>
<td>Itchy</td>
</tr>
<tr>
<td></td>
<td>Watery or mucoid (stringy and ropy) discharge</td>
</tr>
<tr>
<td></td>
<td>Cobblestoning or raised visible bumps (papillary hypertrophia of the palpebral conjunctiva)</td>
</tr>
<tr>
<td></td>
<td>Conjunctival inflammation (chemosis) may occur</td>
</tr>
<tr>
<td></td>
<td>Multiple creases in lower lid</td>
</tr>
<tr>
<td></td>
<td>Seasonal</td>
</tr>
<tr>
<td></td>
<td>Improves on antihistamines</td>
</tr>
<tr>
<td><strong>Lyme disease</strong></td>
<td>Conjunctionitis in about 10% in early infection</td>
</tr>
<tr>
<td><em>(see Section 11.22)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Subconjunctival haemorrhage</strong></td>
<td>Bleeding beneath the conjunctiva</td>
</tr>
<tr>
<td></td>
<td>Painless, harmless</td>
</tr>
<tr>
<td></td>
<td>Associated with minor trauma, hypertension, increased venous pressure as in coughing, sneezing, vomiting, straining</td>
</tr>
</tbody>
</table>
| **Pinguecula or pterygium** | Triangular band of fibrosis next to the cornea is a pinguecula; if encroaching on the cornea, a pterygium  
Present for weeks but may become acutely inflamed  
Painless although may feel gritty or dry  
Might decrease visual acuity if advanced and encroaches on the central part of the cornea (astigmatism) |
|-----------------------------|--------------------------------------------------------------------------------------------------|
| **Red eye with pain**       | Burning or foreign body sensation  
Lack of tears or occasionally excessive tearing  
Common in children with HIV, Stevens Johnson syndrome, female hormonal diseases, other autoimmune diseases |
| **Keratoconjunctivitis sicca** | Severe eye pain  
Variable degree of decreased visual acuity (depending on location of ulcer) and photophobia  
Haziness or opacification of the cornea (with or without fluorescein uptake)  
Pupillary constriction (secondary to ciliary spasm and iritis)  
Presence of pus or white cells in anterior chamber (hypopyon) |
| **Corneal inflammation or infection (keratitis)** | Foreign body sensation  
History of welding work or extended sunlight exposure  
Pain  
Photophobia  
Tearing |
| **Ultraviolet keratoconjunctivitis** (welder's arc, carbon arc, sunlight) | History of splash or exposure to heat or chemicals  
Burns to eyelid or skin  
Singed eyelashes  
Flat thin haemorrhage or thicker collection of blood |
| **Thermal or chemical keratoconjunctivitis** | Intense pain localized to cornea after an injury  
Evidence of corneal abrasion with fluorescein stain  
Foreign body may be seen directly or on eyelid eversion |
| **Foreign body or corneal abrasion** | Round or oval sharply demarcated border with the base appearing ragged and gray  
Painful  
Blurred vision  
Blue/green mucopurulent discharge with fluorescence in UV light in favour of *P. aeruginosa*  
Herpetic ulcer: dendritic branches on fluorescein staining  
Varicella zoster virus (VZV) ulcer: loss of sensation with shingles on ophthalmic branch of trigeminal nerve typical for VZV  
Hypopyon (sterile pus in lower internal part of cornea) |
| **Acute angle closure glaucoma** (or closed angle) | Sudden loss of vision  
Severe headache and eye pain  
Nausea and vomiting  
Halos around light  
Pupils mid-dilated, vertically oval non-reactive to light (sluggish)  
Very high intraocular pressure >30 mmHg – eye will feel hard on digital pressure |
| **Acute anterior uveitis** (iritis or iridocyclitis) | Acute onset  
Unilateral, painful red eye, blurred vision, direct and consensual photophobia, tearing  
Ciliary (not only conjunctival) injection  
360 degree perilimbal flush |
| **Acute posterior uveitis** (choroiditis or chorioretinitis) | Blurred vision with floaters  
Occasional pain  
Photophobia. |
Manage red eye with no pain

**Acute viral conjunctivitis**
Acute viral conjunctivitis is commonly caused by adenovirus. It is highly contagious and occurs in small epidemics in households, schools and the community.

**Key clinical features**
- Acute onset with painless red eye – little or no photophobia, no visual changes.
- Discharge, matted eyelashes, redness and inflammation (chemosis).
- Monitor for secondary bacterial infection – which is common.
- Suspect herpetic conjunctivitis if there are skin findings, or if there is skin involvement (clusters of vesicles on an erythematous base on the face, eyelids. and mucous membranes typical of herpes simplex virus; shingles along ophthalmic nerve dermatome suggestive of herpes zoster virus). Follow management specific for these conditions (see below and 11.39).
- Clinical diagnosis and culture or smears are not needed.

**Treatment**
- If suspect bacterial coinfection, use gentamicin\(^2\) or chloramphenicol eye drops or ointment.
- Use cold compresses several times a day.
- Give tears substitute such as carboxymethyl cellulose 0.5% drops or 1% gel-tears naturale.

**Prevention**
- Avoid contact between fingers and eyes.
- Meticulous hand washing.
- Separate face and hand towels at home for the affected person.

**Bacterial conjunctivitis**

**Key clinical features**
- Mucopurulent discharge present.
- May occur as a primary infection or is secondary to a viral infection.
- Gram stain of the conjunctival smear will help to identify possible organism.
- Hyper-acute gonococcal infection – sudden onset of extreme inflammation and purulent discharge from the eyes; there may be a history of urethral discharge or other signs of a sexually transmitted infection. This is an ophthalmic emergency. Refer urgently to an ophthalmology unit in case of gonococcal infection as it can rapidly infect the cornea and lead to a severe keratitis or perforation of the cornea. Initiate treatment below in the meantime.
- Trachoma or chlamydial conjunctivitis in endemic areas – usually presents with a chronic red eye with stringy discharge.

**Treatment**
- Conjunctivitis due to *Neisseria gonorrhoeae* requires systemic antibiotics and urgent referral.
  - ceftriaxone 1 gram IM; OR
  - spectinomycin 2 g by deep IM; OR
  - ciprofloxacin 500 mg orally.
- If suspect *Chlamydia trachomatis*, follow instructions in Section 10.11.5.
- If neither of these, for other bacterial conjunctivitis give topical antibiotic drops such as gentamicin eye drops 4–6 times daily.\(^2\)

**Prevention**
When conjunctivitis is associated with an STI, treat sexual partners to minimize recurrence and spread of disease.

---
\(^2\) Gentamicin eye drops are on the WHO EML. An alternative is chloramphenicol eye drops.
**Allergic conjunctivitis**

**Key clinical features**
- Itching is a cardinal sign.
- Watery with minimal discharge.
- Congestion and chemosis (swelling) with papillary reaction.
- May be acute and periodic in seasonal allergic conjunctivitis.
- Mild and chronic in atopic or perennial allergic conjunctivitis.

**Treatment**
- Allergen avoidance.
- Topical sodium cromoglycate drops during the allergy season is the mainstay of treatment and is safe even if given for long periods.

---

**Keratoconjunctivitis sicca**

This is also called dry eye syndrome.

**Key clinical features**
- Burning, foreign body sensation, lack of tears.
- Occasionally excessive tears reacting to irritation.
- Common in premenopausal and menopausal women and collagen vascular diseases.
- In PLHIV, may be a consequence of previous Stevens Johnson syndrome. Common in HIV-positive children.

**Treatment**
- Give tear substitute such as carboxymethyl cellulose 0.5% drops or 1% gel-tears naturale.
- Treat secondary bacterial infection, if present.

---

**Manage red eye with pain**

**Acute angle-closure glaucoma**

This is due to increased intraocular pressure that leads to impairment of the functioning of the optic nerve and causes visual field loss, ultimately leading to blindness. It is important to recognize and refer urgently for treatment to prevent visual loss.

**Key clinical features**
- More common among Asians.
- Usually bilateral disease, but acute onset often unilateral.
- Sudden loss of vision with halos around lights – often worse in the evenings.
- Associated with severe headache, vomiting, eye pain.
- Stage of primary angle closure glaucoma.
- Evidence of ciliary congestion, lid oedema, hazy cornea, shallow anterior chamber.
- A mid-dilated pupil (4 to 6 mm) that reacts poorly to light.
- Intraocular pressure is very high – eye feels stony hard on digital pressure.
- Fundoscopy – "cupping" of the optic nerve.

**Treatment**
- **Urgent referral** to specialist facility for further treatment.
- Start the following medication until the patient reaches referral centre:
  - pilocarpine 1 drop (2% solution) every 10 minutes for 30–60 minutes, then 1 drop every 1–3 hours until intraocular pressure subsides, then 1 drop 4 times daily; PLUS
  - acetazolamide 250 mg orally stat, or IV if the patient is vomiting, then continue oral acetazolamide 500–750 mg per day.

**Corneal ulcer or infective keratitis**
- Common cause of painful loss of vision with red eye.
- Very often follows trauma that could be trivial.
• Offending organisms include bacteria, fungi, virus (such as herpes or facilitated by HIV immunosuppression).

Treatment
• **Urgent referral to specialist**
• **Do not** use steroids for a corneal ulcer as the infection may spread resulting in corneal perforation.
• Start empirical broad spectrum antibiotic drops in all patients – chloramphenicol or gentamicin eye drops 6 times daily.

**Bacterial superinfection of the cornea secondary to trauma**
• Diagnosis can be made by scraping margins of the ulcer and plating for bacterial and fungal cultures. This should be done by a trained ophthalmologist, using a microscope or loupe. Refer for specialist assistance.
• *P. aeruginosa* infection causes a ground glass appearance of the cornea, and may lead to early perforation of the cornea.
• Staphylococcal infections are less dramatic, but may cause loss of vision.

**Treatment**
• **Urgent referral** to specialist facility.
• Initiate empirical antibiotic drops – chloramphenicol or gentamicin hourly or any other available broad spectrum antibiotic drop until the patient reaches the referral centre.
• Give supportive treatment with a mydriatic (atropine eye drops) and *timolol* to reduce intraocular pressure.
• If there is not copious discharge, give an eye patch to rest the eye.

**Fungal ulcers**
• Fungal ulcers are commonly caused by filamentous fungi or yeasts (*candida*).
• May occur in those who work in rural settings or those engaged in agricultural activity and in PLHIV.

**Key clinical features**
• Ulcers may follow trivial trauma.
• Symptoms may be mild even with large ulcers.
• Ulcers are dry, elevated, with feathery margins.

**Treatment**
• **Urgent referral** to tertiary level facility.
• Treat as in bacterial ulcers.

**Herpetic ulcers**
Herpes simplex virus (HSV) is a major cause of blindness worldwide from corneal scarring and opacity after cornea infection, inflammation (keratitis), and ulceration.

**Key clinical features**
• Painful eye with blurred vision and discharge.
• Dendritic ulcers are seen on fluorescein staining of the cornea.
• May coalesce to form geographic ulcers (ameboid shape, often with dendritic extensions at the edges).
• Are usually unilateral.
• Loss of corneal sensation if tested with wisp of cotton wool.

**Treatment**
• **Refer urgently** to tertiary level facility.
• Treat with topical aciclovir ointment and **do not use steroids**.
• If topical aciclovir ointment is not available, give oral aciclovir, 400 mg 5 times daily.
• Administer supportive treatment with topical atropine.
10.11.3 Acute visual loss

- Acute loss of vision is usually secondary to posterior segment diseases.
- All require urgent referral to a specialist facility.
- These conditions may or may not be associated with pain.
- They are usually not associated with “red eye”.

DDx: Acute visual loss

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central retinal artery occlusion</td>
<td>Sudden loss of vision</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
</tr>
<tr>
<td></td>
<td>Fundoscopy – cherry red spot at fovea</td>
</tr>
<tr>
<td>Central retinal vein occlusion</td>
<td>Visual loss less dramatic – painless loss of vision</td>
</tr>
<tr>
<td></td>
<td>Older age</td>
</tr>
<tr>
<td></td>
<td>Known hypertensive, sickle-cell disease or blood dyscrasias, or patient with high intraocular pressure</td>
</tr>
<tr>
<td></td>
<td>Fundoscopy – retinal haemorrhages</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>Photophobia, flashing lights, floaters</td>
</tr>
<tr>
<td></td>
<td>Recent blunt trauma or known sickle-cell disease</td>
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<tr>
<td></td>
<td>High myopia, aphakia</td>
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<tr>
<td></td>
<td>Poor or partial red reflex</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>Visual loss mild to severe</td>
</tr>
<tr>
<td></td>
<td>Following diabetic retinopathy or retinal vein occlusion</td>
</tr>
<tr>
<td>CMV retinitis (see Section 11.10)</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Signs of meningitis or pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Fundoscopy – haemorrhagic retinal necrosis (“pizza” pie appearance)</td>
</tr>
<tr>
<td></td>
<td>Very low CD4 (&lt;100)</td>
</tr>
<tr>
<td></td>
<td>Visual loss may be slower in onset in early CMV disease and may not be noticed by the patients until advanced</td>
</tr>
<tr>
<td>Ocular toxoplasmosis (see Section 11.36)</td>
<td>Unifocal in HIV-negative, multifocal in HIV-positive</td>
</tr>
<tr>
<td></td>
<td>Blurred or hazy vision with floaters – erosions may look like headlights in the fog through the vitreous haze</td>
</tr>
<tr>
<td></td>
<td>Occurs with vitritis</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Females : Males = 2 : 1</td>
</tr>
<tr>
<td></td>
<td>Unilateral rapid visual loss</td>
</tr>
<tr>
<td></td>
<td>Retro-orbital pain with eye movement</td>
</tr>
<tr>
<td></td>
<td>Associated with viral illness, multiple sclerosis, systemic lupus erythematosis (SLE), post-menigitis – TB or cryptococcal</td>
</tr>
</tbody>
</table>

Corneal erosions

Key clinical features

- Areas of epithelial loss without infiltration.
- Usually follows trivial trauma – may be a history of contact lens use or even fingernail trauma.
- Very painful.
- If history of trauma is present, rule out penetrating ocular trauma.

Treatment

- Evert eyelids to look for foreign bodies.
- Treat with antibiotic ointment (tetracycline) and rest with an eye patch.
- Refer to specialist care if there is non-healing or delayed healing, or recurrent erosions.
- Never use traditional medicines.
### Acute congestive glaucoma
- Sudden loss of vision
- Severe headache and eye pain
- Nausea and vomiting
- Halos around light
- Pupils mid-dilated, vertically oval non-reactive to light (sluggish)
- Very high intraocular pressure >30 mmHg or eye feels hard on digital pressure

### Endophthalmitis
- Sudden painful visual loss following intraocular surgery or penetrating trauma or corneal ulcer
- Red eye
- Pus in the anterior chamber (hypopyon)
- Inflammation of all inner layers of the eye.

### 10.11.4 Progressive visual loss
- Painless gradual loss of vision may be a result of various causes.
- Diseases of the anterior chamber are usually amenable to treatment, while diseases of the posterior segment require urgent referral.

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cataract</strong></td>
<td>Old age, history of trauma or as part of a systemic condition</td>
</tr>
<tr>
<td></td>
<td>May be unilateral or bilateral</td>
</tr>
<tr>
<td></td>
<td>Opacities seen</td>
</tr>
<tr>
<td></td>
<td>Fundoscopy – unable to see the fundus; red reflex obscured</td>
</tr>
<tr>
<td><strong>Refractive errors</strong></td>
<td>Common cause of visual loss in children</td>
</tr>
<tr>
<td></td>
<td>Improvement of vision with pinhole technique confirms refractive error</td>
</tr>
<tr>
<td><strong>Corneal dystrophies</strong></td>
<td>Painless loss of vision</td>
</tr>
<tr>
<td><strong>Chronic open angle glaucoma</strong></td>
<td>Late-stage visual loss</td>
</tr>
<tr>
<td></td>
<td>Cupping of optic disc on routine examination</td>
</tr>
<tr>
<td></td>
<td>Intraocular pressure may be raised or normal</td>
</tr>
<tr>
<td></td>
<td>Characteristic visual field changes on manual or perimetry are diagnostic</td>
</tr>
<tr>
<td><strong>Hereditary macular degeneration</strong></td>
<td>Painless central loss of vision</td>
</tr>
<tr>
<td></td>
<td>Visual acuity decreased</td>
</tr>
<tr>
<td><strong>Proliferative retinopathy</strong></td>
<td>Longstanding DM poorly controlled or known sickle-cell disease</td>
</tr>
<tr>
<td>e.g. diabetes mellitus, sickle-cell disease</td>
<td>Other risk factors: hypertensive, nephropathy, pregnancy</td>
</tr>
<tr>
<td></td>
<td>Fundoscopy: presence of microaneurysms, hard exudates, retinal oedema, proliferative retinopathy.</td>
</tr>
</tbody>
</table>

### Cataract
**Key clinical features**
- Opacification of the lens with decreased vision.
- Usually due to advancing age, but may also occur in younger population due to trauma or systemic disease, or may be present at birth or early years.
- Clinically reduced clarity of lens, obscuring the view of the retina.

**Treatment**
- Referral to specialist for surgical extraction of the lens with intraocular lens implantation.

### Primary open-angle glaucoma
**Key clinical features**
- Important cause for irreversible visual loss.
- Early diagnosis of disease is important to prevent visual loss.
- Visual loss in late stages.
**Eye problems**

10.11.5 Geographically confined eye diseases – trachoma

<table>
<thead>
<tr>
<th>Condition</th>
<th>Geographical area</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachoma</td>
<td>Occurs globally. Specifically in: <strong>South-East Asia</strong>: India, Myanmar, Nepal <strong>Africa</strong>: Algeria, Burkina Faso, Chad, Djibouti, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal, Togo, United Republic of Tanzania, Zambia <strong>Eastern Mediterranean</strong>: Egypt, Morocco, Oman, Pakistan, Sudan, South Sudan, Yemen <strong>Western Pacific</strong>: Australia, Cambodia, China, Viet Nam. <strong>Americas</strong>: Brazil, Guatemala, Mexico.</td>
<td>Easily visible corneal opacity over the pupil Pupil margin blurred Substantial prevalence in the community – with severe visual loss and potentially disabling trachomatous lesions such as trichiasis and entropion (see trachoma grading system in text below).</td>
</tr>
</tbody>
</table>

**Trachoma**

Trachoma is the result of infection of the eye with *Chlamydia trachomatis*. Infection spreads from person to person, and is frequently passed from child to child and from child to mother, especially where there are shortages of water, many flies, and crowded living conditions.

**Treatment**
- Referral to specialist facility for detailed evaluation and treatment.
- Start pilocarpine to lower intraocular pressure.

**Refractive errors**
- A common cause of gradual progressive reduction of vision.
- Improvement in vision with pinhole or spectacles likely indicates refractive error.
- Regular and repeated screening, particularly in children and adolescents, to allow timely detection and treatment.
- Short-sighted vision or myopia is the difficulty to see distant objects, while near objects are clear.
- Far-sighted vision (hyperopia and presbyopia) is the difficulty to see near objects. In presbyopia, this is due to loss of accommodation, often after 40 years of age.
- Uncorrected refractive errors are a common cause of headache.

**Treatment**
- Corrective lenses.
- Repeated examinations throughout growth to prevent poor vision, if left uncorrected.

**Proliferative retinopathy**
- This is a disease of the pre-capillary arteriole and venules of the retina.
- In diabetics, increasing duration of diabetes is the most important risk factor. Poor glycaemic control, concomitant HPT, nephropathy, and pregnancy are also significant risk factors.
- In sickle-cell disease, a history of multiple crises will increase the likelihood of retinopathy.

**Treatment**
- Stringent glycaemic control in diabetics.
- Regular eye checks – annually if possible.
- *Referral to specialist centre for laser treatment if available; retinal photocoagulation can be vision-saving.*
Infection often begins during childhood then becomes chronic. If left untreated, irreversible blindness typically occurs between 30 and 40 years of age, mainly in females.

Key clinical features
- Eversion of the eyelid shows red, swollen conjunctiva with follicles (whitish dots 0.2–2 mm) or papillae (visible red dots), scars, which can ultimately cause the in-turning of the upper eyelid (entropion trichiasis).
- Damage to the cornea resulting in corneal opacities.
- Other signs: limbal follicles (follicles at the upper edge of the cornea), herbert's pits (small round clear windows at the upper edge of the cornea), and pannus (gradual opacification of the upper part of the cornea).

### Simplified grading of trachoma disease

- **Trachomatous inflammation (TF):** 5 or more follicles (at least 0.5 mm in diameter) on the upper tarsal conjunctiva
- **Trachomatous inflammation intense (TI):** presents as inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels
- **Trachomatous scarring (TS):** scarring (white fibrosis) of the tarsal conjunctiva
- **Trachomatous trichiasis (TT):** at least one eyelash runs on the eyeball
- **Corneal opacity (CO):** central corneal opacity that is so dense that at least one of the pupil margins is blurred.

### Treatment
The WHO SAFE strategy to eliminate trachoma and prevent blindness includes:
- **Surgery for trichiasis – corrective lid surgery**
- **Antibiotics to treat Chlamydia trachomatis infection in diagnosed patients**
- **Facial cleanliness and promotion of hygiene**
- **Environmental improvement to reduce transmission of Chlamydia trachomatis from one person to another.**
- The mainstay of treatment is tetracycline ointment. Apply 1% ointment directly to both eyes twice daily for 6 weeks
- Give oral azithromycin, 20 mg/kg up to 1 gm once a year as a family treatment or community intervention.
  Refer patients with corneal opacity for specialist care.

### 10.11.6 Eye problems in patients with HIV infection

Ocular manifestations of HIV infection are very common and varied. Simple infections and common eye diseases must be recognized, treated and differentiated from sight-threatening problems that may require referral or specialist management.

These conditions are not specific to patients with HIV, but occur more commonly, with greater severity, and often with atypical features

### Anterior segment and adnexal eye problems in patients with HIV infection

**DDx:** Anterior segment and adnexal eye problems in patients with HIV infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molluscum</strong></td>
<td>Pearly white papules, central umbilication</td>
</tr>
</tbody>
</table>

---


### Eye problems

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molluscum contagiosum</strong></td>
<td>Multiple lesions. Unusually large in patients with HIV and do not resolve spontaneously.</td>
</tr>
<tr>
<td><strong>Papillomata</strong></td>
<td>Skin coloured – hyperpigmented papules or warty lesions. Rough surface, on lids or conjunctiva.</td>
</tr>
<tr>
<td><strong>Herpes zoster ophthalmicus</strong></td>
<td>Vesicular rash, dermalomal distribution – trigeminal nerve. Acute pain, can involve tip of nose (Hutchinson sign). Can cause conjunctivitis, scleritis, keratitis, uveitis, glaucoma, nerve palsy.</td>
</tr>
<tr>
<td><strong>Conjunctival squamous cell carcinoma</strong></td>
<td>Recent papular lesion with rapid increase in size, irregular surface and margins. Grey/white rough foamy fungating appearance in interpalpebral zone. Differs from pterygium with smooth shiny epithelium. Tends to be very aggressive with recurrence if only simple excision used.</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Red purplish cauliflower-like lesion on conjunctiva or eyelid. Can be flat or nodular. Distinguish from subconjunctival haemorrhage.</td>
</tr>
<tr>
<td><strong>Keratoconjunctivitis sicca</strong></td>
<td>Burning, dry, foreign body sensation. Cornea lustreless. Typical stain with Rose Bengal dye.</td>
</tr>
</tbody>
</table>

*Refer to a specialist if molluscum contagiosum, papillomata (warts), conjunctival tumours, or Kaposi sarcoma.*

**Herpes zoster ophthalmicus** – see Section 11.39

**Key clinical features**
- Unilateral vesicles and blisters involving the eye.
- More severe cases have corneal involvement.
- May have an atypical presentation and involve both eyes.
- May cause conjunctivitis, corneal lesions, keratitis, scleritis, uveitis, papillitis, and, in rare instances, retinal necrosis.

**Treatment** (all of the following as appropriate)
- Oral aciclovir 800 mg 5 times daily for 7 days.
- Aciclovir 3% eye ointment applied into the eye every four hours.
- Antibiotic eye ointment (chloramphenicol).
- Antibiotics for secondary skin infection if present.
- Analgesia – paracetamol or stronger analgesics if necessary (see Section 20).
- Amitryptiline 25–50 mg before bed for neuropathic pain.
- Assess for complicated disease and refer.

**Posterior segment eye problems in patients with HIV infection**
- Most HIV-associated posterior segment diseases of the eye are associated with visual loss.
- Loss of vision may be acute in onset and rapidly progressive.
- Early recognition and treatment will help in preventing irreversible loss of vision.
- All HIV-positive patients with any visual complaints require urgent referral to a specialist facility.

**DDx: Posterior segment eye problems in patients with HIV infection**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV retinitis</td>
<td>Painless loss of vision, large areas of retinal necrosis yellowish white, with areas of haemorrhage or necrosis (&quot;pizza pie&quot; appearance). No vitreous haze – fundi are clearly seen. Vascular sheathing – “frosted branch” appearance. Examine the other eye if this is diagnosed in one eye. CD4 &lt;100 – occurs less commonly if &gt;100 (look for other cause of retinopathy).</td>
</tr>
</tbody>
</table>

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Eye problems

10. Acute and subacute by symptom: SEARO 2021
### Optic disc swelling
- If bilateral with normal vision and reflex, then it is papilloedema
- If unilateral with decreased vision, then it is optic nerve disease

### Immune recovery uveitis
- Follows CMV of the eye most commonly, but also associated with other retinal opportunistic infections
- Decreased vision of gradual onset with floaters
- Recent initiation of ART
- Can result in cataract, epiretinal membrane, retinal neovascularisation that may threaten sight
- Poor prognosis – focus on protecting the sight of the other eye

### Chorioretinitis from toxoplasmosis (see Section 11.36)
- Posterior uveitis, may be focal, or diffuse mimicking CMV
- Serology for anti-CMV IgM if available to exclude CMV.

### 10.11.7 Neuro-ophthalmic involvement from mass lesions, TB, or cryptococcal meningitis
- TB and cryptococcal meningitis in HIV-infected patients can result in papilloedema, papillitis, or ocular nerve palsies (see Section 10.7) or may present with other neurological presentations.
- As acute or progressive loss of vision can occur with TB and cryptococcal meningitis, examine the eyes routinely after diagnosis.
- Papilloedema is not associated with early visual loss, but if long-standing, may cause progressive visual loss.
- Papillitis is associated with acute visual loss.
10. Acute and subacute by symptom: SEARO 2021
Most joint pain may be a result of chronic conditions of varying duration. However, a substantial number of patients with joint problems require immediate and ongoing care. Prompt treatment can help limit symptoms, prevent disability, and improve outcomes. Follow a stepwise approach in the evaluation and management of painful joints.

Both laboratory studies and diagnostic imaging can help to evaluate the joint and the joint pain. At the initial evaluation, and at each subsequent re-evaluation, there should be efforts to identify underlying conditions that may need disease-specific management.

### 10.12.1 Clinical approach to a patient with painful joints

**Step 1:** Use Quick Check
To identify severe conditions that require immediate medical or surgical care. Generally, an acute onset of joint pain with a prior trauma or appearance of warmth and swelling could indicate conditions such as dislocation, fracture, or a septic joint that requires more immediate attention. Other indicators of potential musculoskeletal emergency include constitutional symptoms (fever), numbness, or weakness.

**Step 2:** Take a history and examine the patient

**Step 3:** Assess the patient’s HIV status

**Step 4:** Work through the differential diagnosis table

**Step 5:** Perform appropriate investigations

**Step 6:** Initiate treatment and monitor the patient’s response

**History**

- Is there any history of trauma or injury?
- location of the pain:
  - one or multiple joints
  - true joint pain, pain from nearby bone, ligament, tendon, bursa, muscle, or referred pain.
- character of the pain:
  - quality – burning, sharp, constant, intermittent
  - factors which worsen or improve pain
  - diurnal rhythm – worse in the morning and eases at night, or worsens at the end of the day, unrelenting, or nocturnal.
- onset and progression, joints that were affected first
- symmetry of joint involvement
- stiffness
- swelling
- limitation of motion

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- constitutional symptoms, such as weight loss, unexplained fevers, chills, cough, night sweats
- associated problems:
  - weakness or numbness of affected limb
  - gastrointestinal, genitourinary or eye problems.
- family history of joint disease and rheumatic conditions
- history of immunosuppression – HIV, immunosuppressive medicines
- drug history – particularly diuretics
- history of tick bite.

### Examination

#### Specific examination

Assess for:
- erythema (redness) or ecchymosis
- warmth
- evidence of any infective focus – e.g. a septic wound, an ulcer
- crepitus, laxity, gross deformity, tendon, or muscle dysfunction (tested by resisted function)
- joint swelling – hypertrophy or a joint effusion
- sensory changes indicate possible neurological or vascular problems
- range of motion (ROM)
- ability to bear weight
- contractures, bone deformities
- weakness
- pain that is out of proportion to the injury
- limping, if lower extremities are involved
- palpable, bony hypertrophy.

#### General examination

- extra-articular features of joint disease
  - cutaneous nodules
  - cutaneous vasculitis lesions.
- lymphadenopathy
- oedema
- ocular inflammation
- urethritis
- tenosynovitis (tendon sheath effusions)
- bursitis (swollen bursa)
- diarrhoea
- orogenital ulceration.

⚠️ **Assess the patient’s HIV status**

HIV can cause either monoarthritis or polyarthritis at any CD4 count.
### 10.12.2 Diagnosis of single and multiple painful joints

These tables are divided into conditions affecting single joints, and those affecting multiple joints.

**DDx: Single painful joint – patient presenting with monoarthritis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| **Trauma** | History of joint injury or trauma  
            Pain, swelling, ecchymosis  
            Bleeding into joint may be present  
            Decreased range of motion |
| **Bursitis** | Pain with motion and localized tenderness  
                History of acute trauma or repetitive injury to the area  
                Swelling over bursa  
                Often involves knees or elbows  
                If fever or recent bacterial infection, may be septic bursitis |
| **Septic arthritis**  
(usually *Staphylococcus aureus* or streptococcal species) | History of diabetes, IV drug use, sickle-cell disease  
                        Acute onset  
                        Large joint (knee most common, or also hip, shoulder, wrist, or ankle)  
                        May localize to joints with pre-existing arthritis or prior trauma  
                        Systemically ill with fever  
                        Hot tender swollen joint with decreased mobility  
                        **More than one joint may be involved**  
                        High WBC and ESR  
                        Joint fluid WBC >50 000 (>90% neutrophils) |
| **Gonococcal arthritis**  
(see Section 11.15) | Purulent arthritis, usually knees, wrists, or ankles (see septic arthritis)  
                        May have preceding skin lesions: papules and pustules, polyarthralgia, and tenosynovitis  
                        Sexually active, 25% have GU symptoms  
                        Synovial fluid WBC >50 000 (>90% neutrophils) |
| **Gout** | On diuretics  
           Dietary and alcohol overindulgence  
           Previous similar attacks  
           Severe joint pain  
           Redness, hot, tender and swollen  
           Typically affects the base of the big toe  
           Gouty tophi |
| **Rheumatoid arthritis** | Autoimmune  
                       Early morning stiffness lasting over 1 hour  
                       Early stages may present as monoarthritis  
                       Later symmetrical polyarthritis: often hand and wrist involvement  
                       Fixed deformities develop  
                       Extra-articular manifestations: fever, anorexia, malaise, weight loss  
                       Rheumatoid nodules: subcutaneous, usually extensor surfaces  
                       Elevated ESR, CRP, platelet count; low Hb; *positive rheumatoid factor* |
| **Osteoarthritis**  
(degenerative joint disease) | Gradual onset  
                        Usual age of onset over 40  
                        Pain on weight-bearing or activity that is eased by rest  
                        Stiffness  
                        Crepitus  
                        Bony enlargement  
                        Tenderness to palpation  
                        Decreased range of motion  
                        Synovial fluid – clear, WBC <2000/mm³, normal viscosity |
| **Tuberculous arthritis** | Gradual onset joint swelling  
                         Mildly inflamed, presentation may vary based on site  
                         Low-grade fever  
                         Night sweats  
                         Synovial fluid: increased protein, increased WBC – predominantly lymphocytes  
                         Vertebral TB: X-ray of spine may show vertebral collapse |
**DDx: Multiple painful joints**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
</table>
| **Gonococcal arthritis**  
see Section 11.15 | Sexually active  
Genitourinary symptoms  
Systemically ill  
Migratory polyarthralgia or polyarthritis (often asymmetric), tenosynovitis (asymmetric) involving fingers, hands, or wrists  
Skin lesions – papules and pustules  
Septic arthritis may follow dermatitis if untreated |
| **Spondyloarthropathies**  
(ankylosing spondylitis, psoriatic arthritis) | Family history  
Back pain, uveitis, urethritis, gastrointestinal symptoms, and rashes  
Large joints of lower extremities |
| **Rheumatoid arthritis** | Autoimmune  
Early morning stiffness lasting over 1 hour  
Symmetrical polyarthritis: often hand and wrist involvement  
Fixed deformities develop  
Rheumatoid nodules  
High ESR, CRP, platelet count; low Hb; *positive rheumatoid factor* |
| **Osteoarthritis**  
(degenerative joint disease) | Gradual onset  
Usual age of onset over 40  
Pain on weight-bearing or activity that is eased by rest  
Stiffness  
Crepitus  
Bony enlargement  
Tenderness to palpation  
Decreased range of motion  
Fixed deformities  
Synovial fluid: clear, WBC <2000/mm³, normal viscosity |
| **Chikungunya** | Viral illness spread by infected mosquito  
Severe joint pains  
Associated fever and rash  
Occurs in outbreaks or rarely in sporadic cases  
Diagnosed by serum antibody titres or PCR |
| **Lyme disease**  
see Section 11.22 | Late Lyme disease is associated with intermittent or persistent arthritis involving one or a few large joints, especially the knee  
May develop months to a few years after the initial infection  
Arthritis may be initial manifestation of Lyme disease |
| **HIV-associated arthritis** | Usually of limited duration, <6 weeks  
Mono or polyarthritis  
Occurs predominantly in lower extremities  
Can occur at any CD4 count. |

**Perform investigations if required**

**Consider investigations** according to the suspected underlying cause:
- erythrocyte sedimentation rate (ESR)
- *C-reactive protein* (CRP)
- *rheumatoid factor*
- *anti-nuclear antibody*
- *uric acid.*

Arthrocentesis is urgently indicated when there is a warm, red joint with effusion, especially when there is no history of trauma. The aspirated synovial fluid should be sent for cell count, chemistry, microscopy, Gram stain, culture, and crystals.
Table: Characteristics of synovial fluid by diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Appearance</th>
<th>WBC/mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Turbid</td>
<td>5000–50 000</td>
</tr>
<tr>
<td>Non-inflammatory</td>
<td>Clear</td>
<td>&lt;400</td>
</tr>
<tr>
<td>Gout</td>
<td>Turbid</td>
<td>2000–5000</td>
</tr>
<tr>
<td>Pseudo-gout</td>
<td>Turbid</td>
<td>5000–50 000</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>Purulent/turbid</td>
<td>&gt;50 000</td>
</tr>
</tbody>
</table>

Diagnostic imaging
- Plain X-rays remain the choice for the diagnosis of most joint abnormalities.
- *Computed tomography (CT)* and *magnetic resonance imaging (MRI)* may be beneficial when the diagnosis is not clear.

Septic arthritis
Common presentations and features:
- most dangerous cause of acute arthritis; knee the most common site
- usually of bacterial origin, but can be viral, fungal, or mycobacterial
- resulting from bacteremia, soft tissue infection, bite
- much more likely in patients with pre-existing joint disease, especially rheumatoid arthritis
- common organisms implicated are *Staphylococcus aureus* and streptococci
- *N. gonorrhoea* in young adults
- *E. coli* in the elderly, drug users, and very ill patients
- *S. aureus*, *M. tuberculosis*, *Salmonella* spp. and *Brucella* spp. – may cause septic spinal (vertebral) arthritis or osteomyelitis.

Diagnosis
- Commonly a single joint, associated fever
- elevated WBC, ESR, *CRP*
- synovial fluid examination: turbid or purulent, Gram stain or culture, cell count and differential.

Treatment
- Give pain control.
- Give IV antibiotics for 2–4 weeks, depending on the clinical response and host factors:
  - ceftiraxone 1–2 g once daily
  - If Gram-positive cocci are seen on Gram stain or culture grows *S. aureus*, may switch to cloxacillin 2 g every 6 hours.
  - In areas where MRSA is prevalent or diagnosis established, vancomycin 15 mg/kg every 12 hours, or cotrimoxazole (15–20 mg/kg per day of trimethoprim) every 8 hours.
  - If *N. gonorrhoea* is presumed or confirmed, see below.
- Aspiration and joint washout to dryness.

Crystal deposition disease (gout, pseudo-gout)
Common presentations and features:
- Can result from elevated levels of uric acid in the bloodstream where crystals of monosodium urate or uric acid are deposited on the articular cartilage of joints, tendons, and surrounding tissues.
- Usually present as transient painful attacks of acute monoarticular arthritis. Eventually lead to chronic gouty arthritis, and the deposition of masses of urates in joints and other sites, creating tophi.
Can be difficult to distinguish from septic arthritis.

Trauma, alcohol, and dietary overindulgence (meat and fish) increase the risk of gouty attacks.

Pseudo-gout – chondrocalcinosis is a very similar disease, caused by deposition of calcium pyrophosphate rather than uric acid.

**Diagnosis**

- The classic presentation of gout is **podagra** – sudden, unexplained swelling and pain at the base of the big toe on just one foot.
- Gouty tophi, particularly when not located in a joint.
- High uric acid levels support the diagnosis, but low or normal levels do not rule it out.
- Definitive diagnosis is by arthrocentesis and polarized light microscopy of synovial fluid for intracellular crystals; the latter is difficult to perform and requires a trained microscopist:
  - gout – negatively birefringent; needle shaped crystals
  - pseudo-gout – weakly positively birefringent, linear or rhomboid shaped crystals.
- If microscopy is unavailable, a combination of a history of episodic acute monoarticular arthritis, podagra, hyperuricaemia, and rapid relief with colchicine all strongly favour the diagnosis of gout.
- A combination of episodic acute arthritis (especially of the knee), chronic arthritis resembling osteoarthritis, and cartilage or joint capsule calcifications on X-ray favour the diagnosis of pseudo-gout.

**Treatment**

- **Gout**
  - acute: NSAIDs, colchicine; may use corticosteroids if renal insufficiency
  - chronic: urate-lowering agents, colchicine
  - prevention: decreased meat and fish intake, weight loss, avoidance of alcohol
- **Pseudo-gout**
  - acute: NSAIDs, colchicine; may use corticosteroids if renal insufficiency
  - chronic: NSAIDs, colchicine.

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**Osteoarthritis**

This is a degenerative disease and is hereditary, mechanical, developmental, or metabolic.

- It usually presents with joint pain, tenderness, stiffness, inflammation, creaking, and locking of joints.
- Pain worse on weight-bearing, causing restriction in mobility resulting in regional muscle atrophy and lax ligaments.
- Osteoarthritis is the most common form of arthritis and the leading cause of disability.

**Diagnosis**

- Usually a clinical diagnosis, but important to rule out other causes including rheumatoid arthritis and pseudo-gout.
- X-rays can be used to confirm, if diagnosis unclear. Typical findings include:
  - joint space narrowing
  - subchondral sclerosis and cysts
  - marginal osteophytes.

**Treatment**

- Pain control:
  - paracetamol
  - NSAIDs are better than paracetamol for pain, but have a higher risk of GI symptoms
  - opioids only for acute flares or when other treatments fail.
- physical therapy
• exercise
• weight loss.

**Rheumatoid arthritis**

Rheumatoid arthritis is a chronic inflammatory disease.

• It usually begins in peripheral joints and proceeds inward.
• It is more common in females.

**Diagnosis**

• Diagnostic criteria (any four for diagnosis – American College of Rheumatology):
  - morning stiffness of more than 1 hour most mornings for at least 6 weeks;
  - arthritis and soft-tissue swelling of more than 3 of 14 joints or groups of joints, present for at least 6 weeks;
  - arthritis of hand joints, present for at least 6 weeks;
  - symmetric arthritis, present for at least 6 weeks;
  - subcutaneous nodules over bony prominences or extensor surfaces;
  - *rheumatoid factor* at a level above the 95th percentile;
  - radiological changes suggestive of joint erosion on posterior or anterior hand or wrist X-rays.

• Systemic disease may involve:
  - constitutional symptoms including fatigue, low-grade fever, malaise, morning stiffness (loss of appetite and loss of weight are common systemic manifestations seen in patients with active rheumatoid arthritis).
  - Skin, hepatic, renal, heart and blood vessels, eyes, anaemia, neurological.

• Laboratory:
  - Rheumatoid factor is diagnostic, but a negative result does not exclude rheumatoid arthritis;
  - Other tests include *anti-nuclear factor*, ESR, CRP, FBC.

• X-rays:
  - no significant changes in early disease – except for soft tissue swelling;
  - may be bony erosions and subluxation in chronic disease.

**Treatment**

• Pain control:
  - paracetamol
  - NSAIDs are better than paracetamol for pain but have a higher risk of GI symptoms.

• Patients may require referral to a specialist for disease-modifying anti-rheumatic drugs (DMARDs). These drugs reduce the rate of damage to bone and cartilage.

• DMARDs produce symptomatic remissions or delays, or halt progression.
  - NSAIDs and analgesics may also be used to improve pain and stiffness, but they do not prevent joint damage or slow the disease progression.

• physical therapy
• lifestyle modification.

**Gonococcal arthritis**

Gonococcal arthritis is associated with the sexually transmitted disease, gonorrhoea.

Gonococcal arthritis can present:

• as dermatitis-arthritis syndrome with arthralgia, tenosynovitis, and painless non-pruritic dermatitis (papules, or pustules); OR

• a septic arthritis.

Often there is a history of recent unprotected sexual activity or sexually transmitted infection.
Diagnosis
- Gram stain of synovial fluid will show Gram-negative diplococci.

Treatment
- Dermatitis-arthritis syndrome:
  - ceftriaxone 1 g IV or IM for 24 hours after symptoms resolve then cefixime 400 mg orally twice daily to complete total 7–10 days.
- Septic arthritis:
  - ceftriaxone IV for 24 hours after symptoms resolve then cefixime 400 mg orally twice daily to complete total 14–21 days.
  Note: add treatment for *Chlamydia* (doxycycline orally) and joint drainage for purulent arthritis.

See also Section 11.15 Gonorrhoea.

10.12.3 Symptom management
- Analgesia:
  - paracetamol with or without codeine
  - aspirin.
- Anti-inflammatory:
  - NSAIDs – ibuprofen, indomethacin.
- Short-term steroid therapy can be used.
- Topical analgesic:
  - an ibuprofen or diclofenac-containing gel
  - *capsaicin* also is used topically.
- Physiotherapy – hot and cold modalities can be used.
This Section provides an approach to recognizing, diagnosing and managing common problems of the soft and hard tissues of the mouth (oral cavity), as well as the pharyngitis.

Oral disorders may be due to disease processes localized to the mouth (teeth, gums, or mouth mucosa), or they may be signs of an underlying systemic disease, nutritional disorder, or bacterial or viral infection. An unhealthy diet rich in sugars and poor oral hygiene play major roles in localized oral diseases, affecting gums and teeth. People who use tobacco or drink alcohol in excess are particularly at risk of major oral disorders, particularly oral cancer and gum disease.

**Assessment of the mouth**

Assessment of the mouth is quick and easy and should be part of the routine health examination. The examination should be systematic and include all parts of the mouth, including the lips and face. Early management of mouth problems is especially important for HIV-infected patients who are at increased risk of both soft tissue lesions and salivary gland disorders, as well as accelerated gum disease. Rapid detection and referral for special care is important for oral cancer.

### 10.13.1 Clinical approach to disorders of the mouth and throat

<table>
<thead>
<tr>
<th>10.13.1</th>
<th>Clinical approach to disorders of the mouth and throat</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.13.2</td>
<td>HIV and the mouth</td>
</tr>
<tr>
<td>10.13.3</td>
<td>Soft tissue lesions of the mouth (with DDx tables)</td>
</tr>
<tr>
<td>–</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>–</td>
<td>Lichen planus or lichenoid drug reaction</td>
</tr>
<tr>
<td>10.13.4</td>
<td>Oral cancer</td>
</tr>
<tr>
<td>10.13.5</td>
<td>Conditions related to the hard tissue of the mouth</td>
</tr>
<tr>
<td>10.13.6</td>
<td>Gum disease</td>
</tr>
<tr>
<td>–</td>
<td>Gingivitis</td>
</tr>
<tr>
<td>10.13.7</td>
<td>Noma disease</td>
</tr>
<tr>
<td>10.13.8</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>10.13.9</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td>–</td>
<td>Acute streptococcal pharyngitis</td>
</tr>
<tr>
<td>–</td>
<td>Peritonsillar abscess (quinsy)</td>
</tr>
</tbody>
</table>

**Step 1:** **Use Quick Check**

Facial asymmetry, or swelling of the lips with mucosal ulceration should be evaluated urgently as this may be a severe drug reaction (angio-neurotic oedema) needing urgent attention.

**Step 2:** **Take a history – both specific of the mouth and a general medical history**

**Step 3:** **Examine the oral cavity and lips, and also perform a general medical examination**

**Step 4:** **Assess the patient’s HIV status**

**Step 5:** **Classify the mouth problem and work through the relevant differential diagnosis (see DDx tables)**

Look for:
- tooth decay or loss of tooth tissue
- gingival bleeding or dental plaque
- abscess
- ulcerative soft tissue lesions
- soft tissue swelling (lumps and bumps)
- white lesions
- red lesions
- dry mouth
- loosening of teeth.

**Step 6:** **Investigate if necessary**

**Step 7:** **Initiate treatment (or refer) and monitor the response**

Note: Suspect mouth cancer if signs do not resolve with treatment and refer within 3 weeks.
**History**

**Specific history of the mouth**
- What is the duration of the symptoms?
- Has there been a change in the condition?
- Are there associated symptoms (e.g. pain, difficulty biting, chewing or swallowing, difficulty speaking, dryness of the mouth, or pain referred to the ear)?
- Ask about use of dentures and appliances.
- Ask about oral hygiene practices.
- Discuss dietary habits (sugars, frequency of snacking).

**General history**
- Are there symptoms of systemic disease or co-morbidities?
  - constitutional symptoms (fever, night sweats, malaise, lymphadenopathy);
  - systems review for specific system involvement (central nervous system, cough, abdominal complaints);
  - assess the patient’s HIV status;
  - ask about autoimmune conditions and immunocompromising conditions like diabetes.
- Is the patient using any medications (including those bought over-the-counter)? Remember to ask when medications were first started.
- Look for signs and symptoms suggestive of current or prior STIs.
- Ask about tobacco (smoking, chewing), alcohol, and drug use.
- Ask about the patient's diet.

**Physical examination**

Assess the mouth (as below) and then perform a full general physical examination checking for signs of systemic disease.

**Specific oral examination**

Examination of the mouth is easy and non-invasive. Useful items include a tongue depressor or wooden spatula, gauze pads, and a light source. Use mouth mirrors if they are available.

- Inspect the face and neck with the mouth closed – note skin changes, swellings, and blisters. Inspect the lips, paying particular attention to cracks and fissures at the angles of the mouth. Note asymmetries of the face and neck that may indicate swollen salivary glands.
- Palpate lymph nodes including the submandibular and cervical lymph nodes (are they enlarged, movable or fixed, tender or non-tender?). See Section 10.4 Lymphadenopathy for more details.
- Examine the oral cavity (remove dentures if present).
- A systematic oral examination is important so as to not overlook parts of the mouth that are likely to be missed.
  - Undertake a clinical examination of inside of the cheeks, tongue, gums, floor of the mouth, and palate.
  - Palpate any lumps visible during the clinical examination.
  - A two-finger palpation approach with one gloved finger inside the mouth and another on the corresponding facial structure is most useful for noting submucosal irregularities, swelling, or enlarged structures.
  - Examine the oropharyngeal area with the patient’s mouth open wide enough for the tonsillar tissue and upper pharynx to be visible. Gentle depression of the tongue may facilitate this. Remember to examine all sides of the tongue including the sides and floor.
  - Examine particularly the teeth and gums.
An X-ray may be useful in some mouth conditions, such as dental (apical) abscess, ulcerative gingivitis, advanced gum disease, and malignant oral cancers spreading to the jaw.

Examining the mouth is important for:
1. detection of HIV-associated oral disorders that may help to identify the disease in the early stages and oral cancer, which, if not detected early, is lethal;
2. diagnosis and treatment of other common oral disorders, such as dental caries, loss of tooth tissue, gum disease, candidiasis, oral ulcers, and swelling of oral cavity. A differential diagnosis of white and red patches is presented, as some potentially malignant disorders (e.g. leukoplakia and erythroplakia) present as white or red lesions.

**10.13.2 HIV and the mouth**

The majority of people with untreated HIV develop oral manifestations at some time during the illness, and about 50% of PLHIV experience oral lesions.

An examination of the oral cavity is particularly important:
- when HIV is suspected;
- for clinical staging of the disease;
- when monitoring the response to ART;
- as a marker of clinical treatment failure if HIV-associated lesions develop while the patient is on ART.

Some conditions are particularly common in PLHIV, such as candidiasis, oral hairy leukoplakia, Kaposi sarcoma, necrotizing ulcerative gingivitis and advanced gum disease (periodontitis), atypical oral ulceration, and non-Hodgkin lymphoma. Oral candidiasis and oral hairy leukoplakia are HIV clinical stage 3 conditions.

**10.13.3 Soft tissue lesions of the mouth**

Classify the lesion and consult the relevant differential diagnosis tables below. Sometimes, more than one differential diagnosis table may have to be used.

- **White lesions** may be white patches on the tongue (dorsal, ventral or lateral surfaces), inside of the lips and cheek mucosa, palate or tonsils. Attempt to wipe off the lesion with gauze.
- **Red lesions** may be red patches or plaques.
- **Ulcerative lesions** may be either small or large ulcers.
- **Soft tissue swellings** are lumps.
DDx: White lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral candidiasis (pseudomembranous)</strong></td>
<td>Cheesy white lesion on mucosal surface</td>
</tr>
<tr>
<td>See below and (Section 11.4)</td>
<td>Reveals red raw surface when wiped off</td>
</tr>
<tr>
<td></td>
<td>Responds to topical antifungal agents; nystatin or amphotericin</td>
</tr>
<tr>
<td></td>
<td>If recurrent, look for immunosuppressed status, e.g. HIV, diabetes, or cancer</td>
</tr>
<tr>
<td><strong>Chronic hyperplastic candidiasis</strong></td>
<td>Painless white plaques close to the angle of the mouth on the inside of cheek</td>
</tr>
<tr>
<td>(See Section 11.4)</td>
<td>(i.e. buccal mucosa); rarely, dorsal tongue</td>
</tr>
<tr>
<td></td>
<td>No local trauma</td>
</tr>
<tr>
<td></td>
<td>Responds to topical antifungal medication</td>
</tr>
<tr>
<td><strong>Oral hairy leukoplakia</strong></td>
<td>Painless, vertical corrugations along the sides of the tongue, bilaterally –</td>
</tr>
<tr>
<td></td>
<td>washboard-like pattern</td>
</tr>
<tr>
<td></td>
<td>Cannot be wiped off</td>
</tr>
<tr>
<td></td>
<td>Responds to ART</td>
</tr>
<tr>
<td><strong>Lichen planus or lichenoid drug reaction</strong></td>
<td>Lacy white striae or patches on the sides of the tongue or insides of the cheek</td>
</tr>
<tr>
<td></td>
<td>Generally asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Note in history change of medication likely to cause a lichenoid reaction</td>
</tr>
<tr>
<td><strong>Frictional keratosis</strong></td>
<td>White patches on the buccal mucosa, lateral tongue, or lip due to accumulation of keratin</td>
</tr>
<tr>
<td></td>
<td>Presence of friction or chronic irritation such as tissue chewing, broken or sharp teeth, or ill-fitting dentures</td>
</tr>
<tr>
<td></td>
<td>Cannot be wiped off</td>
</tr>
<tr>
<td><strong>Nicotinic stomatitis</strong></td>
<td>White colouration of palate with red dots mostly on the hard palate</td>
</tr>
<tr>
<td></td>
<td>History of heavy smoking – particularly pipes, asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Cannot be wiped off</td>
</tr>
<tr>
<td></td>
<td>Responds to cessation of smoking</td>
</tr>
<tr>
<td><strong>Leukoplakia</strong></td>
<td>Painless patches of keratosis on the mucous membranes including the tongue</td>
</tr>
<tr>
<td></td>
<td>Cannot be wiped off</td>
</tr>
<tr>
<td></td>
<td>Associated with tobacco use, alcohol, HPV</td>
</tr>
<tr>
<td></td>
<td>Exclude trauma as a cause</td>
</tr>
<tr>
<td></td>
<td>Considered potentially malignant; 4–15% of the lesions could progress to cancer</td>
</tr>
</tbody>
</table>

**Oral candidiasis**

Candidiasis is common and is often a reflection of ill health due an underlying disorder, e.g. diabetes, anaemia, or immunodeficiency. It is the most common oral manifestation in PLHIV. It may interfere with taste and eating, which may compromise the general status of the affected person. Either topical or systemic antifungal medication may be used for treatment.

**Treatment**

- Early treatment is warranted as candidiasis causes discomfort and may spread to the pharynx and oesophagus.
- Oral candidiasis in HIV patients usually responds to initial topical therapy (clotrimazole, nystatin, miconozole, see Section 11.4).
- Recurrences are common, and if there is no response in 1 or 2 weeks, systemic agents for both treatment and maintenance therapy may be required. This includes giving fluconazole 200 mg daily for 14 days.
- Initiate ART.

**Prevention**

- Reduce tobacco consumption.
- Reduce diet.
- Maintain good oral hygiene.
- Improve denture hygiene.
### Lichen planus or lichenoid drug reaction

Oral lichen planus is a chronic autoimmune inflammatory condition. It can result from an allergic reaction to food, food additives, fragrances, dyes, dental metals, or other substances.

### Treatment

- Medical treatment focuses on symptom control and removing the offending substance if it can be identified.
- Give pain control if necessary, and high-potency corticosteroid gels or ointments (triamcinolone) need to be applied to lesions.

### DDx: Red lesions in the mouth

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythematous candidiasis</strong></td>
<td>Red patches on palate or on dorsal surface of tongue</td>
</tr>
<tr>
<td>(For treatment see oral candidiasis above and see Section 11.4)</td>
<td>No history of local trauma</td>
</tr>
<tr>
<td></td>
<td>May co-exist with pseudomembranous candidiasis</td>
</tr>
<tr>
<td></td>
<td>Usually asymptomatic – burning sensation may occur</td>
</tr>
<tr>
<td></td>
<td>Responds to topical antifungal medication</td>
</tr>
<tr>
<td><strong>Angular cheilitis</strong></td>
<td>Painful erythaema associated with a crack or fissure at angle of the mouth</td>
</tr>
<tr>
<td></td>
<td>Presence of ill-fitting dentures</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>May be due to candidiasis or Staphylococcus aureus</td>
</tr>
<tr>
<td><strong>Kaposi sarcoma</strong></td>
<td>Single or multiple reddish-blue lesion on palate or gum</td>
</tr>
<tr>
<td></td>
<td>Painless, but may progress</td>
</tr>
<tr>
<td></td>
<td>May coexist with skin lesions</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>HIV-infected</td>
</tr>
<tr>
<td><strong>Atrophic glossitis – nutritional deficiency or anaemia</strong></td>
<td>Generalized loss of papillae on dorsal tongue</td>
</tr>
<tr>
<td></td>
<td>Burning sensation</td>
</tr>
<tr>
<td></td>
<td>Dietary deficiencies</td>
</tr>
<tr>
<td></td>
<td>Pallour</td>
</tr>
<tr>
<td><strong>Contact stomatitis</strong></td>
<td>Diffuse erythaema and sloughing</td>
</tr>
<tr>
<td></td>
<td>Involvement of the gingiva</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>History of contact with, e.g. dentures, food colouring, toothpaste. Responds to withdrawal of allergen</td>
</tr>
<tr>
<td><strong>Geographic tongue</strong></td>
<td>Red lesions with yellow/white border – migratory over time or may change size and shape</td>
</tr>
<tr>
<td></td>
<td>Localized absence of papillae (small hairs on the surface of the tongue)</td>
</tr>
<tr>
<td></td>
<td>Irregularly shaped smooth, red patches to form on parts of the tongue (gives the tongue a map-like, or geographical, appearance)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td><strong>Erythroplakia</strong></td>
<td>Red patches with well-demarcated borders</td>
</tr>
<tr>
<td></td>
<td>Frequently found on the floor of the mouth, the tongue, the soft palate</td>
</tr>
<tr>
<td></td>
<td>Precancerous – carcinoma is found in 50% of the lesions and severe dysplasia in the rest indicating potential for cancer development</td>
</tr>
<tr>
<td></td>
<td>Associated with tobacco use.</td>
</tr>
</tbody>
</table>
**DDx: Ulcerative lesions in the mouth**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
</table>
| **Traumatic ulcer** | Isolated ulcer  
Obvious cause of irritation or trauma  
Resolve within 1–2 weeks after removal of the cause |
| **Aphthous ulcers** | Painful ulcer with a whitish base surrounded by discrete red border  
May be small, large, or multiple ulcers  
Usually limiting – but may be large, deep, and longer-lasting in PLHIV  
Previous episodes  
Responds to topical steroids |
| **Behcet’s syndrome** | Painful recurrent oral and genital ulcerations  
Eye involvement and inflammation of other parts of the body  
Unknown cause |
| **Herpetic stomatitis or gingivitis** | Painful vesicles evolving to ulcers  
Palate or gingiva  
Constitutional symptoms  
Tender regional lymphadenopathy |
| **Herpes labialis** | Starts as burning sensation or pain before onset of blister on lip  
Triggered by sun exposure, stress, or recent illness  
Previous episodes  
Very contagious |
| **Herpes zoster** | Distribution of painful vesicles and ulcers on skin and mucosa  
Lesions do not cross the midline but are limited to:  
• one side of the anterior two-thirds of the tongue  
• one side of the mouth or face  
(see Section 11.39) |
| **Cytomegalovirus (CMV) infection** | Large reddish ulcer with a white border  
Painful  
Pain on swallowing  
(see Section 11.10) |
| **Syphilis** | Primary syphilis – painless ulcer that resolves spontaneously  
Secondary syphilis – painful superficial ulcers or erosions  
Tertiary syphilis – painless, punched out ulcers – gumma  
Other features of syphilis on history and examination  
Positive syphilis serology  
(see Section 11.32) |
| **Tuberculosis** | Large, painful, deep ulcers – involvement of the tongue  
Constitutional symptoms of TB  
AFB present  
Coinfection with HIV  
(see Section 11.31) |
| **Necrotizing conditions of the mouth** | Very painful ulcers – sensitive to touch  
Swollen, red, bleeding gums  
Involvement of the bone with loose teeth or bone involvement, sequestration  
In some populations, may very rapidly lead to noma disease with an outbreak of the necrosis onto the face  
Foul mouth odour  
Advanced immunosuppression  
Consider drug reaction if drugs have recently been initiated – see below in HIV-associated disease  
(see also Section 10.13.7 Noma disease)  
(see Section 10.13.6 below for management of acute necrotizing ulcerative gingivitis, acute necrotizing ulcerative periodontitis necrotizing stomatitis) |
| **Adverse drug reaction** | Recent initiation of new drug or long-term use of immunosuppressants  
Erosions, bullous lesions, or ulcers with crusting of the lips  
Involvement of skin and other mucosal surfaces (conjunctiva, vagina)  
Mostly over buccal mucosa and palate  
Sudden onset |
| **Squamous cell carcinoma** | Persistent ulcer, with rolled margins  
Demonstrates induration at margins or base  
Rapidly increases in size  
High-risk patient – tobacco or alcohol user. |
Approach to persistent mouth ulcers

If mouth ulcers are not responding to empirical treatment, do not resolve in 2 weeks, and other causes are excluded consider other conditions such as:

- neoplasms – squamous cell carcinoma
- autoimmune conditions
- inflammatory bowel disease
- neutropenia.

These conditions may need to be confirmed by a biopsy and other appropriate investigations.

**DDx: Soft tissue swellings in the mouth**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
</table>
| **Dental abscess** (see Section 10.13.5) | Constant pain, history of toothache  
Localised swelling of the face or gums near a tooth  
Pointing or pus discharge  
Pain when tapping or biting on tooth |
| **Denture-induced (reactive) hyperplasia** | Painless soft tissue swelling  
Ill-fitting dentures  
Presence of local irritation or trauma  
Often in locations (e.g. sulcus) where the periphery of the denture is over-extended |
| **Mucocoele or ranula** | Painless cystic swelling, generally blue colour  
Mostly on lip labial mucosa or buccal mucosa |
| **Oral warts or condylomas** | Painless  
White or pink often multiple irregular lesions  
Common during treatment with ART |
| **Kaposi sarcoma** | Reddish-blue swollen tissue on palate or gum (gingival)  
May accompany skin lesions  
Mostly asymptomatic unless ulcerating  
May complicate eating, swallowing, and talking |
| **Non-Hodgkin’s lymphoma** | Focal soft swelling that may be red and inflamed  
Painful  
Rapid enlargement  
Needs histological confirmation (biopsy) |
| **Minor salivary gland tumours** | Slow-growing mass on palate with normal colour  
Mostly on palate or upper lip  
Histological confirmation |
| **Epulis** | Fibrous lump on gum (gingiva)  
Firm, may be single or lobulated, painless  
Overlying mucosa normal in colour  
In pregnancy, inflamed and vascular (pyogenic granuloma) |
| **Fibro epithelial polyp** | Common benign disorder  
Pedunculated or sessile, over-growth of mucosa  
Painless |
| **Squamous cell carcinoma** | Persistent lump, with central ulceration  
Demonstrates induration at margins or base  
Rapidly increases in size  
High-risk subject (tobacco or alcohol user). |
10.13.4 Oral cancer

Oral cancer appears as a growth or an ulcer that does not go away. The most common sites are on the side of the tongue, buccal mucosa and sulci, and the floor of the mouth. Oral cancer can be life-threatening if not diagnosed and treated early, and may spread to regional lymph nodes. Oral cancer is mostly caused by tobacco (smoking or chewing), areca nut (betel quid) and excessive consumption of alcohol. HPV infection is an emerging risk factor, particularly in the young.

Common signs and symptoms of oral cancer include:

- swellings, thickenings, lumps or bumps on the lips, cheeks, tongue, gums, or other areas inside the mouth;
- a persistent ulcer that does not heal within 2 weeks;
- development of white, red, or speckled (white and red) patches in the mouth;
- unexplained bleeding in the mouth;
- unexplained numbness, loss of feeling, and pain or tenderness in any area of the face, mouth, or neck;
- soreness or a feeling that something is caught in the back of the throat;
- difficulty chewing or swallowing, speaking, or moving the jaw or tongue;
- hoarseness, chronic sore throat, or changes in the voice;
- ear pain;
- a change in the way teeth or dentures fit together – a change in bite;
- dramatic weight loss;
- lumps in the neck due to spread of the disease.

Definitive diagnosis requires a biopsy and referral to a specialist.

10.13.5 Conditions related to the hard tissue of the mouth

Dental caries – tooth decay

This condition is primarily caused by the combination of dietary sugars and oral bacteria in plaque, which is a sticky yellow-white coating on the tooth surface. The plaque bacteria (particularly Streptococcus mutans) ferment the sugars and produce acid, which eventually breaks down (decalcifies) the hard tooth tissue. Over time, this results in cavitations of the tooth and may cause increasing pain. Sensitivity related to hot or cold foods or drink is common. If the progression is not stopped the bacterial invasion will ultimately involve the pulp of the tooth (central chamber of the tooth with nerve endings and blood vessels) causing excruciating pain. The infection can spread to the jaw bones and can cause an abscess or even cellulitis.

Dental caries often impair dietary habits and affect nutritional status.

Treatment

Restorative treatment may be expensive or unavailable, and extraction of the tooth may be the only option for treatment. Where it is feasible to restore the tooth, minimally invasive techniques should be used.

Prevention

- Limit intake and frequency of sugars and increase intake of fruit and vegetables.
- Oral hygiene measures, such as tooth brushing, flossing, or use of traditional chew sticks.
- Fluoride added to toothpaste, salt or milk has a preventive effect.

Be aware of dry mouth as a result of medication (including ART), as it increases the risk of tooth decay.
Dental abscess
Dental abscesses are usually related to the spread of infection following the progression of dental caries to the pulp, or advanced gum (periodontal) disease.

Treatment
- Drain the abscess or, if extraction of the tooth is indicated, refer urgently to an oral health professional.
- If the patient has fever, difficulty in opening the mouth, difficulty in breathing, or if the infection is spreading, give antibiotics:
  - phenoxymethyl penicillin 250 mg 4 times a day OR amoxicillin 500 mg–1 g 3 times a day for 5–7 days PLUS metronidazole 500 mg three times a day for five days; OR
  - amoxicillin-clavulanate 875 mg every 12 hours (or 500 mg 3 times daily) in adults.
- Provide adequate pain relief (analgesics).

Supportive measures
- Advise the patient on oral hygiene.
- Soft diet for a few days (soup, yoghurt, jelly, boiled eggs, porridge).

Tooth wear
There are three types of tooth wear: attrition, erosion and abrasion.

Attrition
Loss of enamel or dentine due to excessive masticatory forces, grinding, or bruxism. Flattening of cusps of teeth or loss of incisal edges may lead to shortening of the dentition.

Erosion
The irreversible progressive loss of hard tooth substance is caused by chemical factors, such as acids. Erosion is seen in persons suffering from bulimia due to the reflux of gastric juices into the mouth, in people exposed to an unhealthy environment, e.g. workers exposed to acids, and increasingly observed among people drinking large amounts of carbonated, sugar-containing soft drinks, and among alcoholics due to vomiting of gastric acids.

Abrasion
The irreversible progressive loss of hard tooth substances is caused by mechanical factors other than mastication or tooth-to-tooth contacts. Abrasion mostly is seen due to incorrect tooth brushing, which leads to notching at the junction of the crown and root of the teeth. It can be caused by environmental factors, such as exposure to quartz dust.

Where there is tooth wear (due to any of above), the patient may complain of sensitivity of teeth to hot or cold drinks or food. This is transient but causes considerable discomfort. Use of fluoride pastes and desensitizing toothpaste may help to control symptoms. Abraded cavities may need restoration.

10.13.6 Gum disease
Gingivitis
This is an inflammation of the tissues (gums) surrounding the teeth. It originates from plaque (yellow-white coating on the teeth – often along the gum margin) when toxins produced by plaque bacteria cause inflammation of the gums. Gums become inflamed and red and bleed upon touch. This common condition is reversible through oral hygiene measures, such as regular removal of plaque along the gums. If the plaque is not removed it can harden (calcify) into “calculus”.
Periodontitis

If untreated, gingival inflammation might slowly develop into periodontitis – a breakdown of the tissues holding the teeth in place. A pocket develops between the gum and the tooth spreading toward the root of the tooth. Pain is rare but a bad-smelling breath develops, pus can accumulate, and an abscess could form. Eventually, teeth may loosen, move, and fall out.

**Treatment**
- Professional scaling and removing of plaque and calculus.
- Adjunctive use of antiseptic mouthwash for a short period.
- Extraction of mobile teeth.

**Prevention**
- Proper oral hygiene to remove the plaque along the gum (brushing, flossing or use of chew stick) on a daily basis.

**Risk factors**
- tobacco use
- inadequate oral hygiene (presence of plaque or calculus)
- systemic health conditions, such as diabetes and HIV infection.

**Necrotizing conditions of the mouth**

Under certain conditions, periodontitis may rapidly exacerbate into acute and severe situations.
- Acute necrotizing ulcerative gingivitis (also known as ANUG): limited to the gums.
- Acute necrotizing ulcerative periodontitis (also known as ANUP): destruction of bone supporting the teeth and oral mucosa.
- Necrotizing stomatitis: destruction of cheek, sequestration of bone that can cause patients to be systemically unwell.

These necrotizing conditions are caused by aggressive bacteria, stress, poor nutrition and a decreased immune response, and may occur in PLHIV.

**Symptoms**
- ulcerated or necrotic gums
- considerable pain
- foul-smelling breath
- fever and symptoms of common infection
- intake of food and drink is painful.

**Treatment**
- In a patient with acute necrotizing ulcerative gingivitis or periodontitis, or necrotizing stomatitis, treat with metronidazole 200 mg three times daily for 7–10 days.
- Hydrogen peroxide as a mouthwash, diluted 1:1, for seven days.

**10.13.7 Noma disease**

In non-HIV-infected persons, noma disease occurs mainly in young children living in poverty. Contributing factors are severe malnutrition, poor hygiene, aggressive necrotizing micro-organisms, and general infection (e.g. measles). Low immune status is also a factor, making it an HIV-related condition.

The infection results in rapid, devastating destruction of soft and bony tissues spreading from the inside of the mouth, breaking down through the tissues of the cheek, lips and nose. If untreated, this disease results in high mortality. In survivors, it results in severe facial defects often requiring plastic surgery, which is expensive and often not available.
**Treatment**
- Debridement of necrotic tissue or bony sequestrate.
- Acute nutritional supplementation.
- Instructing the patient in oral care – showing the patient and family how to clean the mouth with saline, peroxide or sodium bicarbonate.
- The acute stage responds readily to antibiotic treatment to control anaerobic organisms.

**Prevention**
Noma disease intervention should raise awareness of the disease. Prevention should focus on improved housing conditions, poverty reduction, improved nutrition, promotion of exclusive breastfeeding, optimum prenatal care, timely immunizations against the common childhood diseases, and access to clean water and sanitation facilities for optimal personal and oral hygiene.

### 10.13.8 Dry mouth
Dry mouth is common in the elderly, in those taking regular medications that contribute to xerostomia, after radiation therapy to head and neck, and in association with connective tissue disorders (e.g. rheumatoid arthritis). Dry mouth is a common symptom in HIV infection.

- Review medications – dry mouth can be a side-effect of hyoscine, morphine, atropine, amitriptyline, furosemide and ART.
- Check for signs of infection.
- Breathing through the mouth can also contribute.
- If there is a persistent problem with lack of saliva, pay close attention to preventive oral care and mouth hygiene. Intake of citrus juice or lemon may induce production of saliva.
- If Candida, treat as suggested earlier and see Section 11.4

Advise the patient to:
- moisten the mouth with regular sips of water,
- maintain good oral hygiene,
- avoid sugary snacks,
- chew sugar-free gum.

### 10.13.9 Pharyngitis
Pharyngitis is common worldwide and presents as an inflammation of the throat caused by various organisms from viruses to bacteria. Respiratory viruses causing the common cold are the most common causes, but herpes simplex virus, coxsackie virus, and Epstein-Barr virus (EBV) can cause acute pharyngitis. Cases caused by viruses usually resolve spontaneously. However, pharyngitis caused by *Streptococcus pyogenes* is a cause for concern. If untreated, this can progress to acute rheumatic fever or glomerulonephritis, both of which can cause significant sequelae. *Corynebacterium diphtheriae* is a less frequent cause of bacterial pharyngitis in areas where there is insufficient childhood vaccination coverage. It can be life-threatening through the formation of membranes in the throat. Pharyngitis can be complicated by tonsillitis and peritonsillar abscess (quinsy).

Key clinical features:
- Pain on swallowing,
- Red throat with enlarged tonsils,
• white deposits (exudates) may be present on the pharyngeal surfaces in bacterial and in some viral cases,
• fever, headache, swollen and painful cervical lymph nodes, myalgias, and runny nose are associated in cases of respiratory virus infection, particularly adenovirus and influenza,
• vesicles and shallow ulcerations are present in herpes or Coxsackie virus infections.

Treatment
- For viral pharyngitis, supportive management with fever reducing agents (paracetamol) is adequate.
- Antibiotic treatment should be reserved for cases of suspected streptococcal pharyngitis.

**Acute streptococcal pharyngitis**

Group A beta-hemolytic streptococcus (GABHS) causes only approximately 10% of adult cases of pharyngitis. Antibiotic treatment of pharyngitis benefits only those patients with GABHS infection.

**Key clinical features**
- high fever
- very inflamed throat with many exudates
- large, tender cervical lymph nodes
- absence of cough.
Other features of the common cold are usually absent (runny nose, sneezing).

**Complications**
- rheumatic fever (see Section 11.28),
- post-infectious inflammation of the kidneys (glomerulonephritis, renal failure – see Section 5.3),
- local extension: ear infection, sinusitis, pneumonia.

**Investigations**
If a streptococcal infection is suspected, use rapid antigen detection test or a culture to confirm, if possible. A score has been developed that gives 1 point each for absence of a cough, swollen and tender cervical lymph nodes, temperature >38°C, tonsillar exudate or swelling, and age <15. A point should be subtracted if age >44. A score of 4 or more may justify empirical antibiotic treatment, although considerable overtreatment will still occur. Follow national guidelines.

**Treatment**
Antibiotic treatment should be reserved for cases of suspected streptococcal pharyngitis. This reduces the risk of rheumatic fever (Section 11.28).

Give:
- benzathine benzylpenicillin G 1.2 million units IM single dose (preferred); OR
- phenoxyethyl penicillin 500 mg PO twice daily for 10 days; OR
- (if allergic to penicillin) erythromycin 250 mg four times daily for 10 days.

---

Peritonsillar abscess (quinsy)

Peritonsillar abscess is usually a disease of older children, adolescents and young adults. The infection can spread to the neck and chest, including the lungs. Swollen tissues may block the airway, which is a life-threatening medical emergency (see Section 3.1).

Key clinical features
- sore throat (may be severe and is usually on one side)
- throat red and swollen on one or both sides
- swollen palate (roof of mouth)
- deviated uvula (shifted away from swelling)
- difficulty and pain when opening the mouth
- difficulty swallowing
- drooling or inability to swallow saliva
- may have facial and neck swelling
- fever
- headache
- tender lymphadenopathy of the jaw and throat.

Treatment
- Needle aspiration or incision and drainage. See instructions in the WHO manual Surgical care at the district hospital.³
- Antibiotics, for total 14 days’ duration:
  - In areas where S. aureus remains susceptible to methicillin and patient is able to take oral medication:
    - amoxicillin 500 mg to 1 g three times daily for 5–7 days PLUS metronidazole 500 mg three times a day for five days; OR
    - clindamycin 300 to 450 mg every 6 hours in adults; OR
    - amoxicillin-clavulanate 875 mg every 12 hours (or 500 mg three times daily) in adults.
  - In areas where S. aureus remains susceptible to methicillin and patient requires IV therapy:
    - clindamycin IV 600 mg every 6 to 8 hours.

10. Acute and subacute by symptom: SEARO 2021
This Section deals with the approach to pallour and anaemia. Anaemia is present when the haemoglobin concentration in the peripheral blood is lower than normal for age, sex, pregnancy and environmental factors.

A patient may present with symptoms of anaemia discovered during a routine examination or investigation of some other condition, or the patient may be symptomatic from the anaemia.

### 10.14.1 Clinical approach to a patient with pallour and anaemia

**Step 1:** Use Quick Check to ensure that there are no serious or life-threatening conditions

Use the Quick Check and be aware that acute blood loss (e.g. trauma or pregnancy states, acute GI bleed) can present with shock.

The chronically anaemic patient may decompensate and present with congestive cardiac failure.

**Step 2:** Take a history and examine the patient

Examine the patient to identify key signs:

- ask about associated symptoms and look for signs that reveal the underlying cause of the anaemia
- ask about and look for any complications of the anaemia.

**Step 3:** Assess HIV status

**Step 4:** Perform investigations

- FBC and peripheral blood smear
- Malaria smear or rapid diagnostic test (RDT) for malaria
- Other special investigations as indicated.

**Step 5:** Classify anaemia and work through the differential diagnosis

- Classify the type of anaemia based on the shape and size of the red blood cells – mean corpuscular volume (MCV)
- Classify the anaemia based on whether one cell line is involved or multiple
- Work through the differential diagnoses found in the attached tables
- Request special investigations or diagnostic tests to confirm the diagnosis or refer to local referral hospital.

**Step 6:** Initiate treatment and monitor response to treatment. Re-evaluate as necessary

---

History

Non-specific symptoms of anaemia
- tiredness, fatigue or loss of energy
- dizziness, light-headedness, syncope or fainting
- shortness of breath, especially on effort
- ankle swelling
- headache
- worsening of any pre-existing symptoms, e.g. angina.

Table: Focus history and examination according to the likely cause of the anaemia

<table>
<thead>
<tr>
<th>Cause of anaemia</th>
<th>History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased loss of red blood cells</td>
<td>• obstetric or gynaecological history, menorrhagia or other vaginal bleeding</td>
</tr>
<tr>
<td>• acute blood loss – haemorrhage from trauma, surgery, obstetric causes</td>
<td>• bleeding from urinary tract</td>
</tr>
<tr>
<td>• chronic blood loss: from GI, urinary or reproductive tracts – like menorrhagia</td>
<td>• bleeding gums, epistaxis, purpura</td>
</tr>
<tr>
<td>• parasitic infestations including hookworm and whipworm, malignancy, chronic</td>
<td>• GI bleed: melena, upper GI bleed, chronic diarrhoea, weight loss, indigestion</td>
</tr>
<tr>
<td>• autoimmune, or inflammatory disorders</td>
<td>• drug history</td>
</tr>
<tr>
<td>Decreased production of normal red blood cells</td>
<td>• history of high risk of exposure to HIV</td>
</tr>
<tr>
<td>• nutritional deficiencies: iron, B12, folate, malabsorption, malnutrition</td>
<td>• drug history</td>
</tr>
<tr>
<td>• viral infection: HIV, HBV, and HCV</td>
<td>• nutritional history</td>
</tr>
<tr>
<td>• bone marrow failure – aplastic anaemia, malignancies (leukaemia)</td>
<td>• socioeconomic status</td>
</tr>
<tr>
<td>• reduced erythropoietin production – renal failure</td>
<td>• psychiatric disorders – anorexia, bulimia</td>
</tr>
<tr>
<td>• chronic illness</td>
<td>• fever, night sweats, weight loss (malignancies, TB, HIV, and others)</td>
</tr>
<tr>
<td>• poisoning of the bone marrow: lead, drugs</td>
<td></td>
</tr>
<tr>
<td>Increased destruction of the red blood cells</td>
<td>• malaria episodes, travels or lives in malaria endemic area</td>
</tr>
<tr>
<td>• infections – bacterial, viral, protozoal, parasitic drugs</td>
<td>• fever, night sweats (malaria or other infections like TB)</td>
</tr>
<tr>
<td>• drugs</td>
<td>• family history, ethnic origins.</td>
</tr>
<tr>
<td>• autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td>• inherited disorders – sickle-cell disease, thalassaemia, G6PD deficiency</td>
<td></td>
</tr>
<tr>
<td>• haemolytic disease of the newborn</td>
<td></td>
</tr>
<tr>
<td>• others: DIC, haemolytic uraemic syndrome, TTP</td>
<td></td>
</tr>
<tr>
<td>Increased physiological demand for red blood cells</td>
<td></td>
</tr>
<tr>
<td>• pregnancy</td>
<td></td>
</tr>
<tr>
<td>• lactation</td>
<td></td>
</tr>
<tr>
<td>• growth.</td>
<td></td>
</tr>
</tbody>
</table>

Examination

Look for underlying diseases, signs of anaemia and related complications.

Signs of anaemia with clinical decompensation
- pale mucous membranes, skin and nail beds
- rapid breathing
- tachycardia
- raised jugular venous pressure
- heart murmurs
- ankle oedema
- postural hypotension – dizziness when the patient gets up from a sitting or sleeping position
- pulmonary oedema
- altered mental state.

Remember a patient may have several causes of anaemia – nutritional, HIV, malaria, parasitic infestation or malignancy.
Signs of the underlying disorder

- weight loss or underweight for their height or age
- angular stomatitis, koilonychia (iron deficiency)
- jaundice (hemolysis)
- purpura and bruising (bone marrow failure, platelet disorders)
- enlarged lymph nodes, hepatosplenomegaly, fever (infection, lymphoproliferative disease, HIV infection)
- lower leg ulcers (sickle-cell disease)
- skeletal deformities (thalassaemia)
- neurological signs (vitamin B12 deficiency)
- fever (malaria).

Investigations

- Haemoglobin (Hb) – confirm the presence of anaemia. Note that normal ranges for Hb are age- and sex-dependant (see table below).
- FBC – look at the red blood cell (RBC) count, haemoglobin, haematocrit (HCT) and RBC indices, the white blood cell count, and differential leukocyte count and platelet count.
- Perform a malaria smear or RDT for malaria.
- Peripheral blood smear:
  - Assess RBC: size, shape, colour (Hb content), polychromasia, rouleaux formation, RBC aggregation, RBC inclusion bodies.
  - Morphological abnormalities of other cells – WBC and platelets – are also reviewed and may show underlying pathologies (e.g. leukaemia, aplastic or megaloblastic anaemia, infections like malaria parasites, or bone marrow failure).
  - If an automated blood-cell analyser is not available, the RBC size should be evaluated on the blood smear to detect microcytosis or macrocytosis.
- Reticulocyte count:
  - Reticulocytes are newly produced red blood cells. A normal response to anaemia is for the marrow to produce reticulocytes and, therefore, increase the RBC count. Therefore, the reticulocytes count is an indicator of the marrow response to anaemia.
  - The reticulocyte count results (given as a proportion of total RBC) can be calculated manually or by an automated machine. The reticulocyte count represents the percentage of total erythrocytes and does not correct for anaemia.
  - The corrected reticulocyte or reticulocyte index (RI) adjusts reticulocyte count for haematocrit, and reflects the bone marrow activity. It can be very useful when a bone marrow aspirate cannot be obtained. The formula for calculating RI is as follows:

\[ RI = \text{reticulocyte count} \times \left( \frac{\text{Hct}}{\text{normal Hct}} \right) \]

A normal reticulocyte count is 0.5%–1.5%. A normal reticulocyte index is 1%–3%.

Reticulocytes can also be identified by Wright Giemsa stains on a peripheral smear.

Red blood cells indices using an automated blood cell analyser

Use MCV to classify anaemia

- **Normocytic anaemia**: MCV within the normal range 80–100 fl.
- **Microcytic anaemia**: MCV below 80 fl.
- **Macrocytic anaemia**: MCV above 100 fl.
### Table: Normal ranges for haemoglobin by age and gender

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Normal Hb range</th>
<th>Anaemic if Hb (g/dl) &lt;</th>
<th>Anaemic if Hct &lt;</th>
<th>Severe anaemia if Hb (g/dl) &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6–12 years</td>
<td>11.5–15.5</td>
<td>11.5</td>
<td>(Hct 34%)</td>
<td>4</td>
</tr>
<tr>
<td>Adult males</td>
<td>13.0–17.0</td>
<td>13</td>
<td>(Hct 39%)</td>
<td>7</td>
</tr>
<tr>
<td>Adult females: non-pregnant</td>
<td>12.0–15.0</td>
<td>12</td>
<td>(Hct 36%)</td>
<td>7</td>
</tr>
<tr>
<td>Adult females: pregnant(*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester: 0–12 weeks</td>
<td>11.0–14.0</td>
<td>11</td>
<td>(Hct 33%)</td>
<td>5</td>
</tr>
<tr>
<td>Second trimester: 13–28 weeks</td>
<td>10.5–14.0</td>
<td>10.5</td>
<td>(Hct 31%)</td>
<td>5</td>
</tr>
<tr>
<td>Third trimester: 29 weeks–term</td>
<td>11.0–14.0</td>
<td>11</td>
<td>(Hct 33%)</td>
<td>6</td>
</tr>
</tbody>
</table>

### Additional tests
- a faecal occult blood test;
- iron studies tests:
  - serum ferritin, which reflects total body iron stores and is the first value to fall in iron-deficiency anaemia;
  - total iron-binding capacity (TIBC), which measures the extent to which iron-binding sites in the serum can be saturated;
  - serum total iron, which measures the serum iron that is bound to transferrin;
  - transferrin percent saturation, which measures the extent to which sites on transferrin molecules are filled by iron ions (serum Fe/TIBC).
- haemoglobin electrophoresis;
- sickling test – for sickle-cell disease;
- serum B12 level;
- direct antiglobulin test for autoimmune haemolytic anaemia;
- bone marrow sampling if it is indicated.

### 10.14.2 Classification of anaemia

Classify the anaemia according to the MCV and the MCHC work through the DDx table below.

Over 60 different allelic variants of thalassaemia occur in countries in South-East Asia. Hb E-beta-thalassaemia is one of the most frequent hemoglobinopathies. The incidence of Hb E approaches 60% of the populations in some regions of South-East Asia. HbE gene prevalence may reach up to 70% locally in northeastern Thailand.²

Inherited haemoglobin disorders (sickle-cell disorders and thalassaemias) can be addressed by programmes that integrate treatment with carrier detection and genetic counselling.³

### DDx: Classification of anaemia based on MCV and MCHC

<table>
<thead>
<tr>
<th>Blood film</th>
<th>Cause</th>
<th>In favour of</th>
</tr>
</thead>
</table>
| Microcytic, hypochromic, Low MCV, small | Acquired
  - iron deficiency
  - sideroblastic anaemia | Pallo...
<table>
<thead>
<tr>
<th>RBC on smear</th>
<th>Low MCHC</th>
<th>anaemia of chronic disease</th>
<th>Spoon-shaped nails (koilonychia) Brittle hair Pica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td></td>
<td>α-Thalassaemia and β-Thalassaemia minor: Usually asymptomatic Mild pallour (low MCV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-Thalassaemia intermedia: Moderate compensated anaemia (Hb 7–10) which may become symptomatic leading to heart failure, pulmonary hypertension Bony expansion when the patient is between 20 and 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-Thalassaemia major: Severe anaemia from infancy, poor growth, progressive bone marrow expansion (thalassaemic face, skeletal deformity), jaundice, leg ulcers, cholelithiasis, splenomegaly Pathological fractures common Often Hb &lt;7 g/dl High unconjugated bilirubin</td>
<td></td>
</tr>
<tr>
<td>Macrocytic, normochromic</td>
<td>Increased MCV, large RBC on smear Normal MCHC</td>
<td>With megaloblastic marrow</td>
<td>Insidious onset Diarrhoea – known as Crohn’s disease, tapeworms, autoimmune disease Sore, burning, red tongue Subacute combined degeneration in B12 deficiency – a neuropathy which presents with symmetric tingling in the hands and feet, loss of sensation in the legs, feet and hands, ataxia and, on examination, absent vibration sense, absent patellar reflexes with extensor plantar reflexes Note: The severity of neurologic findings does not correlate with the severity of anaemia Diarrhoea Smooth tongue Cracks in mouth angles Darkening of the skin and mucous membranes, Modest temperature elevation (&lt;38.9 °C) is common in patients who are folate deficient, despite the absence of any infection See vitamin B12 above as the same presentation Long-term ART use</td>
</tr>
<tr>
<td>Macrocytic, normochromic</td>
<td>With normoblastic marrow</td>
<td>alcohol excess myelodysplasia</td>
<td>Patient may be severely ill – haemolytic crises with fever, chills, pain in the back and abdomen, prostration and shock In severe cases, jaundice, splenomegaly, red/dark urine Chronic haemolysis-pigment gallstones, normal MCV, normal MCHC High reticulocytes High unconjugated bilirubin High LDH Indirect hyperbilirubinaemia High urobilinogen in urine</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>Increased MCV</td>
<td>Haemolytic anaemia</td>
<td>Patient may be severely ill – haemolytic crises with fever, chills, pain in the back and abdomen, prostration and shock In severe cases, jaundice, splenomegaly, red/dark urine Chronic haemolysis-pigment gallstones, normal MCV, normal MCHC High reticulocytes High unconjugated bilirubin High LDH Indirect hyperbilirubinaemia High urobilinogen in urine</td>
</tr>
</tbody>
</table>
### Pallor and anaemia

#### Chronic disorder
- infection including malaria
- malignancy
- autoimmune disorders
- renal failure
- hypothyroidism
- hypopituitarism
- aplastic anaemia
- red cell aplasia
- marrow infiltration

In an area of malaria transmission
- Fever, headache
- Patient maybe severely ill with signs of cerebral malaria, including impaired consciousness or convulsions, respiratory or renal failure
- Generally mild, insidious onset
- Usually few or no symptoms

Associated with HIV, chronic inflammation or autoimmune disorder, renal failure, hypothyroidism

#### Leuco-erythroblastic

Indices may be abnormal due to early and numerous forms of red and white cells

<table>
<thead>
<tr>
<th>Various causes</th>
<th>Metastatic carcinoma, lymphoma, or tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disseminated fungal disease</td>
</tr>
<tr>
<td></td>
<td>Symptoms of anaemia, low platelets and neutropaenia</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly, hepatomegaly, nucleated RBC, and tear drop forms</td>
</tr>
<tr>
<td></td>
<td>Immature WBCs</td>
</tr>
<tr>
<td></td>
<td>High reticulocytes, low platelets</td>
</tr>
<tr>
<td></td>
<td>Bizarre-shaped giant platelets</td>
</tr>
<tr>
<td></td>
<td>Lytic and blastic lesions on skeletal X-ray.</td>
</tr>
</tbody>
</table>

#### 10.14.3 Management of anaemia

**Table: Approach to management of anaemia**

<table>
<thead>
<tr>
<th>Type of anaemia</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Iron-deficiency anaemia | • Seek bleeding site or intermittent loss, and treat  
• Consider bleeding from occult sites which may be due to malignancy  
• Stop NSAIDs or aspirin-containing drugs or other drug with anti-coagulating properties  
• De-worm (consider hookworm; consider *Schistosoma haematobium* – see Section 11.34)  
• Provide iron through iron salts (sulphate, gluconate, fumarate) 60 mg of element iron daily for mild anaemia and 120 mg (plus folic acid 400 µg) for moderate or severe anaemia until Hb is normal and ceases to rise, then continue for 4–6 weeks (see algorithm below). Add ascorbic acid – 1 tablet daily to increase iron absorption  |
| Malaria-related (see Section 8.1.6) | • Consider transfusion for patients with severe malaria and Hb<7 g/dl  
• Test for malaria and, if the result is positive, give antimalarials  
• Watch for associated complications (dehydration, hypoglycaemia, avoid precipitating pulmonary oedema, anticonvulsants for convulsions)  
• Monitor for haemolytic crisis – see Quick Check  |
| Hookworm-related | • Albendazole 400 mg orally once; OR  
• Mebendazole 500 mg orally once or 100 mg orally twice a day for 3 days  |
| AZT-related | • These usually occur within 4 to 12 weeks after ART initiation, but can occur as early as 2–4 weeks  
• AZT-related anaemia is either normocytic (early) or macrocytic (later)  
• Severe anaemia is a rare side-effect of AZT treatment  
• Risk of severe anaemia is enhanced by the patient having a low haemoglobin level before starting therapy  
• If drop of haemoglobin below 7 g/dl or at least 25% from the baseline, substitute another drug for AZT (see HIV guidelines)  |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment/Recommendation</th>
</tr>
</thead>
</table>
| **Macrocytic anaemia (B12 or folate deficiency)** | - Vitamin B12 as 1 mg IM 2–4 times per week until haematological abnormalities are corrected, then once a month. Continue if high demands or malabsorption  
- If neurological involvement, 1 mg IM on alternate days until no further improvement, then 1 mg every two months. Neurological improvement may take up to six months  
- Folic acid 5 mg daily for four months (in pregnancy, continue to term)  
- Because it is impossible to differentiate anaemia due to folic acid deficiency and B12 deficiency based on FBC alone, always give B12 with folic acid. Folic acid given alone can precipitate neuropathy if there is underlying unrecognized vitamin B12 deficiency  
- Try to establish cause of the macrocytic anaemia and treat |
| **Anaemia of chronic disease**                  | - Treat underlying cause, monitor Hb  
- Investigate the cause of anaemia in HIV-infected patients. Consider particularly OIs such as TB, disseminated infections, or malignancies, nutritional deficiencies associated with chronic diarrhoea, medications, e.g. AZT and cotrimoxazole  
- If it is secondary to the infection with HIV itself, treatment with antiretrovirals will result in improvement in the Hb and Hct. Avoid the use of AZT if the Hb is below 8 g/dl |
| **Aplastic anaemia**                            | - Pure RBC aplasia: immunosuppressants like prednisone  
- Cyclosporine or cyclophosphamide where available  
- Refer for specialist care |
| **Myelodysplasia**                              | - Transfuse as necessary |
| **Vitamin C deficiency**                        | - Vitamin C 500 mg daily with folic acid 1 tablet daily as this is occasionally associated with folic acid deficiency |
| **Haemolytic anaemia**                          | - Treat the cause of haemolysis, e.g. malaria  
- Iron replacement may be required because of haemoglobinuria and haemosiderinuria  
- Refer for splenectomy if there is hypersplenism |
| **Auto-immune haemolytic anaemia (AIHA)**       | - Drug withdrawal if drug-induced (plus corticosteroids in severe cases)  
- Corticosteroids  
- Intravenous immunoglobulin may be used when steroids are ineffective  
- Transfuse if there is severe anaemia  
- If corticosteroids fail or patient has a relapse, consider splenectomy |
| **Sickle-cell disease**                         | - Rehydrate  
- Give oxygen if low SpO2  
- Pain relief  
- If indicated, treat malaria  
- Transfuse if there is severe anaemia or symptoms persist  
- See Quick Check Section 3, and below for haemolytic crisis |
| **Thalassaemia (major)**                        | - Planned blood transfusion to suppress erythropoiesis with target Hb 10–12 g/dl  
- Iron chelation therapy and vitamin C 500 mg by mouth daily to promote excretion of iron on the day of chelation, folic acid 5 mg per day  
- Consider referral for splenectomy  
- Long-term prophylactic penicillin  
- Vaccinate against hepatitis B and pneumococcus  
- Endocrine replacement (for hypopituitarism, hypothyroidism, parathyroid failure)  
- Anticoagulants if patient develops clots |
Figure: Summary of initial laboratory investigations and management of anaemia

**Further initial investigations**
- Full blood count (Hb, Hct, blood film) plus white cell count and other relevant indices
- Reticulocyte count
- Thick and thin blood film for malaria parasites or rapid diagnostic test
- Faecal occult blood test

**Provisional diagnosis:** iron-deficiency anaemia

**Check haemoglobin at 4–8 weeks**

**Patient responding.** Haemoglobin rising: reticulocytosis on blood film. Diagnosis probably correct
- Continue iron (ferrous sulphate) treatment for at least three months.

**Patient not responding:** review diagnosis
- Is the patient taking oral iron?
  - Yes
    - Reinforce advice to take oral iron
  - No
Blood transfusion therapy

- Use the proper procedure for transfusing a patient with severe anaemia and congestive heart failure, under furosemide cover. Red cell concentrates, given at slow rate, are preferred over whole blood.

Indications

The only absolute indication for a blood transfusion is acute haemorrhage, leading to shock (see Quick Check). Anaemia in itself is not an indication for a transfusion. The goal of transfusion in haemorrhagic shock is to restore tissue oxygenation. There is no threshold of Hb or Hct value that indicates if transfusion is necessary and no "goal Hb" to attain. Therefore, the decision to administer blood must be based on the symptoms and functional status of the patient, such as:

- clinical evidence of decompensation – heart failure, hypoxaemia (see Quick Check)
- active haemorrhage associated with shock
- haemorrhage that cannot be immediately controlled
- surgical procedures.

Sickle-cell disease

Sickle-cell disease (also known as sickle-cell disorder) is a genetic condition due to inheritance of abnormal haemoglobin genes from both parents. Adolescent and adult patients have long periods of well-being, with occasional acute crises.

Acute crises include vaso-occlusive crises, and lead to pain and infarction. They present as acute bone pain and joint swelling, acute chest syndrome, neurological emergencies (stroke or seizure), arterial and venous thrombotic events (pulmonary embolus), and haematological crisis (splenic sequestration crises, aplastic crises due to infections, folate deficiency, and rarely haemolytic crises).

Chronic complications can occur as a result of prolonged or repeated ischaemia leading to infarction. They include skeletal abnormalities, neurological loss due to stroke, hyposplenism, chronic renal failure, impotence following priapism, loss of lung function, and visual loss.

Laboratory investigations

- Hb of 5–11 g/dl (Hb usually lower than expected relative to symptoms of anaemia)
- Blood film to detect sickle cells, target cells, and reticulocytosis

Additional laboratory tests:

- Sickle solubility or slide test to identify sickle cells
- Haemoglobin electrophoresis to identify abnormal haemoglobin patterns
- HbF quantitation to detect elevation of HbF, which may modify the severity of the disease.

Management

The main aims are to prevent crises and minimize long-term damage when a crisis does occur.

Prevention of sickle crisis

- Avoid precipitating factors including dehydration, hypoxaemia, infection, cold and slowed circulation.
- Give long-term prophylaxis with folic acid 1 mg daily orally.
- Vaccinate with 23-valent pneumococcal polysaccharide vaccine and hepatitis B (see national immunization guidelines).
- Recognize and treat malaria promptly. Haemolysis due to malaria may precipitate a sickle crisis.
- Treat other infections promptly. Adolescents and adults with sickle-cell disease are usually functionally asplenic so have a lifelong risk of pneumococcal infection.
• Consider whether regular transfusion is indicated to maintain a sufficient proportion of normal HbA (about 30% or more) and reduce the frequency of crises and recurrent strokes. Consult a specialist.
• For children and adults with HbSS or HbS-beta0-thalassemia, hydroxyurea is the main preventing therapy for decreasing the incidence rate of acute vaso-occlusive pain. Consult a specialist.

Treatment of sickle crisis
• Rehydrate with oral fluids and, if necessary, intravenous normal saline.
• Give oxygen if low SpO2.
• Give effective pain relief: strong analgesics, including opiates (e.g. morphine) are likely to be needed.
• Treat malaria, if infected.
• Treat bacterial infection with the most appropriate antibiotic in full dose.
• Give transfusion for crises and severe acute anaemia (haemoglobin concentration of <5 g/dl or >2 g/dl below the patient’s normal baseline). Aim for a haemoglobin level of 7–8 g/dl only.
10.15 Abnormal bleeding and bruising

This Section provides an approach to the patient presenting with symptoms or signs of abnormal bleeding and bruising. In addition, it outlines abnormalities seen in laboratory investigations in patients who may present with bleeding. It provides a simplified approach to identifying conditions that can be managed by the district hospital team and distinguishes those that need to be referred for more specialized care or managed in coordination with a specialist.

Normal haemostasis involves the interaction of vessels, platelets and coagulation factors. Bleeding disorders may be due to vascular defects, abnormality of platelets (low platelet count, excessive platelets or defective platelet function), or due to abnormalities of the coagulation or fibrinolytic systems. Bleeding disorders can be inherited or acquired.

10.15.1 Clinical approach to a patient with abnormal bleeding and bruising

History
Focus on the following:

- Symptoms of bleeding
  - what is the duration of the bleeding?
  - is it the first episode or is the bleeding recurrent?
  - how many sites are involved?
  - is the bleeding spontaneous or following trauma?
  - obstetrical or gynaecological history (PPH, abnormal vaginal bleeding).

- History of recent, large volume blood transfusions >10 units, or aggressive IV fluid therapy (may result in dilutional clotting abnormalities)

- History of exposure to drugs or chemicals
  - harmful use of alcohol or illicit substances

Step 1: Perform Quick Check
Use the Quick Check to ensure that there are no serious or life-threatening conditions. Refer to Section 3.1 for management of the severely ill patient with haemorrhagic shock and Section 4 Trauma for how to approach to the acutely injured patient. Also, look specifically for pregnancy or recent delivery, and signs of infection or sepsis.

Step 2: Take a history and examine the patient

Step 3: Assess HIV status

Step 4: Consider the likely differential diagnosis using the differential diagnosis tables

Step 5: Perform investigations

Step 6: Initiate treatment and monitor the patient’s response

---

Abdominal bleeding and bruising

- current or previous use of medications, e.g. warfarin, NSAIDs, aspirin, or traditional, herbal, or alternative medications
- exposure to chemicals at work or in the home.

- Family history
  - relatives with a similar condition
  - relatives with any history suggesting bleeding disorder.

Other symptoms:
- weight loss
- anorexia
- fever and night sweats
- HIV status – CD4 count and treatment history.

Symptoms suggestive of a bleeding disorder
- easy bruising, purpura, and nosebleeds
- excessive bleeding after circumcision, dental extraction or other surgery, or after giving a blood sample or blood donation
- heavy menstruation with clots or perinatal haemorrhage
- dark or bloody stools
- red urine
- episodes of swollen, painful joints or muscles
- excessive bleeding after minor scratches
- bleeding that recurs hours or days after the original trauma
- poor wound healing.

The source and type of bleeding usually suggest the most likely cause. Bleeding from mucous membranes or petechial bleeds suggests a low platelet count or platelet abnormalities, von Willebrand disease (vWD), or vascular defects. Muscle and joint bleeding or bruising may be suggestive of haemophilia A or B.

Examination

Signs of bleeding or blood loss
- pale mucous membranes
- petechial haemorrhages
- purpura or ecchymosis (bruising)
- bleeding from mucous membranes (conjunctiva, gums)
- muscle haematomas
- haemarthroses or deformed joints
- blood on rectal examination
- fundoscopy – retinal haemorrhages.

Note: Skin manifestations of bleeding disorders (e.g. petechial haemorrhages or ecchymoses) are sometimes difficult to see in dark-skinned patients. Examine the mucous membranes, including the conjunctivae, oral mucosa and optic fundi, for evidence of bleeding.

Other signs that may point to underlying or comorbid disease
- splenomegaly
- hepatomegaly
- jaundice
- fever
- tenderness
- lymphadenopathy.
Investigations
For a patient with a suspected bleeding problem:

- Perform FBC.
- Assess whether abnormality is in a single cell line or multiple cell lines:
  - single cell line (isolated low Hb, white cell count, or low platelets):
    - low Hb – anaemia – may be as a result of bleeding, see Section 10.18 Anaemia;
    - high WBC – sepsis or infection, leukaemia (blasts);
    - low WBC count – leukopenia, may be result of an underlying pre-leukaemia or myelodysplastic syndrome;
    - increased MCV – haemolysis, vitamin B12 and folate deficiencies, alcohol misuse or myelodysplastic syndrome – see Section 10.18 Anaemia;
    - low platelets – ensure no false result due to platelet clumping on peripheral blood smear. Repeat the FBC – use citrate or blue tubes if available as this may provide a more reliable result.
  - multiple cell lines (pancytopenia – low Hb, low WBC, and low platelets) indicating total marrow failure or involvement – leukaemia, HIV, marrow infiltration, myelodysplastic syndrome, drugs, aplastic anaemia.
- Peripheral blood smear:
  - Platelets:
    - platelet clumping – platelet count incorrectly low on FBC;
    - large platelets.
  - Red cells:
    - red cell fragments – haemolysis (DIC or TTP/HUS);
    - macrocytic (large red cells; high MCV on FBC) – vitamin B12 and folate deficiency, chronic alcohol use – see Section 10.14 Anaemia;
    - nucleated red cells or a leucoerythroblastic film – marrow infiltration (malignancy, leukaemia or lymphoma);
    - parasitic inclusions (malaria).
  - White cells:
    - increased WBC – infection and sepsis – toxic granulation;
    - decrease WBC – leukopenia. aplastic anaemia or myelodysplasia;
    - blasts – leukaemia – refer for specialized care.
- PT (prothrombin time) and the INR:
  - PT and INR screen for abnormalities in the extrinsic and common pathways of coagulation (factors I, II, V, VII and X). Its main use is for anticoagulant (warfarin) monitoring, and detection of acquired bleeding disorders – especially DIC, liver disease, and vitamin K deficiency. The PT is reported as the international normalized ratio (INR), which reflects the ratio of the patient's PT to the laboratory's control value.
    - Normal range for the PT is between 10 and 13 seconds. An INR >1.5 or a PT ≥3 sec longer than a laboratory’s normal control value is usually abnormal and requires further evaluation.
    - Fill the citrate tube to the line for an accurate result.
- aPTT (activated partial thromboplastin time):
  - The aPTT screens for abnormalities in factors of the intrinsic and common pathways (II, V, VIII, IX, X, XI and XII);
  - A typical normal range is 28 to 34 seconds.
- Crude clotting time:
  - If aPTT or PT (INR) are not available, a crude clotting time will assist to exclude a coagulopathy. It is a crude screening test and not accurate. Confirm abnormal tests with a repeat test and refer patients for further tests if the result is confirmed abnormal.
  - See Section 7.2.18 for details.
  - Exclude medications, e.g. warfarin and heparin.
Additional tests that may be requested depending on the clinical findings include:

- rapid malaria test or malaria blood smear
- occult blood in stool
- pregnancy test
- HIV test and CD4 count
- liver function tests
- renal function (urea, creatinine, and electrolytes)
- ultrasound of the abdomen and pelvis
- bone marrow aspirate or biopsy
- further coagulation tests, such as fibrinogen concentration, fibrin degradation products such as d-dimers, factor assay, platelet function tests.

Figure: Interpretation of initial coagulation investigations

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Clinical features of a bleeding tendency</th>
<th>Laboratory investigations: typical results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin petechiae</td>
<td>Excessive bleeding from venepuncture sites or surgical wounds associated with:</td>
</tr>
<tr>
<td></td>
<td>Bleeding gums</td>
<td>• sepsis</td>
</tr>
<tr>
<td></td>
<td>Excessive bleeding from venepuncture sites</td>
<td>• prolonged hypotension</td>
</tr>
<tr>
<td></td>
<td>Retinal haemorrhages</td>
<td>• trauma</td>
</tr>
<tr>
<td>? Low platelet count or abnormal platelet function</td>
<td>? DIC</td>
<td>? Warfarin (coumarin) overdose</td>
</tr>
<tr>
<td>? DIC</td>
<td>? Warfarin (coumarin) overdose</td>
<td>? Haemophilia A or B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Low</th>
<th>Normal</th>
<th>Low</th>
<th>Normal</th>
<th>Normal/low</th>
<th>Normal</th>
<th>Normal</th>
<th>Normal</th>
<th>Normal</th>
<th>Prolonged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude clotting time (if no other tests available)</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Prothrombin time (PT, INR)</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT)</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal/low</td>
<td>Prolonged</td>
<td>Normal/low</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td></td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal/low</td>
</tr>
<tr>
<td>Fibrinogen concentration</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Normal/low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td>Normal/low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal/low</td>
</tr>
</tbody>
</table>

Reversal of prolonged thrombin time by protamine indicates heparin is absent.
### 10.15.2 Diagnostic approach to active bleeding

Patients who present with active bleeding may or may not have a history of prior episodes with a confirmed diagnosis. Obtain an FBC and classify the bleeding according to whether the platelet count is decreased or normal. Consult with the relevant DDx table below.

**DDx: Bleeding with normal platelet count**

<table>
<thead>
<tr>
<th>Condition</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary inherited causes of bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>von Willebrand disease (vWD)</td>
<td>Family history of the disease Easy bruising, abnormal bleeding after surgical or dental procedures Normal or low platelet numbers, prolonged bleeding time</td>
</tr>
<tr>
<td>Haemophilia</td>
<td>Bleeding into tissues after minimal trauma, e.g. haemarthroses, muscle haematoma Arthropathy may be present Elevated aPTT and normal INR and platelets</td>
</tr>
<tr>
<td><strong>Trauma or local injury</strong></td>
<td></td>
</tr>
<tr>
<td>(see Section 4)</td>
<td>History Bruising or bleeding at localized site Be aware of non-accidental injury patterns (physical abuse)</td>
</tr>
<tr>
<td><strong>Underlying medical conditions or medication</strong></td>
<td></td>
</tr>
<tr>
<td>Renal failure (see Section 11.28)</td>
<td>History of renal disease Decreased urine output Uraemic flapping tremor Raised urea and creatinine</td>
</tr>
<tr>
<td>Liver disease or liver failure (see Sections 8.4, 10.6)</td>
<td>History of chronic liver disease, hepatitis or excessive alcohol use Weight loss Firm liver, jaundice, hepatomegaly and right upper quadrant pain, ascites Splenomegaly Decreased albumin Prolonged INR</td>
</tr>
<tr>
<td>Coumarin-based anticoagulants (warfarin, rat poison) (see Section 3.8)</td>
<td>History of using warfarin or ingesting rat poison Easy bruising, epistaxis, GI bleeding Responds to vitamin K, but may need transfusion of FFP or prothrombin complex for rapid reversal Prolonged INR Normal aPTT and platelets</td>
</tr>
<tr>
<td>Heparin overdose</td>
<td>Usually in patients on heparin infusion Prolonged aPTT</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Long-term steroid use can increase skin and vessel fragility, leading to bruising and bleeding.</td>
</tr>
</tbody>
</table>
### DDx: Bleeding with low platelet count

<table>
<thead>
<tr>
<th>Conditions</th>
<th>In favour</th>
</tr>
</thead>
</table>
| **DIC (disseminated intravascular coagulation)** | Severely ill patient with multiorgan failure  
Predisposing condition, e.g. shock, sepsis, malignancy, or obstetric complications,  
ABO incompatible blood transfusion  
Bleeding from puncture sites  
Gastrointestinal bleeding  
Prolonged INR and elevated aPTT, low platelet count, low fibrinogen level, presence of fibrin degradation products  
Peripheral smear – may have red cell fragments |
| **Sepsis**  
(see Section 3.1.5) | Signs of infection – fever, tachycardia, dehydration, shock  
Identifiable or suspected source of infection |
| **Viral haemorrhagic fever**  
(see Section 11.42, 11.11) | Endemic area or travel  
Fever, headache, malaise, maculopapular rash  
Bleeding tendencies with purpura, petechiae, haematemesis, melaena, or epistaxis  
Patients may be severely ill with shock and organ failure  
Prolonged INR |
| **Thrombotic thrombocytopenic purpura (TTP)**  
(see Section 10.11) | Fever  
Confusion, seizures, intracranial haemorrhage, or coma  
Haemolytic anaemia (jaundice), renal failure  
Venous thromboses at unusual sites  
Abdominal pain  
Usually younger patients <60 years  
HIV-infected  
Drugs (e.g. quinine)  
Associated with haemolytic-uraemic syndrome (e.g. from enterohemorrhagic E. coli)  
FBC: Very low platelet numbers, anaemia  
Peripheral blood film: evidence of haemolysis – RBC fragments on film, high bilirubin, high LDH  
Proteinuria, haematuria, renal impairment  
Normal INR and aPTT |
| **Aplastic anaemia**  
(see Section 10.14) | Recent viral infection,  
History of chemotherapy or chloramphenicol, cotrimoxazole, NSAIDs, carbamazepine, or phenytoin  
Recurrent infections, anaemia  
HIV, hepatitis, and mycobacterial infections  
FBC: persistent pancytopenia  
Low reticulocyte count |
| **Leukaemia (ALL, AML) and deranged clotting/DIC – medical emergency seen in acute promyelocytic leukaemia** | Fatigue, fever, recurrent infections  
Lymphadenopathy, anaemia with or without hepatosplenomegaly  
FBC: pancytopenia; or increased WBC  
Peripheral blood film: blasts |
| **Idiopathic thrombocytopenic purpura (ITP)**  
(a diagnosis of exclusion) | Incidental finding of low platelets in a well patient  
Easy bruising, petechiae, or nose bleeds  
Younger patients  
Women are more commonly affected than men  
No other cause of low platelets (autoimmune, HIV or other viral infection, drugs and alcohol)  
No splenomegaly  
FBC: isolated low platelet count  
Peripheral blood film: large platelets |
| **Myelodysplastic syndromes (MDS)** | Fatigue, anaemia, recurrent infections  
Older patient >60 years  
Platelet count does not respond to steroids  
FBC: pancytopenia  
Peripheral blood film: dysplastic morphological features. |
10.15.3 Diagnostic approach to low platelets with no active bleeding

Decide if only platelets or all cell lines are affected. Exclude artefactual decrease in automated count on FBC with platelet clumping. Look at a peripheral blood film for platelet clumps, large platelets, blasts, increased WBC count (infection or sepsis), and RBC fragments.

Exclude medical causes – consult the DDx table below. If a drug is suspected to be the cause of bleeding or low platelet counts, and other important causes have been excluded (HIV, infection and DIC), then the offending drug should be discontinued if possible. See table below for drugs known to affect platelets. The platelet count should return to normal within a short period of time. If recovery of the platelet count does not occur, a review of the list of other differential diagnoses must be considered.

**DDx: Low platelet count with no bleeding**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>In favour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria (see Section 8.1)</td>
<td>Fever, headache</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Living in or travelled to an endemic area</td>
</tr>
<tr>
<td></td>
<td>Malaria test positive (microscopy or RDT)</td>
</tr>
<tr>
<td>HIV</td>
<td>Other causes excluded – may present as ITP</td>
</tr>
<tr>
<td></td>
<td>Responds to ART</td>
</tr>
<tr>
<td>Metastatic malignancy</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Loss of weight</td>
</tr>
<tr>
<td></td>
<td>Evidence of cancer or known diagnosis of malignancy</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Long-term alcohol use</td>
</tr>
<tr>
<td></td>
<td>Parotomegaly</td>
</tr>
<tr>
<td>Autoimmune conditions</td>
<td>Known diagnosis, e.g. rheumatoid arthritis, systemic lupus erythematosis</td>
</tr>
<tr>
<td></td>
<td>Skin lesions</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td>Medicines</td>
<td>No other medical cause apparent</td>
</tr>
<tr>
<td></td>
<td>Taking medication known to cause low platelets – see table below</td>
</tr>
<tr>
<td>Disseminated fungal infections</td>
<td>Generalized lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Unwell patient: fever, malaise, skin lesions with or without lung involvement</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised patient – CD4 &lt;100</td>
</tr>
</tbody>
</table>

**Table: Medicines affecting platelets**

<table>
<thead>
<tr>
<th>Drugs affecting platelet function (normal platelet counts)</th>
<th>Drugs decreasing platelet count (drug-induced thrombocytopenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• aspirin (up to 7 days);</td>
<td>• heparin-induced thrombocytopenia (HIT) – usually with IV heparin after 4–14 days of use if previous use;</td>
</tr>
<tr>
<td>• heparin;</td>
<td>• anti-TB drugs – rifampin, isoniazid, ethambutol;</td>
</tr>
<tr>
<td>• NSAIDs – diclofenac, ibuprofen (up to 48 hours);</td>
<td>• antibiotics – quinine and quinidine, cotrimoxazole, amphotericin B, nalidixic acid, cephalosporins (cephalothin, vancomycin);</td>
</tr>
<tr>
<td>• clopidogrel (up to 7 days);</td>
<td>• psychotrophic medications – diazepam, haloperidol;</td>
</tr>
<tr>
<td>• penicillins and cephalosporins in high dose; worse with renal failure or low albumin.</td>
<td>• analgesics and anti-inflammatories – paracetamol (acetaminophen), diclofenac;</td>
</tr>
<tr>
<td>Recommendations for elective surgery</td>
<td>• cardiac drugs – methyl dopa, digoxin, amiodarone, hydrochlorothiazide;</td>
</tr>
<tr>
<td>In most surgery, there is no need to stop aspirin or clopidogrel if they are used as monotherapy. If used together, stop the clopidogrel. For cardiac or neurosurgery, stop aspirin 7–10 days pre-surgery; stop clopidogrel 5 days pre-surgery.</td>
<td>• antiretrovirals – IDV, AZT;</td>
</tr>
<tr>
<td></td>
<td>• cimetidine and ranitidine;</td>
</tr>
<tr>
<td></td>
<td>• minoxidil;</td>
</tr>
<tr>
<td></td>
<td>• chlorpromazine;</td>
</tr>
<tr>
<td></td>
<td>• carbamazepine.</td>
</tr>
<tr>
<td></td>
<td>• ibuprofen</td>
</tr>
<tr>
<td></td>
<td>• phenytoin</td>
</tr>
<tr>
<td></td>
<td>• tetracycline</td>
</tr>
<tr>
<td></td>
<td>• glibenclamide</td>
</tr>
<tr>
<td></td>
<td>• fluconazole</td>
</tr>
<tr>
<td></td>
<td>• captopril</td>
</tr>
<tr>
<td></td>
<td>• ampicillin.</td>
</tr>
</tbody>
</table>
Figure: Diagnostic approach to low platelets

Low platelets
Initial investigations

Look at the blood film for:
Platelets clumps, large platelets, blasts
Increase WCC (infection or sepsis)
RBC fragments
?Malaria

Nutritional:
Vitamin B12, folate and iron deficiency
Alcohol

Supporting evidence:
Malnutrition
Gastric surgery
GI malignancy
Inflammatory bowel diseases

Other infections:
HIV
Hepatitis B & C
EBV (monospot)
Malaria

Other diseases:
Liver disease
Malignancy (metastatic)
Autoimmune (SLE)

Exclude
Drugs
Medications

Commonly:
cotrimoxazole, phenytoin, quinine, ceftriaxone, carbamazepine, etc.
See table medicines affecting platelets

Other infections:
HIV
Hepatitis B & C
EBV (monospot)
Malaria

Other diseases:
Liver disease
Malignancy (metastatic)
Autoimmune (SLE)
10. Acute and subacute by symptom: SEARO 2021

**Thrombocytopenia in an HIV-positive patient**
This may be due to HIV itself, but it is important to first exclude possible medical causes and drugs, such as TB treatment, cotrimoxazole. Look for lymph nodes, chest X-ray, skin lesions, sputum.

Consider disseminated fungal infections, lymphoma, ITP, and TTP. Start ART.

**10.15.4 Specific bleeding conditions in detail**

**Disseminated intravascular coagulation (DIC)**
Disseminated intravascular coagulation (DIC) is a pathological activation of coagulation mechanisms that occurs in response to a variety of underlying diseases. Fibrin clots form throughout the body and consume all the available coagulation factors, fibrinogen and platelets. Normal coagulation is disrupted, leading to widespread, uncontrolled bleeding from the skin (e.g. venepuncture sites), the digestive tract, the respiratory tract, and surgical wounds. This in turn stimulates an overproduction of fibrinolytic enzymes to break down the clots formed and an increase in fibrin degradation products. The microvascular thrombi also disrupt normal blood flow to organs (such as the kidneys), leading to multiorgan failure. Red cell fragmentation occurs due to the passage of red cells in the narrowed and damaged microvasculature.

DIC usually is a result of a serious underlying diagnosis (see below), but can in itself become life-threatening, by haemorrhage or thrombosis.

DIC can occur in the following conditions:
- infections: Gram-negative sepsis, *Neisseria meningitidis*, *Streptococcus pneumoniae*, malaria, TB, histoplasmosis, aspergillosis, Lassa fever;
- obstetric: abruptio placentae (premature separation of the placenta from the uterus), retained dead fetus, pre-eclampsia, amniotic fluid embolism, septic abortion or post-partum sepsis;
- massive tissue injury: trauma, crush injury, burns, massive surgery;
- severe hypoxia and acidosis;
- cancers of the lung, pancreas, prostate, breast and stomach, acute myelogenous leukaemia, subtype acute promyelocytic leukaemia;
- miscellaneous: liver disease, snake-bite (see Section 3.9), pancreatitis, shock, heat stroke, ruptured aortic aneurysm, malignant hypertension, pulmonary embolism, subarachnoid haemorrhage, acute haemolytic transfusion reaction.

**Key clinical features**
- often acutely ill
- widespread low-grade haemorrhage or oozing (commonly from the mouth, nose, and venepuncture sites)
- extensive bruising
- shock
- in severe cases, shock, gangrene, coma and renal failure.

**Treatment**
- Manage the patient carefully. Referral to a higher facility may be needed.
- The only effective treatment is the reversal of the underlying causes, e.g. antibiotics for sepsis, removal of retained gestational products.
- Give supportive treatment with fluids to maintain renal perfusion and blood pressure (See Section 3.1).
- Monitor the haemoglobin and consider transfusion when clinically indicated. (See Section 10.14 Anaemia).
• If the INR or aPTT is prolonged and the patient is bleeding, replace red cell losses with the freshest whole blood available, as it contains fibrinogen and most other coagulation factors. Give FFP, as this contains labile coagulation factors – 1 pack/15 kg body weight (4–5 packs in adults). Repeat FFP according to the clinical response.

• If fibrinogen is low or the aPTT or thrombin time is prolonged, also give cryoprecipitate (to supply fibrinogen and factor VIII) – 1 pack/6 kg (8–10 packs in adults).

• If the platelet count is less than 50 x 10⁹/litre and the patient is bleeding, also give platelet concentrates – 4–6 packs (adult).

• If the patient is stable enough for transfer to a higher level of care, this should be arranged immediately as intensive care usually is required.

Idiopathic thrombocytopenic purpura (ITP)

ITP is the condition of having a low platelet count (thrombocytopaenia) of no known cause, i.e. idiopathic. It is a diagnosis of exclusion. Most causes appear to be related to antibodies against platelets, so ITP is known also as immune thrombocytopenic purpura or immune-mediated thrombocytopenic purpura.

ITP usually is asymptomatic, however, a very low platelet count may present with:

• bruises (purpura) and petechiae, especially on the extremities;
• bleeding from the nostrils and bleeding at the gums;
• haematomas in the mouth or on other mucous membranes;
• possible fatal complications due to an extremely low count (less than 5000 per mm³), and may include:
  o subarachnoid or intracerebral haemorrhage;
  o lower gastrointestinal bleeding or other internal bleeding.

Treatment

A platelet count below 20 x 10⁹/litre is generally an indication for treatment. Platelet counts between 20 x 10⁹/litre and 50 x 10⁹/litre are usually evaluated on a case-by-case basis. Admit patients with very low counts, and if the patient presents with significant internal or mucocutaneous bleeding. A count below 10 x 10⁹/litre is potentially a medical emergency as the patient is vulnerable to subarachnoid or intracerebral haemorrhage as a result of a mild to moderate head trauma.

Consult with a specialized centre and consider the following treatments or refer for further management.

• Steroids and intravenous immunoglobulin:
  Treatment usually is initiated with IV steroids (methylprednisolone or prednisone), intravenous immunoglobulin (IVIg) or a combination of these drugs. After the platelet count has increased to a safe level, give an oral steroid, such as prednisone (1–2 mg/kg daily). Most cases respond during the first week of treatment. Gradually reduce the dose of the oral steroid therapy over several weeks. Monitor regularly as 60%–90% of patients relapse after the dose is decreased below 0.25 mg/kg daily.

• Platelet transfusion:
  Platelets can be transfused in an emergency bleeding situation to raise the count quickly in order to start oral steroids. Platelet transfusion alone is not recommended, as platelets usually decrease afterwards due to autoimmune destruction.

• Surgery:
  Splenectomy may be performed although the procedure is potentially risky due to the increased possibility of significant bleeding during surgery. Splenectomy is successful in 60%–65% of cases, but less so in older patients.
  Refer for specialized care if patient does not improve on steroids.
Haemophilia
Haemophilia is a group of hereditary X-linked genetic disorders that impair the body’s ability to control blood clotting or coagulation. It affects men more commonly than women. Haemophilia A has a deficiency of clotting factor VIII, and in haemophilia B, factor IX is deficient. Refer to a specialized centre for diagnosis and management. The patient may be referred back to the district hospital with a supply of required clotting factor concentrates to be administered when needed.

Treatment
There is no cure for haemophilia. It can be controlled with regular infusions of the deficient clotting factor, i.e. factor VIII in haemophilia A or factor IX in haemophilia B.

- Avoid antiplatelet agents such as aspirin and NSAIDs.
- Do not give intramuscular injections.
- Initial management of haemarthrosis includes strong analgesia, ice packs, immobilization, compression, and elevation.
- Do not incise swellings and never incise a joint for haemarthrosis.
- Give clotting factors before surgery, during an active bleed, or after injury and, in some cases, on a regular basis to prevent bleeds.
- In acute bleeding episodes give coagulation factor concentrates as quickly as possible.
- Start physiotherapy as soon as possible after initial treatment to minimize loss of joint function.
- Desmopressin may also be used as it releases stored endogenous factor VIII and von Willebrand factor, so may be useful in mild or moderate haemophilia A. It is not indicated in factor IX deficiency.
- FFP and cryoprecipitate may be used if clotting factor concentrates are not available.

Von Willebrand disease (vWD)
Von Willebrand disease is the most common hereditary coagulation abnormality, although it can be acquired as a result of other medical conditions. There is a qualitative or quantitative deficiency of von Willebrand factor (vWF), required for platelet adhesion.

Key clinical features
- mucocutaneous bleeding, e.g. epistaxis, easy bruising
- menorrhagia
- bleeding after dental extractions
- post-traumatic bleeding.

Treatment
- Patients will need to be referred to a specialized centre for diagnosis and management. They may be referred back to the district hospital for ongoing management with their specific medicines and blood products.
- Bleeding episodes may be managed with desmopressin (although it may become ineffectual after repeated use), factor VIII, or cryoprecipitate, which also contains vWF.
Abdominal bleeding and bruising

10. Acute and subacute by symptom: SEARO 2021
10.16 Splenomegaly

This Section provides an approach to the patient with splenomegaly. Splenomegaly is only rarely symptomatic. In those cases, the patient may present with pain or a heavy sensation in the left upper quadrant. In most cases, splenomegaly is identified during either a focused or complete routine physical examination. Splenomegaly is not considered a diagnosis in and of itself. Rather, it is often a serious sign or indication of an underlying condition that requires identification and treatment.

10.16.1 Clinical approach to a patient with splenomegaly

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<th>Step 6: Initiate treatment and monitor the patient's response. Always consider TB and parasitic infections</th>
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</table>

**History**

- What is the age of the patient? Is there sickle-cell or thalassaemia disease in the family?
- Is the patient from a malaria endemic area or is it malaria season?
- Is the area endemic for histoplasmosis, leishmaniasis, schistosomiasis, or trypanosomiasis?
- What is the nutritional status of the patient?
- Is there pain or heaviness in the left upper quadrant? For how long?
- What is the HIV status of the patient?
- Has the patient had prior TB or recent contact with TB?
- Has the patient had travel or occupational exposure to any of the above infections?
- Are there additional constitutional symptoms?
- Is the patient on any hepatotoxic medications?
- Does the patient drink alcohol?
- Is there any shortness of breath on exertion? Ascites? Swelling of the legs?

**Examination**

**Confirm splenomegaly**

Examination techniques for the spleen:

- Bimanual palpation:
  - Position the patient supine with bent knees.
  - Place the left hand on the lower rib cage and pull the skin upward and taut.
  - As the patient inspires deeply and slowly, use the right hand to stroke upward, starting from the left lower quadrant.
• Record the number of centimetres below the costal margin at a fixed point (e.g. umbilicus) at which the spleen tip is first felt.

• Percussion (Castell’s method):
  • Position the patient supine.
  • Percuss the lowest intercostal space in the anterior axillary line.
  • If the percussion is resonant, the spleen is normal. If it is dull, the spleen is enlarged.

Examine the rest of the body to advance the differential diagnosis
• Skin: look for jaundice, pallor, ecchymoses, spider angioma, caput medusae.
• Neck and lymph nodes: look for the hepatojugular reflex (reflux) (abdominojugular test); feel for lymphadenopathy.
• Heart and lungs: look for signs of heart failure (rales) or heart murmurs.
• Abdomen: check liver for tenderness, enlargement, nodularity, bruits, ascites.
• Extremities: look for joint swelling or tenderness, pedal oedema.
• Neurological exam: check for encephalopathy, reflexes, sensation, proprioception.

Investigations
• FCB and smear: this may indicate infection, disseminated disease, or malignancy. Smear will show evidence of haemolysis.
• Malaria thick smear; tests for other parasites.
• Liver function tests; thyroid function tests if clinically indicated.
• Sputum examination and chest X-ray for TB (see Section 15).
• Ultrasound to confirm splenomegaly, and assess for discrete lesions in the spleen.
• Recommend HIV testing.

10.16.2 Use the DDx table to establish a likely differential diagnosis

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<tr>
<td>Rheumatoid arthritis, systemic lupus erythematosus, drug reactions, thyrotoxicosis, ITP, other autoimmune and collagen vascular diseases (see Sections 10.12)</td>
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<td>Splenic enlargement due to response to infection</td>
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<tr>
<td>Disease</td>
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<td><strong>Subacute bacterial endocarditis</strong> (see Section 11.12)</td>
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<tr>
<td><strong>Splenic abscess</strong></td>
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<td><strong>Other bacterial, viral, fungal, parasitic infections</strong></td>
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### Splenic enlargement due to abnormal splenic or portal blood flow

| Non-specific cirrhosis (see Sections 10.5a, 10.6, 11.16) | Hepatomegaly  
Liver tenderness  
Nodular liver edge  
Other stigmata of liver disease  
Chronic hepatitis B infection  
Look for hepatomegaly  
History of alcohol or hepatotoxic substances or medications (e.g. bush tea, INH) or chronic hepatitis B infection |
|----------------------------------------------------------|--------------------------------------------------------------------------------|
| Hepatic schistosomiasis (see Section 11.29)               | History of "swimmer’s itch"  
Fever, chills, cough, myalgia  
Bloody diarrhoea, abdominal pain |
| Splenic artery aneurysm or splenic vein obstruction       | No hepatomegaly  
If splenic vein obstruction happens acutely, spleen will be tender |
| Splenic enlargement due to unknown etiology               | |
| Berylliosis                                               | Occupational exposure  
Shortness of breath |
| Idiopathic splenomegaly                                  | No compelling evidence of another underlying condition. |

### 10.16.3 Management of splenomegaly

The management of splenomegaly requires the management of the underlying cause (see Sections cross-referenced in the DDx Table above). Splenectomy may be performed to correct cytopaenias when the cause is congestive destruction of blood cells. However, if the cause of cytopaenia is marrow failure, splenectomy is contraindicated as the hyperplastic spleen is the body’s only source of new blood cells.
### 11. Multisystem communicable diseases (in alphabetical order)

(Note: Sexually transmitted infections, HIV, TB, sexually transmitted infections (except GC and syphilis) and genitourinary complaints appear in multiple Sections but their management should be found in national guidelines.)

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11. Multisystem diseases (in alphabetical order)
This Section includes diseases that affect multiple organs and body systems, including opportunistic infections, neglected tropical diseases, other infectious diseases, renal problems, and other common problems such as urinary tract infection and sinusitis. Some multi-system communicable diseases are presented in Section 8 including malaria and dengue.

11.1 Amoebiasis
Amoebiasis results from infection with the non-invasive *Entamoeba dispar* or the invasive *Entamoeba histolytica*, and is the third most common cause of death from parasitic disease. It is most commonly contracted through ingestion of live cysts found with faecally contaminated water, food or hands. Foodborne infection is caused by faecally contaminated soil or water that is used for growing vegetables.

It is endemic in most developing countries. Some patients become chronic asymptomatic carriers who can excrete up to 15 million cysts a day, thereby enabling the spread of amoeba to new hosts.

Acute amoebic colitis can be confused with bacterial diarrhoeas caused by *Campylobacter, E. coli, Salmonella, Shigella* and cholera.

11.1.1 Intestinal amoebiasis

Key clinical features:
- Gradual development of lower abdominal pain and mild diarrhoea.
- Malaise, weight loss and diffuse lower abdominal or back pain.
- If caecum is involved, signs and symptoms will mimic those of appendicitis (right lower quadrant pain).
- Full dysentery develops in some patients with passage of 10–12 stools per day. Stools are mostly blood and mucus.

Severe gastrointestinal disease:
- occurs mostly in children
- characterized by high fever, profuse diarrhoea and abdominal pain.

Complications or unusual presentations:
- amoebic liver abscess
- amoebic colitis can be confused with inflammatory bowel disease
- amoeboma (tender abdominal mass).

Investigations
Stool examination:
- Fresh stool specimens must be examined for trophozoites typical of *E. histolytica*. Cysts of both entamoeba species are very similar; therefore, trophozoites that have ingested red blood cells are diagnostic of *E. histolytica*.

If available, ultrasonography can establish the presence of a liver abscess (due to amoeba or bacteria).

Treatment
Supportive management of dysentery, as well as oral or intravenous rehydration, are both very important. Specific treatment is divided into two groups:
To eradicate invasive disease:
- metronidazole 750 mg 3 times daily for 7–10 days; OR
- *tinidazole* 4 tablets (2 grams) by oral route once daily for 3 days.

To eradicate cysts:
- It is recommended to follow all treatment of confirmed amoebiasis with eradication of cysts, although these agents may not be routinely available. If they are not available, relapse rates are high, and another course of a luminal agent may be warranted:
  - diloxanide 500 mg orally 3 times daily for 5 days; OR
  - *iodoquinol* 650 mg orally 3 times daily for 20 days; OR
  - *paromomycin* 25–35 mg/kg/day orally divided in 3 daily doses for 7 days.

Indications for aspiration are:
- the need to rule out other causes of abscess
- no clinical response after 3 to 5 days
- threat of imminent rupture of the abscess
- prevention of left lobe abscess rupture into pericardium.
This relies on the availability of an ultrasound with an expert operator.

**11.1.2 Amoebic liver abscess**
Amoebic liver abscess is caused by an often delayed extra-intestinal infection by *E. histolytica*. Amoebic infection is spread by ingestion of food or water contaminated with cysts. About 10% to 15% of patients with amoebic liver abscess present with only fever.

**Key clinical features**
- Involves clinical tenderness over the liver.
- Amoebic liver abscess is not usually associated with diarrhoea (although the source is usually the colon).
- In endemic areas, the course is often subacute with haepatomegaly and weight loss.
- Fever is present in 30% of cases, and may be the only presenting symptom.
- May be complicated by pleuro-pulmonary involvement when the abscess extends from the liver into the lung area.

**Investigations**
- An ultrasound of the liver can show abscesses.
- Serology: positive serology means invasive amoebiasis and generally will revert to negative after 6–12 months. The presence of a liver abscess usually means that the etiology is amoeba rather than bacteria.
- A negative stool examination for amoebic cysts or trophozoites does not exclude an amoebic liver abscess.
- Aspiration of the abscess with Gram staining (and culture if available) may be useful to differentiate the amoebic abscess from a pyogenic abscess. Caution should be used in aspirating cysts, as an anaphylactic reaction can occur in cases of echinococcal cysts. The decision to perform a liver abscess aspiration should take into account this risk. Trophozoites are rare in liver aspirates (since they are in the capsule of the abscess and not in the aspirated necrotic centre).
- Routine haematology and chemistry tests are rarely helpful, although about 75% of patients will have WBC count of more than 10 000 cells/µl. Liver enzymes are often normal or only mildly elevated. Alkaline phosphatase levels are often elevated and can remain so for months.
Treatment
- metronidazole 750 mg orally or IV 3 times daily for 5–10 days; OR
- single dose tinidazole 2 g (should not be used in patients with HIV infection).

Most patients will respond well to treatment with metronidazole, with a decrease in fever within 72 hours. The advantage of metronidazole is that if the etiology of the liver abscess is bacterial, this treatment will generally still work (if the bacteria is sensitive). Indications for aspiration (if possible under ultrasound guidance) are:
- need to rule out other causes of abscess
- no clinical response after 3–5 days
- threat of imminent rupture of the abscess (superficial abscess)
- prevention of left lobe abscess rupture into pericardium (very rare).

11.2 Bartonellosis
(Carrion's disease, cat scratch disease, oroya fever, peliosis hepatitis, trench fever, verruga peruana, bacillary angiomatosis)
Bartonella spp cause a wide variety of diseases that include trench fever, cat-scratch disease, peliosis hepatitis, oroya fever and verruga peruana. These clinical entities are not considered AIDS-defining, but they are seen with increased frequency in PLHIV and patients with advanced immunosuppression. Bartonellosis is difficult to diagnose and is largely a diagnosis of exclusion in patients with a fever of unknown origin, skin papules, lymphadenopathy, hepatosplenomegaly, maculopapular skin lesions fatigue and malaise.

11.2.1 Oroya fever and verruga peruana
These entities are caused by B. bacilliformis, and are commonly encountered in the Andes mountains because the vector that transmits the disease is a sandfly. Both entities are a spectrum of the same illness. Oroya fever presents predominantly in patients who have never encountered the disease before and verruga peruana is the manifestation of the disease in patients who have been exposed in the past. Oroya fever is associated with profound anaemia that is usually the cause of death.

11.2.2 Cat scratch disease
Cat scratch disease is a self-limited illness caused by B. henselae. It is associated with scratches from young domestic cats infested by fleas. A majority of cases occur in children, but adults, particularly patients with immunosuppression due to AIDS or who are pregnant, are also affected. Enlargement of the lymph nodes can persist for several months and therefore, mimic a malignancy. Diagnosis is mostly clinical.

Key clinical features
- localized papule at the area of the cat scratch;
- tender lymph nodes in the region draining the area of the cat scratch develop after 1 to 2 weeks;
- nodes may become suppurative with bacterial superinfection common;
- systemic symptoms are limited to malaise, anorexia, and weight loss.

Complications
- neurological: meningitis, encephalitis, seizures, transverse myelitis;
- granulomatous hepatitis and splenitis;
- endocarditis;
- osteomyelitis.
Investigations
- serologic tests can be positive in 60–70% of patients;
- biopsy of the affected lymph node, if available, will reveal stellate necrosis.

Treatment
This condition is usually self-limited, but systemic symptoms may be debilitating. Patients with complicated disease should be treated:
- doxycycline 100 mg twice daily for 10–14 days; OR
- azithromycin 500 mg orally daily for 5 days; OR
- ciprofloxacin 500 mg daily for 10–14 days.
Neurological disease and endocarditis need combined and/or longer treatment. Use caution with ciprofloxacin, as it may partially treat undiagnosed TB.

11.2.3 Trench fever
Trench fever is caused by *B. quintana*, and is associated with infestation with body louse. It is, therefore, a disease of overcrowding and poverty. It occurs throughout the world.

Key clinical features
- sudden onset of headache, meningitis
- persistent or relapsing fever
- bacteraemia can persist for weeks
- localized findings are uncommon.

Complications
- endocarditis may develop with prolonged bacteraemia.

Investigations
- blood culture may reveal the cause, but the organism grows very slowly.

Treatment
- Antibiotic treatment needs to be prolonged to eradicate bacteria and to prevent relapse:
  - doxycycline 100 mg twice daily for 4 to 6 weeks; OR
  - erythromycin 2000 mg daily for 4 to 6 weeks; OR
  - azithromycin 500 mg daily for 4 to 6 weeks.

11.2.4 Bacillary angiomatosis
Bacillary angiomatosis can be caused by both *B. henselae* and *B. quintana* in persons who are immunocompromised. It was first described in PLHIV, but has since been seen in other patients who do not seem to have a dysfunctional immune system. The disease classically involves the skin, but can spread to other areas including the liver (then it is called peliosis hepatis). Bacillary angiomatosis can easily be confused with Kaposi sarcoma, angiomas, and pyogenic granulomas.

Key clinical features
- Vascular nodules or papules or small tumours that are red or purple, and resemble Kaposi sarcoma.

Complications
- Dissemination: fever, abdominal pain, weight loss, malaise.
- PLHIV can also have signs of central nervous system abnormalities such as brain lesions or psychiatric conditions.
- Skin lesions are not always evident in disseminated disease.
- Peliosis hepatis is associated with pain when palpating the liver.
**Investigations**
Diagnosis is mostly clinical, but in cases where there may be confusion with Kaposi sarcoma, one of the following may help differentiate the two:
- a blood culture may yield organisms in disseminated disease;
- a definitive diagnosis is done by examination of a biopsy that usually reveals tiny bacteria associated with new vessels (angiomas).

**Treatment**
Treatment needs to be prolonged, especially in cases where relapse has occurred. Patients with liver disease require intravenous treatment. Effective antibiotics include:
- erythromycin 2000 mg per day orally for three weeks; OR
- doxycycline 100 mg per day for three weeks.
In patients with liver disease, intravenous antibiotics are recommended. Macrolides and tetracyclines are generally preferred to other antibiotics.

11.3 Brucellosis¹,²,³ (Mediterranean fever)

Brucellosis, also known as “Mediterranean fever” or “Malta fever”, is caused by infection with gram-negative aerobic coccobacilli of the *Brucella* species. *B. melitensis* is the most virulent and invasive. Transmission to humans occurs through direct contact of broken skin with infected animal tissue, through inhalation of infectious aerosols, or ingestion of infectious milk or dairy products. Brucellosis is predominantly an occupational disease and a disease of nomadic herdspeople. Sporadic cases and sometimes large outbreaks occur after consumption of raw milk and milk products. Animals involved are cows, sheep, goats, swine and occasionally dogs. Human-to-human transmission occurs rarely, through blood transfusion or sexual contact.

Brucellosis is endemic in the Mediterranean countries, North and East Africa, West Asia, South and Central Asia, and South and Central America. The disease is often unrecognized and frequently underreported.

**Key clinical features**
The patient has a history of recent exposure to known or probable source of brucellosis:
- ingestion of unpasteurized milk or milk products
- unprotected contact with potentially infected animal tissues, blood, or vaginal discharge
- incubation period is variable from a few days to weeks and months.

Brucellosis is a systemic disease with confirmed intermittent or irregular fever (undulant fever of varying duration). Clinical manifestations are non-specific. The term “localized” is used when symptoms related to a specific organ predominate. The disease has acute, subacute and chronic presentations:
- acute brucellosis: (50% of the cases);
- untreated or unrecognized acute disease may become localized:
  - may present as either:
    - mild infection that resolves without treatment in 3 to 6 months,
    - sudden onset fever, chills, sweating,
    - gradual onset headaches, malaise, extreme fatigue with intermittent or absent fever.
other clinical features include:
- myalgia and depression (common),
- anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain, haematuria, cough,
- enlarged liver, spleen and lymph nodes;

• subacute localized disease:
  - localized disease (granulomas, vasculitis) can affect any organ:
    - bone and joint involvement (most common) causing sacroiliitis, spondylitis, paraspinal abscesses, osteomyelitis, suppurative arthritis,
    - genitourinary involvement – orchitis, epididymitis,
    - CNS involvement – meningitis, encephalitis, depression,
    - CVS involvement – endocarditis (commonest cause of death),
    - respiratory involvement – bronchitis, lung abscess, effusions,
    - abdominal involvement – liver granulomas,
    - skin involvement – rashes, papules, erythema nodosum,
    - ophthalmic involvement – uveitis, iridocyclitis (see Section 10.12);

• chronic brucellosis:
  - persistence of local or systemic disease; or
  - relapses of local or systemic disease.

Investigations
To demonstrate the presence of *Brucella*, the following steps are necessary:

• isolation of *Brucella* from blood, bone marrow, pus or other tissues:
  - blood culture – requires special technique and long incubation period, and is often negative in long-standing disease;
  - PCR for *Brucella*;

• serological tests for *Brucella* antibodies in blood or other tissue: combine Rose Bengal test for agglutinating antibodies (IgM, IgG, IgA) with a test for non-agglutinating antibodies (Coombs-IgG, ELISA-IgG);

• X-rays to demonstrate joint disease (blurred joint margins, widened sacro-iliac space, destruction of vertebrae).

The diagnosis of brucellosis at district hospital level is difficult, and is generally made through a combination of patient risk factors and clinical presentation. Do not forget to look for tuberculosis.

Treatment
Use two or more antibiotics in combination:
doxyccycline 200 mg daily for 45 days PLUS streptomycin 1 g IM daily (or gentamicin 5 mg/kg daily) for 15 days (preferred); OR
doxyccycline 200 mg daily for 45 days PLUS rifampicin 15 mg/kg/day (600–900 mg) for 45 days (alternative).
Longer courses may be needed for endocarditis and CNS involvement, but this should generally be managed at regional referral hospital level.

Surgical drainage of abscesses may be needed.
11.4 Candidiasis

Candidiasis is a fungal infection most commonly caused by *Candida albicans*. Candida is part of the normal human flora and is found in the mouth, vagina and gastrointestinal tract. Predisposing factors that can lead to infection are:

- wide-spectrum antibiotic use
- diabetes
- HIV
- pregnancy
- skin maceration, or a break in the natural skin or mucosal barrier.

Candidiasis can be limited to mucous membranes or can occasionally spread through the blood or be deeply invasive.

Key clinical features

Oral candida:
- white deposits that adhere to the mucosa in the mouth and that can extend into the oesophagus;
- difficulty with swallowing;
- persistent oral candida is a WHO stage 3 condition indicating the need to initiate ART (see Section 10.13 Mouth problems).

Skin infection:
- red macerated skin if infection occurs in skin folds under breasts or around the anus;
- usually associated with itching.

Vaginal candidiasis:
- white itchy discharge;
- sometimes associated with pain on urination.

Oesophageal candidiasis:
- can be asymptomatic;
- often associated with chest pain and difficulty swallowing;
- oesophageal candidiasis (and candida of trachea, bronchi, or lungs) is a WHO stage 4 condition, indicating the need to initiate ART (see Section 10.5b Painful or difficult swallowing).

Candida can be a deeply invasive disease. Fungemia can occur mainly through infection of intravenous devices or urinary catheters and can spread throughout the whole body. There are a few organs that are very prone to be invaded after bloodstream infections. These are the eyes, causing blurred vision and showing white cotton ball lesions on fundoscopy, and the liver and spleen, particularly in patients recovering from very low WBC. These situations require specific treatment.

Investigations
- A wet smear can identify the fungus with pseudo-hyphae (branching structures).
- A culture of the likely source will often yield a positive result.

Treatment

Approaches to management depend on the location and severity of the infection. Topical agents are preferred for the skin, but invasive candidiasis needs to be treated with systemic antifungals. Patients with AIDS who have recurrent episodes of candidiasis benefit from having each episode treated separately. Medications to be used depend on where the candidiasis is found:

- Oral:
If recurrent or HIV-infected patient: Oral fluconazole 100–150 mg daily for seven to 14 days is recommended as the preferred treatment.4 When fluconazole is not available or contraindicated, alternatives include topical therapy with:
- nystatin suspension or pastilles, or clotrimazole troches.clotrimazole troche (dissolving tablet) twice daily for seven days; OR
- nystatin: one tablet 500 000 IU 4 times daily; tablets should be sucked and retained in the mouth for as long as possible; therapy should be continued for at least 48 hours after symptoms have resolved; OR
- miconazole gum patch once daily for seven days; case reports also mention its efficacy in treating oesophageal thrush; OR
- miconazole oral gel: 60 mg 4 times daily for seven days.

*Prompt ART initiation is recommended in all HIV-infected adults (including pregnant and breastfeeding women), adolescents and children with oropharyngeal candidiasis.

- **Skin:**
  - Use measures to reduce wetness or moisture and decrease friction.
  - Topical application of an antifungal cream such as nystatin, cotrimazole, terbinafine, or miconazole cream for 5 to 7 days.

- **Vaginal:**
  - **Antifungal treatments include:**
    - miconazole 200 mg vaginal suppository, once daily for three days; OR
    - clotrimazole 200 mg intravaginally daily for four days; OR
    - clotrimazole 500 mg intravaginally in a single dose; OR
    - fluconazole 150 mg orally in a single dose (fluconazole is not recommended in pregnancy);
    - alternative (but less effective) is nystatin 100 000 unit vaginal table daily for 14 days. If this has already been treated topically, re-treat with oral drugs (consider more intensive dosing of fluconazole 150 mg orally, repeated three days later). In severe cases (extensive vulvar erythema, oedema, excoriation and fissure formation), extend topical treatment to 7–14 days, or fluconazole 150 mg, repeated after three days.

- **Oesophagus:**
  - fluconazole tablet 100 mg or 200 mg daily for 14 to 21 days; OR
  - itraconazole 200 mg daily, can be increased to a maximum of 400 mg daily, for 10–14 days; the capsules should be taken with food or an acid drink (such as a cola) to increase their bioavailability; OR
  - ketoconazole: 200 to 400 mg daily if fluconazole is not available, until remission is obtained. Ketoconazole is associated with hepatotoxicity. Ketoconazole should not be co-administered with nevirapine. When administered with lopinavir/r, the dose of ketoconazole should not exceed 200 mg daily.

- **Disseminated disease:**
  - Removal of prosthetic devices including catheters is recommended for the management of invasive candida infections.
  - Give fluconazole 400 mg daily (orally or IV if patient cannot swallow) for 14 days after the last fever.

- **Stopping fluconazole:**
  - Long-term administration of fluconazole may result in the development of drug resistance.
  - Patients stable on ART with immunological (CD4 count >100 cells/mm³) or clinical evidence of immune recovery and no evidence of candidiasis should stop fluconazole.

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11.5 Chikungunya\textsuperscript{5,6,7}

Chikungunya (CHIK) is a debilitating zoonotic disease of humans caused by the chikungunya virus (CHIKV). It is transmitted by infected \textit{Aedes} spp. mosquitoes, which bite during the day. Chikungunya outbreaks have occurred in all countries in the South-East Asia Region. Outbreaks are most likely to occur in the post-monsoon period when the vector density is high, though in some places there is endemic co-circulation with dengue. Acute symptoms are similar to dengue, leptospirosis, scrub typhus, Zika, malaria – consider the differential diagnosis (see Section 8.1). Co-infections can occur – CHIKV with dengue, scrub typhus or malaria.

**Transmission**
Transmitted by the bite of an infected female \textit{Aedes aegypti} or \textit{Aedes albopictus} mosquito.

**Key clinical features**
Incubation 1–12 days (average 2–7).
Not life-threatening.

**Acute phase, usually <1 week, but sometimes biphasic**
- Abrupt onset of high fever, nausea, intense polyarthralgia, myalgia, backache, headache.
- Joint pains usually symmetric in both arms and legs; large joints most commonly symptomatic. Joints may become swollen and painful to the touch. In some, ankles, wrists and small joints of the hand are the worst affected.
- Skin rash in 50% – macular or maculopapular; often short-lived.
- Infrequent: stomatitis, oral ulcers, exfoliative dermatitis.

**Post-acute phase, from resolution of fever to end of the third month**
- Can be temporarily disabling and debilitating when joint pain or arthritis (synovitis with or without effusion) +/- tenosynovitis, bursitis and fatigue persist and slowly regress.
- Decompensation of pre-existing osteoarthritis and tendinitis can lead to oedema, entrapments, joint stiffness and neuropathic pain.

In some patients, a chronic phase – without return to patient’s preexisting status, which can last a few months to several years.

Uncommon serious complications, usually in patients with comorbidities or advanced age, include myocarditis, uveitis, retinitis, hepatitis, acute renal disease, severe bullous lesions, (meningo-)encephalitis, Guillain-Barré syndrome, myelitis, and cranial nerve palsies.

**Investigations**
RT-PCR on blood – not all need to be tested during an epidemic.
ELISA for IgM and IgG anti-CHIKV antibodies. Rapid antibody tests are used in some settings, but they perform less well.
CBC, platelets (thrombocytopenia <100, uncommon – unlike dengue).

**Treatment**
Treatment is supportive.

There is no specific antiviral treatment and no effective vaccine.

\textsuperscript{5} Guidelines on Clinical Management of Chikungunya Fever, WHO SEARO, 2008
\textsuperscript{7} Chikungunya http://origin.searo.who.int/entity/emerging_diseases/topics/Chikungunya/en/
Symptomatic management (see Section 12). Special considerations:
- Assess for dehydration and rehydrate, preferably oral (see Section 8.3).
- Manage pain: paracetamol with additional analgesics if needed. Avoid aspirin.
- Control inflammation with anti-inflammatories.
- If disabling peripheral arthritis lasting several months, some may require short course corticosteroids\(^8\) (other antirheumatic drugs have also been used).

Treat serious complications.
During recovery – mild forms of exercise, physical therapy. Encourage active hand movements and proper posturing of joints.

**Infection prevention and control**
Standard precautions.
To avoid further transmission, patients during the first few days of symptoms should stay in a screened place or sleep under an impregnated bednet.

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11.6 Coronavirus: SARS-CoV-2 (COVID-19) and MERS CoV

Coronaviruses are RNA viruses that cause respiratory diseases in humans, from mild cases causing the common cold to more severe causes of respiratory illness e.g. SARS, MERS, and now, COVID-19. SARS, the disease caused by SARS-CoV-1 virus, has not been transmitted since 2004.

11.6.1 COVID-19

COVID-19 is a viral respiratory disease caused by SARS-CoV-2, a novel coronavirus, that was first identified in Wuhan, People’s Republic of China in December 2019 and has led to a global pandemic.

Transmission

The origin of SARS-CoV-2 (earlier called nCoV-2019) is still unclear. It is thought that the virus came from a bat host and then was transmitted to humans from an intermediary animal, but this origin is still being studied.

There is human-to-human transmission of this virus, mainly through:

- Droplet and contact transmission – through direct, indirect or close contact by inhalation of respiratory droplets or saliva from an infected person sneezing, coughing, talking or singing.
- Fomite transmission – contact with contaminated objects/surfaces and then touching one’s own mouth, nose or eyes.
- Airborne transmission – the virus can be aerosolized through aerosol-generating medical procedures such as intubation, extubation, CPR, bronchoscopy, manual ventilation, etc. There is concern for aerosolization of the virus in enclosed indoor, crowded, poorly ventilated spaces e.g. restaurants, fitness classes, nightclubs, choir practice halls, offices and places of worship.

There is also evidence that the virus is spread through pre-symptomatic (person infected with COVID-19 but is yet to develop symptoms) and asymptomatic transmission (person infected with COVID-19 and does not develop symptoms).

Key clinical features

Mild disease (40%) of people with COVID-19:

- fever (83%–99%)
- cough (59%–82%)
- fatigue (44%–70%)
- anorexia (40%–84%)
- non-specific symptoms: headache, sore throat, nasal congestion
- GI symptoms: nausea, vomiting, and diarrhoea preceding onset of respiratory symptoms have been reported
- loss of smell (anosmia) or taste (ageusia) preceding onset of respiratory symptoms have also been reported
- atypical symptoms seen in older people and immunosuppressed – reduced alertness, confusion, reduced mobility, loss of appetite, and absence of fever
- mental health manifestations – anxiety, depression, sleep problems.

Moderate disease (40%):

- pneumonia.

Severe disease (15%)

- severe pneumonia, requiring oxygen support.

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Critical disease (5%):
- ARDS
- sepsis and septic shock
- thromboembolism – e.g. acute pulmonary embolism, acute coronary syndrome, acute stroke.

Other severe complications include:
- multiorgan failure, including acute kidney and cardiac injury, acute liver injury
- neurological manifestations–mengingo-encephalitis, encephalopathy, agitation, delerium. Neurological problems have been reported without respiratory symptoms.

Risk factors for severe disease include older age (older than 60 years), diabetes, cardiac disease, cerebrovascular disease, hypertension, chronic lung disease, dementia, mental disorders, immunosuppression, obesity, smoking, cancer and chronic kidney disease. Also pregnancy, obesity (body mass index [BMI] of 30 kg/m\(^2\) or higher), increasing maternal age, non-white ethnicity, chronic conditions and pregnancy-specific conditions, e.g. pre-eclampsia.

**Multisystem inflammatory syndrome in children (MIS-C)** is a rare but serious condition associated with COVID-19. It occurs in children and adolescents 0–19 years with fever \(\geq 3\) days **AND** at least two of the following: rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including ECHO findings, elevated troponin/NT-proBNP); evidence of coagulopathy (PT, PTT, elevated D-dimers), acute GI problems (diarrhoea, vomiting or abdominal pain); **AND** elevated inflammatory markers (ESR, CRP or procalcitonin) **AND** no other obvious microbial cause of inflammation (e.g. bacterial sepsis, staphylococcal or streptococcal shock syndromes) **AND** evidence of COVID-19 or likely contact with COVID-19 patient.\(^{10}\)

**Investigations (See Section 7)**\(^{11,12}\)
- **RT- PCR or other NAAT:**
  - Upper respiratory sample – oro/nasopharyngeal swab or wash. Sensitivity improves when combined nasopharyngeal and oropharyngeal swabs.
  - Lower respiratory specimen – sputum (if produced) and/or endotracheal aspirate or bronchoalveolar lavage in mechanically ventilated patients (later in course of disease, patients with severe disease and strong clinical suspicion in patients with negative URT sample).
  - Viral RNA has been detected in other sites – faeces, blood, ocular fluid, urine, cerebrospinal fluid and brain tissue in case reports. Faecal samples can aid in diagnosis if appropriately validated by receiving laboratory. Also consider postmortem specimens if deceased.
  - Optimal detection continues to be respiratory material and therefore the frequent choice for diagnosis.
- **Antigen-detecting rapid diagnostic tests (Ag-RDT)**\(^{13}\): Point-of-care test detects SARS-CoV-2 protein from nasal, nasopharyngeal or saliva samples. Results obtained generally in 10 to 30 minutes; sensitivity lower compared with NAAT but specificity is high. Tests recommended by WHO are those with \(\geq 80\%\) sensitivity and \(\geq 97\%\) specificity compared with NAAT reference assay in settings “where NAAT is unavailable or where prolonged turnaround times preclude clinical utility”. These tests may be useful in certain situations

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\(^{13}\) WHO. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. Interim guidance. 11 September 2020.
outbreaks in institutions such as schools, early case detection in health facilities during widespread community transmission and testing of asymptomatic contacts of cases. It is recommended where possible that positive samples or a subset get sent to laboratories for NAAT confirmatory testing for ongoing validation.

- **Antibody test-paired serum sample** (acute and convalescent): May support diagnosis once validated serology tests are readily available. Serology may be useful in certain clinical situations:
  - infection suspected but Rt-PCR result negative – antibody test-paired serum sample (acute and convalescent – 2 to 4 weeks later) may support diagnosis once validated serology tests are readily available
  - late presentation patient or prolonged symptoms who may also have received mRNA vaccine.
- See figure below for diagnostic flow for detection of SARS-CoV-2 infection:

![Diagnostic Flow Diagram for the Detection of Acute SARS-CoV-2 Infection in Individuals with Clinical Suspicion for COVID-19](image)

- Test for other respiratory pathogens as appropriate (note that a positive test for another pathogen does not rule out COVID-19 as co-infections do occur).
- Other investigations based on clinical presentation – See Section 3.2.
Treatment\textsuperscript{10, 14}

Treatment for COVID-19 is mainly supportive.

- Mild disease – isolate at home or community facility or health-care facility; educate on symptomatic treatment, advise on signs/symptoms to return to hospital, advise on IPC – see c p.12 and Section 6.12
- Moderate disease/pneumonia – isolate in hospital if possible (preferred if high-risk) or community facility or home; provide supportive care, IPC – see Section 8.2; advise on signs/symptoms to return to hospital, symptom management, and IPC if at home, and educated on awake proning; pulse oximetry monitoring at home is recommended – see Quick check p.12 and Section 6.12.
- Severe/critical disease – isolate at hospital, shared decision-making, use care bundles to improve care, oxygen therapy, awake proning, VTE prophylaxis, escalate respiratory treatment as appropriate, empirical antibiotics, cautious intravenous fluids if no evidence of tissue hypoperfusion, awake proning, monitor electrolytes/metabolites/inflammatory markers, corticosteroids, symptom control and palliative care – see Sections 3.0, 3.1, 3.2, 3.3, 12.
- Experimental or emerging therapies continue to be studied for COVID-19 through clinical trials – recommended for select patients and should be given based on national protocols; See the living guidelines on WHO or BMJ website or MAGICapp.\textsuperscript{15}

Infection prevention and control

Standard plus droplet plus contact precautions.

Add airborne precautions for aerosol generating procedures – see Section 6.0.

Source control for the patient – masking, respiratory hygiene.

Post-acute COVID-19 – also termed ‘post-COVID-19 syndrome,’ ‘long haulers,’ or ‘long-COVID’\textsuperscript{10}

This description is for patients who develop symptoms during or after infection with acute COVID-19 that continue for 12 weeks or longer without an explanation of alternative diagnosis. Global data has shown consistently that persistent symptoms of COVID-19 exist after acute illness. In a cohort of 1733 adult patients with COVID-19 in Jin Yin-tan Hospital (Wuhan, People’s Republic of China) that were discharged after acute illness, 76% (1265 of 1655) patients had at least one symptom that persisted at six months; 50% of patients had residual chest imaging abnormalities.\textsuperscript{16} Data from the United Kingdom shows that more than 20% of patients who have tested positive for COVID-19 had symptoms longer than five weeks and over 10% have had symptoms for 12 weeks or longer.\textsuperscript{17} Common symptoms include fatigue and breathlessness.\textsuperscript{10}

There is some evidence from prior coronavirus outbreaks that some lung damage could persist. For example, 38% of patients who recovered from SARS had reduced lung diffusion capacity even 15 years after infection.\textsuperscript{18} One study indicated that 40% of people recovering from SARS


\textsuperscript{17} Venkatesan P. NICE guideline on long COVID. \textit{The Lancet Respiratory Medicine}. 2021(9):2-129.

had chronic fatigue 3.5 years after being diagnosed.\textsuperscript{19} Long-term pain, fatigue, depression, sleep disturbances and PTSD have all been associated with SARS-CoV-1.\textsuperscript{10}

As COVID-19 is a novel disease, it is hard to define this post-acute COVID-19 as related to complications of hospitalization for severe disease or for critical disease, e.g. post-ICU syndrome or from the virus itself.

Symptoms range and include the following:\textsuperscript{20,21}

- General – severe fatigue, fever, pain
- Respiratory – breathlessness, cough
- Cardiovascular – chest tightness, chest pain, palpitations
- Neurological – “brain fog,” loss of memory or concentration, headache, peripheral neuropathy, dizziness, delirium (for older patients), sleep disturbance
- Gastrointestinal – abdominal pain, nausea, diarrhoea, anorexia/reduced appetite (older)
- Musculoskeletal – joint pain, muscle pain
- Psychological/psychiatric – depression, anxiety
- ENT – tinnitus, earache, sore throat, dizziness, loss of taste or smell
- Dermatological – skin rash.

These persisting symptoms are not necessarily linked to illness severity of acute COVID-19.

**Assessment/Investigations\textsuperscript{17,20}**

Important to include a multidisciplinary team and tailor to patient’s signs and symptom.

- assess functional limitations – work/school, activities of daily living (ADLS), exercise etc, include sources of anxiety, days missed, financial;
- assess sleep, mood
- laboratory may include: FBC, kidney function tests, liver function tests, CRP, TSH; HbA1c if peripheral neuropathy
- imaging depending on symptoms – chest x-ray, CT head
- other: exercise tolerance test, e.g.\textsuperscript{1} min sit to stand test – record heart rate, oxygen saturation and level of breathlessness, check orthostatics if patient feels dizzy, 3 min active stand test or 10 minute if suspect postural tachycardia
- pulmonary function tests (anecdotal observation: symptomatic/objective mismatch), cognitive testing.

**Treatment\textsuperscript{20,21}**

Provide ongoing follow-up at discharge from hospital or health facility from acute COVID-19 illness – what to watch out for and when to return.\textsuperscript{10}

- This may include but not limited to: difficulty breathing, oxygen desaturation if pulse oximetry available, chest pain, palpitations, confusion; also breathlessness after exercise or climbing stairs.
- Offer different platforms for follow-up – phone consultation, videocall, or in person.
- If symptomatic- use multidisciplinary assessment/teams/rehabilitation to provide integrated coordinated care, rehabilitation specialists, occupational therapy, physiotherapy, clinical psychology and psychiatry.


\textsuperscript{21} CDC. CDC Clinician outreach and communication activity (COCA) webinar: Long COVID: Clinician experience with post-acute COVID-19 care. 28 January 2021.
• Provide advice on self-management, symptom monitoring, also supported self-monitoring, e.g. HR, pulse oximetry if makes sense:
  o set realistic goals
  o who to contact.
• Support groups – local, social media groups, online FB, other apps.
• Provide information as more is known.
• Discuss support for back-to-work or school – phased return an option?
• Ongoing olfactory dysfunction – may improve on own or if ongoing after 2 weeks, consider treatment, e.g. olfactory training: deliberate sniffing a set of odorants for 20 seconds each at least twice daily for at least three months or longer; efficacy of treatment is not established.  
  
  22
• “brain fog” – address bloodwork abnormalities; may be attention problems – cognitive rehabilitation, meditation, breathwork.
• Fatigue – pacing of exercise, short duration activity.
• Sleep problems – sleep hygiene, sleep aids.
• Address mental health – see mhGAP.

Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by MERS-CoV, a novel coronavirus that appeared in 2012. MERS has a clinical spectrum of diseases ranging from asymptomatic to mild to severe pneumonia and death. Case-fatality ratio is 35.5%.

Transmission
Dromedary camels are the reservoir host for MERS-CoV. The exact transmission from infected camels to humans is unknown. Human cases have occurred through close human-to-human transmission in health-care settings and in family clusters. Outbreaks have occurred in Saudi Arabia, United Arab Emirates, and Republic of Korea. Cases continue to occur and have been reported in 27 countries around the world since 2012. To date, sustained human-to-human transmission has not been documented.

Introduction of MERS by returning travellers is an ongoing risk. Over 0.4 million people go on Hajj pilgrimage to Mecca from the SEA Region annually, with 95% of them from Bangladesh, Indonesia and India.

Key clinical features
Incubation period 2 to 14 days:
- fever – may be absent in 15% of hospitalized cases.
- cough
- shortness of breath
- myalgias
- some have GI symptoms – nausea, vomiting, diarrhoea
Pneumonia is common. Complications include ARDS, septic shock and multiorgan failure leading to death. Risk factors for mortality include older age and chronic lung disease. Other risk factors for severe disease include diabetes, renal failure and immunocompromised persons. Infections in children are uncommon.

Investigations
RT-PCR
- Lower respiratory tract specimen collection – bronchoalveolar lavage, sputum and tracheal aspirates.
- Upper respiratory tract – nasopharyngeal/oropharyngeal swab.
- Viral loads have been observed to be higher in the lower respiratory tract. Wherever possible, it is recommended that both upper and lower respiratory tract specimens be collected.
- Test for other respiratory pathogens as appropriate.
Serology – only if RT-PCR not available for confirmation of infection, maybe of value for identifying probable cases or prior infections (interval between illness onset and sample collection is 21 days); paired serum samples should be collected 3–4 weeks apart, with the first being taken during the first week of illness.

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23 Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected: Interim Guidance, WHO, January 2019.
24 WHO. MERS Situation Updates. Available at : https://www.who.int/emergencies/mers-cov/en/
**Treatment**
Treatment is currently supportive; there is no specific treatment or vaccine. Isolate in hospital. Oxygen therapy, escalate respiratory care as needed [refer for mechanical ventilation] IV fluids, monitor for and manage septic shock, empirical antibiotics, symptom control and palliative care- see clinical management summary\(^{12}\) and details of care in Sections 3.0, 3.1, 3.2, 12].
For discharge, repeat URT and LRT samples every 2 to 4 days until there are two negative results in a clinically recovered patient at least 24 hours apart.

**Infection prevention and control**
People at high risk of disease should avoid contact with camels, their urine, drinking raw camel milk or uncooked meat.
Health workers: standard plus droplet plus contact precautions to prevent direct or indirect transmission. Add airborne precautions for aerosol generating procedures – see Section 6.0.
11.7 Crimean-Congo Haemorrhagic Fever\textsuperscript{26,27}

The causative agent of Crimean-Congo haemorrhagic fever (CCHF) is a Nairovirus, a group of related viruses in the Bunyaviridae family. It is the only VHF with human-to-human transmission documented so far in the SEA Region.

CCHF is a significant threat for the Region, which has a high human and animal density, poorly guarded human–animal interface, widespread distribution of the vector, and the Hyalomma tick, in eight out of 11 SEA Region countries, and weak animal health and vector surveillance systems.\textsuperscript{28} An outbreak occurred in India in 2011.\textsuperscript{29}

Although only two SEA Region countries have reported CCHF in humans (India and Bangladesh), the vector (different species of the Hyalomma tick) exists in Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Myanmar, Nepal and Thailand.\textsuperscript{28}

Transmission

Transmission of the CCHF virus to humans can occur in several ways:

- A bite from an infected tick or crushing a tick against the skin. Ixodid (hard) ticks, especially those of the genus Hyalomma, are both a reservoir and a vector for the CCHF virus. Numerous wild and domestic animals, such as cattle, goats, sheep and hares, serve as amplifying hosts for the virus.
- Contact with the blood of an infected animal. Animal herders, livestock workers and slaughterhouse workers in endemic areas are at risk of CCHF.
- Human-to-human transmission through contact with infectious blood or body fluids in the community or in hospitals. Aerosol generating procedures have also resulted in cases of secondary nosocomial infection of health workers.
- Documented hospital spread due to improper sterilization of medical equipment, re-use of injection needles and contaminated medical supplies.
- Possible vertical transmission from a mother to her child has been reported. The risk of exposure during breastfeeding is unclear, although considered high.

Key clinical features

Early and late clinical signs vary, with a wide spectrum of disease severity from mild to fatal outcome (case fatality rate 5%–30%). An estimated 88% of infections are subclinical.\textsuperscript{2} Incubation period depends on the mode of acquisition. It ranges from 2-14 days but is usually 3–7 days. The documented maximum after a tick bite is 9 days and after contact with infected blood or tissues, 13 days.

Sudden onset with initial signs and symptoms including headache, high fever, chills, anorexia, lethargy, joint and back pain, abdominal pain and vomiting, sometimes jaundice, and in severe cases changes in mood and sensory perception. In approximately 30% of patients, hepatosplenomegaly can also be found.

Ask the patient about exposure to ticks, to wild animals and livestock, travel to an area or village endemic for CCHF, or contact with a CCHF case.

\textsuperscript{26} This section borrows from the VHF pocket guide- World Health Organization. Clinical management of patients with viral haemorrhagic fever: a pocket guide for front-line health workers: interim emergency guidance for country adaptation. February 2016.
\textsuperscript{28} Roots for resilience: a health emergency risk profile of the South-East Asia Region, WHO SEARO 2017.
The initial clinical manifestations are non-specific and mimic many common infections, making CCHF difficult to diagnose early. Thus, it is important to understand the case definition and expand differential diagnosis to include other causes of fever and non-specific symptoms (for example, malaria, typhoid, acute gastroenteritis/shigellosis, respiratory infections, urinary tract infections, other viral hemorrhagic fevers).

The haemorrhagic period is usually short (2–3 days, but it can be up to 2 weeks), develops rapidly, and usually begins between the third and fifth days of disease. Haemorrhagic manifestations of CCHF are common and range from petechiae to large haematomas on the mucous membranes and skin. The most common bleeding sites are the nose (epistaxis), gastrointestinal system (haematemesis, melena and intra-abdominal bleeding), uterus (excessive menstrual bleeding), other vaginal bleeding, urinary tract (haematuria), respiratory tract (haemoptysis) and ecchymoses. Uncontrolled bleeding at injection sites can also be seen, and bleeding from other sites, including cerebral haemorrhage, has been reported.

Adverse prognostic indicators and risk factors include age greater than 60 years, rapid progression of clinical status and laboratory values, somnolence and platelets <50 000 mm$^3$ or prolonged aPTT.

Laboratory tests return to normal levels within approximately 5–9 days among surviving patients.

**Investigations**
Definitive diagnosis by RT PCR; IgG and IgM enzyme-linked immunosorbent assay (ELISA); antigen detection kits; or virus isolation by cell culture.

Laboratory features of CCHF include thrombocytopenia, leukopenia, elevated liver enzymes, and prolonged bleeding times.

Handling and processing specimen require suitably equipped laboratories under maximum biological containment conditions and trained staff collecting samples.

**Treatment**
Other than ribavirin treatment and possibly the support for the coagulation system with blood component therapy, clinical management in health facilities are the same for Ebola and CCHF. See Optimized Supportive Care for Ebola Virus Disease$^{30}$ and detailed guidance on management of fluids, shock, electrolytes, etc. in Sections 3.0–3.1- 3.2; 11.11; and the VHF pocket guide.$^{31}$

Ribavirin can be given early in the course of CCHF although its efficacy has not been proven by a randomized controlled trial, and there are differences in opinion on its clinical effectiveness in the published literature.

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**Ribavirin dose for CCHF**

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV*</td>
<td>30 mg/kg (maximum 2 grams)**</td>
<td>Loading dose, followed by:</td>
</tr>
<tr>
<td>IV</td>
<td>IV* 15 mg/kg (maximum 1 gram) **</td>
<td>Every 6 hours for 4 days, followed by:</td>
</tr>
<tr>
<td>IV</td>
<td>IV* 7.5 mg/kg (maximum 500 mg)**</td>
<td>Every 8 hours for 6 days</td>
</tr>
</tbody>
</table>

* Dilute ribavirin in 150 ml of 0.9% saline and infuse slowly.

** Reduce the dose in persons known to have renal insufficiency (creatinine clearance <50 ml/minute).

Major adverse effects due to short-term ribavirin therapy are rare but require monitoring. The main side-effect is a dose-dependent, mild-to-moderate haemolytic anaemia that infrequently necessitates transfusion and disappears with cessation of treatment. Haemoglobin/haematocrit and bilirubin levels should be checked at initiation of ribavirin therapy and then every few days, with consideration of transfusion of packed red blood cells if significant anaemia develops. Rigours may occur when ribavirin is infused too rapidly. See formulary or VHF Pocket Guide for contraindications and other side-effects.

**Infection prevention and control**

Standard plus contact plus droplet precautions (see Section 6).

Institute screening and isolate suspected, probable and confirmed cases.

If an isolation area is not available or if advance preparations have not been done, immediately set aside a single room. This room should have an adjoining toilet or latrine, good ventilation, screened windows and restricted access.

**Reporting, contact tracing and education**

Immediate reporting.

Contribute to contact tracing and early case-finding.

Epidemiology investigation to find the source.

Help educate community on reducing risk of tick-to-human transmission.

**Post-exposure prophylaxis with ribavirin**

Post-exposure prophylaxis should be considered for those exposed to CCHF. This should be limited to high-risk close contacts of the patients and laboratory and health workers, defined as one of the following:

- penetration of skin by a contaminated sharp instrument (e.g. needle stick injury);
- exposure of mucous membranes or broken skin to blood or bodily secretions (e.g. blood splashing in the eyes or mouth);
- participation in emergency procedures without appropriate personal protective equipment (for example, resuscitation after cardiac arrest, intubation or suctioning); or
- prolonged (hours) and continuous contact in an enclosed space without appropriate personal protective equipment.

In estimating infection risk, note that the most infectious patients are those with severe clinical conditions, usually late in the course of illness. Prophylaxis should not be used when the only exposure was during the incubation period or during convalescence after fever has subsided.

The prophylaxis dose is oral ribavirin 35 mg/kg loading dose (maximum 2.5 g) followed by 15 mg/kg (maximum 1 g) every 8 hours for 10 days.33

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33 Bausch, DG et al. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa Fever, Ribavirin Postexposure Prophylaxis, CID 2010, 51:1435-1441
11.8 Cryptococcosis

This infection is most commonly caused by Cryptococcus neoformans, particularly in HIV-positive patients with advanced immunodeficiency (CD4 cell count generally <100/mm³). However, patients who have been on long-term steroid therapy, as well as other immunosuppressive drugs, are also at risk. Notably, other species of Cryptococcus (e.g. Cryptococcus gattii) are increasingly recognized as a cause of cryptococcosis in immunocompetent individuals. Typically, infection is acquired by inhalation of the fungus into the lungs. Cryptococcus is found in most areas with a relatively warm climate, but is not restricted to the tropics. In the South-East Asia Region, an estimate of over 140 000 cases of Cryptococcus neoformans occur in HIV-infected people annually.

Cryptococcal meningitis or meningo-encephalitis is the most common presentation in HIV-positive patients, and is associated with a universal mortality without treatment. Non-meningeal presentations of cryptococcosis include pneumonia, skin lesions, and lymphadenitis. Approximately 43 200 cases of cryptococcal meningitis occur in HIV-infected patients each year in Asian and Pacific countries.

Key clinical features

- Sub-acute meningitis: headache increasing over days to weeks, fever, photophobia, nausea, seizures, confusion, irritability, blurred vision, sixth cranial nerve palsy, papilloedema on retinal exam are common. Nuchal rigidity is often not marked.
- Coma, or a reduced level of consciousness are associated with a poor prognosis.
- Lung infections: chest pain and cough in a minority of patients, but often no fever.
- Skin lesions: disseminated disease is associated with papular lesions with an umbilicated, centrally depressed area (similar appearance to molluscum contagiosum), which can become ulcerated.

Complications

- Intracranial pressure can become raised (increasing headache, vomiting, cranial nerve palsy).
- Cryptococcomas can develop in the brain, more commonly in patients who are not immunocompromised.
- Coma, cerebral oedema, and death follow if it is untreated, usually due to elevated intracranial pressure.
- Hydrocephalus, blindness, dementia, and personality change can occur as permanent sequelae.

Investigations

- A lumbar puncture and CSF examination is the most useful investigation with rapid cryptococcal antigen assay (preferred diagnostic approach):
  - elevated opening pressure (more than 20 cm H₂O in 70% of patients),
  - rapid cryptococcal antigen (lateral flow assay or latex agglutination test that examines the presence of capsular antigen) – results in the rapid test in <24 hours.

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Other CSF findings:
- white blood cell counts in CSF counts are variable but with a lymphocytic predominance; however, WBC counts may be normal,
- lower or normal glucose level,
- mildly elevated or normal CSF protein.

*If access to cryptococcal antigen assay is not available and/or rapid results not possible, perform lumbar puncture with CSF India ink test:*

- Presence of encapsulated yeast forms on an India ink stain of the CSF is the most widely available diagnostic test (sensitivity 82%–85%, but may be negative if low fungal burden).
- If lumbar puncture not accessible or contraindicated (e.g. significant coagulopathy, suspected space-occupying lesion based on focal CNS signs preferably confirmed by CT, recurrent seizures, major spinal deformity or patient refusal):
  - rapid serum, plasma or whole-blood cryptococcal antigen assay can be obtained.
  - If cryptococcal antigen assay is not available and/or rapid access to results are not available: refer for further investigation and treatment.
  - A positive CSF fungal culture is the definitive test, but is not widely available and may take some days so rapid testing for diagnosis is preferred.
  - Cryptococcus can be cultured in the blood in 70% of cases.
  - Microscopy and culture from non-meningeal cryptococcal sites – visualization of encapsulated yeasts or positive culture from skin scraping or biopsy, sputum, urine, lymph node FNA, or biopsy.
- Chest X-ray – similar to PCP (bilateral diffuse interstitial infiltrates).

**Screening and prevention**
- Screen for cryptococcal antigen in HIV-infected adults or adolescents with CD4 cell count < 100 mm$^3$ and consider for those with CD4 cell count <200 mm$^3$. Screen before initiation or reinitiation of ART.
- If cryptococcal antigen positive – evaluate for cryptococcal symptoms and provide pre-emptive therapy with fluconazole 800 mg orally each day for adults; 12 mg/kg/day for adolescents for two weeks to prevent progression to invasive cryptococcal disease. Follow pre-emptive treatment with consolidation and maintenance fluconazole therapy (see below). If symptoms present, perform lumbar puncture.
- If cryptococcal antigen screening not available and CD4 cell <100 mm$^3$ – treat with primary prophylaxis with fluconazole, follow national guidelines.

**Anti-fungal treatment**
If the patient has meningitis or pneumonia, treatment with a regimen containing amphotericin is preferred. Given potential life-threatening adverse events (e.g. severe hypokalaemia) associated with amphotericin therapy, however, amphotericin-containing regimens should not be used without adequate laboratory monitoring (i.e. electrolytes and kidney function) and the use of pre-hydration and electrolyte replacement prior to amphotericin administration (see Box below for further details of safe administration of amphotericin B).

The following therapies for *cryptococcal meningitis* are recommended:

**Induction**
- amphotericin B 1 mg/kg/day PLUS flucytosine 100 mg/kg/day divided into four doses per day for seven days, followed by oral fluconazole 1200 mg daily (12 mg/kg/day for adolescents up to max of 800 mg) for seven more days; OR
- fluconazole 1200 mg daily for adults or 12 mg/kg/day for adolescents PLUS flucytosine 100 mg/kg/day divided into 4 doses/day for two weeks; OR
11. Cryptococcosis

- amphotericin B 1 mg/kg/day PLUS fluconazole 1200 mg daily for adults, 12 mg/kg/day for adolescents (up to a max of 800 mg daily) for two weeks. Clinical response should be assessed daily during induction therapy. Routine use of and adjunctive corticosteroid during the induction phase is NOT recommended.

Consolidation
- fluconazole 800 mg daily for adults, 6–12 mg/kg/day for adolescents (up to max of 800 mg daily) for 8 weeks following the induction phase.

Maintenance (or secondary prophylaxis)
- fluconazole 200 mg daily for adults, 6 mg/kg/day for adolescents.

Note: Toxicity monitoring, pre-emptive hydration and electrolyte replacement should be included in induction phase to minimize treatment toxicity with amphotericin B containing regimens and flucytosine.

Recommendations for safe administration of amphotericin B

- To reduce risk of thrombophlebitis, use large peripheral veins or a central venous catheter, changing venous access sites frequently and infusing over longer periods.

- Protect against life-threatening adverse events:
  - Monitor renal function and electrolytes (e.g. serum potassium, serum creatinine, fluid intake and output, and daily weight) prior to initial treatment and then at least twice weekly. Monitor haemoglobin at baseline and weekly. Consider monitoring of full blood counts if on flucytosine.
  - One hour prior to administration of each amphotericin infusion, administer 1 litre of IV normal saline solution over 2–4 hours.
  - Add one ampoule (20 mmol) of potassium chloride with each litre of IV saline solution plus one to two 8 mEq KCL tablets orally twice daily. An additional one 8mEq KCL tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250 mg tablets of magnesium trisilicate twice daily).
  - Use with caution in renal impairment. If creatinine increases by ≥2 fold from baseline value, switch to liposomal amphotericin (3 mg/kg/day) if available.
  - If liposomal amphotericin not available, either skip an amphotericin B dose or increase pre-hydration to one litre 8 hourly. Once creatinine improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B. If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day. Monitor creatinine daily.
  - If significant hypokalaemia (K <3.3 mol/l) – manage by increasing potassium supplementation to 40 mEq KCL by IV infusion and/or one-two 8-mEq KCL tablets orally thrice daily. Monitor potassium daily.
  - If elevated creatinine (increase by ≥ 2 fold from baseline) increase pre-hydration to 1 l every 8 hours and consider temporarily omitting a dose of amphotericin B:
    - once creatinine improves, restart amphotericin B at 0.7 mg/kg/day and consider alternate-day amphotericin B.
    - if creatinine continues to increase – consider discontinuing amphotericin B and continue fluconazole at 1200 mg/day (adjust if significant renal impairment), especially if seven doses of amphotericin B have been received.
  - If severe anaemia – transfuse. Consider discontinuing amphotericin B prematurely in second week.

- Minimize acute infusion reactions (e.g. fever, chills, headache, hypotension):
  - Infuse the initial dose slowly over 3–6 hours.
  - Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute infusion reactions (and in whom continued treatment with amphotericin is essential).
  - Reactions become less frequent over time.
Control of raised intracranial pressure (ICP)
- Patients with suspected cryptococcal meningitis should have an initial lumbar puncture and early repeat lumbar puncture with assessment of CSF opening pressure. If increased intracranial pressure, see box below. Symptoms/signs of raised ICP – headache, nausea ± vomiting, changes in vision or hearing, changes in mental status, papilloedema, seizures, cranial nerve palsies, other focal neurological signs
- Educate and inform the patient about the importance of baseline and follow-up lumbar punctures (i.e. improves treatment outcomes).
- Measure the intracranial pressure (see Section 7.4.2).

### Treatment of raised intracranial pressure (ICP) in cryptococcal meningitis:
Patients should have frequent lumbar punctures (days 3, 7, 10 and 14 of induction phase) to remove approximately 20–30 mls of CSF relieving the pressure and avoiding the development of blindness and other long-term complications.

- Raised ICP contributes to early mortality and residual morbidity.
- Raised ICP is present in >50% of patients.
- Repeated spinal taps lower ICP, reducing mortality and morbidity, as well as reducing severe headaches.
- If initial opening pressure is normal, repeat LP in 1–2 weeks or if worsening headache, and visual or hearing disturbances.
- If initial opening pressure is >25 cm H2O, tap up to 30 ml spinal fluid to achieve pressure <20 cm H2O (or halving the baseline pressure if extremely high).
- For persistent symptoms of raised intracranial pressure, perform daily taps until the opening pressure is normal (<25 cm H2O) for at least 2 days.

Delay initiation of ART
Due to the high risk of IRIS with CNS disease, which may be life-threatening, in HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy, and

- after 4-6 weeks from initiation of treatment:
  - consider ARV and fluconazole drug interactions when choosing ART regimen
  - Persistent or recurrent symptoms
  - Review patient history and treatment regimen for adequate induction, consolidation and maintenance (regimen, dose, duration) and adherence. There is fluconazole drug resistance that can occur with people who have history of prolonged fluconazole treatment.
  - Perform lumbar puncture to assess opening pressure and CSF examination to exclude possible co-infection.
  - Consider cryptococcal immune reconstitution syndrome (IRIS) for patients who have started ART- see below.
  - Send CSF for prolonged fungal culture (2 weeks incubation).
  - For patients who have relapse of cryptococcal meningitis, re-treat starting with induction treatment regimen.
  - Manage raised intracranial pressure as above.
  - Reinforce adherence.

If ART has not been started, initiate ART after 4-6 weeks of repeat antifungal treatment.
Cryptococcal IRIS

Patients with advanced immune deficiency can develop IRIS after the initiation of ART as a result of partial immune restoration. Cryptococcal meningitis is a common infection implicated in IRIS. It occurs in patients with latent or recently treated cryptococcal meningitis who then develop inflammatory meningitis, headache or focal signs. Cryptococcal IRIS can develop between one week and eight months after a patient starts ART, but typically within 1–6 weeks. It is usually accompanied by a significant CD4 increase and a viral load (VL) decrease.

**Diagnosis**

In addition to the above history, look for:
- recent initiation of ART or switch to a more potent second-line regimen.
- recent treatment for cryptococcal meningitis.
- history of long-standing mild headache prior to ART commencement.

In addition to the above examination look for:
- lymphadenopathy.
- increased intracranial pressure.

**Investigations**

CSF results can be difficult to interpret, especially if the patient has recently been treated for cryptococcal meningitis. The CrAg and India ink test remain positive for many months after treatment and do not distinguish between live and dead organisms. Diagnosis will therefore often be based on the patient’s history and examination findings.

- **CSF:**
  - positive cryptococcal antigen (if recently treated will still be positive – does not indicate new infection)
  - cryptococcal culture usually negative.
- **VL or CD4:**
  - significant decrease in VL
  - increased CD4.

**Treatment**

- continue ART
- manage raised ICP
- consider re-start of cryptococcal treatment from induction phase (as above)
- consider steroids if meningitis is life-threatening or focal neurology exists.

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11.9 Cysticercosis (pork tapeworm disease) – see also Section 11.35 Taeniasis

Taeniasis and cysticercosis are two different diseases caused by the same organism. Taeniasis is an intestinal infection caused by the large adult tapeworms *Taenia solium* (pork tapeworm) and *Taenia saginata* (beef tapeworm). Note that this is different from porkworm disease, which is trichinellosis (Section 11.39).

Cysticercosis is caused by the larval stage of *Taenia solium* that can invade any tissue and produce a variety of clinical pictures ranging from asymptomatic to fatal disease. Morbidity and relevant clinical symptoms are almost exclusively caused by neurocysticercosis and less often by ocular infection. *T. solium* is the cause of 30% of epilepsy cases in many endemic areas where people and roaming pigs live in close proximity. In high-risk communities it can be associated with as many as 70% of epilepsy cases.37

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Higher prevalence is found in areas with poor sanitation and where untreated wastewater is used in agriculture. Cysticercosis is found where *T. solium* is found.

**Key clinical features**

* Clinical manifestations vary greatly because the cysticerci can occur in any number, and in almost any organ:
  * common sites: brain, muscles, subcutaneous tissue.
  * In some endemic regions particularly in Asia, infected people may develop visible or palpable subcutaneous nodules.\(^{38}\)
  * other sites: eye, orbit, liver, lung.
* Cysticerci cause varying degrees of calcification, oedema, and granuloma formation.
* Neurological symptoms are the most common reason for presentation, except in Asia where subcutaneous presentation is as common.
* Neurocysticercosis presentations:
  * can be asymptomatic
  * adult onset seizures or epilepsy (most common presenting symptom)
  * chronic headaches
  * neurological deficits (focal or non-focal)
  * dementia
  * neuropsychiatric problems (altered mental status, behaviour changes)
  * vomiting
  * visual defects (due to neurological, meningeal, or ocular involvement)
  * muscular pseudohypertrophy in massive, multicystic infection

- radiculopathy (due to spinal cysticerci)
- fever is uncommon (investigate for other causes if fever is present)
- other presentations include chronic stroke, febrile meningitis, hydrocephalus with raised intracranial pressure.

- Presentations in other organ systems:
  - muscle and subcutaneous tissue cysticerci:
    ◦ usually asymptomatic
    ◦ may have nodules that can be seen or felt
    ◦ can have pain.
  - eye: retinal and vitreal involvement may affect vision.
  - orbital involvement.
  - liver: often asymptomatic, an incidental finding on radiological imaging, when enlarged can:
    ◦ cause right upper quadrant pain
    ◦ compress bile ducts causing cholestasis
    ◦ rupture into or simply communicate with the biliary tract causing biliary colic.

**Investigations**

Diagnosis and staging of suspected neurocysticercosis require CT or MRI imaging that may require referral to obtain. Overdiagnosis is possible, so combination with ELISA testing is useful. EEG is helpful for patients with seizures.

- Demonstration of the parasite:
  - larvae seen in biopsy of subcutaneous nodules, liver cyst aspirate (definitive diagnosis);
  - fundoscopy for intraocular larvae (definitive diagnosis);
  - stool examination is of limited use as not all patients with cysticercosis will have an intestinal infection;

- Eye exam and fundoscopy to look for papilloedema and nystagmus (signs of neurocysticercosis);

- X-ray to demonstrate muscle and subcutaneous cysts, which appear as small cigar-shaped opacities;

- Serological tests:
  - ELISA on CSF for anticysticercal antibodies or cysticercal antigens (antigen is only positive in active infections). Negative serology (including antibody or antigen testing in the CSF) does NOT rule out neurocysticercosis, especially in single lesions.

**Treatment**

Medical and surgical treatment generally depends on the location, number, and characteristics of the cysticerci which need to be determined with advanced imaging (MRI, CT). Imaging is also necessary to establish if there is a reason to withhold cysticidal treatment, for example in cysticercotic encephalitis (heavy intraparenchymal parasite burden), and to assess for stages of the disease where cysticidal treatment does not seem to be beneficial (calcified lesions). Patients with suspected neurocysticercosis should therefore be referred to a tertiary facility for further management.

Empirical treatment of neurocysticercosis without imaging should be avoided. However, if no imaging is available at the referral hospital, the clinician has to be aware that there is a risk of exacerbating symptoms under cysticidal treatment due to increasing inflammation, which can be life-threatening. Steroids should be given in such circumstances. This is especially the case for cysticercotic encephalitis (heavy intraparenchymal parasite burden), when parasitic treatment is controversial and treatment of symptomatic disease usually consists of only steroids.

A standard adult treatment regimen for uncomplicated cysticercosis would entail:

- Antiparasitic treatment:
o albendazole 15 mg/kg daily for 8 days (preferred); OR
o praziquantel 50 mg/kg daily for 14 days (alternative second choice; is less effective and has more interactions with steroids and antiepileptics than albendazole; is contraindicated when antiepileptic drugs are given, or in the case of ocular cysticercosis).

- Corticosteroids are usually added to antiparasitic treatment; a starting dose of dexamethasone 8–10 mg daily or prednisone 40 mg daily and titrated as inflammation changes. Length of treatment with corticosteroids is not well-defined.

Also recommended for symptom management:
- analgesics for headaches;
- antiepileptics (phenytoin, carbamazepine, valproate, phenobarbitol) for seizures (levels may be lowered when given concomitantly with praziquantel);
- mannitol may need to be given temporarily for raised intracranial pressure.

### 11.10 Cytomegalovirus (CMV)

CMV is in the human herpes family of viruses, and as such is characterized by its potential for latency and disseminated infection. It causes a wide spectrum of diseases in older children and adults. It is distributed worldwide and, if acquired in utero, is associated with congenital malformations. Transmission is predominantly through repeated and prolonged contact, but it is most commonly transmitted through sexual contact. In addition, the virus has been found in breast milk, saliva, faeces and urine.

After acquisition, CMV persists for life, and can be reactivated if the immune system is weakened, such as by HIV or organ transplantation. CMV is difficult to diagnose and requires pathological examination of specimens for definitive diagnosis. In areas where these examinations are not available, diagnosis relies on its typical clinical presentation (in case of CMV retinitis) that is not explained by other conditions. CMV also can cause a mononucleosis syndrome, more commonly caused by Epstein Barr virus.

There are several syndromes caused by CMV.

#### CMV in persons with decreased immunity

CMV causes retinitis and disseminated disease in HIV-infected patients whose CD4 counts are below 100. In the era of antiretroviral therapy, this is seen less often. However, it is important to note that CMV retinitis and colitis can occur in the first few weeks after starting antiretroviral therapy, or can worsen as part of IRIS.

If blindness has occurred in one eye due to CMV or other causes, the other eye should be examined carefully for signs of CMV infection before starting antiretroviral therapy. Relapses are uncommon if CD4 counts have increased due to treatment of HIV disease. Since disseminated CMV infection is only seen in patients who are severely immune deficient, immune reconstitution through the prompt initiation of ART in HIV-positive individuals is key to managing this disease.

**CMV retinitis** – see Section 10.11 Eye problems

#### Key clinical features

- painless loss of vision
- floaters, visual field defects, or black spots
- no vitreous haze – fundi clearly seen
- vascular sheathing – “frosted branch” appearance
- examine the other eye if this is diagnosed in one eye
CD4 <100 – occurs less commonly if >100, then look for other cause for retinopathy.

**Immune-recovery uveitis**
- Follows CMV of the eye most commonly, but also associated with other retinal opportunistic infections.
- Decreased vision or gradual onset with floaters.
- Follows recent initiation of ART.
- Decreased vision, floaters, visual field defects, or black spots.

**Investigations**
- Fundoscopic examination (by an ophthalmologist or trained clinician) shows typical yellow-white areas of peri-vascular infiltrates contrasting with red areas of intraretinal haemorrhage, typical yellow-white areas of retinal necrosis, peri-vascular infiltrates, with areas of haemorrhage or necrosis (“pizza pie” or cheese appearance).
- Other investigations are not helpful in this presentation.

**Complications**
- retinal detachment
- immune reconstitution vitreitis is a vision-threatening complication of antiretroviral therapy initiation in the absence of effective anti-CMV treatment of active retinitis.

Note: Although long-term anti-CMV treatment is costly, a strategy of having limited amounts of CMV drugs available for use while immune reconstitution takes place with ART in patients presenting with CMV end-organ disease may limit adverse consequences of CMV immune reconstitution syndromes.

**Treatment**
- Antiretroviral therapy plus:
  - ganciclovir 5 mg/kg IV twice daily for 3 to 4 weeks, if available; OR
  - oral valganciclovir 900 mg twice daily with food for 14 days, followed by 900 mg daily maintenance therapy until CD4 count is more than 100–150 for six months.
- Co-administration of AZT with ganciclovir requires caution and careful monitoring because of additive bone marrow toxicity (anaemia and neutropaenia).
- If vision is threatened, intraocular ganciclovir implants may be available from a specialist clinician; anaesthesia is required for insertion.
- Relapses should be treated with a repeat of the induction dose of the same regimen.

**Gastrointestinal CMV**
Suspect CMV gastrointestinal disease in patients with GI complaints that do not respond to common bacterial, antifungal therapy, and aciclovir (for suspected herpes simplex oesophagitis or proctitis), and for those who have a CD4 below 100. In case of simultaneous CMV retinitis, suspect other locations of CMV infection.

**Key clinical features**
- fever
- oesophagitis: retrosternal pain and pain when swallowing
- gastritis: substernal or burning epigastric pain
- pancreatitis: epigastric pain radiating to the back
- small bowel disease or colitis: abdominal pain, weight loss and diarrhea (bloody or non-bloody).

**Complications**
- Perforation or bleeding are possible.
• Initiation of antiretroviral therapy in the setting of untreated CMV end-organ disease can be associated with immune reconstitution syndromes that may rarely result in intestinal perforation.

Treatment
• antiretroviral therapy PLUS ganciclovir 5 mg/kg IV twice daily for 3 to 4 weeks, if available.
• Co-administration of AZT with ganciclovir – with caution and careful monitoring because of additive bone marrow toxicity (anaemia and neutropaenia). Oral valganciclovir 900 mg twice daily may be used if not contraindicated because of suspected malabsorption, ileus or inability to swallow.

Neurological CMV – see Section 10.10a Neurologic problems

Key clinical features
• CMV polyradiculitis: ascending polyradiculopathy (affecting several nerve roots) – progressive leg weakness, then bladder and bowel dysfunction.
• CMV encephalitis: rapidly progressive delirium, cranial nerve dysfunction, nystagmus, and ataxia.

Investigations
A lumbar puncture reveals a raised protein, low glucose, and increased WBC, which can be monocytes or neutrophils. Note that these findings may be similar to those found in TB meningitis. The diagnosis should be suspected in patients with a CD4 count below 50 who present with the clinical features of encephalitis or polyradiculitis as described above. In resource-enhanced settings, the diagnosis can be confirmed by CMV PCR of the spinal fluid.

Treatment
• Antiretroviral therapy PLUS prompt initiation of ganciclovir, if available, 5 mg/kg IV twice daily for 3 to 6 weeks.
• Subsequent maintenance with oral doses of valganciclovir 900 mg daily can halt neurological progression, although established neurological deficits are rarely reversible.
11.11 Ebola virus disease

Ebola virus disease (EVD) is a severe illness which can be rapidly fatal, and has a high mortality rate. Ebola virus is highly infectious and there are recorded instances of international spread of Ebola virus infection from the West African outbreak in 2014 to 2016 via air travel to Lagos, Nigeria, and Dallas, USA.

Ebola virus disease has never occurred in the SEA Region. However, due to international travel, local preparedness and rapid containment if a case is detected are important, even though the likelihood of importation into the SEA Region is low.39

Clinicians can contribute to event-based surveillance and timely early warning (see Section 9). Ask a travel history and include in your differential diagnosis if travel from country with outbreak and signs/symptoms are suggestive. Assure routine use of standard IPC precautions and prepare to increase these precautions to include contact and droplet precautions (see Section 6) and to isolate a suspected case (with an isolation unit ready). Such local capacities for disease detection and control are important rather than relying only on border control. With adequate preparation, introduction of the virus can be contained before a large outbreak develops.

Capacity-building for local containment and coordinated and expedited international cooperation are essential to reduce the risk of global transmission.

Transmission

Direct contact (such as through broken skin or mucous membranes of the eyes, nose or mouth) with:

- Blood or body fluids (urine, saliva, sweat, feces, vomit, breastmilk and semen) of a person who is sick with or died from EVD. Viral load and infectiousness of these fluids increase as patient become more ill. The dead body is highly infectious.
- Objects (such as clothes, linens, used needles and medical equipment) contaminated with body fluids from a person who is sick with or died from EVD.
- Infected forest-dwelling African fruit bats (probable reservoir host) or nonhuman primates (such as apes and monkeys; intermediate hosts who also suffer epidemics and die). Direct infection where African fruit bats have contaminated fruit or the bat is eaten as bushmeat.

Sexual intercourse: spread by semen from a man who recovered from EVD, up to 12 months after clinical recovery

Pregnant mother who has survived EVD, to fetus, baby: Breastmilk positive by RT-PCR up to nine months.

Key clinical features40

Incubation period is 2–21 days, no transmission of disease until symptomatic.

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40 Clinical management of patients with viral haemorrhagic fever: A pocket guide for frontline health workers; interim emergency guidance for country adaptation. WHO, February 2016
Haemorrhage is seen in less than a third of patients with Ebola. It is usually not large in volume, so it is important to know other signs and symptoms.

Early symptoms: sudden onset non-specific febrile illness with sudden fever, malaise, weakness, headache, myalgia, arthralgia, anorexia, conjunctivitis (sometimes hiccups), sore throat.

Followed by gastrointestinal symptoms: nausea, vomiting and diarrhoea (watery or bloody) (particularly severe in the 2014–2016 West African outbreak).

Late symptoms: Broad spectrum of severity which can progress to multi-organ acute complication with hypovolemic and septic shock, metabolic acidosis, respiratory distress, electrolyte abnormalities, renal insufficiency, internal and external bleeding (puncture site oozing, bleeding gums, conjunctival haemorrhage, ecchymoses, petechiae, epistaxis, GI bleeding), confusion, seizures and death.

In pregnant women: miscarriage.

Investigations
- RT-PCR detects acute infection.
- IgG and IgM detect recent infection (within the previous several months).

Daily biochemistry to check for electrolyte abnormalities, features of acute kidney injury, leukopenia early in course and leukocytosis, thrombocytopenia, deranged LFTS (elevated AST, ALT), disseminated intravascular coagulation (DIC).

All samples should be considered highly infectious; use full Ebola PPE when collecting and triple pack samples.

Treatment

Guidance on the key elements of supportive care of EVD listed below can be found in Optimized supportive care for Ebola virus disease: clinical management standard operating procedures as well as detailed guidance on interventions in specific Sections of this Manual.

Fluid resuscitation
- rapid fluid boluses IV if severe dehydration, septic, hypovolaemic or haemorrhagic (uncommon) shock – SBP<90 or other signs poor perfusion (Quick Check p.6).
- manage septic shock with fluids and vasopressors according to protocol (Section 3.1).
- oral rehydration in patients who can drink – treat dehydration with ongoing fluid loss with Fluid Plans B and C (Section 8.3).
- maintenance of fluids orally or through IV.

Electrolyte monitoring and correction
- daily biochemistry laboratories during acute phase of illness and haematology on admission and as needed.
- appropriate and timely correction of electrolyte abnormalities (see Section 5.2).

Glucose monitoring and management
- serum glucose checked at least three times a day with vital signs.
- intravenous (IV) glucose management as needed (Quick Check p. 28).

Treatment of potential co-infections
- empiric antibiotics on admission with re-assessment after 48 hours.
- empiric antimalarial medication until the treatment course is finished or malaria testing is negative (Section 8.1.6).

Nutrition
- enteral nutrition should be provided and advanced as tolerated.
- IV dextrose provided for patients that cannot take oral food and with evidence of hypoglycaemia.

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11. Multisystem diseases: SEARO 2021
Symptomatic care and prevention of complications
  • symptomatic care of fever, pain and nausea (see Sections 3.0 and 12).
  • prevention of catheter associated infections and pressure ulcers.

Management of complications

Systematic assessment and re-assessment of all EVD patients
  • staffing ratio of one or more clinicians for four patients.
  • assessments (evaluation of each patient) performed at least three times per 24 hours.
  • close monitoring of patients to allow recognition of and reaction to acute changes in condition.

Although no licensed treatment, there are many investigational therapies to which access can be provided. Provide access to and safe delivery of investigational therapies, coupled with optimized supportive care.

Infection prevention and control\(^{42}\)
  • Standard plus contact plus droplet precautions:
    o airborne precautions if aerosol generating procedure.
  • Close supervision of donning and doffing full Ebola PPE (see Section 6) including double gloves, gown or coverall and apron, face mask, eye protection (goggles or face shield), head cover and boots.
  • Strict isolation of patients and their body fluids and excreta, with restricted access.
  • Cohort patients in specific areas, keeping suspect and confirmed cases separate.
  • Regular and rigorous environmental cleaning, decontamination of surfaces and equipment, management of soiled linen and of waste.
  • Assure supplies for frequent hand hygiene – before and after all patient contact, contact with potentially infectious material, and before putting on and upon removal of PPE, including gloves.

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\(^{42}\) Interim Infection Prevention and Control Guidance for care of patients with suspected or confirmed filovirus haemorrhagic fever in health-care settings, with focus on Ebola, WHO Geneva, December 2014.
11.12 Endocarditis

Endocarditis is an infection of one or more of the heart valves. Risk factors include pre-existing heart valve disease that may be congenital or rheumatic heart disease. Conditions that are associated with bacteraemia, such as intravenous drug use or intravenous lines may also cause endocarditis. Bacterial endocarditis is always fatal without treatment, due to destruction of the heart valves and heart failure.

Key clinical features
- May present with a fever without a clinically evident focus.
- New or changing cardiac murmur.
- A precipitating event, such as a dental abscess or tooth extraction, can rarely be identified.
- Can present with symptoms suggestive of embolization of the infection to distant sites, most commonly the vertebrae (presenting with back pain), brain (presenting with focal weakness or other neurological signs). Small emboli may also be seen in the fingers or elsewhere on the skin. Complications of endocarditis are usually associated with a poor prognosis.

Investigations
- ECG is usually normal or shows non-specific findings such as tachycardia. Abscesses of the aortic ring may present as heart block.
- Blood cultures are commonly positive. Common causative organisms include: *Staphylococcus aureus* and *Streptococcus viridans*.
- Echocardiography may show valvular regurgitation (most commonly mitral and aortic) that may be visualized. If it is large, valvular vegetations may be visible.
- Look for the possible source of bacteraemia, based on the type of bacteria isolated (e.g. dental abscess).

Treatment
- Treatment includes antimicrobial therapy, supportive care for complications (e.g. heart failure), and specialist advice, if available.
- Referral for cardiac surgical consultation for complications of a destroyed heart valve (such as intractable heart failure, shock, progressive heart block, recurrent emboli, or persistent positive blood cultures) is recommended.
- If blood culture results are available, treatment should be guided by the results of culture and antibiotic susceptibility tests.

Empirical treatment options include:

Native valve:
- benzylpenicillin 12 to 18 million units in divided doses plus gentamicin 1 mg/kg IV 3 times daily (preferred); OR
- ceftriaxone IV/IM 2 g daily plus gentamicin 1 mg/kg IV 3 times daily (alternative if mild allergy to penicillin); OR
- *vancomycin* IV 30 mg/kg daily in two equally divided doses plus gentamicin 1 mg/kg IV 3 times daily (alternative if severe allergy to penicillin or if methicillin-resistant *Staphylococcus aureus* is suspected – recent admission to hospital, intravenous drug use).

Prothetic valve:
- *vancomycin* IV 30 mg/kg daily in two equally divided doses PLUS gentamicin 1 mg/kg IV 3 times daily PLUS rifampicine orally 600 mg daily.

The duration of treatment depends on antibiotic susceptibility; generally courses of two to six weeks are required.

Treat the source of bacteraemia if identified (e.g. removal of an infected tooth).
If the patient has a non-anaphylactic allergy to penicillin (for example, skin rash only), then ceftriaxone can be used. Vancomycin is only recommended for patients allergic to penicillin and ceftriaxone, or for S. aureus resistant to cloxacillin (MRSA).

Dosing of gentamicin and vancomycin should be guided by levels, especially in the presence of renal dysfunction. When these drugs are used in a district hospital for endocarditis, there should be collaboration with a referral hospital that provides specialist guidance and laboratory analysis of drug levels if possible.

- For gentamicin, monitor creatinine and gentamicin levels at least once per week. Aim for peak serum concentrations 3–4 mcg/ml and trough <1 mcg/ml when 2–3 divided doses are used; when given in a single daily dose, pre-dose (trough) levels should be <1 mcg/ml and post-dose (peak, 1 hour after injection) levels should be approximately 10–12 mcg/ml.
- For vancomycin, adjust dose to achieve peak serum concentrations (1 hour after infusion completed) of 30–45 mcg/ml and pre-dose (trough) concentration of 10–15 mcg/ml. The dose should not exceed 2 g per 24 hours unless levels are inappropriately low.

Treatment options for native valve endocarditis where blood cultures are available are shown in the following table. Other regimens are required when blood cultures grow highly resistant viridans streptococci, S. pneumoniae, enterococci, or fastidious Gram-negative bacilli, or when blood cultures are negative but endocarditis is highly suspected (for example, based on echocardiography).

<table>
<thead>
<tr>
<th>Table: Treatment options for viridans streptococci and S. aureus43</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillin-susceptible viridans streptococci (minimum inhibitory concentration (MIC) ≤0.12 mcg/ml)</strong></td>
</tr>
<tr>
<td><strong>4-week regimen (for patients &gt;65 years old or with impairment of the 8th cranial nerve or renal function)</strong></td>
</tr>
<tr>
<td>- benzylpenicillin 12–18 million units (7.2–10.8 g) per 24 hours IV in four or six equally divided doses OR</td>
</tr>
<tr>
<td>- ceftriaxone 2 g per 24 hours IV/IM in one dose OR</td>
</tr>
<tr>
<td>- vancomycin 30 mg/kg per 24 hours IV in two equally divided doses</td>
</tr>
<tr>
<td><strong>2-week regimen (for non-complicated cases; not for patients with known cardiac or extracardiac abscess or for creatinine clearance &lt;20 ml/min or impaired 8th cranial nerve function)</strong></td>
</tr>
<tr>
<td>- benzylpenicillin 12–18 million units (7.2–10.8 g) per 24 hours IV either continuously or in six equally divided doses OR ceftriaxone 2 g per 24 hours IV/IM in one dose AND</td>
</tr>
<tr>
<td>- gentamicin 3 mg/kg per 24 hours IV/IM in one dose or in two to three equally divided doses</td>
</tr>
<tr>
<td><strong>Strains of viridans streptococci relatively resistant to penicillin G (MIC &gt;0.12 mcg/ml and &lt;0.5 mcg/ml) in patients with normal renal function</strong></td>
</tr>
<tr>
<td>- benzylpenicillin 24 million units (14.4 g) per 24 hours IV in four or six equally divided doses OR ceftriaxone 2 g per 24 hours IV/IM in one dose for 4 weeks AND</td>
</tr>
<tr>
<td>- gentamicin 3 mg/kg per 24 hours IV/IM in one dose or in two to three equally divided doses for 2 weeks OR</td>
</tr>
<tr>
<td>- vancomycin (alone) 30 mg/kg per 24 hours IV in two equally divided doses for 4 weeks</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td>- Sensitive to cloxacillin (MSSA)</td>
</tr>
<tr>
<td>- cloxacillin 12 g per 24 hours IV in four or six equally divided doses for 6 weeks</td>
</tr>
<tr>
<td>- Resistant to cloxacillin (MRSA)</td>
</tr>
<tr>
<td>- vancomycin 30 mg/kg per 24 hours IV in two equally divided doses for 6 weeks.</td>
</tr>
</tbody>
</table>

11.13 Fascioliasis\textsuperscript{44,45,46}

Fascioliasis is caused by infection with the trematodes \textit{Fasciola hepatica} and \textit{Fasciola gigantica}. It is transmitted to humans through ingestion of contaminated water or food – usually uncooked vegetables to which the parasite’s larvae are attached. The lifespan of the adult worm in humans is about 9–13 years. Sheep and cattle are important definitive hosts of \textit{Fasciola} species, humans are accidental hosts.

Fascioliasis is a global disease, and human cases have been reported from more than 75 countries worldwide. Recognized areas of high transmission are the highlands of South America, the Nile Valley, the Caspian Sea basin, as well as East Asia and South-East Asia.\textsuperscript{47} No country can be considered free from the risk of fascioliasis.

**Key clinical features**

These vary by the phase of the infection. After the symptomless incubation period, fascioliasis can be roughly divided into acute (when immature worms migrate through liver) and chronic (when mature worms are lodged in bile ducts). Chronic fascioliasis can, however, be further divided into four phases, for a total of six phases. Re-infection and new infections can result in an overlap of phases.

- **Incubation phase**
  - Lasts from ingestion of metacercariae to appearance of the first symptoms
  - Can last a few days to a few months.

- **Acute or invasive phase**
  - Lasts 2–4 months
  - Immature worms migrate through the liver and digest hepatic tissue
  - Worms may deviate and migrate through other organs causing ectopic fascioliasis
  - Worms cause haemorrhage and inflammation proportionate to the number of worms. Dying worms cause necrosis and scarring
  - Common symptoms: fever, abdominal pain, gastrointestinal disturbances, rashes, and respiratory symptoms
  - Less common symptoms: enlarged liver or spleen, ascites, anaemia, and jaundice
  - Complications: subcapsular haematoma of the liver, haemobilia (haemorrhage in bile), acute intra-abdominal bleeding, pneumothorax
  - Symptoms of acute phase usually disappear when the worms reach the bile ducts.

- **Latent phase**
  - Lasts months to years
  - Mature worms start laying eggs during this phase
  - Many patients are asymptomatic or have non-specific symptoms, such as gastrointestinal disturbance and intermittent biliary obstruction
  - Complications arise from worms living in the bile ducts for years causing fibrosis, hyperplasia, and thickening of the duct walls.


**Chronic (obstructive) phase**
- Common bile duct obstruction caused by parasites, parasite fragments, or debris in the common bile duct
- Symptoms include biliary colic (from obstruction, spasm, or distension of the common bile duct), epigastric pain, fatty food intolerance, nausea, intermittent jaundice, pruritus, right upper-quadrant abdominal pain and fever
- Complications: gallbladder swelling, pancreatitis, jaundice, cholestatic hepatitis, and secondary bacterial infection with cholangitis and cholecystitis.

**Advanced chronic phase**
- Characterized by stones in the gall bladder and common bile duct, bacteria in the bile (mainly *E. coli*, *E. faecalis*, *Klebsiella pneumoniae*), and chronic cholangitis and cholecystitis
- Worms stop laying eggs during this phase.

**Ectopic fascioliasis**
The worm can affect other sites of the body causing painful migrating erythematous itching swellings. Frequent sites include:
- the subcutaneous tissue often of the abdominal wall muscles
- lungs, heart, the genitourinary tract can be affected.

**Post-infection phase**
- Characterized by complications such as cirrhosis and growth deficiencies
- Stones cause chronic recurrent gallbladder obstruction, and eventually a dilated, atonic gallbladder
- Ectopic worms die and form calcifications or granulomas in ectopic sites, such as the gastrointestinal tract (most commonly), subcutaneous tissue, heart, blood vessels, lung and pleural cavity, brain, orbit, abdominal wall, dorsal spine, appendix, pancreas, spleen, lymph nodes (mostly inguinal and cervical), skeletal muscle, epididymis, uterus, ovaries, and breasts
- Worms are no longer present in the liver during this phase.

Note: Patients with fascioliasis often are co-infected with other parasites, and there is a significant association between fascioliasis and giardiasis (*Giardia intestinalis*) due to the common transmission pathway (drinking of contaminated water).

**Investigations**
- Stool examination for eggs. Eggs can also be found in duodenal aspirates and bile specimens.
  - Detection of eggs or antigens in the stool:
    - Detection of eggs:
      - Kato-Katz or conic-cup sedimentation technique
      - Specific but not sensitive, therefore more than one stool sample is needed
      - Negative during incubation phase and acute phase
      - Easy to miss early infections
      - Negative in ectopic fascioliasis.
    - Detection of specific worm antigens in stool (e.g. FES-Ag) is more sensitive than detection of eggs. It can only be used in chronic fascioliasis.
- Serology (ELISA)
  - Detects circulating antibodies to fasciola antigens (e.g. Fas2 and CL1) or uses monoclonal antibodies to detect circulating fasciola antigens
  - Can be used in incubation, acute, and chronic phases, as well as in ectopic fascioliasis
  - Highly sensitive and specific.
• Haematological findings:
  o Eosinophilia is present in the acute phase, not always in the latent and chronic phases
  o Anaemia due to blood loss in the bile (haemobilia), direct blood-sucking by the worm, and possibly increased destruction and decreased production of red blood cells.
• Liver function tests may be abnormal during the acute phase.
• Ultrasound
  o Acute phase: migrating hypoechogenic liver foci and splenomegaly
  o Chronic phase: crescents, sludge, calculi, tender gall bladder, decreased contractility of the gallbladder. The sensitivity for diagnosis less than 15%.
• Examination of surgically removed specimens – macroscopic and histological.

Staging
Staging of the disease relies on interpretation of the clinical presentation, and the following criteria on stool examination (using Kato-Katz or conic-cup sedimentation) and serology.
• stool (–) and serology (–): no infection or infection resolved
• stool (–) and serology (+): acute or ectopic infection; infection resolved; biliary obstruction; intermittent egg shedding
• stool (+) and serology (+): chronic phase
• stool (+) and serology (–): long-term chronic phase (Ab titres eventually becoming negative)

Treatment
• Triclabendazole 10 mg/kg as a single dose. This should be available at the regional hospital level.
• In case of treatment failure (see below for criteria), re-administer triclabendazole 10 mg/kg, followed by another dose 12–24 hours apart (giving a total dose of 20 mg/kg).

Primary criteria of treatment failure
This includes any of the following by day 60 after treatment:
• detection of eggs in stools
• persistence of FES-Ag in stools
• crescents seen on ultrasound examination.

Additional criteria of failure
• persistence of nausea, pruritus, abdominal pain
• increase of anti-fasciola antibodies
• persistence of eosinophilia
• persistence of IgE.

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11.14 Filariasis, lymphatic (elephantiasis)

The term filariasis refers generally to disease caused by the lymphatic-dwelling filarial worms *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. *Wuchereria bancrofti* is the most common, whilst *Brugia malayi* causes most of the remainder of infections worldwide. The filarial parasite is transmitted by mosquitoes.

There are two principal forms of the infection: one found in most areas of the world, where microfilariae circulate in the blood at night (the highest concentrations being between 10 pm to 2 am); the other, where microfilariae circulate continuously in the blood (but with the highest concentrations during the day), found mainly in the Pacific Region.

The SEA Region has made substantial progress with mass drug administration (MDA) scaled to all endemic districts in India, Indonesia, Myanmar, Nepal and Timor-Leste; MDA stopped in all endemic districts and under surveillance in Bangladesh and validated as having eliminated LF as a public health problem and under surveillance in Maldives, Sri Lanka and Thailand.49

**Progressive filariasis**

In progressive filariasis, the clinical features depend on the clinical stage.

**Key clinical features**

1. **Asymptomatic amicrofilaraemic stage**
   - Some people living in endemic areas have no clinical signs and no detectable microfilaria in the blood despite significant exposure to infective larvae. Some of these might be immune while others harbour adult parasites in their lymphatics.
   - Laboratory tests are not able to determine whether such individuals are immune or recently infected, but the circulating antigen test (ICT card test) can identify those with established infections but who are amicrofilaraemic.

2. **Asymptomatic microfilaraemic stage**
   - There may be no symptoms for months to years, despite circulating microfilariae. These people are an important reservoir of infection.
   - Blood surveys and other procedures will detect infection in these people.
     - Blood must be taken at the correct time of day, depending on when the maximal microfilaraemia is for the prevalent species.
     - Use Giemsa-stained smears or haemolyzed blood in a counting chamber for visualization of the microfilaria and species identification.
     - DEC provocative test (2 mg/kg). After taking DEC, microfilariae enter the peripheral blood within 15 minutes. This method is not used if ICT is available.
     - Immuno-chromatographic test (ICT), also called the “card test”, to detect filarial antigen using finger-prick blood taken any time of day.
     - Ultrasonography to visualize living adult worms in the lymphatics of the female breast or scrotum. Adult worms show constant thrashing movements, referred to as the “filarial dance”.

3. **Stage of acute manifestations**
   In the initial months and years following infection, patients may have recurrent episodes of acute inflammation in the lymph nodes or vessels of the limb and scrotum. These are generally related to bacterial and fungal superinfections of tissue compromised by reduced lymphatic function.

49 Global Programme to eliminate lymphatic filariasis: progress report, 2017. WER No. 44, 2018, 93, 589–604
Clinical manifestations:

- Filarial fever (ADL-DLA):
  - Acute adenolymphangitis (ADL): high fever, lymphatic enlargement in the area where the adult worm resides, transient local oedema, tenderness and redness of overlying skin. Ulceration can occur.
  - Dermatolymphangioadenitis (DLA): high fever, chills, muscle aches, and headache with inflammatory skin changes in the area of infection.
- Lymphangitis
- Lymphadenitis
- Epididimo-orchitis.

4. **Stage of obstructive (chronic) lesions**

- These take 5–15 years to develop. They result from permanent damage to lymph vessels by the adult worms. This often manifests as hydrocoele and limb lymphoedema.
- Recurrent inflammatory reactions to the worms cause dilation of the lymph vessels, which results in oedema. The stages of lymphoedema are outlined below.

<table>
<thead>
<tr>
<th>Stages of lymphoedema</th>
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<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
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<tr>
<td>• swelling reversible at night</td>
<td></td>
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<tr>
<td>• skin folds: absent</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: smooth, normal</td>
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<tr>
<td><strong>Stage II</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
</tr>
<tr>
<td>• skin folds: absent</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: smooth, normal</td>
<td></td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
</tr>
<tr>
<td>• skin folds: shallow</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: smooth, normal</td>
<td></td>
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<tr>
<td><strong>Stage IV</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
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<tr>
<td>• skin folds: shallow</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: irregular, occasional knobs or nodules</td>
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<tr>
<td><strong>Stage V</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
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<tr>
<td>• skin folds: deep</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: smooth or irregular</td>
<td></td>
</tr>
<tr>
<td><strong>Stage VI</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
</tr>
<tr>
<td>• skin folds: absent, shallow, deep</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: wart-like lesions on foot or toes</td>
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<tr>
<td><strong>Stage VII</strong></td>
<td></td>
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<tr>
<td>• swelling not reversible at night</td>
<td></td>
</tr>
<tr>
<td>• skin folds: deep</td>
<td></td>
</tr>
<tr>
<td>• appearance of skin: irregular</td>
<td></td>
</tr>
<tr>
<td>• needs help with daily activities, dependent on family or health-care system.</td>
<td></td>
</tr>
</tbody>
</table>
Occult or cryptic filariasis, presenting as tropical pulmonary eosinophilic (TPE) syndrome

Occult filariasis results from hyperresponsiveness to filarial antigens derived from microfilariae.

Key clinical features
- Classical manifestations: paroxysmal cough and wheeze, scanty sputum, occasional haemoptysis, adenopathy, chronic interstitial lung disease, recurrent low-grade fever, weight loss.
- Occurs more commonly in males.

Investigations
In late disease, the diagnosis is often made clinically because the clinical signs are so suggestive.
In early disease, when the differential diagnosis is broad and treatment would be most useful, the following tests may be used to help make a diagnosis:
- extreme elevations of the eosinophil count in peripheral blood,
- high number of eosinophils in respiratory secretions,
- rarely, demonstration of microfilariae in peripheral blood or lung biopsies,
- blood must be taken at the correct time of day, depending on when maximal microfilaraemia is for the prevalent species,
- use Giemsa-stained smears or haemolysed blood in a counting chamber for visualization of the microfilaria and species identification,
- DEC provocative test (2 mg/kg). After taking DEC, microfilariae enter the peripheral blood within 15 minutes,
- immunochromatographic test (ICT), also called the “card test,” to detect filarial antigen using finger-prick blood taken any time of day,
- ultrasonography to visualize living adult worms in the lymphatics of the female breast or male scrotum. Adult worms show constant thrashing movements, referred to as the “filarial dance”,
- chest X-ray may show interstitial thickening and diffuse nodular mottling of tropical pulmonary eosinophilia.

Treatment
- **Recommended regimen** for lymphatic filariasis in clinical settings:
  - diethylcarbamazine citrate (DEC) 6 mg/kg daily in three divided doses after food for 12 days (24 days for tropical pulmonary eosinophilia syndrome):
    ◊ kills the adult worms and reduces microfilaraemia
    ◊ treatment should be repeated every six months as long as the person remains microfilaraemic or has symptoms.
  - Note: DEC should not be used in areas where onchocerciasis or loiasis is co-endemic, due to possible severe adverse reactions. Patients should be examined for coinfection before using DEC.

For interruption of transmission through mass drug administration, WHO now recommends a three-medicine MDA regimen in countries without onchocerciasis:
- ivermectin (200 mcg/kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in certain settings.

Previously MDA with a two-medicine regimen (DEC 6 mg/kg body weight, plus albendazole 400 mg, yearly in countries without onchocerciasis) was used to interrupt the transmission cycle when conducted annually for 4–6 years with effective coverage of the total population at risk.
Morbidity management and disability prevention (MMDP) is the WHO-recommended strategy to alleviate suffering and prevent further progression of disease. The following basic package of care should be made available for patients: surgery for hydrocele (in W. bancrofti-endemic areas), treatment for episodes of adenolymphangitis, management of lymphoedema to prevent episodes of adenolymphangitis and progression of disease.

Surgery can alleviate most cases of hydrocele. Clinical severity and progression of the disease, including acute inflammatory episodes, can be reduced and prevented with simple measures of hygiene, skin care, exercises, and elevation of affected limbs. People with lymphoedema must have access to continuing care throughout their lives, both to manage the disease and to prevent progression to more advanced stages.

- **Supportive treatment and prevention of acute adenolymphangitis (ADL) attacks:**
  - hydration and rest
  - antipyretics and analgesics.

- **Treatment and prevention of lymphoedema**
  - Hygiene measures for the affected limb:
    - wash twice daily with soap and clean water and dry well
    - keep nails short and clean
    - elevate the affected limb at night
    - wear comfortable footwear
    - prevent and treat entry lesions.
  - Frequent exercise of the affected limb to promote lymph flow:
    - standing on toes, flexing and circling ankles while sitting.
  - Elevation
  - Use of antibiotic or antifungal agents:
    - antiseptic, antibiotic, and antifungal creams for small wounds and abrasions
    - systemic antibiotics or antifungals in severe cases
    - surgical treatment of hydrocele.
11.15 Gonorrhoea

Gonorrhoea is a sexually transmitted disease caused by *Neisseria gonorrhoeae* which can manifest itself in many different ways. In 2012, an estimated 78 million cases of gonorrhoea occurred among 15–49-year-olds globally.

**Key clinical features**

**In men**
- Acute urethritis: purulent urethral discharge with pain on urination (dysuria).
- Complications: epididymitis, prostatitis, and fistula formation.

**In women**
- Mucopurulent discharge from the cervix with dysuria is the most frequent presentation.
- Urethritis (inflammation of the urethra and often the bladder) causes “internal” dysuria.
- Infection of the fallopian tubes (salpingitis), infection of the uterus (endometritis), and pelvic inflammatory disease (PID). Fever, abdominal pain, and cervical tenderness are common.
- Pelvic peritonitis (with nausea and vomiting) and perihepatitis (jaundice and abdominal pain) are less common.
- Infertility due to scarring can occur and can lead to an ectopic pregnancy.

**In men or women**
- Rectum: acute pain, difficulty passing stools, purulent discharge. Can occur in women or men who have sex with men.
- Pharynx: mild symptoms with cervical lymph node enlargement.
- Eyes
  - In adults, this results from contamination from a genital site. Characterized by swollen eyelids, severe redness, and swelling of the conjunctiva, which can lead to corneal ulcers.
  - Complications include corneal ulcers and perforation, infection of the whole eye (panophthalmitis), and blindness.
- Disseminated gonococcal infection:
  - This is the result of the bacteria passing into the blood and infecting distant sites. It is more common in women, and menstruation is a risk factor for dissemination of bacteria.
  - Fever, chills, and painful joints.
  - Skin lesions: pustules and papules, often with some blood in them, located on the limbs.
  - Septic arthritis: involves 1–2 medium joints (knees, wrists, ankles, elbows).

**Investigations**
- NAAT – on samples such as urine, vulvovaginal, cervical and urethral swabs; sensitivity is >90%.
- A Gram stain of urethral discharge in men reveals Gram-negative diplococci in the cells (only 50–70% of asymptomatic infections in men will be positive on gram stain).
- A culture can be done, but requires a special medium for inoculation, as well as immediate processing for a good yield.
- In a setting without diagnostic laboratory, the diagnosis is usually clinical.

**Treatment**
Resistance to antibiotics has emerged in many parts of the world, particularly to the quinolones and are, therefore, no longer recommended. Check the latest information for the region in which

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the infection was acquired before choosing a regimen. If data on local resistance not available, WHO recommends dual therapy over single therapy for people with genital or anorectal gonorrhoea.

Gonorrhoea (genital and anorectal) without dissemination can be treated with (for adolescents 10–19 years old and adults, patients with HIV, and pregnant women):

**Dual therapy**
- ceftriaxone 250 mg IM – 1 dose PLUS azithromycin 1 g orally – 1 dose; OR
- cefixime 400 mg orally – 1 dose PLUS azithromycin 1 g orally – 1 dose
  *Single therapy* (base on local resistance data)
- ceftriaxone 250 mg IM – 1 dose OR
- cefixime 400 mg orally – 1 dose OR
- spectinomycin 2 g IM – 1 dose.

Oropharyngeal gonococcal infection:

**Dual therapy**
- ceftriaxone 250 mg IM – 1 dose PLUS azithromycin 1 g orally – 1 dose; OR
- cefixime 400 mg orally – 1 dose PLUS azithromycin 1 g orally – 1 dose.

**Single therapy** (base on local resistance data; treatment failure has been observed on single therapy)
- ceftriaxone 250 mg IM – 1 dose.

Gonococcal infection after treatment failure:
- If re-infection suspected, re-treat with above WHO regimen, provide partner treatment, and re-inforce sexual abstinence or condom use.
- If treatment failure after following a non-WHO recommended regimen, re-treat with WHO recommended regimen.
- If treatment failure after WHO recommended single therapy, re-treat with WHO recommended dual therapy regimen.
- If treatment failure with availability of resistance data, treat according to susceptibility.
- If treatment failure after WHO recommended dual therapy, treat:
  - ceftriaxone 500 mg IM – 1 dose PLUS azithromycin 2 g orally – 1 dose; OR
  - cefixime 800 mg orally – 1 dose PLUS azithromycin 2 g orally – 1 dose; OR
  - gentamycin 240 mg IM – 1 dose PLUS azithromycin 2 g orally – 1 dose; OR
  - spectinomycin 2 g IM – 1 dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally – 1 dose

*Chlamydia* is a common coinfecting agent, and additional treatment directed at *Chlamydia* is important in patients who receive treatment for gonorrhoea (azithromycin 1 g orally – 1 dose OR doxycycline 100 mg twice daily for 7 days; if pregnant, azithromycin 1 g orally – 1 dose OR amoxicillin 500 mg orally three times daily for 7 days, OR erythromycin 500 mg orally four times daily for 7 days).

**Guinea worm disease (dracunculiasis)** – see Section 10.1 Skin problems

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11.16 Hepatitis – viral

Viral hepatitis can be caused by five different viruses: hepatitis A, B, C, D or E. All cause a wide range of symptoms, from asymptomatic infections to fulminant disease. In addition, the bloodborne viruses (B, C and D) can cause chronic liver disease, leading to cirrhosis and liver cancer. Hepatitis A and E are the most common causes of acute hepatitis.

In the SEA Region, approximately 39 million people live with chronic hepatitis B and 10 million people with chronic hepatitis C. An estimated 410 000 people in the Region die annually due to viral hepatitis, with chronic complications associated with HBV and HCV accounting for 78% of the total.\(^{52}\) Although advances in water and sanitation have reduced the burden of hepatitis A and E in the Region, outbreaks of waterborne and foodborne hepatitis due to hepatitis viruses A and E continue.

For example, in Nepal, hepatitis E (HEV) has become the predominant type of acute hepatitis both in adults and children, in sporadic and epidemic forms. Hepatitis E (HEV) outbreaks occur sporadically due to faecal contamination of water and poor sanitation, with a relatively high mortality rate (0.2%–4%), which is particularly high in pregnant women (10%–25%).\(^{53}\) In Nepal, hepatitis E outbreaks have occurred in 1973, 1981–1982, 1987, 1995 and 2014.\(^{54}\) Outbreaks are either focal (a large number of cases occur over days to weeks in a well-defined small population) or epidemic.\(^{55,56}\) During these outbreaks, a maternal mortality rate of 21%–25% was reported. During an epidemic in Biratnagar in 2014, HEV IgM prevalence was as high as 94%–100% in acute hepatitis patients.\(^{57}\)

### 11.16.1 Summary of transmission, prevention and management of acute hepatitis

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Hepatitis A and E</th>
<th>Hepatitis B and C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faecally contaminated water</td>
<td>Exposure to infected blood or body fluids through sexual contact, blood transfusions, reuse of contaminated needles and syringes, and transmission from mother to child</td>
</tr>
<tr>
<td></td>
<td>Person-to-person</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnant women are at high risk of acquiring the disease, and it is also more frequently fulminant in the third trimester of pregnancy. There is a high risk of mother-to-child transmission. Pregnant women and young children are at high risk for poor outcomes</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical features common to all causes of acute hepatitis**

The clinical features of acute hepatitis are similar for all types of viral hepatitis:

- First: nausea, anorexia, vomiting, fatigue, malaise, headaches, muscle aches, sometimes fever
- Clinical jaundice develops 1–2 weeks later (yellow skin and eyes and dark urine)
- Enlarged, tender liver with right upper quadrant pain and discomfort
- Complete recovery can take many months

\(^{52}\) Singh PK: Towards ending viral hepatitis as a public health threat: translating new momentum into concrete results in South-East Asia, Gut Pathogens, 2018


### Investigations common to all causes of acute hepatitis

**Liver function tests**
- AST and ALT are elevated (at least three times higher than normal). The degree of elevation does not correlate well with the severity of disease.
- Alkaline phosphatase is usually mildly elevated or remains normal.
- Bilirubin levels are elevated ranging from 4.96 mg/dl to 19.88 mg/dl (85–340 umol/litre).
- Coagulation studies
- **Elevated PT (prothrombin time).** The degree of prolongation reflects the severity of the liver damage present.

### Specific investigations

**Hepatitis A**
- Anti-HAV IgM antibodies present within 10 days of the start of illness

**Hepatitis B**
- **Diagnosis of acute hepatitis B requires dosage of HBs Ag and anti-HBc IgM antibodies**
  - Screening of high-risk groups for hepatitis B requires dosage of HBs Ag and anti-HBs
- **HBs Ag (antigen)**
- **anti-HBc (total antibodies)**
- **anti-HBs (antibodies)**
- **Acute infection**
  - +
  - +/-
  - -
- **Chronic infection (carriage)**
  - +
  - +
  - -
- **Past infection (cured)**
  - -
  - +
  - +
- **Vaccinated**
  - -
  - -
  - +

**Ag HBs (antigen) is a marker of carriage and thus contagiousness.**
**Anti-HBc total antibodies is a marker of infection; specific dosage of IgM is helpful to distinguish between acute (IgM are positive) and chronic (IgM are negative) infection.**
**Anti-HBs antibodies is a marker of recovery from a past infection or immunity due to vaccination.**

*See Section 11.16.2 for continued assessment and diagnosis, treatment and monitoring of chronic HBV infection of a patient who is HBsAg+ (reactive).*

**Hepatitis C**
- Anti-HCV antibodies can be detected within 6–8 weeks of the onset of illness. If antibodies are positive, this needs to be confirmed with HCV RNA as 25% patients will clear HCV on their own.
- **See Section 11.16.3 for continued assessment of a patient who is either Anti-HCV+ (reactive) HBsAg+ (reactive).**

### Treatment common to all causes of acute hepatitis

**Supportive care (fluid management, and treatment of encephalopathy and coagulopathy in severe acute illness).**
No specific drug treatment is indicated.

### Prevention

**Treatment of chronic hepatitis B and C—see Section 11.6.2 and 11.6.3 below and current WHO and national guidelines**

**Hepatitis A**
- **Primary prevention**
  - Active immunization with hepatitis A vaccine for persons at risk who are older than 12 months
  - Three vaccinations are required with several schedule options (see package insert)
- **Secondary prevention**
  - (Post-exposure prophylaxis for exposed contacts)
  - Active immunization with hepatitis A vaccine (two doses give life-long protection).
  - The vaccine is safe in pregnant women and should be given in case of exposure to the disease.
  - A combination hepatitis A and B vaccine is available
- **Other preventive measures**
  - Handwashing and other enteric precautions

**Hepatitis B**
- **Primary prevention**
  - Active immunization with hepatitis B vaccine, anytime from birth
  - Three vaccinations required with several schedule options (see package insert)
- **Secondary prevention**
  - Active immunization with hepatitis B vaccine
  - OR
  - Passive immunization with immunoglobulin is indicated in two specific clinical situations: occupational post-exposure prophylaxis, or infants born to mothers who are HBsAg-positive.
  - Active and passive immunization have equivalent efficacy in exposed individuals. Active immunization has the added advantage of providing extended protection
The vaccine is safe in pregnant women and should be given in case of exposure to the disease. A combination hepatitis A and B vaccine is available.

**Other preventive measures**
- Condom use for sexual contact
- No sharing of injecting drug equipment
- Harm reduction interventions including opioid substitution therapy.

<table>
<thead>
<tr>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccine is available</td>
</tr>
<tr>
<td>Injecting drug users are at highest risk</td>
</tr>
<tr>
<td>Men who have sex with men are at highest risk of sexual transmission</td>
</tr>
<tr>
<td>More common in areas with high prevalence of injecting drug users, tribal scarring, tattooing, and unscreened blood products</td>
</tr>
<tr>
<td>Prevention interventions include condom use, harm reduction measures, and blood product safety.</td>
</tr>
</tbody>
</table>

11.16.2 Diagnosis, treatment and monitoring of chronic HBV infection of a patient who is HBsAg + (reactive).

This summary algorithm is from 2017 WHO guidelines on hepatitis B and C testing.\(^\text{58}\) Use this full guideline, the 2015 Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection,\(^\text{59}\) and your national guidelines on clinical management and the role of the district hospital. As appropriate, refer to the appropriate level for treatment initiation and ongoing care.

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\(^{58}\text{WHO guidelines on hepatitis B and C testing, 2017}\)

\(^{59}\text{Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, WHO, 2015}\)
11. Multisystem diseases: SEARO 2021

HEPATITIS B SURFACE ANTIGEN (HBsAg)
Single RDT\(^2\) or laboratory-based immunoassay\(^3\)

1. SEROLOGICAL TESTING
   - HBsAg + (reactive)
     - Report positive
     - Compatible with HBV infection
   - HBsAg – (non-reactive)
     - Report negative
     - No serological evidence of HBV infection

2. ASSESSMENT OF STAGE OF LIVER DISEASE
   - HBV DNA NUCLEIC ACID TEST (NAT) (quantitative)
     - (to further guide who to treat and not treat, if no evidence of cirrhosis)
   - PRESENCE OF CIRRHOSIS
     - Yes
       - ALL AGES
         - >30 years (in particular)
         - ALT\(^6\) Persistently abnormal
         - HBV DNA >20,000 IU/mL

     - No
       - AGE <30 years
       - ALT\(^6\) Persistently normal
       - ALT\(^7\) Persistently normal
       - HBV DNA <2000 IU/mL

   - INITIATE ANTIVIRAL THERAPY\(^8\) AND MONITOR
     - Tenofovir or entecavir
     - Entecavir in children aged 2–11 years

   - DEFER TREATMENT AND MONITOR
     - HBV DNA >2000–20,000 IU/mL
     - HBV DNA <2000 IU/mL

3. MONITORING
   - DETECTION OF HCC in persons with cirrhosis or HCC family history (every 6 months)
     - Ultrasound and serum AFP
   - TREATMENT RESPONSE AND/OR DISEASE PROGRESSION (every 12 months)
     - ALT, HBV DNA and HBsAg
     - Staging of liver disease (clinical criteria and NITs (e.g. APRI in adults or TLE)
   - TOXICITY MONITORING in persons on treatment (baseline and every 12 months)
     - Renal function and risk factors for renal dysfunction

11.16.3 Diagnosis, treatment and monitoring of chronic HCV infection
Use the following algorithm which does not require genotyping (except for adolescents) given the availability of pan-genotypic drugs. Also refer to the 2018 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection\(^60\) and your national guidelines on clinical management and the role of the district hospital. As appropriate, refer to the appropriate level for treatment initiation and ongoing care. Direct-acting antivirals have made cure possible and the cost of treatment has been markedly reduced.

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\(^60\) Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection, WHO, 2018
### Hepatitis

#### 1. Multisystem diseases: SEARO 2021

<table>
<thead>
<tr>
<th>Step</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>CONDUCT ANTI-HCV ANTIBODY TESTING</strong>&lt;br&gt;Use rapid diagnostic test or laboratory-based immunoassay</td>
</tr>
<tr>
<td></td>
<td>Anti-HCV +</td>
</tr>
<tr>
<td>2</td>
<td><strong>PROCEED TO SUPPLEMENTARY TESTING</strong>&lt;br&gt;Use HCV RNA (qualitative or quantitative) or HCV core antigen (cAg)</td>
</tr>
<tr>
<td></td>
<td>HCV RNA test + or cAg +</td>
</tr>
<tr>
<td></td>
<td>HCV infection</td>
</tr>
<tr>
<td>3</td>
<td><strong>START TREATMENT</strong>&lt;br&gt;The following should be assessed prior to treatment initiation&lt;br&gt;• Assess liver fibrosis with non-invasive testing, e.g., APRI, FIB-4 to determine if there is cirrhosis&lt;br&gt;• Assess other considerations for treatment (comorbidities, pregnancy, potential drug–drug interactions)</td>
</tr>
<tr>
<td></td>
<td>≥18 YEARS WITHOUT CIRRHOSIS&lt;br&gt;• Sofosbuvir/velpatasvir 12 weeks&lt;br&gt;• Sofosbuvir/daclatasvir 12 weeks&lt;br&gt;• Glecaprevir/pibrentasvir 8 weeks*</td>
</tr>
<tr>
<td></td>
<td>≥18 YEARS WITH COMPENSATED CIRRHOSIS&lt;br&gt;• Sofosbuvir/velpatasvir 12 weeks&lt;br&gt;• Glecaprevir/pibrentasvir 12 weeks*&lt;br&gt;• Sofosbuvir/daclatasvir 24 weeks&lt;br&gt;• Sofosbuvir/daclatasvir 12 weeks**</td>
</tr>
<tr>
<td></td>
<td>ADOLESCENTS (12–17 YEARS)***&lt;br&gt;• Sofosbuvir/ledipasvir 12 weeks in genotypes 1, 4, 5 and 6&lt;br&gt;• Sofosbuvir/ribavirin 12 weeks in genotype 2&lt;br&gt;• Sofosbuvir/ribavirin 24 weeks in genotype 3</td>
</tr>
<tr>
<td>4</td>
<td><strong>MONITORING</strong>&lt;br&gt;• Assess cure: sustained virological response (SVR) at 12 weeks after the end of treatment (HCV RNA SVR, qualitative or quantitative nucleic acid test (NAT))&lt;br&gt;• Detection of hepatocellular carcinoma (HCC) in persons with cirrhosis (every 6 months) with ultrasound or AFP</td>
</tr>
</tbody>
</table>
11. Multisystem diseases: SEARO 2021

11.17 Histoplasmosis

This is an infection caused by the fungus *Histoplasma capsulatum* that is found in moist surface soil containing bat or bird droppings. The infection is acquired through inhalation. Patients can become ill after acute infection, or due to reactivation of a latent infection. Histoplasmosis is endemic in many regions worldwide, including Asia.

**Key clinical features**
- In the immunocompetent host: mild symptoms in a majority of cases include cough, fever, and malaise.
- In the chronic form: there is a gradual onset of productive cough, weight loss, and night sweats.
- In the disseminated form: fever, weight loss, enlarged liver, spleen, and lymph nodes, anaemia, and papular skin lesions can also occur. Pulmonary involvement is observed in 50% of cases.

It is important to differentiate histoplasmosis from PCP pneumonia (see Section 8.2 *Pneumocystis jiroveci* pneumonia), and tuberculosis.

Histoplasmosis generally occurs late in the course of HIV infection when the CD4 count is <100.

**Investigations**
- Laboratory findings are non-specific.
- A definitive diagnosis is by a culture of blood or affected tissue, but takes 4–6 months for a result.
- *Histoplasma antigen can be tested for in urine or blood and has high sensitivity, but the test is often unavailable.*
- Direct microscopy on Wright-stained smears is a cheap, easy to conduct method, but has a low sensitivity (less than 10%). If combined with blood cultures, it has sensitivity of up to 88%.
- If there are pulmonary symptoms, the chest X-ray is abnormal in 50%–70% of cases, showing mainly a diffuse interstitial image or reticulo-nodular infiltrates. However, other abnormalities also are possible.

**Treatment**
- All PLHIV with histoplasmosis should be treated with ART.

If there are mild clinical symptoms, and a single focus of disease other than the CNS:
- initially, itraconazole 200 mg three times daily for three days; then itraconazole 200 mg twice daily with food for 6–12 months.
- fluconazole 800 mg daily is a safe and moderately effective induction therapy for mild or moderately severe disseminated histoplasmosis in patients with AIDS.

In severely ill patients with or without immunosuppression, the first recommended option is:
- amphotericin B 0.7 mg/kg IV until clinical improvement (usually at least 14 days), and then continue with itraconazole 200 mg twice daily for 6–12 months.

If there is CNS involvement:
- same as severely ill patients, except that amphotericin B treatment should be continued for at least four to six weeks.
Note: During treatment with amphotericin B, check the serum creatinine and electrolytes regularly. Also, be aware of a possible reaction during the infusion (fever, chills) which can be prevented by pre-treatment with paracetamol or corticosteroids. See advice on amphotericin administration in Section 11.8.

**Secondary prevention**
Itraconazole 200 mg daily needs to be administered for at least 1 year, and can be discontinued if the CD4 count rises above 150. If the CD4 count drops again, itraconazole therapy must be resumed.

Note: Fluconazole 400 mg daily is less effective than itraconazole 200 mg to 400 mg daily or amphotericin B 50 mg IV given weekly as maintenance therapy to prevent relapse.
11.18 Hydatid disease (cystic echinococcosis)\textsuperscript{61, 62}

Echinococcosis or hydatid disease is a parasitic disease caused by tapeworms that affect humans and animals, more commonly dogs, horses, sheep and rodents. Both cystic and alveolar echinococcoses develop when humans ingest eggs of \textit{Echinococcus granulosus} or \textit{E. multilocularis} which are shed in the faeces of dogs harbouring adult stages of these tapeworms. Humans are “accidental intermediate hosts” – the infection is acquired by ingestion, but humans are not involved in transmission. Echinococcosis has a global distribution and causes serious morbidity and death if left untreated. \textit{E. granulosus} is more prevalent worldwide, causing unilocular cystic disease while \textit{E. multilocularis} causes budding proliferating cysts.

**Clinical features**

Hydatid cysts often develop in the liver but can also affect the lungs, brain, spleen, kidney, muscles, central nervous system and bone.

- Liver cysts are often asymptomatic when small but may cause right upper quadrant abdominal pain; a palpable mass when large; and jaundice if the bile duct is obstructed.
- Rupture or leakage of a cyst may cause fever, urticaria, bronchospasms or anaphylactic reaction. A liver cyst may rupture into the peritoneal cavity, pleural space, biliary ducts or the vascular system of the liver. Secondary bacterial infection can lead to formation of a liver abscess.
- Pulmonary cysts can be seen on chest x–ray and may rupture to cause cough, chest pain, shortness of breath, bronchospasm, bloody mucoid sputum with fragments of membrane and haemoptysis. Spontaneous cyst rupture into a bronchus may be accompanied by complete emptying and resolution. However, incomplete emptying may lead to formation of a lung abscess.
- Cysts in the heart can lead to cardiac tamponade.
- Cysts in the brain or spinal cord can cause neurological sequelae.
- Bone cysts may cause pathological fractures.
- Ocular cysts may occur.

**Differential diagnosis includes:**

- amoebic liver abscess
- pyogenic liver abscess
- hepatic cysticercosis
- hepatoma or other malignancy
- other causes of liver mass and obstructive jaundice
- pulmonary tuberculosis (TB).

**Investigations**

- Ultrasound is the technique of choice; usually complemented by CT-scan or MRI.
- Chest X-ray: for pulmonary cysts, may show calcified cysts.
- Serological tests.
- Needle aspiration under ultra-sound or CT-scan guidance.

This procedure is both investigational and therapeutic (see below). The material aspirated should be examined as follows:

- Macroscopy: appearance, whether purulent or blood stained, smell, consistency,
- Microscopy: for pus cells, protoscoleces, brood capsules, hooks or amoebic trophozoites,

\textsuperscript{61} Echinococcosis (23 March 2020) https://www.who.int/news-room/fact-sheets/detail/echinococcosis Accessed 10 June, 2020

\textsuperscript{62} Elizabeth Sentongo, Makerere University, Uganda
• Gram stain,
• Aerobic and anaerobic culture and testing for bacterial sensitivity to antibiotics.

**Treatment**
A symptomatic liver cyst should be managed at a regional hospital
• Treatment comprises mainly surgical intervention or percutaneous treatment and/or high-dose, long-term therapy with albendazole or mebendazole.
• Percutaneous treatment requires a surgeon and a radiologist; the anaesthetist should be on standby in case of an anaphylactic reaction.
• The haemoglobin level, bleeding and coagulation indices should be within normal limits.
• Radiology should exclude connection between the cyst and the biliary tree.

The PAIR procedure, which has largely replaced open surgery, includes chemotherapy and involves:
• Percutaneous access to the liver cyst – under ultrasonographic guidance.
• Aspiration of the cyst contents – through a large bore cannula.
• Introduction of a protoscolicidal agent – ethanol or hypertonic saline.
• Reaspiration of the ethanol/content mixture and closed short-term drainage.
• Chemotherapy with albendazole started at least four days before surgery then continued for four weeks after surgery or mebendazole four days before surgery then continued for three months after surgery.

Lung cyst (alveolar echinococcosis) requires major surgery – lobectomy, wedge resection – followed by albendazole. If confined, radical surgery can be curative.

**Influenza** – see Section 8.2 Chest symptoms: Cough and shortness of breath
11.19 Leishmaniasis

Leishmaniasis is a disease caused by infection with protozoa called Leishmania, and is transmitted to humans by infected sand fly bites and in some cases by contaminated blood transfusions. The two clinical types – cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) – are outlined below.

In a surveillance report from 2015, three countries in the SEA Region were endemic for cutaneous leishmaniasis (with 1284 reported cases) and five countries (9250 reported cases) for visceral leishmaniasis.

11.19.1 Cutaneous leishmaniasis (Aleppo boil, oriental sore)

In the Eastern Hemisphere cutaneous leishmaniasis (CL) is caused by L. infantum, L. major, L. tropica, and L. aethiopica. In the Western Hemisphere CL is caused by L. braziliensis, L. mexicana, and L. guyanensis complex. L. donovani, L. infantum and L. chagasi usually cause visceral disease but can also cause cutaneous disease. Mucosal lesions are mainly due to L. braziliensis and L. panamensis.

Key clinical features
Cutaneous leishmaniasis is a disease of the skin and mucous membranes. There are different clinical forms of CL: localized CL, diffuse CL, and mucosal leishmaniasis. The typical features of each are outlined below.

Cutaneous lesions
- Occur mainly on exposed body parts (face, neck, arms, legs).
- May be single or multiple with regional lymph node enlargement.
- Are usually painless.
- If secondarily infected, they can be painful and itchy.

Localized cutaneous leishmaniasis
- Papule at the site of the bite (like an insect bite).
- If papule persists, it develops into either:
  - a small nodule
  - an ulcer with a flat base and raised border
  - the nodulo-ulcerative form (broad-based ulcer with crust).
- Leishmaniasis recidivans is localized CL that is characterized by a chronic solitary lesion that expands slowly and often reoccurs. The lesion can continue for many years, causing severe disfigurement.

Diffuse cutaneous leishmaniasis
- Coalescence of papules and nodules to form plaques.
- Chronic and very difficult to treat.

Mucosal leishmaniasis
- Is the most severe form of CL, causing severe disfigurement and mutilation of the face.

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Nasal lesions cause discharge, bleeding, obstruction, deformity, and destruction of cartilage with collapse of the nose.

Oropharyngeal lesions: difficulty chewing and swallowing, bleeding gums, toothache, loose teeth, perforation of the hard palate.

Involvement of mucosa can follow:
- primary infection (with \textit{L. major} or \textit{L. donovani}); OR
- dissemination of cutaneous leishmaniasis; OR
- treatment for visceral leishmaniasis (post-kala-azar dermal leishmaniasis).

\textbf{Investigations}

Demonstration of the parasite:
- microscopic identification of intracellular amastigote in Giemsa-stained specimens from lesions;
- culture of extracellular promastigote on specialized media;
- Montenegro test (leishmanin skin test):
  - intradermal injection of killed amastigotes, measure skin induration after 48–72 hours (more than 5 mm is positive);
  - useful in established disease;
- PCR on a skin biopsy;
- serology tests are of little use because of very low antibody levels in CL.

\textbf{Treatment}

- Spontaneous healing is mainly observed in “old world” CL after several months (\textit{L. major}: 40%–70\% after three months, 100\% after 12 months; \textit{L. tropica}: 1\%–10\% after three months, 68\% after 12 months, close to 100\% after three years).

- The decision to treat is based on the species, the potential for dissemination, as well as the location, number, and size of the lesions, and previous treatment used if any. With the exception of \textit{L.major}, CL of the old World is commonly treated with local treatment (for exceptions see below). Because of the risk of developing mucocutaneous leishmaniasis, CL of the New World is commonly treated with systemic treatment.

- Solitary lesions are common.
- Small, localized lesions usually heal without treatment other than wound care.
- Diffuse and mucosal lesions are usually severe and difficult to treat.

- First-line treatment uses a daily combination of intramuscular injections of generic sodium stibogluconate (SSG) 20 mg/kg and paromomycin 15 mg/kg for 17 days. Second-line treatment uses either amphotericin B deoxycholate 1 mg/kg intravenously on alternate days for 15 doses or liposomal amphotericin B (Ambisome) 3mg/kg intravenously daily for 1–7 days or on days 1–5, 14 and 21.

- \textbf{Local treatment}
  
  This needs to be adapted according to species, and the clinical characteristics – site, size, number of lesions, whether open or nodular, whether superinfected, and the immune status of patients.
  - local infiltration (1 to 5 intralesional injections, every few days or weekly) with pentavalent antimonials, with or without cryotherapy (preferred); OR
  - paromomycin ointment (15\% paromomycin plus 12\% methyl benzethonium chloride ointment twice daily for up to 20 days); OR
  - thermotherapy (1 or 2 applications of localized heat (55 \degree C for 5 minutes) using a thermal device), with or without cryotherapy with liquid nitrogen (-195 \degree C) applied to the lesion once or twice weekly up to six weeks.
Systemic treatment
- pentavalent antimonials (meglumine antimoniate or sodium stibogluconate) 20 mg/kg daily IV/IM for 21 days; OR
- liposomal amphotericin B 3 mg/kg for six doses (up to 30 mg/kg total dose if needed); OR
- pentamidine – only recommended if no other treatment available, due to severe side-effects and toxicity (except for L. guyanensis for which it is the preferred choice); OR
- miltefosine 150 mg daily (or 2.5 mg/kg daily if weight less than 25 kg) for 28 days; OR
- fluconazole 200 mg orally daily for six weeks; OR
- ketoconazole 600 mg orally daily for 28 days.

11.19.2 Visceral leishmaniasis (kala-azar)

Most SEA Region cases currently are in foci in Bangladesh, India and Nepal.

Key clinical features
Visceral leishmaniasis is a systemic disease; however, infection is often not clinically apparent. Malnutrition and HIV infection predispose to the development of overt clinical disease (see Section 11.20.3 HIV/leishmaniasis coinfection below).

Possible clinical presentations include:
- fever – irregular and prolonged (more than 2 weeks)
- weight loss, which can be severe with wasting
- enlarged spleen (often massive) and enlarged liver (relatively unusual)
- cough, diarrhoea
- generalized lymphadenopathy may occur
- anaemia, leukopenia, neutropenia, thrombocytopenia
- skin lesions that occur after treatment – post-kala-azar dermal leishmaniasis – see below.

Investigations
- Blood investigations:
  - low platelet count or pancytopenia (in advanced disease)
  - low albumin level.
- Demonstration of the parasite:
  - microscopic identification of parasite on Giemsa-stained smear from spleen, bone marrow, lymph node aspirates
  - spleen aspirates are highly sensitive but extremely invasive, require training and a blood transfusion service
  - culture of organism from aspirated or biopsied material.
- Serology
  - the rk39 rapid diagnostic test
    - There are several commercially available rK39 dipstick types: the DiaMed IT-Leish (DiaMed AG, Switzerland) and the Kalazar Detect (Inbios Ltd, Seattle, USA).
    - the direct agglutination test (DAT) performed by a trained laboratory technician.
- A negative serology result does not rule out leishmaniasis in HIV patients and those with other immunocompromising conditions due to low sensitivity, more so when the clinical and geographic attributes are correspondent.

Treatment
- First-line treatment uses a daily combination of intramuscular injections of generic sodium stibogluconate (SSG) 20 mg/kg and paromomycin 15 mg/kg for 17 days. Second-line treatment uses either Amphotericin B deoxycholate 1 mg/kg intravenously on alternate days
for 15 doses or Liposomal Amphotericin B (Ambisome) 3mg/kg intravenously daily for 1–7 days or on days 1–5, 14 and 21.

- Mortality in untreated patients is very high (almost certain), so effective therapy is very important. The treatment of visceral leishmaniasis depends on the geographical location, the parasite species involved, and other conditions of the patient (e.g. age, pregnancy, HIV co-infection). Preferred treatment can change rapidly based on new combination drug regimens and sensitivity of the parasite. For detailed information refer to the WHO Technical Report Series 949, *Control of leishmaniases*.63

- Treatment also includes high-protein nutritional intake, ferrous sulphate, folic acid, vitamin A and vitamin C supplementation, and an empirical dose of albendazole against intestinal helminths. Spleen size, weight and the haemoglobin level should be monitored and evidence of co-existent infection (respiratory, intestinal and malarial) screened for on admission and regularly throughout treatment. Patients should be followed up at 6, 12 and 18 months post-discharge.

### Table: Treatment options for visceral leishmaniasis and post-kala-azar dermal leishmaniasis

<table>
<thead>
<tr>
<th>Geographical area and disease form</th>
<th>1st preference</th>
<th>Alternative options by rank of preference</th>
</tr>
</thead>
</table>
| Indian subcontinent (Bangladesh, Bhutan India, Nepal)  
Anthroponotic visceral leishmaniasis caused by *L. donovani* | Liposomal amphotericin B: 3–5 mg/kg over 3–5 days up to a total dose of 15 mg/kg by infusion, or 10 mg/kg as a single dose by infusion | 1. Combinations (co-administered)  
- liposomal amphotericin B (5 mg/kg by infusion, single dose) plus miltefosine (7 days, as below)  
- liposomal amphotericin B (5 mg/kg by infusion, single dose) plus paromomycin (10 days, as below)  
- miltefosine plus paromomycin, both for 10 days, as below  
- amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 15–20 doses  
2. Miltefosine; for people aged ≥12 years and <25 kg body weight, 50 mg/day; 25–50 kg body weight, 100 mg/day; >50 kg body weight, 150 mg/day; orally for 28 days (treatment failures reported from Nepal)  
Or paromomycin: 15 mg (11 mg base) per kg body weight per day IM for 21 days  
3. Pentavalent antimonials: 20 mg Sb5+/kg per day IM or IV for 30 days in areas where they remain effective: Bangladesh, Nepal and the Indian states of Jharkhand, West Bengal and Uttar Pradesh. |
| Post-kala-azar dermal leishmaniasis in Bangladesh, India, and Nepal | Liposomal amphotericin B: 3–5 mg/kg per day in 3–6 infusions, up to a total dose of 18–21 mg/kg, or pentavalent antimonials: 20 mg Sb5+/kg per day IM or IV for 28 days | Amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 20–30 doses, for a total dose of 2–3 g |
11.19.3 Leishmania/HIV coinfection

The HIV pandemic has modified the natural history of leishmaniasis disease with a dramatic impact on its clinical course and response to treatment. Coinfection has been reported in many countries.

Impact of coinfection

Both HIV and VL target similar immune cells, causing damage to the immune system and a drop in CD4 count. Coinfected patients often present late with low CD4 counts and high HIV viral loads. Coinfection increases the risk of developing overt VL disease, and reduces response to treatment. The risk of VL relapse is increased with a low CD4 count, and VL relapse inhibits CD4 recovery in a patient on ART.

See HIV guidelines for current case management.

11.20 Leprosy

Leprosy is a chronic infection caused by *Mycobacterium leprae*. It most commonly affects the skin and peripheral nerves as well as the eyes and upper respiratory tract. Untreated leprosy can cause progressive and permanent damage with deformities and disabilities. Leprosy affects people of all races and ages and both sexes. The most effective way of reducing further transmission of the disease, as well as, preventing disabilities in leprosy, lies in early diagnosis and treatment with multidrug therapy (MDT). Leprosy is curable and treatment in the early stages can prevent disability.

Elimination as a public health problem (defined as prevalence of leprosy at less than one case per 10 000 population) has been achieved globally and by most countries at national level. Some countries, particularly in specific regions (i.e. states, districts and provinces with large populations), continue to have substantial number of new cases indicating ongoing transmission. In the South-East Asia Region such countries include Myanmar, Nepal, India, Indonesia and Sri Lanka. In 2019, the SEA Region reported 71% of all global cases; two countries – India and Indonesia – contributed 92% of these cases. Hence the continued importance of clinicians at district hospital level being able to diagnose, treat and manage complications.

A WER report presented data on the point prevalence of leprosy registered cases on the last day of 2018 and new cases detected in 2019 (a proxy for incidence) and included data from 11 SEA Region countries. The prevalence rate per million population was 53.8 in the SEA Region. The regional proportions of new cases in 2019 were: 71.3% (143 787) in the SEA Region, 14.8% (29 936) in the Region of Americas, 9.9% (20 205) in the African Region, 2.1% (4211) in the Eastern Mediterranean Region, 1.9% (4004) in WPR and 42 in EUR. The presence of visible deformity or grade 2 disability (G2D) at the time of diagnosis indirectly indicates delayed detection. The number of new G2D cases showed a significant decrease, particularly in the SEA Region, from 8792 in 2015 to 4817 in 2019 (nearly 45%), suggesting case detection campaigns have resulted in earlier detection.

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It is believed that *M. leprae* spreads from person to person primarily as a nasal droplet infection. Untreated leprosy patients discharging bacilli are considered to be the main source of infection. Persons living in the same household or who otherwise are in frequent contact with an untreated patient have the greatest risk of being exposed to the bacilli.

The infectiousness of a leprosy patient is related to the size of the bacillary population in the body. The first supervised dose of MDT reduces the load of viable bacilli to such low levels that it is no longer possible to cultivate the organism in an animal model. In public health terms, this implies that infectiousness becomes negligible after the start of MDT.\(^{68}\)

The incubation period is generally 5 to 7 years but can be longer. Most individuals exposed to the bacteria do not develop the disease. The different clinical manifestations are due to differences in the immunological defence of the body.

**Key clinical features**

Leprosy should be considered in people with any of the following symptoms and signs:
- pale or reddish patches on the skin (the most common sign)
- loss or decrease of feeling in the skin patch, i.e. temperature, touch and pain
- loss of sweating
- numbness or tingling of the hands or feet
- weakness of the hands, feet or eyelids
- painful or tender nerves
- swellings or lumps in the face or earlobes
- painless wounds or burns on the hands or feet.

If one is not sure of the diagnosis, the person with suggested symptoms and signs should be referred to the next level. They should not registered as a case.

**Diagnosis of leprosy** is based on careful clinical examination of the patient and when necessary backed by bacteriological examination. Leprosy is diagnosed when at least one of the following cardinal signs is present:

(i) definite loss of sensation in a pale (hypopigmented) or reddish skin patch;
(ii) thickened or enlarged peripheral nerve with loss of sensation and/or weakness of the muscles supplied by that nerve; or

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\(^{68}\) Report of the Tenth Meeting of the WHO Technical Advisory Group on Leprosy Control. New Delhi, WHO Regional Office for South-East Asia, 2009 [SEA-GLP-2009.5].
(iii) presence of acid-fast bacilli in a slit-skin smear  

**History should include:**
- General information on the patient – complete name, gender, place, date of birth, full address distance from home to health unit, occupation;
- Contact information – other leprosy cases and contacts in the household and family or neighbourhood or in the workplace;
- Main complaints – date of onset, sites of the lesions, disability experienced, subsequent changes and development of the disease, treatment received.

**Physical examination needs:**
- adequate light (preferably day light) because it is difficult to see the lesion in poor light,
- enough privacy for the person to feel at ease.

To ensure that no important sign is missed the entire skin surface should be examined systematically.

The skin should be examined (with consent) for:
- presence of skin lesions (patches or nodules)
- number of skin lesions
- loss of sensation on the skin lesions (patches).

Peripheral nerves should be examined for:
- enlargement or thickening
- tenderness (pain on touch)
- nerve function assessment.

During all clinical assessments look for disabilities:
- examine feet for dryness, fissures, cracks, blisters, and ulcers on the sole or between toes
- examine hands for dryness, injury, dry cracks or fissures.

**Classification of leprosy**
Classification of leprosy (grouping of cases for treatment purposes) is important to classify the type of leprosy because it determines the treatment regimen and the appropriate messages to give to the patient before administration of treatment. In relation to this, there are two treatment groups:

**Paucibacillary leprosy (PB)** – These are patients who have one to five skin lesions in total, without demonstrated presence of bacilli in a skin smear (skin-smear negative).

**Multibacillary leprosy (MB)** – These patients have more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions.

All patients with a positive skin smear must be classified as MB irrespective of the number of skin lesions.

When an individual with very low body resistance is infected with leprosy bacilli, the bacilli will multiply freely in the body and the person will develop the more diffuse or severe form of the disease, i.e. MB leprosy.
Treatment
MDT is a combination of medicines that is very safe and effective for treatment of leprosy. To prevent the emergence of drug resistance, patients should never be treated with a single drug.

WHO now recommends a 3-drug regimen of rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment of six months for PB leprosy and 12 months for MB leprosy. The same blister pack can be used for treatment of both types of leprosy. Some countries have continued 2 drug treatment for paucibacillary patients.

Other important information for the patient:
- MDT is distributed free of charge to all those who need it – both the treatment and consultation.
- The drugs are all taken orally; the daily drugs should be taken in a single dose on an empty stomach.
- The drugs are given out in blister packs which provide four weeks of treatment (28 days). Explain how the tablets must be taken at home, e.g. for an adult patient:
  - once a month: Day 1: 2 capsules of rifampicin (300 mg X 2) + 3 capsules of clofazimine (100mg X 3) + 1 tablet of dapsone (100 mg),
  - once a day on days 2–28: 1 capsule of clofazimine (50 mg) + 1 tablet of dapsone (100 mg).
- It is crucial that patients understand which drugs they have to take once a month and which every day. A health worker or other accompanying person (if health worker is not available) should ensure the patient takes the monthly dose of three drugs. There are different packs with the same drugs but in smaller doses for children.
- Warn the patient that the urine will be red for some hours after taking the rifampicin —this is normal. In MB, skin may darken due to clofazimine and the pigmentation may return to previous skin colour after the treatment is finished, particularly if originally of darker skin.
- Discuss how often the person should attend: monthly or less often depending on access and disease status.
- Discuss that leprosy is no longer infectious once treatment has started. However, close contacts may already have been infected and are at risk of developing the disease;
hence they should be brought for examination at the next visit. Preventive treatment is available.

- Discuss that leprosy reactions can occur and can be treated. If there are signs of leprosy reactions, the patient should quickly report back to the clinic if:
  - patches can suddenly become red and swollen again;
  - there may be pain or numbness in the limbs;
  - there may be weakness of hands or feet;
  - there may be eye problems: loss of vision, pain or redness.

- MDT is safe for women and their babies during pregnancy and breastfeeding.
- MDT can be given to HIV-positive patients, those on antiretroviral treatment and to patients on treatment for TB. If a leprosy patient is on treatment for TB, the MDT regimen should omit rifampicin as long as the TB regimen contains rifampicin.

### Side-effects of MDT drugs and their management:
MDT is safe and serious side-effects are very rare.

<table>
<thead>
<tr>
<th>Side-effects of MDT</th>
<th>Drug responsible</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red coloured urine</td>
<td>rifampicin</td>
<td>Reassure the patient that this is normal for rifampicin. This is taken once monthly – it lasts for only a few hours after taking the drug</td>
</tr>
<tr>
<td>Darkening of the skin</td>
<td>clofazimine</td>
<td>Counsel – this is due to clofazimine. The darkening is harmless and will disappear within a few months of completing therapy. Encourage the patient to take the medicines regularly.</td>
</tr>
<tr>
<td>Gastrointestinal irritation e.g. abdominal pain, diarrhoea, nausea</td>
<td>All three, increased with high dose of clofazimine</td>
<td>Give drugs with food</td>
</tr>
<tr>
<td>Anaemia</td>
<td>dapsone</td>
<td>Give iron and folic acid</td>
</tr>
<tr>
<td>Itchy skin rash</td>
<td>dapsone</td>
<td>Stop dapsone and refer</td>
</tr>
<tr>
<td>Allergy, urticarial</td>
<td>dapsone or rifampicin</td>
<td>Stop both and refer (see Section 10.1 Skin)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>rifampicin</td>
<td>Stop rifampicin and refer</td>
</tr>
<tr>
<td>Shock, purpura, renal failure</td>
<td>rifampicin</td>
<td>Stop rifampicin and refer</td>
</tr>
</tbody>
</table>

*Other drugs are available for use if one or more of the standard drugs have been stopped but they are also associated with serious adverse effects and must be managed by specialists.

### Treatment of drug-resistant leprosy – regimens for these patients should be started by specialists at the referral level.

Leprosy patients with rifampicin resistance may be treated using at least two of the following second-line drugs: clarithromycin, minocycline or a quinolone (ofloxacin, levofloxacin or moxifloxacin), plus clofazimine daily for six months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months.

Leprosy patients with resistance to both rifampicin and ofloxacin may be treated with the following drugs: clarithromycin, minocycline and clofazimine for six months followed by clarithromycin or minocycline plus clofazimine for an additional 18 months.
Prevention of leprosy through chemoprophylaxis for contacts

WHO Guidelines for the diagnosis, treatment and prevention of leprosy 2018 recommends single-dose rifampicin as chemoprophylaxis for all contacts: both household and social contacts living in the neighbourhood and sharing the workplace.

National programmes are recommended to counsel persons affected by leprosy for examination of all contacts and to administer single-dose rifampicin for all contacts as chemoprophylaxis. The national programmes should ensure high coverage of contact screening of all detected patients.

Single-dose rifampicin (SDR) may be used as leprosy preventive treatment for contacts of leprosy patients (adults and children aged 2 years and above), after excluding leprosy and tuberculosis (TB) disease, and in the absence of other contraindications.

<table>
<thead>
<tr>
<th>Age/weight</th>
<th>Rifampicin single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 years and above</td>
<td>600 mg</td>
</tr>
<tr>
<td>10–14 years</td>
<td>450 mg</td>
</tr>
<tr>
<td>Children 6–9 years (weight ≥20 kg)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Children &lt;20 kg (&gt;2 years)</td>
<td>10–15 mg/kg</td>
</tr>
</tbody>
</table>

Complications

The complications of leprosy can be grouped as follows:

- Leprosy reactions (see Classification and management below)
- Effects of nerve damage (see Prevention of disability, below)
- Complications of advanced disease:
  - eye complications
  - facial deformities (now rare) including:
    - sunken nose,
    - loss of eyebrows (madarosis)
    - so-called “lionine” face.
- Psychosocial complications
- Disabilities as well as negative beliefs and prejudices concerning leprosy are the main causes of psychosocial problems for leprosy affected persons. Negative attitudes are also observed among health service providers including doctors. People suffering from psychosocial problems may need to be referred for counselling and other help.

Classification of leprosy reactions

Leprosy reactions are immune-mediated with inflammation episodes that can be self-limiting or severe and prolonged. They are the underlying cause of most leprosy disability. A reaction is the sudden appearance of symptoms and signs of inflammation in the skin lesions of a person with leprosy. There is redness, swelling and sometimes tenderness of the skin lesions, new skin lesions may appear. There may also be swelling, pain and tenderness of nerves often accompanied by impairment of nerve function.

Reactions can occur before, during or after completion of (MDT). There are two types of reaction:

- Reversal reaction (or Type 1 reaction)
- Erythema nodosum leprosum (ENL or Type 2 reaction)

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69 WHO Guidelines for the Diagnosis, treatment and prevention of leprosy, 2018, https://apps.who.int/iris/bitstream/handle/10665/274127/9789290226383-eng.pdf?ua=1

Apart from PB patients with single lesions, most other patients have a risk of getting reversal reactions. Only a small group of MB patients with a high load of bacilli are at risk of developing ENL reaction.

Both types can be divided into mild or severe; severe reactions require treatment with corticosteroids.

Signs of severe (Type 1) reversal reaction:
If any of the following signs is found, the reaction should be treated as severe:
• nerve function impairment, i.e. loss of sensation or muscle weakness
• pain or tenderness in one or more nerves
• silent neuritis
• a red, swollen skin patch on the face or overlying another major nerve trunk
• watering in eyes and inability to close eyes
• a skin lesion anywhere that becomes ulcerated
• presence of constitutional symptoms like fever
• oedema of the hands, feet or face.

Signs of Severe (Type 2) ENL reaction
If any of the following signs is found, the reaction should be treated as severe:
• inflamed subcutaneous nodules in the skin anywhere in the body; usually 1–2 cm in diameter
• pain or tenderness in one or more nerves, with or without loss of function
• ulceration of enl nodules
• watering, redness and of the eyes, with or without loss of visual acuity
• painful swelling of the testes (orchitis) or of the fingers (dactyliitis)
• marked arthritis or lymphadenitis.

Management of leprosy reactions
All patients who develop reactions while on MDT should have the MDT continued without alteration of dosage. Both types of reactions can be precipitated or their response to treatment adversely affected by other concurrent conditions, e.g. malaria, intestinal worms or tuberculosis. Patients should be carefully screened for these and appropriate treatment given.

Mild reversal reactions
Patients not showing any of the signs of severity listed above may be managed in the treatment centre symptomatically with aspirin or another NSAID. If after one week’s treatment there is no apparent improvement the patients should be managed as having severe reaction.

Severe reversal reactions
Patients with severe reaction must be referred to the regional referral level where they can be treated and monitored effectively. Recent (within the last six months) loss of function in one or more peripheral nerves is the main reason for steroids to be prescribed in leprosy. Nerve function should be monitored on a regular basis.

Management of severe reversal reactions

Steroid treatment
Those should be treated with a course of prednisolone usually lasting 12 to 24 weeks. The prednisolone should be prescribed by someone properly trained in using them.

In general, the starting dose should be between 0.5 and 1.0 mg per kg of body weight per day. In most settings 0.5 mg/kg daily would be an appropriate starting dose for a first course, meaning 30 or 40 mg daily for most adults. Recent studies suggest that a course lasting 20 weeks gives the best results, starting at either 30 mg or 40 mg, depending on body weight.

Because of the prolonged treatment with the prednisolone, patients must be assessed for potential side-effects. As soon as nerve tenderness decreases, patients with muscle weakness or paralysis should be taught exercises to strengthen the affected muscles and prevent joint stiffness.

Table Recommended prednisolone regimen for Type 1 reactions in PB or MB patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>1–2</th>
<th>3–4</th>
<th>5–8</th>
<th>9–12</th>
<th>13–16</th>
<th>17–20</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg</td>
<td>40 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg</td>
<td>30</td>
<td>30 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg</td>
<td></td>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Physiotherapy
- In the acute phase, rest the affected limb; consider splinting at night.
- After acute phase pain is reduced, execute passive stretching to preserve range of motion followed by active exercise to regain strength.
- Soak and oil dry skin to prevent cracking.

Management of severe ENL reactions
ENL reactions are complex medical problems requiring careful management by experienced clinicians. Short courses of prednisolone are often used.
The patients should be treated with prednisolone starting with 60 mg as a single daily dose. After a few days the dose can be lowered and, in general, the prednisolone can be stopped after a period not exceeding four weeks. The patient’s condition should be assessed before the dose of prednisolone is decreased. A few countries still allow the use of thalidomide with strict controls and the safeguards needed to prevent the occurrence of its well-known teratogenic effects. Refer to the national protocol.

In patients with recurrent attacks of ENL or those needing corticosteroids for longer, clofazimine should be started and prednisolone gradually withdrawn. It is important to ensure that the patient has no worm infestation, especially Strongyloidiasis, before giving high doses of prednisolone. Immune suppression can cause dissemination of Strongyloides.

Prevention of disability (PoD) and self care

<table>
<thead>
<tr>
<th>Problem</th>
<th>Signs</th>
<th>Secondary effects</th>
<th>Aims of PoD action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness of eye closure</td>
<td>Dryness</td>
<td>Impairment of vision</td>
<td>Preservation of sight</td>
</tr>
<tr>
<td></td>
<td>Ulceration of cornea</td>
<td>Blindness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scarring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of sensation in the hand</td>
<td>Dryness, cracking and ulceration</td>
<td>Loss of tissue, joint stiffness</td>
<td>Keep the skin in good condition and avoid injury</td>
</tr>
<tr>
<td>Weakness and deformity of the hand</td>
<td>Visible deformity</td>
<td>Contracture and fixed deformities</td>
<td>Preserve muscle strength and preventing contractures/deformities</td>
</tr>
<tr>
<td>Loss of sensation and ulceration of the foot</td>
<td>Dryness, cracking and ulceration</td>
<td>Chronic infection</td>
<td>Keeping the skin in good condition  Provision of protective footwear  Prevention of injury</td>
</tr>
<tr>
<td>Weakness and deformity of the foot</td>
<td>Foot drop</td>
<td>Ulceration and permanent deformity</td>
<td>Preserve muscle strength and preventing contractures and deformity</td>
</tr>
</tbody>
</table>

### Assessment and recording of disabilities

Disability is a broad term covering any impairment or activity limitation.

Every new case of leprosy must be assigned a “Disability Grade” which depicts the condition of the patient at diagnosis. The grade is on a scale of 0, 1 or 2. Each eye, hand and foot is given its own grade, so the patient actually has six grades, but the highest grade is used as the disability grade of that patient.

### Definitions of disability

**Hands and feet:**

Grade 0 – No anaesthesia* (palms and soles) or no visible deformity or damage
  - Grade 1 – Anaesthesia* (palms and soles) but no visible deformity or damage

Grade 2 – Visible deformity or damage

Visible damage includes wounds, ulcers, shortening of fingers and/or toes as well as deformity due to muscle weakness, such as a foot drop or a claw hand.

**Eyes:**

Grade 0 – No eye problems due to leprosy; no evidence of visual loss
Grade 1 – Eye problem due to leprosy present, but vision not severely affected as a result (vision 6/60 or better; can count fingers at six meters)
Grade 2 – severe visual impairment (vision worse than 6/60; inability to count fingers at 6 metres), lagophthalmos, iridocyclitis, corneal opacities

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(* not to be confused with the loss of sensation in a skin patch)

Only leprosy-related impairments should be graded.

**Care for people with disabilities due to leprosy**

Interventions are carried out at the following levels:
- Home-based care including those activities that can be done by the person at home
- Local health facility
- Referral services (requiring the input of specialists).

**Table: Assessment and management of disabilities by health facility level**

<table>
<thead>
<tr>
<th>District hospital</th>
<th>Referral hospital or district hospital with trained staff</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment of disabilities</strong></td>
<td>• Determine grade 1 disability at least by asking the patient about loss of sensation in the hands and the feet and observing dryness of hands&lt;br&gt;• Look for signs of visible deformity (Grade 2 disability) e.g. wounds or ulcers on the hands or feet, redness of the eye&lt;br&gt;• Record the visible deformity&lt;br&gt;• Refer the patient to the facility where disability care services are being provided</td>
</tr>
<tr>
<td><strong>General role in disability management</strong></td>
<td>• Discuss the management of the disability problems of their patient with the District Supervisor but eventually take over the responsibility for implementation of interventions&lt;br&gt;• Instruct and assist the patient in carrying out the relevant home care activities described above</td>
</tr>
<tr>
<td><strong>Problems with eye closure</strong></td>
<td>• Provide protective cover for the eyes or goggles&lt;br&gt;• Provide artificial tears or prescribed eye ointment (not containing steroids) if the eyes are very dry&lt;br&gt;• Treat conjunctivitis with antibiotics&lt;br&gt;• Refer more serious eye problems to an Ophthalmology Clinical Officer or the nearest eye clinic</td>
</tr>
<tr>
<td><strong>Problems with the hand</strong></td>
<td>• Review to assess the implementation of expected home care activities and advise as necessary&lt;br&gt;• Refer if required</td>
</tr>
</tbody>
</table>
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| Problems with the foot | • Review to assess the implementation of expected home care activities and advise as necessary  
| | • Take foot maps for protective footwear or arrange for these to be taken by the DTLS or trained community-based rehabilitation (CBR) worker  
| | • Refer if required. | • Remove thick callus and trim ulcers with a scalpel blade  
| | • Management of severe infections of foot ulcers  
| | • Surgical management of chronic ulcers  
| | • Provision of orthopaedic appliances including those for foot drop  
| | • Surgical correction of foot drop. |

Self-care at home

It is important that individual patients are given self-care instructions that are relevant to their particular situation and that they are supported to practice self-care at home. The WHO SEARO leprosy eLearning course include modules on self-care and counselling.74

Such support may be provided by:

- health workers
- family members
- other people affected by leprosy or living with disabilities from other causes. Self-care groups are a good medium for people with self-care needs to meet together regularly to discuss the practicalities of self-care.

Self-care for patients having problems with eye closure:

- inspect the eye in a mirror to check for redness (if no mirror, ask a neighbour to check)  
- learn to blink frequently to keep the eyes moist and exercise the lids  
- wear a hat with a large brim and/or sunglasses to prevent dust from getting into the eyes  
- use a sheet or mosquito net to cover the head at night.

Self-care for patients with hand or foot problems:

- inspect daily for signs of injury  
- soak the hand/feet in water for about 30 minutes every day  
- use a rough stone to smoothen the dead skin  
- apply oil or petroleum jelly when the skin is still wet to prevent the skin from drying out.  
- use a clean cloth to cover any open wound  
  - walk as little as possible and walk slowly; take frequent rests (foot care).  
  - if foot ulcers are present, rest is essential.  
  - if there is any muscle weakness (e.g. foot drop), passive stretching and active exercises help to prevent contracture and may lead to some strengthening.

The value of appropriate footwear for people affected by leprosy:

The use of appropriate footwear is important for preventing ulceration among people with loss of feeling in the feet. The shoes should be locally available, socially acceptable and used whenever the patients are on their feet and walking.

74 Go to: https://searo.labs.enablingdimensions.com/login/index.php and set up an account to access the modules. Modules include: Suspect and Referral; Diagnosis of Leprosy; Counselling for Leprosy; Treatment for Leprosy; Reaction and Neuritis in Leprosy; Management of Disabilities in Leprosy; Self-care in Leprosy; and Laboratory diagnosis
Most people do not require special footwear – the right shoes bought in the market can be just as effective. Sports shoes are often very appropriate. Alternatively, sandals or shoes with a firm under-sole and a soft insole may be used.

They should fit comfortably; Velcro straps are easier to use than other types of fastenings and heel straps are needed for sandals. Some people need specially designed prosthesis or assistive devices.

Networks or persons affected by leprosy
It has increasingly been recognized that people who have personally experienced the disease are important partners in their treatment and control of leprosy.

Persons affected by leprosy have formed networks and/or organizations with membership of individuals with experience of leprosy. Inclusion of persons affected by leprosy is an important component of the Global Leprosy Strategy 2016–2020, which was duly endorsed by national programmes, Inclusion in planning and implementation of leprosy control activities was successful in many countries, particularly bringing up the users’ perspective in leprosy control.

This has resulted in awareness raising and advocacy with elected representatives, as well as reduction in disabilities and discrimination. Networks of persons affected by leprosy also facilitates their peers to access welfare measures and social entitlements. Their agenda includes fighting stigma and ensuring that the human rights of persons affected are respected. ‘Guidelines for strengthening participation of persons affected by leprosy in leprosy services – 2011’ were brought out by WHO following a series of consultations involving persons affected by leprosy and representatives of national leprosy programmes.

75 Guidelines for strengthening participation of persons affected by leprosy in leprosy services -2011;
https://apps.who.int/iris/bitstream/handle/10665/205169/B4726.pdf;jsessionid=A60754FD8E24B6AB1F4015A948F5148D?sequence=1
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11.21 Liver abscess

Liver abscesses are usually due to bacteria or the parasite *Entamoeba histolytica* (see Section 11.1). Bacterial liver abscesses are usually caused by multiple species of bacteria. In Asia, *Klebsiella* is an increasingly recognized cause of liver abscesses, which may spread to other sites, including the eye.

**Key clinical features**
- Fever without an obvious focus.
- Pain in the right upper quadrant may be present, but may only be elicited by percussion over the lower ribs on the right.
- Jaundice is uncommon unless there is obstruction of the biliary tree. Tenderness in the right upper quadrant under the costal margin on inspiration (Murphy’s sign) is more suggestive of acute cholecystitis due to gall stones.

**Investigations**
- Positive serology for amoeba means invasive amoebiasis, which generally will revert to negative after 6–12 months. In the presence of a liver abscess, it thus usually means that the etiology is amoeba rather than bacteria.
- A negative stool examination for amoebic cysts or trophozoites does not exclude an amoebic liver abscess.
- Ultrasound may demonstrate an echolucent cavity in the liver.
- Aspiration may be diagnostic; pink pus is suggestive of an amoebic abscess, while purulent, offensive smelling pus may be suggestive of a bacterial infection. Pus aspirated should be sent for microscopy and culture.

**Treatment**
If amoebic liver abscess is suspected: see Section 11.1.
If bacterial liver abscess is suspected, use:
- ampicillin 1 g IV 8 hourly plus metronidazole 400 mg orally; OR
- ceftriaxone 1 g IV daily plus metronidazole 400 mg orally is another option in penicillin-allergic patients;
- minimum duration of treatment is two weeks with IV antibiotics followed by minimum of 4–6 weeks of oral antibiotics, depending on the clinical response. Patients who respond quickly can change to oral antibiotics (amoxicillin-clavulanate) and metronidazole to complete therapy after two weeks. Aspiration of large abscesses (more than 5 cm) may be therapeutic, or necessary if the response to IV antibiotics is poor.
Lyme disease is a spirochetal infection transmitted by the bite of infected ticks of the *Ixodes ricinus* complex. It is a bacterial infection caused by six species in the spirochete family *Borrelliaceae*. It is caused primarily by *Borrelia burgdorferi* in the United States, and primarily *Borrelia afzelii*, *Borrelia burgdorferi*, and *Borrelia garinii* in Europe and Asia. Unlike North America and western Europe, where most infections are acquired from the bite of a nymphal tick, in Asia and Asiatic Russia transmission to humans is mainly by the adult stage of the tick.

Lyme is the most common tick-borne disease currently in the USA, Canada and Europe and reported also in Russia, Japan and People’s Republic of China, and foci of Lyme borreliosis in forested areas of Asia. There are reported cases from Nepal and multiple reports now from both North and South India of Lyme disease. The *Ixodes* tick is common in the Himalayas.

**Transmission**

Bite from an *Ixodes* tick infected with a *Borrelia*.

**Key clinical features**

Lyme disease has a broad spectrum of clinical manifestations, divided into three phases, although their clinical features can overlap and some patients present with late disease with no history of early Lyme disease signs and symptoms.

**Early localized:** Characteristic erythema migrans (EM) skin lesion (see Section 10.1) usually in 7 to 14 days after a tick bite (range 3–30 days). As EM expands, some central clearing often develops with a target or bull's eye appearance. This is different from the early erythema from an allergic reaction to the tick bite site. EM happens with or without systemic symptoms resembling a viral syndrome with fatigue, anorexia, headache, neck stiffness, myalgias, arthralgias, regional lymphadenopathy and, in a minority, fever. Most people do not recall the tick bite.

**Early disseminated:** Multiple EM lesions (usually days to weeks) and/or neurological and/or cardiac findings (usually weeks to several months) after the tick bite.

- Neurological features include lymphocytic meningitis (see Section 10.8), peripheral neuropathy or cranial nerve palsies especially Bell’s palsy (see Section 10.7), radiculopathy, and rarely cerebellar ataxia or encephalomyelitis. A classic triad of acute neurological abnormalities is meningitis, cranial neuropathy (especially facial nerve), and motor or sensory radiculoneuropathy.
- Cardiac manifestations include atrioventricular heart block, sometimes with mild myopericarditis, and rarely, sudden cardiac death.
- Ocular manifestations — conjunctivitis in about 10% in early infection. Rarely other manifestations described in case reports: keratitis, iridocyclitis, retinal vasculitis, choroiditis, optic neuropathy, and uveitis.

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78 Lyme on WHO web: https://www.who.int/ith/diseases/lyme/en/
79 Pun et al: First report of Lyme disease in Nepal. JMM Case Reports 2018;5
**Late Lyme disease:** Develops months to a few years after infection. Associated with intermittent or persistent arthritis involving one or a few large joints, especially the knee (sometimes preceded by migratory arthralgias) (see Section 10.12), and/or rarely a subtle encephalopathy or polyneuropathy.

**Investigations**

In a Lyme endemic area, diagnosis of early disease is based only on erythema migrans skin lesion. Serological tests are insensitive in first few weeks of infection and may remain negative if patient is given early antibiotics.

In patients with suspected early disseminated or late Lyme disease, serological testing is warranted to support the diagnosis. A two-tier conditional strategy should be used to support the diagnosis of Lyme disease: initial enzyme-linked immunosorbent immunoassay (ELISA) or immunofluorescence assay, followed by a Western blot; or a modified algorithm that uses two ELISAs to improve the sensitivity and specificity of serological testing.81

CSF or synovial fluid may be needed to support a diagnosis of Lyme disease in patients with aseptic meningitis, radiculoneuritis or arthritis.

**Treatment82**

**Early localized:** Doxycycline 100 mg orally twice daily for 10 days OR amoxicillin 500 mg orally three times daily for 14 days, OR cefuroxime axetil 500 mg orally twice daily for 14 days.

**Early disseminated** with isolated facial nerve palsy, meningitis, or radiculoneuropathy: Doxycycline 100 mg twice daily for 14 days, OR more serious disease such as encephalitis or symptomatic, second- or third-degree atrioventricular block or PR interval>300 milliseconds – ceftriaxone 2 g IV once daily for 14–28 days

Arthritis without neurological problems – doxycycline 100 mg orally twice daily for 28 days or amoxicillin 500 mg three times daily for 28 days or ceftriaxone 2 gm IV once daily for 14–28 days

Late, delayed or inadequate treatment may lead to complications. Complete response to treatment may be delayed beyond the treatment duration. Relapse has occurred with all of these regimens; patients with objective signs of relapse may need a second course of treatment.

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81 Lyme disease- diagnosis- UpToDate, accessed 10 June 2020.
82 Lyme disease- treatment- UpToDate
11.23 Meliodosis

Meliodosis is an infection caused by the facultative intracellular gram-negative bacterium, *Burkholderia pseudomallei*.

Meliodosis occurs predominantly in South-East Asia, northern Australia, South Asia, and People's Republic of China, but also many other countries now that more studies have been done. Northeastern Thailand and parts of northern Australia are "hyperendemic" for melioidosis, with seasonal peaks in the wet seasons. The disease affects mostly rice farmers and patients with underlying conditions including diabetes, cancer, and alcoholism. In endemic areas, *B. pseudomallei* is a common cause of human pneumonia and septicaemia.

**Transmission**
- Percutaneous – during exposure to wet soil or contaminated water (reaches lungs by hematogenous route).
- Inhalation of contaminated water, especially during heavy rain.
- Ingestion.

Rarely transmitted human-to-human. No documented animal- or insect- to human transmission, although it can infect many animals and insects.

**Key clinical features**

*Most B. pseudomallei* infections are likely subclinical. The clinical presentations are varied:83

**Localized infection:** Presents as an ulcer, nodule or skin abscess, and may result from inoculation through a break in the skin. May have fever and general muscle aches. The infection may remain localized, or may progress rapidly through the bloodstream. Parotid abscess is a common manifestation in children.84

**Acute respiratory infections:** This is the most common form of presentation of the disease and can range from mild bronchitis to severe pneumonia. The onset of pulmonary melioidosis is typically marked by a high fever, headache, anorexia, and general muscle soreness. Chest pain is common, but a nonproductive or productive cough with normal sputum is the hallmark of this form of melioidosis. Cavitary lesions may be seen on chest X-ray, similar to those seen in pulmonary tuberculosis. A more subacute illness leading to bronchiectasis is also described, as with tuberculosis.

**Bacteremia, septic shock:** Patients with underlying risk factors such as diabetes and renal insufficiency are more likely to develop bacteremia, which often results in septic shock. The symptoms of bloodstream infection may include fever, headache, respiratory distress, abdominal discomfort, joint pain, muscle tenderness, and disorientation. This is typically an infection with rapid onset, and concurrent abscesses may be found throughout the body (see Disseminated infection below).

**Disseminated infection:** Disseminated melioidosis presents with abscess formation in various organs of the body, and may or may not be associated with sepsis. Organs involved typically include the liver, lung, spleen and prostate; involvement of joints, bones, viscera, lymph nodes, skin or brain may also occur. Disseminated infection may be seen in acute or chronic melioidosis. Signs and symptoms, in addition to fever, may include weight loss, stomach or chest pain, muscle or joint pain, and headache or seizure. The most common clinical manifestations are pneumonia and localized skin infection.

In those with clinical disease, bacteremia occurs in around half the cases and septic shock in up to a quarter. Case-fatality ratio is up to 40%.

Geographical differences have been described: encephalomyelitis appears to be restricted to northern Australia (about 4% cases) and is rarely reported elsewhere; parotid abscess is common in children in South-East Asia, but not in Australia.

**Investigations**
- Culture is the main way to diagnose. (Culture, as available, of blood, sputum, urine, abscess fluid, and swab of ulcer/skin lesion/throat/rectum.) For non-blood specimens, special culture media may be required – especially urine.
- Gram stain of sputum and abscess pus may reveal gram-negative bacilli of *B. pseudomallei*. The organisms often have a characteristic bipolar staining with a "safety pin" appearance.
- Serological testing alone is not a reliable method of diagnosis.
- Chest X-ray
  - in acute pneumonia: discrete, diffuse or patchy lobar or multilobar consolidation, necrotizing lesions, and pleural effusions
  - in chronic melioidosis: can mimic TB. Cavitating, nodular, or streaky infiltrates with fibrotic changes.

**Treatment**

Can be refractory to treatment with relapses after years or decades and extensive antibiotic resistance. Treatment depends on presentation and phase of treatment. Intravenous therapy – ideally for at least 10 days in septicemia/disseminated infection (cases without fever can take up to nine days to resolve):
- Ceftazidime 2g every 6–8 hours
  OR
- Meropenem 1g every 8 hours.

**Oral antimicrobial therapy** – as continuation therapy (≥3 months; 6 months if neurological disease or osteomyelitis), or for localized disease (in order of preference):
1. Cotrimoxazole 160/800 x 2 tablets every 12 hours if weight >60 kg; 80 mg/400 mg x 3 tablets every 12 hours if 40–60 kg
  OR
2. Amoxicillin/clavulanic acid (co-amoxiclav) 500 mg/125 mg x 3 tablets every 8 hours if weight >60 kg; 500 mg/125 mg x 2 tablets every 8 hours if <60 kg (may be difficult to tolerate!)
  OR
3. Doxycycline 100 mg every 12 hours

*B. pseudomallei* is resistant to penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin and streptomycin.

**Prevention**

Avoid direct contact with soil and water: wear protective footwear where necessary. Boiled or UV-treated water is advised.

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85 Eighth World Melioidosis Congress, 2016: presenting an emerging infectious disease in the context of “One Health.”

WEEKLY EPIDEMIOLOGICAL RECORD, NO. 46, 18 NOVEMBER 2016


https://doi.org/10.1016/j.ijantimicag.2014.01.005.


11.24 Microsporidiosis

Microsporidia are a group of protozoa that can cause diverse clinical manifestations, most notably in immunocompromised patients. In patients with AIDS, they can cause chronic diarrhoea. The implementation of effective anti-retroviral therapies has reduced the incidence in PLHIV considerably.

Cases are also known to occur in immunocompetent individuals. The clinical manifestations vary according to the causal species and route of infection. Disseminated infection can be fatal. Of all of the manifestations of microsporidiosis, *Enterocytozoon bieneusi*-associated diarrhoea is the most common.

Key clinical features
- subacute or chronic, watery, non-bloody diarrhoea
- sometimes abdominal pain and cramping, nausea, vomiting and weight loss.

Disseminated disease:
- cholecystitis and biliary tract infections, hepatitis and peritonitis
- kerato-conjunctivitis
- infections of the lungs, muscles, and brain.

Investigations
Modified trichrome stain identifies spores in stool specimens – but this requires specific expertise and is often not available at district level.

Treatment
- At present, there is no effective treatment for microsporidia. In patients with AIDS, starting antiretroviral therapy as soon as possible is important.
- Albendazole has been reported to decrease diarrhoea (but does not eradicate the organism) in patients with AIDS, while in immunocompetent individuals it may resolve symptoms.
- Give cotrimoxazole prophylaxis to patients with AIDS.
- Supportive symptomatic treatment (hydration – see Section 8.3 for recommendations for rehydration and antidiarrhoeal drugs).

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doi:10.1097/QCO.0b013e32834aa152
11.25 *Mycobacterium avium* complex (MAC)

*Mycobacterium avium complex* (MAC) is often a life-threatening disease in PLHIV, but can also occur as a more limited, pulmonary form in HIV-negative individuals, commonly those with underlying chronic lung disease – typically COPD or bronchiectasis. In patients with HIV infection, MAC is primarily of concern in those with very low CD4 counts (typically less than 50), or in WHO stage 4 disease, and is usually generalized. Localized manifestations, mainly in lymph nodes, can be seen, especially in IRIS. MAC shows important regional variations in reported incidence, though globally the species in this complex are the most commonly found non-tuberculous mycobacteria.

**Key clinical features**

Disseminated disease – usually in AIDS or other immunosuppression:
- prolonged fever and night sweats
- wasting
- enlarged liver and spleen
- gastrointestinal symptoms such as diarrhoea, abdominal pain
- symptoms of anaemia
- localized disease – including cold abscesses (as in tuberculosis)
- meningitis
- generalized lymphadenopathy, papulo-pustular eruption on trunk and extremities.

Pulmonary disease – most common presentation in immunocompetent individuals:
- chronic cough
- other symptoms vary: fever, weight loss and haemoptysis can occur, but less commonly than with tuberculosis.

**Investigations**

The diagnosis of MAC in PLHIV is often made by exclusion in a patient with symptoms compatible with disseminated TB or MAC, who fails to respond to TB medicines (without macrolides), and when other causes of insufficient treatment response, such as poor adherence, or multidrug-resistant TB have been ruled out.
- FBC – severe anaemia, leukopenia and thrombocytopenia due to bone marrow infiltration.
- LFTs – high alkaline phosphatase (more than 2 times ULN) and gamma GT levels (more than 3 times ULN).
- Definitive diagnosis is made by either blood or bone marrow culture, or both, but this may not be possible in resource-limited settings. (This is further complicated in immunocompetent individuals, by MAC being a common environmental contaminant.)

**Treatment**

- For disseminated disease in PLHIV: empirical TB treatment plus a macrolide, until confirmation that the patient does not have TB. (Localized disease in immunocompetent individuals is nuanced and best managed by a specialist centre.)
- **Initiation of ART** is the preferred treatment for MAC in many resource-constrained settings.
- Treatment of MAC may not be possible at the district level due to lack of access to the definitive treatment.
  - At least 2 drugs should be used to avoid the emergence of resistance:
    - ethambutol 15 mg/kg/day (higher than the dose for TB) for six months;
    - PLUS either
    - clarithromycin 500 mg twice daily for six months; OR
    - azithromycin 500 mg daily for six months (this is the preferred option if the patient is on ART because of drug-drug interaction).
Some recommend addition of rifabutin 300 mg/day, but this is prone to drug-drug interactions (check for dose adjustments needed), and benefits from adding this are unclear now that ART is widely available.

- Emphasis on symptomatic treatment (hydration, antidiarrhoeal drugs).

**MAC and ART**

ART should be started within two weeks of starting MAC therapy, where available. If the patient develops MAC IRIS when on ART (often with regional lymphadenopathy, liver lesions, bone lesions or hypercalcaemia), many experts recommend the continuation of ART, and close monitoring of the patient, plus treatment with steroids (20–40 mg/day prednisolone for 4–8 weeks) if necessary.³⁰,³¹

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11.26 Nipah

Nipah virus (NiV) was first identified during an outbreak of disease that took place in Kampung Sungai Nipah, Malaysia, in 1998, and was named after this village. The Nipah virus is a paramyxovirus (genus Henipavirus) with the bat as a natural animal reservoir, particularly fruit bats of the *Pteropus* genus. These bats are locally abundant in South Asia and are migratory.

The outbreak in Malaysia was initially thought to be of Japanese encephalitis (JE) but there were inconsistencies: encephalitis among adults rather than children; high number of patients had been vaccinated against JE; the clustering of cases in the same household; and a history of illness in pigs belonging to the affected farmers.

**Transmission:** There have been several modes of transmission.

- **Bats to pigs to humans:** In the 1998 Malaysian outbreak of acute encephalitis, Nipah virus from bats spread to pigs, with subsequent transmission between pigs, followed by transmission to humans exposed to infected urine and/or respiratory secretions of infected pigs.
- **Bats contaminating raw date palm sap consumed by humans (no intermediate host):** Associated with consumption or collection of foodstuff, such as raw or partially

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93 https://www.cdc.gov/vhf/nipah/outbreaks/distribution-map.html
fermented date palm sap, which was contaminated with bat saliva and/or excreta containing Nipah virus. Evidence from Bangladesh show viral spillovers from bats to humans happen regularly, providing an opportunity for a more highly transmissible strain to infect and adapt in humans.95

- **Human-to-human**: Close and direct, unprotected contact with infected patients, especially those with respiratory symptoms, has been implicated as a transmission risk. This was responsible for most of the cases in the Kerala outbreak in India in May-June 2018.96 The relative contribution of this mode of transmission has varied between outbreaks. From 2001 to 2008, around half of the reported Bangladesh cases were due to human-to-human transmission through providing care to infected patients.

- **(Bats to) horse to humans**: Both human-to-human and horse-to-human transmission (slaughtering horses or consuming infected horse meat) were identified in the Philippines outbreak in 2014.

Nipah virus can also infect other animals such as cats, dogs, goats and sheep, but these have not yet served as an intermediate host to humans. The virus has caused severe disease in animals such as pigs with significant economic losses for farmers.

**Key clinical features**

- Incubation period: four to 14 days but reports of as long as 45 days.97 Fever with altered sensorium (mental status changes) with rapidly progressing ARDS along with epidemiological indications, such as clustering of cases in the family or health-care facility; exposure to date-palm sap; exposure to bats, animals, or similar cases, are good indicators that the illness may be Nipah.

Range of clinical presentations, from asymptomatic infection to acute respiratory syndrome and fatal encephalitis:

- sudden onset of febrile illness, sometimes with GI symptoms;
- headache, drowsiness, disorientation, confusion, abnormal movements, seizures. These signs and symptoms can progress to coma within 24 to 48 hours;
- variable occurrence pneumonia, other respiratory symptoms (sometimes a presenting complaint), some progressing to acute respiratory distress syndrome (ARDS). Some patients have a respiratory illness during the early part of their infections, and half of the patients showing severe neurological signs also showed pulmonary signs;98
- myocarditis in some critically ill patients;
- other signs and symptoms—variable between outbreaks.

Encephalitis, the most important complication, has a high mortality rate. About 60% of patients rapidly become critically ill, with high mortality (40% to 75%, as high as 100%).99 In many patients, encephalitis and/or meningitis develop three to 14 days after the initial illness.

Most patients surviving acute encephalitis make a full recovery but about 20% have late sequelae such as personality change or seizure disorder. A few relapse or develop delayed-onset encephalitis and some late deaths, even years after exposure.²⁷,¹⁰⁰

Investigations
The diagnosis can be confirmed only with a real-time PCR test. RT-PCR (or virus isolation) from blood, CSF, urine, oropharyngeal secretions, bronchial wash if collected early in disease or, if rapid death and only tissue available, from brain or spleen (also by immunohistochemistry of tissues post-mortem) may confirm diagnosis. Later in disease, IgM and IgG antibodies in serum or CSF by ELISA or serum neutralization assay¹⁰¹ may be considered.

CSF abnormalities are similar to other acute viral CNS infections (see Section 10.8). Magnetic resonance imaging of the brain may reveal multiple small subcortical and deep white matter lesions, without surrounding oedema, similar to other acute CNS infections. Use sample collection precautions and safe transport.

Treatment¹⁰²,¹⁰³
Intensive supportive care including management of:
- raised intracranial pressure (see Section 3.4.3);
- septic shock (see Section 3.1);
- respiratory distress requiring oxygen (see Quick Check p. 20 and Section 3.2) and sometimes mechanical ventilation; and
- management of seizures (see Quick Check p. 28 and Section 10.9).

No specific treatment or vaccine. Several experimental therapies are in pre-clinical development or phase 1 clinical trials. Ribavirin has been tried.

Infection prevention and control
Strict IPC measures:
Standard plus contact plus droplet precautions (see Section 6). Airborne precautions if aerosolizing procedures.¹⁰⁴
Respiratory isolation.

In patients with respiratory illness: if cough, sneezing or other signs of respiratory illness – also use source control. The patient should wear a mask and practice respiratory hygiene (see Section 6).

As it is almost impossible to identify the first case of Nipah in most settings except when there is a clear exposure, it is important that standard precautions including respiratory hygiene be practised at all times.

Pneumococcus—see Section 8.2 Chest problems

¹⁰⁴ Public Health England advises same as MERS - contact plus airborne for all
11.27 Rabies, animal bites and PEP\textsuperscript{105,106,107,108}

11.27.1 Rabies elimination strategy

Rabies is a fatal viral disease that can affect all mammals. The causative agent is a neurotropic RNA virus of the family Rhabdoviridae and genus \textit{Lyssavirus}. The rabies virus (RABV) is transmitted through inoculation of saliva, usually from the bite of an infected animal. The disease is almost always fatal once clinical signs appear, from acute progressive encephalitis.

The burden of disease is disproportionately borne by rural poor populations, with approximately half of all cases attributable to children under 15 years. In the WHO South-East Asia Region, more than 26,000 people die annually. Eight of the Region’s 11 Member States are endemic (the exceptions being the Democratic People’s Republic of Korea, Maldives and Timor-Leste) and account for around 45% of the global burden.\textsuperscript{109}

Up to 99% of the deaths are due to exposure to dogs, which are the major reservoir and transmitter of rabies, but transmission by wild animals such as bats, foxes, wolves, jackals, racoons, skunks and mongoose) is also possible (RABV infection of rodents is very uncommon and there are no reported human rabies cases from rodent bites).

**Vaccinate dogs:** The best way to eliminate rabies is by vaccinating dogs, with herd immunity achieved with at least 70% vaccination coverage. Mass dog vaccination is supported by a “One Health” approach with significant progress in many countries in the SEA Region. The regional goal is to reach zero human deaths from dog-mediated rabies by 2030.

**Vaccinate people after a Category II or III exposure.**

11.27.2 Rabies post-exposure wound care and prophylaxis after animal bites

After an exposure the following measures should be undertaken:

- Wound care for any scratches, abrasions, bites, or licks on broken skin is the most important immediate procedure in the prevention of rabies:
  - \textit{immediately} scrub with alkaline soap/detergent and water, and flush with water for 15 minutes followed by
  - povidone-iodine or benzalkonium chloride 1%–4% or ethanol should be used on the wound, if available.
  - See Section 4 for additional information on bite management:
- Decide on post-exposure prophylaxis (vaccination) and rabies immunoglobulin (RIG) use depending on type of contact. These should be started as soon as possible after recognized exposure.

**Categorize the type of contact with the rabid animal and decide if vaccine and RIG**

The indication for post-exposure vaccination with or without rabies immunoglobulin depends on the type of contact with the rabid animal.


\textsuperscript{106} Weekly epidemiological record: Rabies vaccines: WHO position paper. April 2018 No 16, 2018, 93, 201–220


\textsuperscript{108} WHO SEARO: Strategic framework for elimination of human rabies transmitted by dogs in the South-East Asia Region. Delhi, 2012

Types of contact are:
Category I – touching or feeding animals, animal licks on intact skin (no exposure)
Category II – nibbling of uncovered skin, minor scratches or abrasions without bleeding (exposure)
Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks; or exposure and direct contact with bats (severe exposure).

Treat according to category of contact:
Category I – no treatment is required (no vaccine, no RIG)
Category II – immediate vaccination
Category III – immediate vaccination and administration of rabies immunoglobulin.

Post-exposure prophylaxis

As for all vaccines, appropriate staff training is needed to ensure correct storage, reconstitution and injection technique.

Human rabies PEP vaccination and RIG, if no prior rabies vaccination
In category III exposure, both rabies vaccine and rabies immunoglobulin (RIG) should be used. In category II exposure, only vaccination is necessary.

Rabies immunoglobulin
Human rabies immune globulin 20 IU/kg or equine rabies immunoglobulin 40 IU/kg (mostly injected at the site of the bite). If any is left over, inject IM at a distant site. This can be given up to seven days post-exposure if not available immediately.

Vaccination
Since 1984, WHO recommends modern, concentrated, purified cell culture and embryonated egg-based rabies vaccines (CCEEVs) for both PEP and PrEP.

All CCEEVs should have the recommended potency of at least 2.5 international units (IU) per single intramuscular immunizing dose (0.5 ml or 1.0 ml volume after reconstitution, depending on the type of vaccine). These are currently only available in single-dose vials.

CCEEVs can be administered either by intradermal (ID) or IM injection.

- Intramuscular schedules
For the IM route, one dose is one vial of vaccine per patient. All intramuscular injections must be given into the deltoid region. The vaccine should never be administered in the gluteal region.

The PEP schedule of vaccination options depend on the vaccine manufacturer.

Most vaccine manufacturers recommend:
- a 1-site IM 5 dose regimen on days 0, 3, 7, 14, and 28; OR
- a 4-dose Zagreb regimen – 2 site IM on day 0 (right and left deltoid) and 1-site IM on days 7 and 21.

An alternative 4 dose regimen for healthy, full immunocompetent exposed person who has received high-quality RIG is a WHO-prequalified rabies vaccine at 0, 3, 7 and 14 days.\(^{110}\)

- **Intradermal schedule**
  In order to reduce the cost of post-exposure treatment, intradermal (ID) multisite regimens using a fraction of the intramuscular volume per intradermal inoculation site have been developed. The dose is 0.1 ml of CCEEV (irrespective of the vaccine brand). This means a 0.5 ml vial provides five doses; a 1.0 ml vial provides 10 doses. Intradermal can be used in both Category II and III exposures.

  Some manufacturers additionally include the 2-site ID Thai Red Cross regimen, with four clinic visits on days 0, 3, 7 and 28. This is a WHO-recommended option as it saves costs, doses and time.

  Evidence shows that intradermal route of administration produces a strong immunological response and is safe. For information on which vaccines are recommended for intradermal use, see:

**Observation or laboratory examination of the animal:** Apparently healthy dogs and cats who are the origin of the exposure should be kept under observation for 10 days. Dogs and cats that are suspected of being rabid, as well as wild animals, should be humanely killed and their tissues examined in the appropriate laboratory.

Note that vaccine treatment can be stopped if the animal remains healthy through the observation period of 10 days or if the animal is proven negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

**If prior pre- or post-exposure vaccination**
For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or post-exposure treatment with cell-derived rabies vaccines, immediate thorough wound cleaning, as above, then two intramuscular doses of a cell-derived vaccine separated by three days are sufficient; ideally the first dose is given on the day of exposure. Rabies immunoglobulin treatment is not indicated in such cases. The same rules apply to persons vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml.

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\(^{110}\) https://www.who.int/ith/vaccines/rabies/en/ accessed 8 June 2020
11.27.3 Pre-exposure vaccination (PrEP) for populations at high risk of exposure

Pre-exposure vaccination is recommended for:
- those in rabies diagnostic and research laboratories;
- veterinarians;
- individuals at high risk of exposure such as stray dog handlers, park or wildlife officials, or bat handlers;
- travellers with extensive outdoor exposure in rural areas – such as may occur while running, bicycling, hiking, camping, backpacking, etc. – may be at risk, even if the duration of travel is short;
- individuals travelling to isolated areas or to areas where immediate access to appropriate medical care is limited or to countries where modern rabies vaccines are in short supply and locally available rabies vaccines may be unsafe and/or ineffective;
- children living in or visiting countries or areas at risk, where they provide an easy target for rabid animals.

- Pre-exposure vaccination is administered as one full dose vaccine given three times, IM or 0.1 ml intradermal, on days 0, 7, and 21 or 28. A few day’s variation is acceptable. If receiving chloroquine prophylaxis, the dose should be IM rather than ID (CQ can reduce antibody response).
- Immunized individuals still need to get two post-exposure (after a bite) booster doses (see above).
- Professional groups at high risk of exposure to live virus (laboratory researchers and technicians) should have their antibody level checked regularly every six months and receive a booster when the level is <0.5 IU/ml.

11.27.4 Rabies disease

Incubation period

The incubation period is relatively long (ranging from three weeks to three months) but can be as long as several years in rare cases. The closer the inoculation site is to the central nervous system, the shorter is the incubation period. It is important to note that in cases of exposure to bats, often a bite cannot be identified and the patient may be unaware or unsure whether exposure at the time had occurred.

Key clinical features

Patients often manifest the two more common clinical forms of rabies:
- the encephalitic or furious form, or
- the paralytic or dumb form.

A less common presentation is the atypical or non-classic form of rabies associated with bites from bats. Atypical or non-classic rabies is increasingly being identified. Ascending paralysis, similar to Guillain-Barré syndrome, occurs in some cases and makes diagnosis more difficult.

Rabies virus causes encephalitis as do several other etiologies (see Section 3.4) so a differential diagnosis and, if possible, laboratory tests should be performed to exclude other treatable conditions.

Clinical disease is recognised in five stages:
- The incubation period:
  - is one to 3 months in the majority of cases. This can range from days to months to longer than one year. Bites sustained on or close to the head cause faster progressing disease than bites sustained on the lower extremities.

111 WHO web ref above- cross reference
The prodromal period:
- this consists of non-specific symptoms and signs and lasts for a few days to seven days,
- neuropathic pain and paresthesias (pins and needles sensation) occur at the bite site.

The acute neurologic phase:
- the highly neurotropic rabies virus replicates in muscle tissue and enters peripheral nerves, spreading via the peripheral nervous system to the spinal cord then brain then to many tissues including the salivary glands.
- the phase directly follows the prodromal period and lasts up to seven days.
- confusion, delirium, altered mentation, agitation, hallucinations result.

Encephalitic rabies: Excitation predominates in many cases with hypersensitivity or spasms in response to touch, noise, visual, or olfactory stimuli. The following are suggestive:
- hydrophobia (fear of water) – water can be offered for diagnostic purpose. As this progresses, the offer of water leads to pharyngeal spasms and involuntary refusal with gagging,
- aerophobia (fear of air),
- hypersalivation with difficulty swallowing the excessive saliva,
- periods of agitation alternating with lucidity.\(^\text{112}\)

In paralytic rabies, phobic spasms occur in only half of patients. In early paralytic rabies, piloerection and myoedema may occur at percussion sites on the chest, deltoid muscle, and thigh (percussion myoedema).

Autonomic system dysfunction: enlarged pupils, increased production of saliva, tears and perspiration.

Coma:
- This stage directly follows the acute neurological phase; there is generalized flaccid paralysis, then respiratory and circulatory failure.
- Occurs after several days to 1 week.
- Hypoventilation, loss of temperature control, heart dysfunction can lead to death

Death:
- Most patients die within days after passing into coma.

Investigations
In the early phase, most laboratory tests are non-specific and may not be available. Diagnosis often rests on history of exposure and typical neurological findings.

- Antemortem investigation can be done on serial specimens of saliva, skin biopsy (such as the nape of the neck), serum and CSF. Polymerase chain reaction (PCR) analyses may demonstrate viral antigen in the sample. In late disease antibody to the rabies virus may be detected in serum and CSF.
- CSF: increased white cells (lymphocytes), mildly increased protein — this is not distinctive from other encephalitides Laboratory confirmation is usually postmortem.

Post-mortem investigation uses brain and other nerve tissues. The Negri bodies are not always demonstrated. Fluorescent antibody testing on brain tissue is the gold standard for rabies diagnosis. Direct rapid immunohistochemistry tests, enzyme-linked immunosorbent assays, and RT PCR are also used.

Treatment
There is no effective specific treatment for rabies. It is almost always fatal once clinical signs occur. Even with skilled critical care in an ICU, recovery is exceedingly rare and has only occurred in cases where very intensive respiratory and cardiac support were available and

usually in young, previously healthy patients who had received one or more PEP doses. Chance of survival is very low and usually with serious neurological deficits. Less than a dozen cases have been documented globally. Six documented cases of survival (albeit with severe neurological deficits) have been reported in India.30

**Palliative care**113,114

The short clinical course of rabies entails much suffering, whether excitation or paralysis is predominant. Patients remain conscious, are often aware of the nature of their illness, and are often very agitated, especially when excitation is predominant. They are often isolated, because of the perceived risk of transmission even though this is almost nil. Health workers should know that even though the patient with rabies will die, they can effectively alleviate the suffering of the patient and family, at no risk to themselves.

Patients with rabies should receive adequate sedation and comfort with emotional and physical support, preferably in a private room.

Due to hydrophobia, oral medicines are not feasible. Furious cases with hydrophobia and several days of fever will often be dehydrated and suffering from thirst. Give IV fluids (being careful to immobilize the limb with a splint to prevent needle displacement) or by subcutaneous or intraperitoneal infusion. Restraints stimulate agitated patients and can be loosened or removed as soon as the patient is sedated. Spastic signs and anxiety can be alleviated with diazepam which is also a muscle relaxant, anticonvulsivant and sedative. Diazepam can be administered IV or intrarectal (see Quick Check page 28). Alternatives are midazolam, barbiturates and possibly haloperidol. Repeated IV morphine can relieve severe agitation and phobic spasms and control pain.

In some countries, the patient is taken home, where religious rites or other spiritual care can be administered. Home-based palliative care can and should be delivered at home (with subcutaneous or rectal administration of medicines).

Avoid intubation and other life support measures when the diagnosis is certain.

**Health worker safety**

Human-to-human rabies transmission has never been documented except extremely rarely from infected tissue or organ transplantation. However, given that secretions may contain the virus, as a precaution, medical and nursing staff should wear a mask, gloves and goggles.

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114 Tarantola A et al: Caring for patients with rabies in developing countries – the neglected importance of palliative care. Tropical Medicine and International Health Volume 21 No 4 April 2016
Rheumatic fever (RF) occurs as a complication of group A streptococcal infection (pharyngitis). It is currently rare in industrialized countries, but is still an important cause of disease in the developing world. About 3% of patients who have acute streptococcal infection will go on to develop RF. Acute rheumatic fever usually occurs between the ages of 5 and 15, although it is also seen in adults up to the age of 40.

Key clinical features
The diagnosis of RF is mostly clinical, based on the Jones criteria.

Jones criteria: This involves either two major criteria, or one major and two minor criteria, plus evidence of previous streptococcal infection.

- Major criteria
  - Carditis: sinus tachycardia, mitral valve disease, pericardial rub, enlarged heart.
  - Migratory polyarthriti: extremely painful inflammation of medium joints (ankles, wrists, elbows, knees) over a few days.
  - Sydenham’s chorea: uncoordinated jerky movements affecting the face and limbs with loss of fine motor skills and problems with walking.
  - Subcutaneous nodules: a rare manifestation, nodules are found over the extensor surfaces of joints, mostly in patients with long-standing disease.
  - Erythema marginatum: also rare, a vanishing macular rash with rounded borders, usually found on the trunk.

- Minor criteria
  - Clinical: fever, arthralgias.
  - Laboratory: elevated ESR, prolonged PR interval on ECG.

Investigations
- ECG can show increased PR interval.
- Echocardiography for valvular heart disease is helpful, if available.
- Throat culture can yield streptococci in up to 40% of patients.
- Anti-streptolysin (ASO) titres are elevated in 80% of patients.

Treatment
Antibiotics are effective in primary prevention (see Section 10.17), treatment of acute rheumatic fever, and for secondary prophylaxis. For all three situations, benzathine benzyl penicillin is recommended as the preferred first-line therapy. Evidence shows that this antibiotic can reduce recurrences and that IM therapy is better than oral therapy for this outcome. However, oral phenoxymethyl penicillin is an alternative if injections are unacceptable or not possible. In patients with hypersensitivity to penicillins, erythromycin is the recommended antibiotic.

- Anti-streptococcal antibiotic treatment
  - benzathine benzylpenicillin G 1.2 million units single dose (preferred);
  - phenoxymethyl penicillin 500 mg twice daily for 10 days; OR
  - erythromycin 250 mg four times daily for 10 days, if allergic to penicillin.

- Symptomatic therapy
  - salicylates escalating to a maximum dose of 2 grams four times daily for 4–6 weeks with a tapered dose at the end. Note: gastric protection is required.
  - steroids may be useful for patients with severe carditis complicated by congestive heart failure.

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Secondary prophylaxis

- With carditis – prophylaxis for 10 years or until age 25:
  - benzathine penicillin G 1.2 million units every four weeks; OR
  - phenoxyymethyl penicillin 250 mg orally twice daily; OR
  - sulfadiazine 1 g orally once daily; OR
  - erythromycin 250 mg twice daily, if penicillin allergy.
- In valvular disease, prophylaxis is given up until 40 years of age or lifelong.
- Without carditis
  - As above for a minimum of five years or until age 21.

Rickettsial diseases: see 8.1

Scabies (the seven-year itch): see Section 10.1.2 Skin problems
11.29 Schistosomiasis (bilharziasis)\(^{44, 116, 117, 118, 119}\)

Schistosomiasis or "bilharziasis" is a disease caused by blood flukes. Schistosomiasis affects about 200 million people worldwide, and 650 million people live in endemic areas in Africa, South America, the Caribbean, the Eastern Mediterranean, South-East Asia, and the Western Pacific. The number of deaths, considered to be at least 20,000 per year, is likely to be underestimated due to delayed morbidity. There are five main species of schistosome that cause disease in humans: *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*.

In the SEA Region, two species of *Schistosoma* cause disease. Myanmar and Thailand are endemic for *S. mekongi* and Indonesia for *S. japonicum*.

Larvae (cercariae) enter the body via intact skin in contact with infested water, usually while swimming, washing, wading or working. Adult worms develop in the liver, live in the veins around the gastrointestinal and genitourinary tracts, and produce eggs that are deposited around the body. Genitourinary disease is caused by *S. haematobium* and intestinal disease by *S. mansoni*, *S. japonicum*, *S. intercalatum* and *S. mekongi*.

**Key clinical features**

Deposited and trapped eggs result in granulomas and scarring in the surrounding tissues. Symptoms are related to the number and location of the eggs and duration of disease. The clinical features of the four disease stages are:

1. **Stage of invasion:**
   - Cercarial dermatitis ("swimmers itch"):
     - an itchy maculopapular or urticarial rash that occurs after cercariae penetrate the skin and migrate underneath (cercaria from non-human schistosomes may also cause a dermatitis, but do not go on to cause disease),
     - occurs within 24 hours of exposure.

2. **Stage of maturation**
   - Acute schistosomiasis ("Katayama fever")
     - usually occurs 4–8 weeks after infection when egg production starts,
     - more common in travellers to endemic areas,
     - usually a mild, self-limited systemic upset but can be severe enough to cause neurological manifestations,
     - symptoms and signs include: fever, chills, cough, muscle aches, prostration, abdominal pain, vomiting, diarrhoea, generalized lymphadenopathy, weight loss, enlarged liver and spleen, confusion, decreased level of consciousness, and spinal cord involvement (myelopathy).

3. **Stage of established infection**
   - It may be asymptomatic or have symptoms related to inflammation or granuloma formation around deposited eggs, leading to organ dysfunction. Symptoms include:
     - intestinal and hepatic: abdominal pain, diarrhoea with or without blood, tender enlarged liver, enlarged spleen (*S. mansoni*),

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\(^{117}\) Schistosomiasis website: http://www.who.int/schistosomiasis/en/


\(^{119}\) Insert Asian schistosomiasis article 2019
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- urinary: supra-pubic pain, urinary frequency, dysuria, terminal haematuria (S. haematobium).
- Lesions of this stage may resolve spontaneously or after anti-schistosomal treatment.

4. Stage of late infection
- Chronic schistosomiasis occurs if granulomas do not resolve and there is progression to fibrosis. Chemotherapy may no longer be effective at this stage.
  - intestinal disease:
    - liver: portal hypertension, periportal hepatic fibrosis, worsening liver function, liver failure, ascites, oesophageal varices with risk of fatal bleeding liver cirrhosis and liver cancer;
    - intestine: chronic diarrhoea, intestinal polyps, ulcers and strictures, protein-losing enteropathy, colorectal malignancy.
  - urogenital disease:
    - renal: kidney stones, hydronephrosis, hydroureter, recurrent bacterial infections, bladder calcification and ulceration, bladder papillomas, bladder cancer, kidney failure; deposition of antigen-antibody complexes causing nephrotic syndrome;
    - genital tract: pain on ejaculation, blood in semen, absent sperm (men); painful intercourse, contact bleeding, lower back pain, infertility (females); entry point lesions for sexually transmitted infections.

Other manifestations
- Lungs:
  - eggs may embolize to the pulmonary vessels causing acute necrotizing arteriolitis, pulmonary hypertension, or cor pulmonale,
  - adult worms may embolize to the lungs on starting therapy causing transient bronchospasms.
- CNS: Neuroschistosomiasis may be spinal cord or cerebral
  - egg deposits in the brain and spinal cord can cause epilepsy and transverse myelitis,
  - adult worms may aberrantly migrate to the spinal cord and brain.
- Other sequelae: anaemia, retarded growth.

Investigations
- Urine
  - inspection of urine for visible blood
  - dipstick for microscopic haematuria and proteinuria
  - microscopic examination of urine sediment or urine filtration through nylon filters
  - antigen detecting assays
  - CCA urine for S. mansoni (in mansoni subgroup).
- Stool
  - macroscopic inspection for blood
  - direct microscopy (qualitative) or Kato-Katz thick smear (quantitative) for demonstration of schistosome eggs
  - antigen detecting assays.
- Blood
  - markedly raised eosinophil count (rarely present in people living in endemic areas)
  - anaemia from chronic loss of blood
  - thrombocytopenia with hepatosplenic disease.
- Serum
  - antigen detection – circulating anodic antigen (CAA) or circulating cathodic antigen (CCA) are detected in active infection
  - antibody detection – cannot distinguish between old and present active infection.
Other sites to demonstrate eggs
  o biopsy samples – rectum (rectal snip), intestine, liver, urinary bladder, genital tissue
  o speculum examination – eggs appear as "sandy patches" on the cervix, often with associated contact bleeding
  o bronchoscopy washings.

Treatment

• Acute schistosomiasis:
  o is potentially dangerous and difficult to diagnose (before egg laying)
  o treatment should be started if infection is clinically suspected
    ◊ praziquantel 40 mg/kg as a single dose
  o if CNS involvement is suspected, refer patient to tertiary level for further investigation and treatment.

• Patients with eggs on microscopy of urine and stool, or examination of tissue specimens:
  o antischistosomal therapy is required
    ◊ praziquantel 40 mg/kg as a single dose
    ◊ dose may need to be repeated if there is still evidence of infection at follow-up microscopy after four weeks.

Mild and transient adverse events following treatment may occur: abdominal pain or discomfort, nausea, skin rash and headache are the most frequent. To minimize their occurrence and severity, treatment should be administered between meals.

Note: Current public health strategies for the control of schistosomiasis include largescale annual population-based preventive chemotherapy interventions in endemic areas where the prevalence of infection is estimated at more than 10%. School-based treatment is provided every two years where prevalence of infection is 1%-9%.
11.30 Sinusitis

Sinusitis is defined as inflammation of one or more of the paranasal sinuses. Sinusitis is acute if it has lasted less than four weeks, subacute if it has lasted four to eight weeks, and chronic if it has lasted more than eight weeks.

The most common pathogens associated with acute bacteria sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In some regions of the world, these organisms may be resistant to penicillin. Chronic sinusitis may also be associated with *Pseudomonas aeruginosa* and anaerobe bacteria.

**Key clinical features**

- **Acute sinusitis:**
  - nasal congestion, purulent nasal discharge, facial pain, headache, postnasal drainage, and cough,
  - fever, malaise, and sore throat,
  - oedema and erythema of the nasal mucosa, and purulent secretions.

- **Chronic sinusitis:**
  - more subtle presentation,
  - nasal congestion, postnasal drainage, slight headache, and fatigue.

Sinusitis commonly follows an upper respiratory tract infection with nasal congestion and the blocking of the sinus drainage passageway or underlying allergic rhinitis. Recurrent bacterial sinusitis in PLHIV is a WHO clinical stage 2 condition. An anatomical predisposing factor may be present, e.g. nasal polyposis or deviated nasal septum; surgery may be considered in these instances.

**Complications**

- facial or periorbital swelling,
- visual changes or neurological signs that could suggest intracranial involvement (mainly intracranial infections).

**Investigations**

- the diagnosis of acute sinusitis is usually made clinically,
- sinus X-rays have significant false positives and false negatives, and are not recommended.
- if available, in case of chronic or complicated sinusitis a CT scan limited to the sinuses may be useful to look for an underlying cause.

**Treatment**

For acute uncomplicated sinusitis:

- normal saline irrigation (1/4 spoon of salt in a cup of water) and washout using a syringe without needle or neti pot (frequently sterilized and using sterilized water).
- short-term use (3–5 days) of topical decongestants (e.g. *phenylephrine* and *oxymetazoline*).
- oral NSAID.

For sinusitis lasting for more than seven days in spite of these local measures:

- amoxicillin 1000 mg three times daily for seven days; OR
- amoxicillin-clavulanate 875 mg twice daily for seven days; OR
- oral cephalosporin for seven days, in particular if the patient has mild allergy to penicillin;
- if the patient is severely allergic to penicillin: cotrimoxazole double strength tablets orally twice daily for seven days.

For chronic sinusitis or sinusitis not responding fully to a 10–14-day course of antibiotics:

- check if local measures to drain sinuses are applied correctly;
- nasal or oral corticosteroids may be beneficial in chronic sinusitis, especially in case of concomitant nasal polyps or mucosal swelling, or in sinusitis due to allergy.
11.31 Strongyloidiasis

Strongyloidiasis is caused by the intestinal parasite *Strongyloides stercoralis* or *Strongyloides fuelleborni* (found sporadically in Africa and Papua New Guinea), which has the ability to replicate in the human body and cause overwhelming infection. The worm is acquired through contact with contaminated soil, linen and clothing, or water-containing larvae. The larvae penetrate the skin or mucous membranes.

The genus *Strongyloides* is referred to as “threadworms” in the Americas. *Strongyloides stercoralis* is a nematode or round worm with a thread-like or filamentous form (filiform). The parasitic adult female worm is an almost transparent larva about 2.2–2.5 mm in length with a diameter of 50 μm. It lives in tunnels between the enterocytes in the duodenum and proximal jejunum and moves threaded in the epithelium leaving trails of dark eggs behind as it migrates through the intestinal mucosa, and hence is frequently referred to as the threadworm.

The majority of patients with strongyloidiasis have uncomplicated disease. As many as 50% of patients remain asymptomatic and can survive decades undiagnosed. Symptomatic infections typically manifest in the gastrointestinal, pulmonary and dermatological systems. Severe symptoms may develop and death may ensue, especially in individuals who are immunocompromised.

Strongyloides hyperinfection syndrome usually occurs in immunocompromised hosts and may require hospitalization and intensive care in disseminated infection. Patients with hyperinfection syndrome often have complications of sepsis, shock and acute respiratory distress syndrome (ARDS). Any patient suspected of disseminated disease should receive care in a facility properly equipped for intensive management.

**Key clinical features**

- **Skin:**
  - transient dermatitis when larvae penetrate the skin, usually in the feet;
  - intensely itchy dermatitis (larva currens) radiating from the anus, perineal area, buttocks and trunk;
  - stationary wheal lasting 1 to 2 days;
  - migrating larvae under the skin produce a red, serpiginous rash that moves across the trunk at several centimetres per hour.
- **Lungs:**
  - cough and wheeze as larvae migrate through the lungs.
- **Gastrointestinal:**
  - symptoms result from the female adult worm in the intestinal mucosa;
  - epigastric pain aggravated by food;
  - nausea, vomiting, diarrhoea, constipation;
  - GI bleeding, weight loss.

**Complications**

- Small-bowel obstruction with heavy infestation.
- *Strongyloides* hyperinfection syndrome:
  - severe wasting;
  - secondary peritonitis;
  - secondary Gram-negative sepsis with acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC);
  - diffuse pulmonary infiltrates on chest X-ray;
  - coma and death.
Disseminated strongyloidiasis, heavy worm loads and hyperinfection syndrome can occur in immunocompromised patients with HIV. There is also a risk of developing hyperinfection syndrome in patients taking high-dose steroids. All patients starting high-dose steroids (equivalent 0.5 mg/kg prednisolone) and cytotoxic therapy should receive treatment for strongyloidiasis before commencing. Pregnant women with suggestive symptoms should be screened and treated if infected.

Investigations
- Eosinophilia
- Identification of the parasite (larvae):
  - stool microscopy or wet mount
  - sputum examination in patients with pulmonary symptoms
  - duodenal aspirate.
- Serology tests for larval stage antigens are sensitive (positive in 80%–85% cases) but not specific, and may indicate past infection or cross-reaction with other nematode antigens not routinely available in limited-resource settings.

Treatment
- Drug of choice:
  - ivermectin 200 micrograms/kg stat or 200 micrograms/kg daily for 2 days.
- Less effective:
  - thiaibendazole 25 mg/kg twice daily for 3–7 days; OR
  - albendazole 400 mg twice daily for 3 days.

Empirical therapy may be considered in patients with signs and symptoms suggestive of strongyloidiasis infection. Following which, maintenance therapy once monthly is necessary to suppress symptomatic infection (albendazole 400 mg or ivermectin 6 mg once monthly).
Syphilis is caused by *Treponema pallidum*. Patients with HIV and syphilis may have accelerated or atypical disease.

**Transmission**
- sexual contact
- blood transfusion
- transplacentally from a pregnant woman to her foetus.

**Key clinical features**

**Early syphilis**

**Primary syphilis**
- Usually presents as a single *painless* chancre (genital ulcer) often with regional lymphadenopathy, at the site of inoculation.
- Chancres are usually on the genitals but may be found in the anal canal or mouth and often resolve without treatment.

**Secondary syphilis**
- Presents weeks to months after the initial infection.
- Papulosquamous (papular and scaly) rash which is generalized, and characteristically involves palms and soles but can also affect mucous membranes (mucous patches) and lymph nodes.
- Condylomata lata – flat top papules (wart-like) on the genitals, axillae, breasts.
- Constitutional symptoms of secondary syphilis include malaise, sore throat, headache, fever, and anorexia.

**Early latent syphilis**
- Asymptomatic.
- Infection for less than two years, characterized by positive syphilis serology.

**Late syphilis**

**Late latent syphilis**
- Asymptomatic.
- Infection for more than two years, characterized by positive syphilis serology.

**Tertiary syphilis**
- This may progress within a year of initial infection or after latent infection for up to 30 years.
- It usually involves skin (cutaneous gummas), heart (cardiosyphilis, e.g. aortitis), and neurosyphilis.
- Neurosyphilis can occur at any stage and is tertiary when it follows on secondary syphilis:
  - early neurosyphilis is meningeal or meningovascular, and may present with symptomatic meningitis or meningitis with stroke, cranial nerve dysfunction, auditory or ophthalmic problems;
  - late neurosyphilis presents with general paresis (dementia) and *tabes dorsalis* (ataxia, incontinence, pain, and optic atrophy with Argyll-Robertson pupils).

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Investigations

Direct:
- Dark field microscopy is definitive, but difficult to perform. See characteristic morphology and motility of the spirochete in lesion exudate or tissue.
- Direct fluorescent antibody (DFA) test – spirochetes stained with fluorescein-labelled anti T. pallidum globulin and detected through fluorescence microscope.
- Nucleic acid amplification test (NAATs) – detect T. pallidum DNA by PCR from specimen of any lesion exudate, tissue or body fluid.

Serology - becomes positive 2–3 weeks after the appearance of a chancre.
- Non-treponemal (diagnostic) tests- RPR and VDRL
  - These detect anti-lipid IgM or IgG antibodies and are not highly specific for syphilis as can cross-react with other conditions (false-positive).
  - Also false negative if tested early in first four weeks; if negative at three months after chancre, this excludes syphilis diagnosis.
  - Quantitative non-treponemal tests correlate with disease activity and are used to follow response to treatment as the titre decreases and the test becomes non-reactive (e.g. look for four-fold change or higher in titre for positive response to treatment from 1:16 to 1:4).
- Treponemal (confirmatory) tests – T. pallidum haemagglutination assay (TPHA), T. pallidum particle agglutinations assay (TPPA) and fluorescent treponemal antibody absorbed (FTA-ABS) as well as the new rapid tests, usually remain reactive for life (85%).
- Rapid treponemal tests are becoming increasingly available. Results are available in 10 – 15 minutes, sensitivity (85%–98%), specificity (93%–98%); detect treponema-specific antibodies in whole blood or serum. These tests are specific to syphilis (but do not differentiate between venereal and endemic syphilis). A positive test will not distinguish between active infection and infection that has been previously treated.
- Increasingly, countries have begun to adopt rapid syphilis tests (RSTs) that allow for point-of-care testing in settings with limited laboratory resources. Rapid dual HIV/syphilis tests are now available for use in ANC settings. Currently one rapid dual HIV/syphilis test is WHO prequalified.121

- Neurosyphilis is difficult to diagnose, particularly in HIV-infected patients:
  - positive CSF VDRL
  - increased CSF protein
  - CSF pleocytosis (>5 WBC/μl and probably >20 WBC in PLHIV).

Treatment

For early syphilis (primary, secondary and early latent syphilis (<2 years duration))
- Give a single dose of benzathine penicillin G, 2.4 million U IM (for adolescents, adults or pregnant women). This is preferable to procaine penicillin (1.2 million units IM once daily for 10 days):
  - add 5 ml sterile water to a vial containing 1.2 million units = 1.2 million units/6 ml total volume. Give 12 ml (6 ml in each buttock);

OR

Alternative treatment only for non-pregnant, penicillin-allergic patients or if benzathine (or procaine) penicillin not available (e.g. due to stock-outs):
- doxycycline 100 mg orally twice daily for 14 days or ceftriaxone 1 g IM once daily for 10–14 days or in special circumstances azithromycin 2g once orally.

Alternative treatment **only for pregnant, penicillin-allergic patients** (where penicillin desensitization is not possible) or benzathine (or procaine) penicillin are not available (due to stockouts):
- erythromycin 500 mg orally four times daily for 14 days (with caution) or ceftriaxone 1 g IM once daily for 10–14 days or azithromycin 2 g once orally
If the patient is pregnant, plan to treat the newborn. Remember to treat the partner.

**For late syphilis (late latent syphilis (>2 years duration) or syphilis of undetermined duration):**
- benzathine benzyl penicillin G, 2.4 million U IM once weekly for three consecutive weeks (the interval between doses should not exceed 14 days; this is preferable over procaine penicillin 1.2 million units IM once daily for 20 days)); OR
- doxycycline 100 mg orally twice daily for 30 days (if penicillin allergy or stock-outs in non-pregnant patient); OR
- **if pregnant with penicillin allergy**- erythromycin 500 mg orally four times daily for 30 days.

**For neurosyphilis:**
- aqueous benzyl penicillin G, 2–4 million U IV q 4h for 14 days; OR
- procaine benzyl penicillin, 2.4 million U IM once daily, PLUS probenecid 500 mg orally four times daily for 10–14 days.

**Monitoring treatment**
- VDRL titres should decline fourfold over 6–12 months after treatment.
If titres do not decline, rule out neurosyphilis with a CSF examination.
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Syphilis

Positive syphilis screening test
- Perform treponemal-specific test

Positive treponemal-specific test
- Establish stage of infection: obtain quantitative nontreponemal test titres

Signs or symptoms of primary or secondary syphilis
- Early latent syphilis
  - Penicillin G benzathine, 2.4 million units IM (single dose)

No clinical signs or symptoms (latent syphilis)
- Late latent syphilis
  - Penicillin G benzathine, 2.4 million units IM once a week for 3 weeks (3 doses)

Signs or symptoms of tertiary (late) syphilis, or patient is HIV-positive or otherwise immunocompromised
- Lumbar puncture
- Signs, symptoms, or CSF findings consistent with neurosyphilis
  - Yes
    - No penicillin allergy
      - Desensitization
        - Aqueous crystalline penicillin G, 3 million to 4 million units IV every 4 hours for 10 to 14 days; or Penicillin G procaine, 2.4 million units IM once daily; plus 500 mg of probenecid orally 4 times daily for 10 to 14 days
  - No
    - Penicillin allergy
      - Involve appropriate subspecialists, penicillin G benzathine, 2.4 million units IM once a week for 3 weeks (3 doses)

Negative treponemal-specific test
- Primary syphilis suspected
  - Obtain quantitative nontreponemal test titres
  - Penicillin G benzathine, 2.4 million units IM (single dose)
- False-positive test result
  - Consider other causes

Prevention

Sexual transmission – occurs generally during primary, secondary or early latent stage – education on condoms, avoid multiple sexual partners, avoid sexual contact with infected persons, and early testing and treatment if develop ulcer.

Screen all pregnant women for syphilis at the first antenatal visit. Maternal-to-child transmission can occur several years after untreated infection and causes congenital syphilis leading to early foetal deaths/stillbirths, neonatal deaths, preterm/low-birth-weight babies in addition to bullous rash, hepatosplenomegaly, meningitis, chorioretinitis, and inflammatory problems in eyes, ears, joints and skeletal malformations.

11.33 Taeniasis (pork tapeworm disease)

(See also Section 11.9 Cysticercosis – a different and more serious disease caused by the same organism.)

Taeniasis and cysticercosis are two different diseases caused by the same organism. Taeniasis is an intestinal infection caused by the large adult tapeworms *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm) and *Tania asiatica*. Cysticercosis, caused by the larval stage of *Taenia solium*, is an extraintestinal larval disease involving the tissues and manifestations in the brain and eye, which are the main reasons for morbidity. On the other hand, taeniasis in an intestinal form plays an important role as a reservoir for direct transmission to other humans.

Humans become infected after ingesting raw beef or pork containing larvae. The larvae develop into adult worms in the gut and cause the intestinal infection (taeniasis). In *T. solium* infection, the eggs produced by the adult worm are passed out in the stool. Humans can also become infected with *T. solium* eggs due to faecal-oral ingestion from poor hygiene or ingesting contaminated food or water, or eating undercooked pork or beef. The eggs develop into cysts in different parts of the body (cysticercosis) including the muscles and the central nervous system (neurocysticercosis). Neurocysticercosis causes serious morbidity in endemic areas. Even vegetarians can become infected due to poor hygiene or infected salt.

Only *T. solium* causes major health problems. Beef tapeworm has become rare due to changes in animal husbandry, promotion of toilet use, and change in meat preference.

The diagnosis and treatment of taeniasis and cysticercosis are markedly different, and thus are considered separately.

A review in 2015 estimated areas where full transmission of the life-cycle of the parasite occurs or is likely to occur, particularly as indicated by the presence of porcine cysticercosis. This suggested that most SEA Region countries are endemic for *T. solium*. Only *T. solium* causes major health problems. Beef tapeworm has become rare due to changes in animal husbandry, promotion of toilet use, and change in meat preference.

Key clinical features
- The majority of intestinal infections with adult worms are asymptomatic.
- Suggestive symptoms include:
  - early morning abdominal pain, nausea, and vomiting,
  - history of passing proglottids (motile segments of the worm) in stool or underwear.

Investigations
Stool examination:
- observation of proglottids or other tapeworm fragments,
- observation of eggs in stool or on anal swabs.

Treatment
Tapeworm carriers, identified by positive stool examination, should always be treated even when asymptomatic (epidemiological indication). Treatment of taeniasis by *Taenia solium* is important to prevent neurocysticercosis and as a tool to assist in controlling or stopping the parasite transmission cycle. The treatment can be done on an individual bases, or as mass

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drug administration depending on the local circumstances and the control approaches being implemented. Treatment of patients living in an endemic area with suggestive symptoms or history of eating raw pork or beef should be considered even if stool examination is negative.\textsuperscript{124}

- Both praziquantel and niclosamide are effective:
  - praziquantel:
    - contraindication: presence of ocular cysticercosis;
    - adults more than 60 kg: 5–10 mg/kg as a single dose;
    - patients 30–60 kg: 300 mg as a single dose;
  - niclosamide:
    - no contraindications, avoid alcohol during therapy;
    - adults: 2 g in a single dose;
    - children less than 35 kg: 1 g as a single dose.

Without treatment, the tapeworm usually dies in 2–3 years.

11.34 Talaromycosis (penicilliosis)

This refers to infection due to the dimorphic fungus *Talaromyces marneffei* (previously named *Penicillium marneffei*). It causes disease primarily in immunosuppressed individuals, most commonly due to advanced HIV infection (88% of cases; usually CD4 count <100 cells/mm³), and is an AIDS-defining illness. Talaromycosis is most commonly reported in Viet Nam, southern People’s Republic of China, the Kingdom of Cambodia, and a number of WHO South-East Asia Region countries: Bangladesh, northern/northeastern India, Indonesia, Myanmar and northern Thailand. It is a systemic infection, with haematogenous dissemination from initial inhalation to the lungs leading to involvement of a wide range of sites in the body.

**Key clinical features**

Talaromycosis can start as a non-specific subacute illness, with few features differentiating it from other common infections such as tuberculosis, histoplasmosis and enteric fever.

**The most common features are:**

- fever (~80%)
- cutaneous lesions (40%–70%): mostly umbilicated with central necrosis on the face, trunk and extremities – late, but most specific to talaromycosis. Sweet’s syndrome also common – up to 30% in patients without HIV.
- hepatomegaly (up to 70%)
- lymphadenopathy (30%–40%)
- cough and/or shortness of breath – usually due to pneumonia (~40%)
- gastrointestinal symptoms, most commonly diarrhoea (up to 30%)
- anaemia & thrombocytopaenia
- raised aminotransferases, with AST:ALT (SGOT:SGPT) ratio of ~2.

**Complications/unusual manifestations:**

- Anaemia can be severe, with need for repeated transfusions.
- Central nervous system involvement (<1%; meningitis and/or encephalitis) – high mortality (80%).
- Concurrent infections common: up to 60% patients with HIV infection have another opportunistic infection.

**Investigations**

Microscopy can allow a presumptive diagnosis in endemic regions. Round/oval yeast-like organisms measuring 3–6µm are typically found within macrophages or extracellularly in skin lesion scrapings, lymph node/bone marrow aspirates, or tissue, using Giemsa, Wright or GMS stains.

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They may be seen on Wright-stained blood smears if fungaemia is high. A clear midline septum when cells are dividing differentiates *T. marneffei* from *Histoplasma* and *Candida*.

Definitive diagnosis, where available, is by histopathological identification in biopsy specimens or positive culture from a clinical specimen, e.g. bone marrow (highest yield – 100%), skin lesions (90%) or blood (70% yield). It grows slowly (5–14 days) but readily in standard and Sabouraud media. Serological (antibody/antigen) and PCR-based methods are being developed but not yet widely used, due to concerns over sensitivity (and specificity, for galactomannan).

**Treatment**

Ideal therapy: Liposomal amphotericin B: 3 to 5 mg/kg/day IV for two weeks, then itraconazole 200 mg PO twice daily for 10 weeks, then maintenance therapy/secondary prophylaxis (if specialist/local guidance recommends) with itraconazole 200 mg PO daily.

**Alternatives to induction therapy with liposomal amphotericin B – in order of preference:**
- Deoxycholate amphotericin B 0.7 mg/kg/day IV.
- Voriconazole 6 mg/kg IV every 12 hours for one day, then 4 mg/kg IV every 12 hours.
- Itraconazole 600 mg per day orally for three days, then 400 mg per day.

Note that toxicity from deoxycholate amphotericin B is common; voriconazole is expensive (oral formulations cheaper and have been used) and prone to drug-drug interactions; and itraconazole is less effective and also prone to interactions.
Tetanus is a neurological disease caused by a powerful toxin that is produced by *Clostridium tetani* growing in necrotic tissue under anaerobic conditions. This organism is found in the soil and animal dung, and is introduced through wounds or injuries. Tetanus can also occur after abortions, childbirth, surgery, injections (both medicinal and injecting drug use – see Section 17 Substance use), burns, chronic wounds and infections, ulcers and frost-bite. The disease is preventable by adequate vaccination, and clean delivery and aseptic cord care practices, but there are still many cases reported every year, particularly in resource-limited settings where neonatal tetanus cases constitute the bulk of the cases being reported.

**Key clinical features**

**Generalized tetanus**
- The incubation period is usually 3–21 days (median 8 days) after injury.
- Increased tone in muscles, often starting in the jaw (commonly called "lockjaw"), with difficulty swallowing, stiffness and pain in the neck, shoulder, back or abdominal muscles.
- Painful muscle spasms; in severe tetanus, arched back (opisthotonus) and generalized spasms can cause difficulty breathing.
- Fever is usually absent or low-grade, or may develop if frequent spasms occur.
- Mental status is preserved.
- Autonomic dysfunction: hypertension or hypotension, tachycardia, dysrhythmias, high temperature, sweating may be seen.

**Local tetanus**
- Occurs only in muscles around the site of the wound.
- No further CNS involvement occurs and mortality rates are very low, around 1%.

**Cephalic tetanus**
- Local tetanus of the head, usually after a middle-ear infection or head injury. This form of tetanus is very uncommon and carries a high mortality rate.

**Investigations**
- Diagnosis is only clinical. There is no diagnostic test.
- A high WBC may be present.

**Treatment**
- Tetanus can be fatal if not treated.
- Antibiotics reduce the amount of bacteria, hence stopping toxin production.
  - metronidazole 500 mg four times daily (every six hours) for 10 days; OR
  - benzylpenicillin 2–4 million units every six hours for 10 days.
  - tetracyclines, macrolides, clindamycin, cephalosporins and chloramphenicol are also effective.
- Antitoxin lowers mortality, but only binds to the toxin that is still circulating. This is urgent.
  - human tetanus immunoglobulin (TIG) 500 units IM; OR
  - equine tetanus immunoglobulin (not preferred, can produce serum sickness and hypersensitivity reactions).
- Administer tetanus vaccine with age-appropriate dose. Further doses are then needed (second dose at 1–2 months, third dose at 6–12 months).

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• Manage spasms:
  o IV diazepam given in increments of 5 mg and titrated to control spasms – large doses (up to 500 mg per day) may be required initially; OR
  o lorazepam in 2 mg increments OR
  o phenobarbital to a maximum of 1000–1500 mg in adults;
  o chlorpromazine 50–150 mg IM every 4–8 hours (adults), or magnesium sulphate can be used alone (or with diazepam) 5 g IM or 75 mg/kg IV loading dose, then 2–3 g per hour until spasm control is achieved (monitor for toxicity). See Quick Check page 37.
• For severe autonomic dysfunction:
  o labetalol (alpha and beta blocker), clonidine, magnesium sulphate, or morphine may be tried.
• Intensive care
  o Drugs used to control spasm and provide sedations can result in respiratory depression.
  o Ventilatory support is crucial, and severe cases need to be referred for intensive care.
  o If spasm, including laryngeal spasm, is impeding or threatening adequate ventilation, mechanical ventilation is recommended when possible. Early tracheostomy is preferred as endotracheal tubes can provoke spasm and exacerbate airway compromise.
• Adequate fluids and nutrition – tetanus spasms cause high metabolic demands. Good nutrition can enhance survival.

With good supportive care (including nutritional support and good nursing care), patients whose spasms can be controlled usually survive with few or no long-term effects.

Prevention
• See tetanus toxoid vaccine dosing schedules.
• Ensure high coverage with the primary vaccination series with DTP in infancy.
• Ensure high coverage with the booster doses at 4–7 years, in adolescence and in pregnancy (see Section 19).
• Ensure skilled attendants at birth with aseptic cord care practices.
• After acute injury in non-vaccinated persons:
  o wash wound with soap and water; THEN
  o tetanus immune globulin 250 units IM once; AND
  o initiate an age-appropriate primary vaccination series.
• All previously vaccinated persons need a booster dose every 10 years.
  o For children >7 years, adolescents, and non-vaccinated adults: Td vaccine 0.5 ml IM at 0, 4–8 weeks, and 6–12 months.

11.36 Toxoplasmosis

Toxoplasma gondii is a parasite that can cause a variety of illnesses in humans. It is acquired from the ingestion of oocysts, from stools of household pets, or cysts present in undercooked meat. It can be transmitted through blood transfusions and transplacently from an infected mother to the fetus. The parasites invade the blood stream and form cystic aggregates in tissues. Usually, the patient’s immune system can control the acute infection and dormant cysts develop mainly in the retina and CNS, but also in the heart and lungs. In PLHIV and in fetuses, the poorly functioning immune system leads to a more aggressive primary infection. Dormant cysts are reactivated when CD4 counts drop below 100. Acquired infection in a pregnant woman can be transmitted to the unborn child and cause serious disease and possibly the death of the child.

Key clinical features
In patients who have normal immunity:
• many cases do not have any symptoms
• cervical lymph node enlargement may occur
fatigue, muscle pain, rash and sore throat may occur.

In PLHIV (usually subacute)
- focal findings – cranial nerve deficits, motor deficits, visual field loss, and aphasia are common;
- altered mental status, fever, seizures, headaches;
- meningeal irritation is infrequent.

See Section 10.11 on chorioretinitis.

Investigations
- Serology: simultaneous presence of IgG and IgM denotes acute infection. The absence of IgG makes infection unlikely (negative predictive value 94–97%).
- Encephalitis: CSF findings are usually normal; a slight increase in the white cell count or protein may be seen. Glucose remains normal.
- Multiple or single ring-enhancing lesions may be seen on computed tomography (CT) of the brain, although this form of imaging is rarely available in non-specialized centres.

In HIV-infected patients with a suggestive clinical picture and a positive toxoplasmosis serology OR normal CSF findings, toxoplasmosis treatment should be started.

Treatment
Option 1
Because of its wide availability, cotrimoxazole should be the first option treatment for CNS toxoplasmosis.
- Give cotrimoxazole 2 double-strength tablets two times daily for six weeks.
- If severely ill and not able to take oral medication, cotrimoxazole IV can be used.

Option 2
Pyrimethamine and sulfadiazine:
- pyrimethamine 100–200 mg loading dose once, then 50 mg once daily for six weeks, PLUS sulfadiazine 4 to 6 grams four times daily for 6 weeks, PLUS folinic acid 10–25 mg daily for six weeks (not folic, even though folinic acid is often not available).

Supportive management
If intracranial pressure is elevated (papilloedema, vomiting), prednisolone (40 mg four times daily) or dexamethasone (4 mg four times daily) can be administered. Use of prednisone 40 mg four times daily to manage cerebral oedema can be used at the discretion of the provider, if TB is excluded.

In the case of empirical treatment, a response can be expected after seven days of treatment in about 3/4 of patients or after 14 days in almost all patients. If no improvement occurs, reconsider the diagnosis.

Secondary prevention
- cotrimoxazole, 1 double-strength tablet daily until CD4 >200 for at least six months.

Primary prevention
All HIV-positive patients with a CD4 <200 should receive cotrimoxazole, 1 double-strength tablet daily until their CD4 count is >200 for at least six months. This will protect them from both toxoplasmosis and PCP.
11.37 Trichinellosis (porkworm disease)

Trichinellosis or pork worm disease is caused by the roundworm *Trichinella*. The disease has been reported worldwide, the prevalence of human infection being highest in the People’s Republic of China, Thailand and in parts of South America and Central Europe. The species that infect humans include *T. spiralis* and *T. pseudospiralis*.

The life-cycle starts when man eats meat with encysted larvae. Digestive juices dissolve the cyst capsule to release larvae which penetrate the intestinal epithelium, mature and mate. Newborn larvae traverse the intestinal wall, enter lymphatics and the circulation and are distributed to various tissues. The larvae encyst in muscle and may remain viable for years. Most infections are acquired through ingestion of inadequately cooked pork or wild game.

The incubation period varies with the number of ingested larvae, the *Trichinella* species and the host’s immune status. Mild infections can be subclinical, shorter incubation periods are associated with more severe disease. The age, sex and general condition of the individual affect the course of disease.

Three phases of infection may be recognised with heavy infection:

- **Intestinal stage**: This initial stage is easily misdiagnosed, may be asymptomatic or manifest upper abdominal pain, nausea, vomiting and transient diarrhoea, malaise and low-grade fever. The symptoms abate.

- **Migratory stage**: Adult-derived larvae penetrate the intestines, enter the circulation and disseminate. The symptoms, usually the first to be clinically apparent, are myalgia, paralysis, periorbital and/or facial oedema, conjunctivitis, fever and skin rash.

- **Muscle stage**: Key findings are subungual splinter, conjunctival and retinal haemorrhages, chemosis and ocular pain. Pain, tenderness, swelling and weakness occur as larvae enter skeletal muscles, usually accompanied by high fever, body rashes and respiratory upset. Severe pain can restrict movement, breathing or swallowing. Transient migration of larvae through cardiac muscle can cause severe myocarditis with a high mortality.

**Key clinical features**
The direct trauma of larvae encysting in muscle cells and the predominantly eosinophilic immune reaction are responsible for most clinical features.

- A diagnosis of trichinellosis should be considered in patients with periorbital oedema, myositis and eosinophilia.
- There may be a history of ingesting inadequately cooked meat, especially pork.
- Acute trichinellosis may be fatal with myocarditis, encephalitis or pneumonia.
- Infections often resolve even when encysted larvae remain viable; some larvae die and calcify.

**Investigations**

- Parasitological diagnosis by:
  - demonstrating larvae in muscle biopsy best taken from symptomatic muscles, or
  - direct microscopy of muscle tissue compressed between microscope slides,
- elevated serum muscle enzymes – creatine phosphokinase and lactate dehydrogenase,
- hypergammaglobulinemia,
- marked peripheral blood eosinophilia (eosinopenia may be due to secondary bacterial infection),
- myoglobinuria on urinalysis,
- calcified densities indicating old infection on plain X-rays of the extremities.

**Treatment**

- Most infections are self-limited and specific therapy may not be necessary.
- Give analgesics and antipyretics as needed.
- Corticosteroids may be required in myocarditis and encephalitis.
- If myocarditis, encephalitis or respiratory muscle involvement, give mebendazole or albendazole:
  - mebendazole 200–400 mg three times daily for three days, then 400–500 mg three times daily for 10 days OR
  - albendazole 400 mg twice daily for 10 to 15 days.

**Typhoid fever:** see Section 8.1 Fever
11.38 Urinary tract infection

Urinary tract infections (UTI) can be limited to the lower urinary tract causing cystitis or can spread to the upper urinary tract or kidney and cause pyelonephritis. Risk factors include sexual intercourse, diabetes, pregnancy, menopause, instrumentation, and anatomical or functional abnormalities of the urinary tract including obstruction. The most common organisms include Gram-negative bacteria (*Escherichia coli*, *Proteus*, *Klebsiella*) and some Gram-positive organisms.

**Key clinical features**
Of lower urinary tract infection:
- suprapubic abdominal discomfort and tenderness
- pain on urination
- urinary frequency
- urinary urgency
- haematuria (blood in urine).

Of upper urinary tract infection:
- fever >38 °C
- loin pain and tenderness
- associated systemic symptoms: nausea, vomiting.

**Investigations**
- Microscopy of a clean, fresh, uncentrifuged specimen of urine. Cases of UTI will usually show more than 10 white cells per high-powered field, or a dipstick will show a positive result for leucocytes or nitrites.
- If possible, obtain a midstream urine sample for culture.

**Treatment**
Uncomplicated lower urinary tract infection:
- Treat with oral antibiotics for three to five days. Options include:
  - trimethoprim 300 mg daily for three days, amoxicillin with clavulanic acid 500 mg plus 125 mg twice daily for five days; OR
  - nitrofurantoin 100 mg twice daily for five days.
- If an organism is resistant to these antibiotics on culture, then it may be appropriate to use:
  - ciprofloxacin 500 mg twice daily for three days, if available.
- If treatment fails or a relapse occurs, treat as for a pyelonephritis or upper urinary tract infection.
- If the patient is pregnant, use either:
  - nitrofurantoin 100 mg twice daily for five days; OR
  - amoxicillin with clavulanic acid 500 mg thrice daily for three to seven days.

Upper urinary tract infection:
- Mild: can be treated with ciprofloxacin or trimethoprim as above for lower tract infection, but continue treatment for 7–10 days.
- Severe: as in high temperature, pain, debility, and inability to maintain oral hydration, and in pregnancy. Options include:
  - ciprofloxacin 500 mg orally twice daily (if no vomiting); OR
  - ceftriaxone 1 g daily; OR
  - if these two options are not available: ampicillin 1 gm IV, eight hourly, plus gentamicin 4–6 mg/kg IV daily.

Avoid quinolones in pregnancy.
Patients treated initially with intravenous therapy can be changed to oral antibiotics once afebrile for 24 hours and improvement has been noted. Treatment should be for 10–14 days in total.

**Monitoring of upper urinary tract infection (pyelonephritis)**
Patients should improve within 2 to 3 days with effective treatment. Failure to improve within 48–72 hours of antibiotics may suggest a complication such as renal abscess or obstruction or infection with a resistant organism. If available, a renal ultrasound may be beneficial to assess for complications.

**Complications of upper urinary tract infection (pyelonephritis)**
Infection of the upper urinary tract with obstruction of the kidney (e.g. renal calculi) requires insertion of a nephrostomy to relieve the obstruction. A renal abscess may require surgical drainage.
11.39 Varicella/zoster

The varicella virus causes two distinct syndromes in humans: a primary illness called chickenpox, which most often occurs in children and is relatively benign, and a second distinct syndrome called herpes zoster, which occurs in older adults and is due to reactivation of the dormant virus in the nerves. Herpes zoster causes significant morbidity due to the intense and sometimes long-standing pain that it causes. It has become more significant in recent years due to its propensity to affect patients with HIV infection. Herpes zoster in a young person is highly predictive of HIV infection and is a WHO clinical stage 2 condition.

11.39.1 Chickenpox

Key clinical features
- Prodrome of fever, malaise, nausea, “flu-like” illness.
- 2–5 days later a generalized, itchy rash appears.
- Crops of papules-vesicles, then crusted lesions, appear all over, sparing the palms and soles.
- Lesions co-exist in different stages of progression, i.e. new papules appear when older lesions are already crusted.
- Intense itching occurs.

Complications are more often seen in patients who acquire the infection as adults, and particularly in pregnant women.
- Pneumonia can be severe: difficulty breathing, low SpO₂ and infiltrates on chest X-ray; occurs in 10% of pregnant women (see Sections 10.6 and 3.2.4).
- Encephalitis is due to a necrotizing vasculitis that is seen in HIV-positive patients.
- Hepatitis with increased liver function tests can also be seen.
- Haemorrhagic syndromes can also accompany varicella in adults. These range from mild to life-threatening.

Varicella in pregnancy carries a high risk of complications.
- If acquired before 28 weeks of gestation, it will cause congenital abnormalities in the child (also called congenital varicella syndrome).
- If acquired around the time of birth, it can cause neonatal varicella, which carries a high rate of pneumonia and other complications.

Treatment
Antiviral therapy depends on age, pregnancy and immune status.
- In children without immune deficiency <12 years:
  o aciclovir is not recommended.
- In “high-risk” children >12 years with chronic pulmonary or cutaneous disorders or on corticosteroid treatment:
  o oral aciclovir 20 mg/kg.
- In HIV-positive children and children with disseminated disease:
  o IV aciclovir 10 mg/kg thrice daily for seven days.
- In adults including pregnant women:
  o oral aciclovir 800 mg five times daily for seven days.
- In immunocompromised adults or those with disseminated disease:
  o IV aciclovir 10 mg/kg thrice daily for seven days; OR
  o high-dose oral aciclovir, if no IV available.
Treatment should be started as early as possible, ideally less than 24 hours after the start of symptoms. For oral treatment, the value of starting after 24 hours is not well established.

**Follow infection control precautions – see Section 6.**

### 11.39.2 Herpes zoster

**Key clinical features**
- Painful vesicular rash in a dermatomal distribution of a nerve supply that does not cross the midline.
- Pain sometimes comes before the appearance of the rash.
- Vesicles form in groups and progress to crusted lesions after a few days.
- Most common areas: trunk, particularly the flanks, and forehead.
- Can involve the eye and cause corneal scarring and blindness.
- HIV patients have more frequent multidermal involvement, involvement of the trigeminal nerve and presence of systemic symptoms, and have a higher risk of disseminated disease.
- Myelitis, meningitis, and encephalitis with headache, fever, neck stiffness, altered motor and sensory function.
- Guillain-Barre syndrome.

**Complications**
- Blindness due to corneal involvement.
- Post-herpetic neuralgia: chronic pain in the area where the lesions occurred that can last for months to years after the acute episode.

**Treatment**
- Local lesion care including treatment of secondary bacterial infections.
- Chlorhexidine.
- Calamine or topical or oral antihistamine preparations to reduce itching (no topical steroid creams) (see Section 20 Palliative care).
- Good hygiene is the key, and daily bathing with soap and clean water is recommended.
- Isolation of the patient to avoid spreading the virus. Contact should be avoided until all lesions are crusted over.
- Paracetamol if there is fever.

Herpes zoster infection:
- Aciclovir 800 mg five times daily for seven days can be considered for all adults, and is recommended for all HIV-positive adults. Start aciclovir within 72 hours from the onset of symptoms.

Ophthalmic involvement:
- oral aciclovir 800 mg five times daily for seven days and aciclovir 3% eye ointment applied into the eye every four hours.

Pain management (zoster):
- paracetamol or stronger analgesics if necessary;
- amitriptyline 25–50 mg before bed for neuropathic pain and post-herpetic neuralgia.

Prevention or post-exposure prophylaxis:
If available, varicella immune globulin should be administered to pregnant women or persons at high risk of severe disease after exposure. Varicella vaccine is available for prevention in some areas.
11.40 Viral haemorrhagic fevers

Although commonly grouped together by their similar presentation, the pathogens that cause Viral haemorrhagic fevers (VHF) syndromes are very diverse. All are characterized by fever, malaise, and hypotension that can lead to shock and to coagulation defects that manifest as a tendency to bleed.

Viral haemorrhagic fever is a general term for a severe illness, sometimes associated with bleeding, that may be caused by a number of viruses. The term is usually applied to disease caused by viruses of the following taxonomic virus families:
- Arenaviridae (Lassa, Lujo, Junin, Guanarito, Sabia, Machupo and Chapare)
- Bunyaviridae (Crimean-Congo haemorrhagic fever [CCHF], Rift Valley fever and hantaviruses)
- Filoviridae (Ebola and Marburg)
- Flaviviridae (yellow fever, dengue, Omsk haemorrhagic fever, Kyasanur forest disease and Alkoruma haemorrhagic fever).

Of these, only Ebola, Marburg, CCHF, Lassa fever and Lujo have human-to-human transmission. The death of health workers is often the first sign that a VHF outbreak has begun, and early recognition and implementation of measures to protect health workers is one of the main objectives of early outbreak management.\(^\text{130}\)

Dengue and yellow fever also have haemorrhagic manifestations but are not transmitted directly from person to person. Except for dengue fever (see Section 8.1 Fever), all the agents of VHF are zoonotic pathogens. Thus, the risk of infection is strongly influenced by the local environment and ecology, and exposure to infected animal vectors (e.g. through occupational exposure, consumption of food, or inhalation of aerosols contaminated by infected animal excretions).

Thus far, only dengue and CCHF have occurred in the South-East Asia Region. There is a risk of importation of Ebola and yellow fever by air travel or other transport when cases are occurring in other regions. There is some serological evidence of hantavirus in rodents in India, Indonesia, Myanmar, Sri Lanka and Thailand.\(^\text{131}\)

Refer to specific other Sections in this manual for these four VHFs: dengue (Section 8.1.7), CCHF (Section 11.7), yellow fever (Section 11.43) and Ebola (Section 11.11).

**Key clinical features**
- fever
- headache
- myalgia
- abdominal discomfort, nausea, vomiting
- erythematous rash (may be difficult to see in dark skin)
- haemorrhagic manifestation (typically conjunctival haemorrhage, oozing from puncture sites, ecchymoses, petechiae, purpura, and occasionally gastrointestinal haemorrhage)
- oedema.

A careful search should be made for evidence (clinical or laboratory) of other infections, such as typhoid or malaria, that could mimic the effects of a VHF. In addition, dually-infected patients have been reported during some outbreaks.

\(^{130}\) Clinical management of patients with viral haemorrhagic fever: A pocket guide for frontline health workers; interim emergency guidance for country adaptation. WHO, February 2016

\(^{131}\) A brief guide to emerging infectious diseases and zoonoses. WHO SEARO, 2014
Any acute illness, especially febrile illness, not clearly due to a common pathogen or which is unresponsive to initial empirical therapy, should raise concerns about VHF. This is especially true if there is unexplained bleeding or rapid deterioration of the patient's condition.\(^{132}\)

### Standardized case definitions: acute haemorrhagic fever – see Section 9

<table>
<thead>
<tr>
<th>Acute haemorrhagic fever syndrome</th>
<th>Suspected case: Acute onset of fever of less than three weeks duration in a severely ill patient AND any two of the following: haemorrhagic or purpuric rash; epistaxis (nose bleed); haematemesis (blood in vomit); haemoptysis (blood in sputum); blood in stool; other haemorrhagic symptoms, and no known predisposing factors for haemorrhagic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmed case: A suspected case with laboratory confirmation or epidemiological link to confirmed cases or outbreak.</td>
</tr>
<tr>
<td>Note: During an outbreak, case definitions may be changed to correspond to the local event.</td>
<td></td>
</tr>
</tbody>
</table>

### Laboratory investigations
- Full blood count (may demonstrate lymphopaenia, thrombocytopaenia, or rise in haematocrit due to haemoconcentration);
- Evidence of disseminated intravascular coagulation (elevated fibrin split products and D-dimer).

### Treatment
Intravenous ribavirin may be effective against Crimean-Congo haemorrhagic fever and hantaviruses, based on small case series. Consult with the national programme and experts on its use.

### Supportive care
- Hypotension and shock must be carefully monitored and treated judiciously with intravenous fluid (Lactated Ringer's solution or normal saline). If the patient is in shock, see septic shock management in Section 3.1.5. Overhydration may precipitate pulmonary oedema.
- Pain control.

### Infection prevention and control
For suspected VHF with human-to-human transmission:
- Use standard plus contact plus droplet precautions (see Section 6) plus airborne precautions if risk of exposure to aerosols (e.g. during intubation, bronchoscopy).
- Isolate infected patients from others to the extent possible.
- Minimize invasive procedures (including blood draws) to limit the risk of occupational exposure.

For those without human-to-human transmission, standard precautions are sufficient.

\(^{132}\) Clinical management of patients with viral haemorrhagic fever: A pocket guide for frontline health workers; interim emergency guidance for country adaptation. WHO, February 2016
11.41 Yellow fever

Yellow fever is caused by a flavivirus and is transmitted by mosquito bites. It is found in sub-Saharan Africa and South America. Yellow fever can be prevented by vaccination, but several hundred cases are still reported every year.

No case has been diagnosed in the South-East Asia Region. However, the vector *Aedes aegypti* is present (the same vector as in dengue, Zika and chikungunya) and the population has no immunity. These are conditions that would support local transmission. Urban yellow fever outbreaks are occurring, raising the risk of spread by air and other transport (vector control measures are required in various forms of transport by IHR (2005).

Yellow fever is a classic viral haemorrhagic fever and is difficult to identify, particularly in the early stages when signs and symptoms are not specific. It can be confused with more common diseases such as malaria, viral hepatitis and leptospirosis (when jaundice), dengue, other arbovirus diseases, and Ebola virus disease (when haemorrhagic), as well as with poisoning.

**Key clinical features**

**Incubation period:** 3 to 6 days

**Acute phase:** fever, malaise, backache, muscle aches, headache, nausea and vomiting. This phase improves after 3–5 days.

**Remission for 1–2 days**

**Toxic phase:** affects about 15% of patients.
- Recrudescence of high fever.
- Liver damage with jaundice, abdominal pain, and nausea with vomiting.
- Bleeding can be severe: gastric bleeding (black vomit), ears, eyes and nose can be affected.
- Kidney failure follows, with decreased urine production and confusion due to increased blood urea.

**Severe disease:** 50% of patients in the toxic phase die within 10–14 days.

**Investigations**
- Liver function tests: high bilirubin (conjugated) and elevated AST and ALT.
- Blood leukocyte counts are decreased early on, but can be high at terminal stages.
- Urine protein levels are increased.
- Blood urea nitrogen increases in severe cases with renal failure.

**Treatment**
Supportive treatment is essential. Although there is no recognized drug therapy available for yellow fever, good and early supportive care improves survival rate.

---

Patients should be managed in hospital in severe cases. Treat dehydration. If the patient is in shock, see septic shock management in Section 3.1.5. Mortality is relatively high, but those who recover do so without any residual organ damage.

**Infection prevention and control**
Health workers should use standard precautions. The patient needs to stay under mosquito nets during the day to limit spread to others through bites of mosquitoes.

**Prevention of international spread**
Notification of cases are required by the International Health Regulations (2005). Travellers should present yellow fever vaccination certificates if they have been in a country with yellow fever transmission.
12. Palliative care: symptom management and end-of-life care

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### 12. Palliative care: symptom management and end-of-life care

| 12.1 Assess pain (acute or chronic) | 12.10 Manage other symptoms using other Sections of this manual |
| 12.2 Manage pain | 12.11 Preventive interventions for all patients |
| 12.3 Adjuvant mediations | 12.12 Special considerations in palliative care for PLHIV |
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| 12.8 Symptom management: hiccups | |
| 12.9 Symptom management: trouble sleeping | |

Palliative care is a multifaceted, integrated approach to improving the quality of life of patients and their families facing the problems associated with life-threatening illnesses such as COVID-19.\(^1\) It focuses on prevention and relief of suffering through assessment and management of the following stressors:\(^2\)

- physical
- psychosocial
- spiritual

Palliative care includes symptom management during both acute and chronic illness and end-of-life (terminal) care. This includes management of pain and other symptoms such as nausea, vomiting, itching, etc.\(^3\) This section also addresses symptoms associated with severe COVID-19 disease including breathlessness, cough, fever and agitation. The current approach to palliative care has evolved to fit with Figure B, rather than the original dichotomous version shown in Figure A, where patients receive curative-restorative care until this fails and then receive palliative care. It is meant to be part of people-centred health services and should be accessible to all patients.\(^4\)

---

2. WHO. Integrating palliative care and symptom relief into the response to humanitarian emergencies and crises. 2018. Available at https://apps.who.int/iris/handle/10665/274565
4. See https://www.who.int/health-topics/palliative-care
When providing palliative care, both specific treatment for the illness and treatment to relieve symptoms are needed, and these can be delivered in hospital or as part of home-based care. There are certain interventions for symptom control that may be possible only in a hospital setting.

### 12.1 Assess pain (acute or chronic)

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. There are two types of pain:

- **Nociceptive pain** is due to the stimulation of pain receptors in the tissues. It can be subdivided into somatic pain which arises from the skin, muscles, bones and joints, or visceral pain which originates from the internal organs. This pain is often described as sharp, dull, aching, throbbing or spasmodic.
- **Neuropathic pain** is caused by damage to the central or peripheral nervous system. Such pain is often described as burning, tingling, stinging or “pins and needles” pain.

Chronic pain is associated with a chronic pathological process. General features include:

- gradual or ill-defined onset,
- ongoing for months or years,
- often not accompanied by physical signs that may be present with acute pain (e.g. swelling, bruising) but the patient may report fatigue and functional limitations,
- may be accompanied by low mood/depression.

#### Assess the patient for pain

Assessment is vital for successful pain management.

- Remember that “pain is what the patient says it is”. Pain is always subjective; it is important to believe the patient.
- Determine the cause of the pain by history and examination. This is important for new pain and any change in pain. Ask the following questions:
  - Where is the pain? When did it start? Was there an event or injury?
  - What makes it better or worse?
  - What are you taking for the pain?
  - Can you describe the nature of the pain? For example, is the pain sharp, dull, shooting, tingling, stinging, colic or muscle spasms? This helps to ascertain the type of pain.

---

• How often do you have the pain? Assess whether there is a psychological or spiritual component to the pain?
• Use other Sections in this manual to determine if there is an infection or other problem causing the pain that is reversible with treatment. Prompt diagnosis and treatment of infection, if present, is important for pain control. Evaluate the location of the pain to see if there are physical signs that can be observed or elicited – swelling, redness, erythema, pain on passive or active motion.

Assessment tools
Assessment is an ongoing process and should be carried out regularly to ascertain the pattern of the individual’s pain and monitor the effectiveness of any treatment.

There are a variety of assessment tools that can be used. The simplest and easiest to use are body diagrams and pain intensity scales.

• Body diagrams
  o body diagrams are used to document the site of pain,
  o patients mark the site(s) of their pain on the body diagrams.

• Pain intensity scales
  o pain rating scales are simple scales that help to follow the course of the patient’s pain and the effect of any treatment given,
  o among the most commonly used scales are the numeric pain intensity scale or numerical rating scale (NRS) and the Wong-Baker FACES pain rating scale.6,7

The patient is asked to rate the pain along the pain intensity scale (shown above) or to grade the pain with the FACES scale (especially for children) or with the hand scale (with no fingers meaning no pain, 1 finger very mild pain, and 5 fingers the worst possible pain) (shown below). It is important to record the ratings given by the patient, noting the intensity of the pain, the time and the date. This will help to track whether the patient’s pain is responding to treatment.

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The Critical Care Pain Observation Tool can be used in severely ill patients who are not able to communicate.⁸

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial Expression</strong></td>
<td>No muscular tension observed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Presence of frowning, brow lowering, orbit tightening and levator contraction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>All of the above facial movements plus eyelid tightly closed</td>
<td>2</td>
</tr>
<tr>
<td><strong>Body movements</strong></td>
<td>Does not move at all (does not necessarily mean absence of pain)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slow, cautious movements, touching or rubbing of pain site, seeking attention</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pulling tube, attempting to sit up, moving limbs/thrashing, not following</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>commands, striking at staff, trying to climb out of bed</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle tension</strong></td>
<td>No resistance to passive movements</td>
<td>0</td>
</tr>
<tr>
<td>Evaluation by passive flexion and</td>
<td>Resistance to passive movements</td>
<td>1</td>
</tr>
<tr>
<td>extension of upper extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strong resistance to passive movements, inability to complete them</td>
<td>2</td>
</tr>
<tr>
<td><strong>Compliance with the ventilator</strong></td>
<td>Alarms not activated, easy ventilation</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Alarms stop spontaneously</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asynchrony: blocking ventilation, alarms frequently activated</td>
<td>2</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td>Talk in normal tone or no sound</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sighting, moaning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td>2</td>
</tr>
<tr>
<td><strong>Vocalization (extubated patients)</strong></td>
<td>Talking in normal tone or no sound</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sighting, moaning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Crying out, sobbing</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: Gélinas et al. 2006.⁹

### 12.2 Manage pain

**Manage pain with analgesics, adjuvants and non-medical treatments**

- The aim is to relieve pain as quickly as possible and to keep it under control.
- Pain can be managed in several ways:
  - with analgesics, according to the analgesic ladder,
  - with adjuvant medications (drugs that are not analgesics but can be helpful in pain management) e.g. antidepressants, anticonvulsants, steroids,
  - with non-pharmacological treatments.
- It is important to regularly reassess the need for pain medication and other interventions. Regular grading of the pain, using the above assessment tools, will help to see whether the pain is being managed or not.
- Any new problems should be investigated as appropriate.


• Use the ABCDE steps for pain assessment and management:
  o A – ask about pain regularly
  o B – believe the patient and family in their reports of pain and what relieves it
  o C – choose pain control options appropriate for the patient, family and setting
  o D – deliver interventions in a timely, logical, and coordinated fashion
  o E – educate and empower patients and their families; enable them to control their course to the greatest possible extent.

• Use the WHO guidelines for Cancer Pain Relief, i.e. by mouth, by the clock, by the individual, and by the ladder:
  1. By mouth
     • If possible, give analgesics by mouth, as it is the easiest route.
     • Rectally is an alternative.
     • Consider continuous IV infusion or intermittent or continuous subcutaneous infusion in a hospital or home setting, under supervision.
     • Avoid IM, as it is painful and shows no added benefit.
  2. By the clock
     • Give painkillers at fixed time intervals (by clock, radio or sun).
     • Give painkillers regularly to prevent the pain from returning; do not give analgesics for chronic pain on an as-required basis.
     • The next dose should be given before the effect of the previous dose wears off.
     • For breakthrough pain, give an extra “rescue” dose (same dosing as the four-hourly dose) in addition to the regular schedule.
     • Start with a small dose, and then titrate the dose against the patient’s pain until the patient is comfortable.
  3. By the individual
     • Link the first and the last dose of the day with waking and sleeping times.
     • Write out the drug regimen in full or present it in a drawing.
     • Teach patients and their families how and when to take the prescribed medication.
     • Check to be sure that the patient and family or assistant at home understands the regimen.
     • Ensure that pain does not return and that the patient is as alert as possible.
  4. With attention to detail
     • Ideally, the patient’s analgesic medicine regimen should be written out in full for patients and their families to work from, and should include the names of the medicines, reasons for use, dosage and dosing intervals.
     • Patients should be warned about possible adverse effects of each of the medicines they are being given.
  5. By the analgesic ladder – for adults
     • The choice of which analgesic to take should be guided by the WHO 3-step analgesic ladder for cancer pain.
     • The 3 steps of the ladder represent mild, moderate, and severe pain.
     • It is usual to start an individual on an analgesic from the first step and then progress up the steps as needed. However, some patients present with severe pain that requires going straight to a step 3 analgesic.
     • It is important to note that, if pain is not controlled by a step 2 analgesic, do not change to another stage 2 analgesic but instead move up to a step 3 analgesic.
     • Step 2 and step 3 opioids should not be used at the same time.

---


• If no codeine is available, aspirin every four hours can be combined with paracetamol every four hours or paracetamol with ibuprofen. Overlap the times so that one is given every two hours. Do not give aspirin and ibuprofen together.
• Adjuvant medications that are helpful for pain can be combined with these drugs (see next sub-section).

* Avoid aspirin in the presence of bleeding or if patient is less than 16 years old. Do not use aspirin and ibuprofen together.

General issues to consider:
• The correct dose of analgesics is the dose that gives the best sustainable balance between symptom relief, function, and adverse effects.
• Although there is a maximum dose for most analgesics, this is not the case for morphine. It has no maximum dose or ceiling. From a low initial dose, it can be increased slowly until pain relief is obtained.
• The choice of analgesic is determined by the severity, site and type of pain.
• The aim is to improve quality of life, balancing pain with physical and mental functioning.
• Consider the concept of “total pain,” i.e. that pain can be physical, psychological, social, spiritual or cultural. These are all overlapping components that result in the “total” pain experienced by the individual.
• Treat the underlying disease where possible.
• If treatment of the underlying condition reduces pain or improves prognosis, consider reducing or ceasing opioids.

The following is a guide to the use of various analgesics:

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Starting dose in adults</th>
<th>Range</th>
<th>Side-effects and cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol (also lowers fever)</td>
<td>1 gram every 4–6 hours, but no more than 4 grams in 24 hours. If &lt;50 kg give 2 g in 24 hours</td>
<td>Only 1 tablet may be required in elderly or the very ill, or when combined with an opioid. Mild pain might be controlled with doses every 6 hours</td>
<td>Do not exceed 4 grams in 24 hours (more can cause serious liver toxicity)</td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid) (anti-inflammatory and lowers fever)</td>
<td>600 mg (2 tablets of 300 mg) every 4 hours</td>
<td>300–900 mg (1–3 tablets of 300 mg) every 4–6 hours Maximum 4 grams daily</td>
<td>With or after food</td>
</tr>
</tbody>
</table>
**Ibuprofen** (anti-inflammatory and lowers fever)  
200–400 mg  
3–4 times daily  
Maximum daily dose of 2.4 grams  
With or after food. Avoid use if gastric problems. Stop if epigastric pain, indigestion, black stools, petechiae or bleeding. Avoid if any bleeding or renal impairment. **Do not give to children under 16 years**

**Opioid for mild to moderate pain** (give in addition to aspirin or paracetamol)

| **Codeine** (if not available, consider alternating aspirin and paracetamol) | **Codeine phosphate**  
30 mg every 4 hours | **Codeine phosphate**  
30–60 mg every 4 hours. Maximum daily dose for pain 240 mg. Consider switch to morphine when a dose of 180 mg is reached | Unless diarrhoea, give regular laxative to avoid constipation |

**Opioid for moderate to severe pain**

| **Oral morphine:**  
5 mg/5 ml or 50 mg/5 ml or tablets. Give by mouth. If necessary, can be given IV/IM/SC | Initially, morphine sulphate 5–10 mg every 4 hours, increased by 30%–50% if pain persists. If elderly/frail/renal impairment start with 2.5-5mg | According to pain  
**There is NO ceiling dose** | Unless diarrhoea, give regular laxative to avoid constipation. Excessive dosage can reduce respiratory rate |

**STEP 2**

<table>
<thead>
<tr>
<th><strong>STEP 2</strong></th>
<th><strong>STEP 3</strong></th>
</tr>
</thead>
</table>

**Specific considerations regarding the use of oral morphine in pain**

- Either immediate-release oral morphine solution or tablets can be used, as available.
- Start with a low dose, e.g. 5–10 mg every four hours or lower; if elderly/frail/renal impairment, start with a lower dose and/or increase the dosing interval.
- Increase the dose of oral morphine solution if pain persists, e.g. 5 mg → 10 mg → 15 mg → 20 mg as doses every four hours. Increase in 30%–50% dose increments; anything less is not effective.
- Ensure that a breakthrough dose is prescribed initially, in case of pain, before the next dose is available. The breakthrough dose should be one sixth of the total 24-hour opioid dose.
- Explain to the individual that there are potential side-effects with morphine, which include constipation, nausea, and drowsiness.
- Respond to the side-effects of morphine as appropriate (see below).
- Always prescribe a laxative at the same time as the oral morphine, unless the individual has persistent diarrhoea.

**If patient has a morphine side-effect:**

<table>
<thead>
<tr>
<th></th>
<th>Then manage as follows:</th>
</tr>
</thead>
</table>
| **Constipation** | • Increase fluids.  
• Give stool softener at time of prescribing plus stimulant (senna).  
• Prevent by prophylaxis (unless diarrhoea, TB on PAS, or HIV) |
| **Nausea or vomiting** | • Give an antiemetic: |
Misconceptions surrounding morphine have often limited its use in palliative care and led to unnecessary suffering. If necessary, reassure the individual that when used appropriately morphine is a safe and effective analgesic. Although morphine has addictive potential, this is hardly ever a problem when a patient has true physical pain, and their morphine use is regularly monitored and titrated against the pain. Physical tolerance can develop, but this is easily overcome by steadily increasing the dose, and this does not usually lead to drowsiness or respiratory depression; neither does it hasten death. There is no ceiling dose.

### Teach patient and family how to give pain medications

- Explain frequency and importance of giving pain medications regularly — do not wait for the pain to return.
- Advise on important side-effects, including when to call or return to health facility.
- Write out instructions clearly. For example:

#### Reduction or cessation of opioids

The above guidelines assume to a certain extent that the pain is progressive and that for adequate control it will require stronger medication, in higher doses; and that due to the life-
threatening nature of the underlying condition, continued opioid treatment for the rest of the patient’s life does not pose any problem.

There are a number of situations in which it might be necessary or desirable to reduce or even cease opioids, moving back down the pain ladder:

- Reduction in pain severity due to treatment of the underlying condition.
- Treatment of the underlying condition leads to cure or an improvement in prognosis.
- Adverse effects of opioids are affecting quality of life.
- There is evidence of abuse or diversion of opioids.
- There is evidence of opioid-induced hyperalgesia (paradoxical response whereby a patient receiving opioids for the treatment of pain could become more sensitive to certain painful stimuli)

If opioids have only been used for a few weeks, treatment can be reduced or stopped rapidly. Chronic opioid treatment should be reduced or stopped gradually. Sudden cessation of opioids will result in a worsening of pain and an opioid withdrawal syndrome, consisting of nausea, vomiting, diarrhoea, anxiety, insomnia, sweating, as well as muscle and joint aches and pains (see section on opioid withdrawal). A general rule of thumb is to start the reduction at not more than 10% per week and adjust as tolerated.

If there is evidence of abuse or diversion of opioids, then consider if the person has developed opioid dependence (see mhGAP). In this case, it may be necessary to provide supervised doses of opioids, preferably with once daily opioids such as methadone. If this is not feasible, then opioid reduction or cessation may be required.

**Non-pharmacological interventions for pain**

- Non-pharmacological interventions that help reduce pain
  - regular limb exercises (can reduce contractures and, therefore, pain)
  - massage
  - acupuncture
  - transcutaneous electrical nerve stimulation (TENS)
  - heat and cold packs
  - deep breathing
  - music
  - yoga
  - traditional practices that are helpful and not harmful; it is important to get to know what can help in the local setting.

- In the light of the concept of total pain, it is important to remember that psychological, social, spiritual and cultural factors can play an important part in the perception and relief of pain.

- Psychological factors
  - Psychological symptoms are often seen in terms of anxiety or depression but may include anger, frustration, withdrawal, etc.
  - Individuals can struggle with pain; it can be hard to accept and understand and can have a significant impact on functional ability and sense of self-worth.
  - Psychosocial support can help the patient to adapt to and cope with the situation and help relieve pain.
  - Psychological interventions that may help reduce pain:
    ◊ psychosocial support and counselling
    ◊ support groups
    ◊ relaxation therapy
    ◊ meditation
    ◊ distraction, e.g. listening to the radio or watching television.

- Spiritual factors
Spiritual distress is an important part of suffering and may manifest as physical symptoms. Spiritual interventions that help reduce pain:
- spiritual support or counselling
- support groups
- prayer (respect the patient’s practise).

Social factors
- Social problems can impact upon the experience of pain, e.g. financial stresses, work pressures, family discordance, worry about the future of children.
- Social interventions that help reduce pain:
  - information
  - supportive counselling
  - practical assistance
  - accessing community resources
  - food support
  - transport issues
  - care of the children
  - life or disability insurances
  - provision for a will
  - discussion around end-of-life care, advanced directives or advance care plan.

Cultural factors
- Individuals from different cultural backgrounds respond to their pain differently.
- Health workers need to be non-judgemental in their response to an individual’s pain and
  - overcome language barriers if possible,
  - be sensitive to culture, ethnicity, gender, sexuality, etc.

## 12.3 Adjuvant medications

### The use of adjuvant analgesics
Adjuvant analgesics are medications whose primary purpose is not as an analgesic but may contribute significantly to pain relief. They can be used on their own or in combination with steps 1, 2, and 3 analgesics. They are particularly useful in neuropathic pain (which is often not very responsive to opioids and NSAIDs), bone pain, smooth or skeletal muscle spasm, and pain related to anxiety.

### Table: Examples of adjuvant analgesics

<table>
<thead>
<tr>
<th>Adjuvant analgesic – Primary drug class</th>
<th>Example</th>
<th>Dose</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline</td>
<td>25–150 mg at night. Start with a low dose and slowly increase if needed.</td>
<td>Nerve pain</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine</td>
<td>Start at 100 mg twice a day; can be increased to 800 mg twice a day.</td>
<td>Nerve pain (if amitriptyline not working or unavailable)</td>
</tr>
<tr>
<td>Muscle relaxants or anxiolytics</td>
<td>Diazepam</td>
<td>5 mg orally 2–3 times daily</td>
<td>Skeletal muscle spasm</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>Ibuprofen</td>
<td>200–400 mg up to three times daily as needed after meals</td>
<td>Bone pain</td>
</tr>
</tbody>
</table>
### Corticosteroids

| Drug                                | Dexamethasone       | 2–4 mg per day for all situations apart from raised intracranial pressure For raised intracranial pressure, start at 16 mg daily and reduce by 2 mg daily to lowest effective maintenance dose | Bone pain
|                                     |                    |                                                                 | Nerve pain
|                                     |                    |                                                                 | Headache due to raised intracranial pressure
|                                     |                    |                                                                 | Pain associated with oedema and inflammation
|                                     |                    |                                                                 | Caution in TB and HIV
|                      |                      |                                                                 |                      

#### Antispasmodic (hyoscine butylbromide)

| Drug                                | Hyoscine butylbromide (also called scopolamine or buscopan) | 10–20 mg tablets up to 4 times per day | Abdominal pain from colic (exclude GI obstruction), muscle spasms in urinary system
|                                     |                                                               |                                  |                      

### Nerve blocks for specific severe pains

Nerve blocks involve the injection of an anaesthetic and corticosteroid around a nerve to alleviate pain in the distribution of that nerve. Nerve blocks can be technically difficult procedures that should be done by experienced clinicians. It may take several weeks before you feel the full effect of the nerve block.

- The most common sites for nerve block are:
  - brachial plexus – interscalene block for shoulder surgeries and procedures
  - sciatic nerve – sciatic nerve block for procedures below the knee
  - femoral nerve – femoral nerve block for femoral shaft fractures, knee procedures
  - most somatic nerves may be targeted depending on the location of the pain.
- Refractory neuropathic pain resulting from herpes zoster may be treated with a block of the relevant thoracic (or other affected) nerve.

### 12.4 Manage acute pain in emergency or acute conditions

Acute pain is usually due to an acute injury or illness or a complicating infection or problem during a chronic illness. Acute pain often is associated with other symptoms, such as sweating, tachycardia, tachypnoea, pupil dilation and anxiety.

- When administering strong analgesics, use a stepwise approach.
- Direct appropriate treatment at the acute injury site or illness while managing associated symptoms such as pain.
- Analgesics need to be provided regularly in both acute and chronic pain and may need to be supplemented with pain medications as needed. For acute pain, patients should be assessed at regular intervals, to evaluate their response and whether repeat doses are required.
- Treat pain early as it will be managed more effectively and often with lower doses of medication.
- Morphine remains the medicine of choice in the management of moderate-to-severe acute pain.
- IM or IV administration of analgesics is more often required in acute pain.

#### Manage acute severe pain

- First use Quick Check and stabilize the circulation.
- Treat the underlying cause of the pain: e.g. immobilize a broken leg.
- IV morphine should be given cautiously in patients in shock as it can lower a patient’s blood pressure. Rather give small, titrated doses of pain medication and reassess regularly.
Morphine dosing is weight-based. The usual dose of morphine is 0.1 mg/kg IV and can be carefully titrated. Maximum single dose should be 8–10 mg IV.

Morphine can depress the respiratory rate. Naloxone reverses the effects of morphine. When administering morphine, it is important to have naloxone available in case the patient is over-sedated.

Monitor responsiveness, airway, respiratory rate, BP and pulse every 15 minutes when administering morphine IV in an acute situation.

- Record in notes: If systolic BP <100 or falls more than 20 mm Hg from previous reading or SpO₂ <90%; or respiratory rate <10/minute, do Quick Check, determine if patient needs more fluids, and give naloxone.
- If continuous monitoring is not possible, give bolus dose, with frequent regular monitoring. IM and subcutaneous dosing are reasonable alternatives for administration, but the patient must be closely observed for delayed absorption.

Assess and monitor acute pain regularly - use the pain scale (see Section 12.1). Once the underlying cause has been treated, the level of pain and the need for analgesia may decrease rapidly.

**Morphine IV infusion for refractory severe acute pain**

- For patients continuing to experience severe pain in the hospital, morphine can be given by carefully monitored IV drip. A strictly controlled rate, with a metal gate-clamp in the IV rather than a roller device (which can become loose), must be guaranteed and closely monitored.
- A bolus dose of 2 mg is given initially, followed by a continuous infusion at 1 mg/hour.
  - The infusion may be titrated hourly as needed for pain control, usually between 5–35 mg/hour.
  - The infusion should be slowed if the patient begins to show signs of somnolence and stopped if there is respiratory depression (RR <16) or hypotension (SBP <90).
- Patients with respiratory depression unresponsive to cessation of the morphine infusion may require naloxone for reversal of opioid overdose.
  - If systolic BP <90 or falls more than 20 mmHg, SpO₂ <90, or respiratory rate <10/minute, do Quick Check, determine if the patient needs more fluids, and give naloxone.
  - Naloxone should be given with great caution, as it will reverse analgesia. See QC p. 27 for acute reversal.
  - See Section 3.6.1 Opioid intoxication or overdose for more on the management of opioid overdose.

**Clinical examples of acute pain and initial analgesia**

Severe “undifferentiated pain” may require morphine for initial management, e.g:

- renal colic from kidney stone
- acute nerve compression
- acute gangrene
- trauma
- perforated peptic ulcer
- sickle cell crisis
- burns
- biliary colic
- pancreatitis.

Pain from the following is usually moderate; give paracetamol with codeine or a NSAID – the latter for both pain control and its anti-inflammatory effects:

- sprained ankle
- broken rib.
Pain from the following is usually mild. Give paracetamol. A NSAID is an option for treatment of mild pain. Do not include aspirin for treatment of mild pain if there is evidence of a viral syndrome or influenza-like illness.

- influenza
- simple headache.

### 12.5 Symptom management: cough or difficulty breathing

#### Difficulty breathing or breathlessness

Use Section 8.2 to first decide if the patient has pneumonia or tuberculosis. Specific advice for COVID-19 is included below. In addition to specific antimicrobial management (antibiotics/antiviral for pneumonia; sputum examination if suspect TB and TB treatment as indicated), do the following:

- **Treat hypoxaemia**
  - If there is hypoxaemia, O₂ can be given continuously in hospital and, depending on availability and affordability of concentrators or O₂ cylinders, at home with training of the patient and family members. If oxygen saturation is normal, there is no evidence for the use of oxygen therapy for breathlessness.

- **Control bronchospasm**
  - Give bronchodilators by a metered-dose inhaler (MDI) with spacer or by nebulizer (MDI preferred with COVID-19 to reduce risk of aerosolization). In terminal care, stop the use of bronchodilators when the patient is not able to use them anymore or has very shallow or laboured breathing.
  - Consider steroids (see Section 3.2).

- **Relieve excessive sputum**
  - If there is a cough with thick sputum try to give steam inhalation or nebulized normal saline 2.5–5 ml four times daily to help loosen secretions so that it is easier for the patient to expectorate.
  - If more than 30 ml/day, try forced expiratory technique (“huffing”) with postural drainage.

If a patient is terminal and is dying from COPD, lung cancer, drug-resistant tuberculosis, or any other terminal pulmonary problem, there are additional measures to relieve dyspnoea.

- For a bothersome cough not responding to codeine, give oral morphine 2.5–5 mg every four hours if required.
- In end-of-life care a small dose of morphine can reduce dyspnoea. Monitor closely but do not let fears of respiratory depression prevent the trying of this drug. Titrate the dose of the opioid to its effect in relieving dyspnoea using a dyspnoea scale or physical signs of dyspnoea.
  - for a patient not on morphine for pain, start with 1–2 mg 4–6 hourly,
  - for a patient already on morphine, increase the dose by 25%. If this does not work, increase by another 25%.
- If there is heart failure or excess fluid with pitting oedema, give furosemide 40–80 mg orally. Refer if no improvement.
- Patients with tuberculosis continue treatment even if terminal. The decision to continue or stop treatment must be a team decision, with the patient having full information on toxicity, resources to continue treatment, and quality-of-life issues. The concept of treatment failure should not be a consideration for stopping treatment, as patients still do convert after years of treatment. See Section 12.11.
• Infection control precautions to protect the family, health workers and other patients are important (see Section 6).

Difficulty in breathing/breathlessness in COVID-19

• Chest tightness and difficulty in breathing are a major part of severe Covid-19 infection. Breathlessness can be helped by oxygen if the patient is hypoxaemic. It is important to monitor SpO2 in these patients. If patient has a normal SpO2 but feels breathless, some techniques may help, e.g. pursed lip breathing or square box breathing.13,14

Square box breathing:
Step 1 – Slowly inhale (count 1-2-3-4) in through nose with focus
Step 2 – Hold breath (count 1-2-3-4)
Step 3 – Slowly exhale (count 4-3-2-1) out through mouth with focus
Step 4 – Hold breath again (count 1-2-3-4) and repeat.

Additional measures include:
• Keeping the face cool with a face cloth dipped in cold water wiped around the mouth, nose and forehead can soothe.
• A window open to keep the room air cool can help. Avoid using fans and nebulizers as they blow the virus around the room.
• Advise patient to sit propped up and lean forward to make breathing easier (see illustrations below). High supported sitting can help with breathlessness, optimize oxygenation and reduce energy expenditure.13 advise patients on self-proning and breathing exercises.

For severe breathlessness a small dose of morphine 1–2 mg can be given by mouth up to every four hours or more often as needed until the breathlessness is less distressing. Monitor for sedation and reduction in respiratory drive.

Make sure these pharmacological palliative treatments do not interfere or contradict specific treatments for severe pneumonia with severe respiratory distress. For example, too much sedation may interfere with cooperation in proning the awake patient.

Additional pharmacological management if unable to swallow or if symptoms are not responsive to previously mentioned measures:  
- morphine 1.5–2.5 mg or fentanyl 25 mcg subcut/IV every two hours
- midazolam 2.5 mg subcutaneous/IV every four hours or lorazepam 0.5–1 mg sublingually every eight hours (if associated agitation or distress)
- if continuous infusion is available start continuous infusion of morphine 15 mg or fentanyl 100 mcg over 24 hours – subcutaneous or IV infusion
- midazolam can be added, 10–30 mg over 24 hours.

**Oropharyngeal and respiratory secretions**
- Noisy breathing is caused by secretions. Although the noise is upsetting, it does not cause pain or make the breathlessness worse. Sometimes fairly simple adjustments of posture and position make a big difference to noisy breathing.
- Decrease volume of fluid intake.
- Advise on active cycle of breathing technique (ACBT) – involve a respiratory physiotherapy team where possible, include a cycle of breathing control, thoracic expansion exercise (deep breathing), and huffing (forced expiratory technique, and then repeat).
- Gravity-assisted drainage – positioning patient to allow gravity to assist in draining mucus from the lung periphery.

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• Give gentle closed suctioning if absolutely necessary.
• Consider pharmacological management, if needed:
  • furosemide orally or intravenously if fluid overload suspected,
  • glycopyrolate 200–400 mcg every two to four hours intravenously or subcutaneously,
  • hyoscine butylbromide 20–40 mg every 2–4 hours (intravenously or subcutaneously),
  • atropine 1% ophthalmic eye drops 1–2 drops sublingually every four hours.

All interventions inducing cough for airway clearance are potentially aerosol-generating procedures -- add airborne precautions; also single-patient-use disposable options are recommended (e.g. positive expiratory pressure device)

Cough

• Patients with comorbidities, frailty, impaired immunity or reduced ability to cough and clear secretions are more likely to develop severe pneumonia and this can lead to respiratory failure and death. Pay attention to positioning and avoid having the patient lying on their back as this makes coughing ineffective.
• Use simple measures first e.g. a teaspoon of honey, anti-tussives, simple menthol lozenges may help to soothe an irritant cough.
• For viscous (thick) secretions with a strong cough use steam inhalations or nebulized normal saline 2.5–5ml four times daily can help to loosen secretions and make it easier for the patient to expectorate. Use appropriate PPE if needed for nebulization.
• Use stronger measures to suppress the cough if it is distressing:
  o codeine linctus 15 mg/5 ml or codeine phosphate tablets 15 mg and 30 mg tablets,
    Give 15–30 mg every four hours as required, up to four doses in 24 hours increase as needed to maximum of 240 mg in 24 hours,
  o morphine sulphate oral solution (MST) 10 mg/5 ml. Give 2.5–5 mg every four hours as needed, increase to 5–10 mg every four hours as needed. If unable to swallow morphine sulphate 1.25–2.5 mg can be given subcutaneous/IV every four hours as needed,
    If the patient is already taking regular morphine, increase their usual dose by a third.
• Avoid cough suppressants in chronic bronchitis and bronchiectasis as this can cause sputum retention and secondary infection.

12.6 Symptom management: fever

Fever

Fever can be a predominant symptom of many infectious diseases, including COVID-19 disease.
• Ensure adequate hydration and keep the patient cool. The use of fans is not encouraged due to the risk of aerosolization.
• When needed use paracetamol, 500–1000 mg orally every six hours for fever. Continue only while the symptoms of fever and the other symptoms are present.

17 NICE. COVID-19 rapid guideline: Managing symptoms (including at the end of life) in the community. 3 April 2020. Available at www.nice.org.uk/guidance/ng163

12 – 16 Symptom management
• If using a non-steroidal anti-inflammatory drug, apply the lowest effective dose for the shortest period needed to control symptoms.

12.7 Symptom management: agitation/anxiety

Aim to control agitation with non-pharmacological measures such as counselling the patient, showing them familiar faces where possible, adequate lighting, orienting them to time and place. Ensure that any sensory deprivation is minimized, e.g. glasses, hearing aids.

When pharmacological measures are required aim to have minimum sedation. Exclude reversible causes using Section 3.4 such as infection, electrolyte abnormalities, constipation, urinary retention, and substance withdrawal.

When needed, assess orientation and consider the use of drug management:

- **If disoriented:**
  - use haloperidol – 1 mg slowly IV or subcut, 1.5 mg orally. Repeat hourly up to maximum dose of 5 mg,
  - if persistent add Midazolam 1 mg slow IV or subcut or start an infusion of midazolam 10 mg with haloperidol 5 mg over 24 hours.

- **If oriented (i.e. anxiety, fear, panic)**
  - and able to swallow give lorazepam 0.5–1 mg orally or sublingually twice daily, alternatively clonazepam 0.25–0.5 mg twice daily;
  - if not able to swallow, give midazolam 2.5–5 mg bolus intramuscularly as needed;
  - if refractory, start a midazolam infusion 10 mg in 24 hours, and add haloperidol 5 mg in 24 hours if still no response.

Note: benzodiazepines can be used with caution in patients with COVID-19. These medicines can be sedating. For patients with respiratory symptoms, choose non-benzodiazepine sedating drugs first, where possible; if not effective or not possible, choose short-acting drugs (lorazepam/midazolam) at lowest dose for the shortest period of time. Monitor respiratory status.

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Adapted from

12.8 Symptom management: hiccup
Assess patient for possible cause of hiccup, such as ascites, organomegaly, or metabolic disorders including uraemia.

Treatment
- Metoclopramide 10 mg every eight hours in combination with an antacid and antiflatulant, e.g. aluminium hydroxide.
- Haloperidol 1.5 mg three times daily for non-responding hiccups.
- If ascites, relieve pressure with abdominal paracentesis if appropriate (see Section 7.4.5).

12.9 Symptom management: trouble sleeping
Consider the following reasons:
- Pain, anxiety, depression, breathlessness (asthma, PND, COVID-19), drug withdrawal and nocturia.

’People with COVID-19 are at higher risk for sleep problems owing to acute stress responses, as well as additional reasons for those who are hospitalized, such as environmental factors, invasive medical procedures (e.g. mechanical ventilation), and the frequent combination of multiple medications possibly disrupting sleep patterns’.

Treatment
- Address the underlying cause of insomnia.
- Psychosocial support and calming communication if stressed or anxious.
- Evaluate medicine regimen.
- Address breathlessness — see section 12.5
- Address pain — give analgesia
- Reduce noise where possible.
- Help block light at night.
- If patient is getting up to urinate at night, consider the cause of the nocturia and treat it.
- Sleep hygiene – avoid caffeine-containing beverages, nicotine and alcohol in the late afternoon and at night.
- Diazepam 5 mg can be used but only in the short term (less than four weeks).

12.10 Manage other symptoms using other sections of this manual

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>8.1</td>
</tr>
<tr>
<td>Peripheral oedema, swelling of limbs</td>
<td>10.3</td>
</tr>
<tr>
<td>Depression</td>
<td>10.6</td>
</tr>
<tr>
<td>Anxiety and agitation</td>
<td>10.7</td>
</tr>
<tr>
<td>Pain on swallowing</td>
<td>10.5b</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>10.13</td>
</tr>
<tr>
<td>Dementia or delirium</td>
<td>3.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8.3</td>
</tr>
<tr>
<td>Incontinence of stool and urine</td>
<td>IMAI-IMCI Palliative care guideline module</td>
</tr>
<tr>
<td>Constipation</td>
<td>10.5d</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>10.5c</td>
</tr>
<tr>
<td>Itching</td>
<td>10.1</td>
</tr>
<tr>
<td>Bedsores</td>
<td>10.1</td>
</tr>
</tbody>
</table>

12.11 Preventive interventions for all patients

This table includes a set of safe, inexpensive medicines, equipment and basic social supports which can prevent and relieve suffering of all types.² (It was developed as a minimum package that should be accessible by anyone affected by a health emergency or crisis.)

### Essential package of palliative care for humanitarian emergencies and crises

| Interventions | Inputs | Equipment | Human resources
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medicines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention and relief of **pain or other physical suffering,**⁴ acute or chronic</td>
<td>Amitriptyline, oral Bisacodyl (senna), oral Dexamethasone, oral and injectable Diazepam, oral and injectable Diphenhydramine (chlorpheniramine, cyclizine, or dimenhydrinate), oral and injectable Flucloxacilone, oral Fluoxetine, oral Furosemide, oral and injectable Haloperidol, oral and injectable Hyoscine butylbromide, oral and injectable Ibuprofen (naproxen, diclofenac, or meloxicam), oral Lactulose (sorbitol or polyethylene glycol), oral Loperamide, oral Metoclopramide, oral and injectable Metronidazole, oral, to be crushed for topical use Morphine, oral immediate release and injectable Naloxone, injectable Omeprazole, oral Ondansetron, oral and injectable Oxygen Paracetamol, oral Petroleum jelly</td>
<td>Pressure-reducing mattresses Nasogastric drainage and feeding tubes Urinary catheters Opioid lock boxes Flashlights with rechargeable batteries (if no access to electricity) Adult diapers or cotton and plastic</td>
<td>Doctors (with basic palliative care training) Nurses (with basic palliative care training) CHWs (if available)</td>
</tr>
<tr>
<td>Prevention and relief of **psychological suffering,**⁵ acute or chronic</td>
<td>Amitriptyline, oral Dexamethasone, oral and injectable Diazepam, oral and injectable Diphenhydramine (chlorpheniramine, cyclizine or dimenhydrinate), oral and injectable Fluoxetine, oral Haloperidol, oral and injectable Lactulose (sorbitol or polyethylene glycol), oral.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention and relief of <strong>social suffering,</strong> acute or chronic</td>
<td></td>
<td></td>
<td>Social workers CHWs (if available)</td>
</tr>
<tr>
<td>Prevention and relief of <strong>spiritual suffering.</strong></td>
<td></td>
<td></td>
<td>Local spiritual counsellors.</td>
</tr>
</tbody>
</table>

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⁴ Based on WHO Model List of Essential Medicines 2015 (88). Acceptable alternative medicines are in parentheses: ( )

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Oral care

Instruct all patients in oral care:

- Use a soft toothbrush to gently brush teeth, tongue, palate and gums to remove debris.
- Use diluted sodium bicarbonate (baking soda) or toothpaste.
- Rinse mouth with diluted salt water after eating and at bedtime (usually 3–4 times daily).
- Petroleum jelly can be used to moisten the lips when dry.

<table>
<thead>
<tr>
<th>Treat dry mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>review medications</td>
</tr>
<tr>
<td>offer sips of drinks</td>
</tr>
<tr>
<td>moisten mouth regularly with water</td>
</tr>
<tr>
<td>let the sick person suck on fruits if able</td>
</tr>
</tbody>
</table>

Preventing bedsores (see also Section 10.1 Skin problems)

Remember that prevention of bedsores is better than cure.

- Help the bedridden patient to sit on a chair from time to time.
- Lift the patient up in the bed (do not drag, as this can break the skin).
- Encourage patients to move their bodies on the bed if able.
- Change the patient’s position on the bed often, if possible every one or two hours. Use pillows, cushions or wedges made from a cut-up foam mattress to support the patient in the position.
- Keep the bedding clean and dry.
- Look for damaged skin (change of colour) on pressure points (the back, shoulders and hips) every day.
- Place extra soft material, such as a soft cotton towel, under the patient.

Preventing pain, stiffness and contractures in muscles, and moving the bedridden patient

- Check range of motion (RoM); move limbs gently.
- Give diazepam if spasms or very spastic.
- Check RoM in the key seven joints on both sides (wrist, knee, elbow, ankle, shoulder, hip and neck).
- Encourage mobilization.
- If patient is immobile, encourage simple range-of-motion exercises (this can also be done at home):
  - exercise limbs and joints on both sides at least twice daily,
  - protect the joint by holding the limb above and below it and supporting as much as possible,
  - bend, straighten and move joints as far as they normally go; be gentle and move slowly, without causing pain,
- Move the bedridden patient safely:  
  - It is better to have two people to safely move a patient up in bed. Using a slide sheet helps to prevent injury and friction, which can scrape or tear skin. A slide sheet can be made out folding a bed sheet in half.
  - First tell the patient what you are doing. The two people moving the patient should stand on opposite sides of the bed.
  - If able, raise the bed so as to reduce strain on your back. Keep bed flat.
  - Roll patient to one side, then place half rolled up, slide sheet against the person’s back.
  - Roll the patient onto the sheet and spread the sheet flat. Make sure the head, shoulders and hips are on the sheet.
  - Grab the sheet at the upper back and hips on the side and then on the count of three with your partner, pull up towards the head of the bed. When done, remove the slide sheet.
  - Transfer from bed to chair:  

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21 Adapted from Mount Sinai Hospital. Available at https://www.mountsinai.org/health-library/selfcare-instructions/pulling-a-patient-up-in-bed
Preventing constipation

- If patient is on opiates – prevent opioid-induced constipation by giving prophylactic laxative therapy e.g. stimulant (senna- 2 tab at bedtime) and daily (or as needed) osmotic laxative polyethylene glycol (PEG). Docusate can be added to soften stools.
- Encourage fluid intake, ambulation and soluble dietary fiber if patient is able.
### Special considerations in palliative care for PLHIV

PLHIV have physical, spiritual, social and emotional care needs. While these needs are substantially altered on effective ART, the need for good palliative care including symptom management and end-of-life care is important.

Pain continues to be a problem in people with HIV infection, compromising overall quality of life, both physically and psychologically. Pain may be due to many different reasons: OIs, malignancies, direct effects of the virus such as distal sensory polyneuropathy and HIV-related myopathy; medication side-effects, IRIS, nonspecific manifestations of late-stage illness, and other, non-HIV-related causes. Identify and treat the underlying cause where possible while at the same time controlling the pain.

Illness in PLHIV and symptoms can be unpredictable. The course of the illness can change. Treatment of infection often improves the patient's condition and results in reduction of pain and other symptoms.

Effective symptom management of ARV therapy side-effects is important to support adherence and respond to serious adverse reactions.

### Special consideration in palliative care for TB patients

Cough, fever, difficulty breathing, and chronic haemoptysis caused by TB may continue for several months after starting TB and MDR-TB therapy. Symptomatic management is summarized above as well as in other Sections of this manual.

Drug-resistant TB (DR-TB) treatment requires adequate support measures to achieve a high level of adherence. These measures include disease education, DOT, socioeconomic support, emotional support, and effective management of adverse effects. The long duration of complicated treatment regimens and the likelihood of adverse effects of second-line anti-TB drugs, particularly when combined with ART treatment, require close attention to management and place demands on the health worker’s skill. It is rarely necessary to stop antituberculosis drugs completely. Ancillary drugs for the management of adverse effects should be available to the patient, without charge for patients with limited financial resources. See specific guidance on managing these adverse effects. The clinical team must communicate closely with the patient and treatment supporter to address adverse effects.

In a very small number of patients treatment of DR-TB fails and all options are exhausted, and a decision is made to suspend therapy and provide only supportive care. The process to stop therapy would usually be made after a number of visits over several weeks, and is made after discussions with the patient. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so and agrees with the supportive care that will be offered. It is advisable to counsel the family.

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**Treat constipation**
- Give laxative. Increase laxative dose (senna or PEG) if patient already on prophylactic laxative treatment unless patient develops abdominal cramping. Once diarrhoea occurs, the dose can be lowered (if on opiates) or stopped.
- If patient has not passed stool in several days, give enema. Do rectal exam for impaction; manual disimpaction may be needed.
Stopping DR-TB treatment is often because the drugs used in DR-TB treatment have significant adverse effects and continuing them while the treatment is failing may cause additional suffering.

A second reason to stop therapy is that it is not working and hence becomes a public health concern. Continuing a treatment that is failing can amplify resistance in the patient’s strain, resulting in highly resistant strains, such as XDR-TB, which may subsequently infect others.

The patient who is taken off treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued, including both environmental controls and personal protection. Health workers and family members at high risk who are providing close patient care should use N95 particulate respirators (N95 masks) over nose and mouth and other infection control interventions when caring for infectious TB patients, particularly in the presence of MDR-TB and XDR-TB (see Section 6).

### 12.14 Special considerations in palliative care for cancer

Cancer patients need symptom management during treatment and at a later stage end-of-life care. In limited-resource countries many patients present late and there is limited access to definitive cancer treatment services, and many patients will only have access to palliative care. Patients with cancer suffer with problems similar to those commonly encountered in other chronic illnesses including HIV and AIDS. HIV infection also predisposes to several cancers. Pain, dyspnoea, wasting, confusional states, psychosocial distress and other debilitating symptoms commonly affect these patients. The principles of palliative care and specific interventions can be applied to the wide range of chronic, potentially fatal disorders.

### 12.15 Special considerations in palliative care for COVID-19

*Beyond surging demand in addition to pre-existing resource limitations, the pandemic has also brought novel challenges to ensuring quality end-of-life care. Most important and always, good care involves having a clear understanding of patients’ goals, values and preferences for treatment.*

This pandemic has shown multiple examples of difficulties in implementing adequate palliative care due to overburdened health systems during COVID-19 surges, restrictions on face-to-face clinical interactions, rapid physiological decline among patients with COVID-19, restrictive visitation rules, insufficient access to staffing, bed space and medications, and equipment. Services at home have also been affected due to shortages in personal protective equipment, medicines and staffing support, and overwhelmed community services.

Quality palliative care services should be integrated with curative treatment in patients with COVID-19. Each institution should include palliative care considerations in hospital planning for COVID-19 treatment. This includes adequately triaging patients based on medical need and goals of care, capacity-building for clinicians in symptom control and management of end-of-life

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conversation, access to essential medicines, multidisciplinary team (e.g. spiritual care providers, social workers, counsellors), and measures to support communication between the patient and family members who may have restrictive visitation (or not at all) due to infection prevention and control precautions related to COVID-19. See WHO steps on “How to practice palliative care”:1

1) Identify if patients have an advance care plan in place, e.g. do they want invasive mechanical ventilation?
   a. Support communication – smartphones or tablets may be needed for family communication while patients are on isolation.

2) Discuss goals of care and care plan as early as possible with patient, family members, and caregivers – cure, maintenance of current level health, comfort? Also discuss location of care – home, hospital, hospice:
   a. consider pharmacological and non-pharmacological interventions for symptom control;
   b. support caregivers through telemedicine and regular follow-up if patient goes home;
   c. support tangible needs as able if patient goes home – medical equipment, food, medications; this may be mobilized through community-based or faith-based organizations;
   d. incorporate spiritual care – refer patient to spiritual provider with permission;
   e. consider alternate care sites or hotlines staffed by palliative care teams to support patients at home or at other sites.22

3) Document goals of care in patient records – this allows for the whole team to be aware of the patient’s wishes.

Similar consensus recommendations for palliative care in patients with COVID-19 were developed through a task force of experts from 15 countries using ‘Convergence of Opinion on Recommendations and Evidence (CORE)’ methodology:23

1. Advance care planning (ACP; discussion of goals and preferences for future medical treatment and care) should be routinely performed or reviewed by clinicians with patients and their loved ones upon diagnosis of serious COVID-19.
2. ACP should be re-evaluated prior to discharge of recovered COVID-19 patients from hospital.
3. Patients presenting with serious COVID-19 and distressing breathlessness despite optimal treatment of underlying causes should be given low-dose opioids for the palliative treatment of breathlessness. Note: Data on effectiveness for breathlessness in COVID-19 are lacking.
4. Patients presenting with serious COVID-19 and distressing breathlessness despite optimal treatment of underlying causes should be given benzodiazepines for the

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12.16 End-of-life care

End-of-life care refers to care when death is imminent. Its duration usually varies from a few hours to several weeks or longer. In some cases, this may be obvious to the health workers, but in other cases even experienced clinicians may be uncertain.

Patients often express a wish to die at home, but this is not always possible. End-of-life care may be provided in the hospital, a hospice-type facility or in the home. Where possible, respect the wishes of the patient and family. Having a patient die at home can be difficult for the family. Caregivers and continued support from the clinical team, and hospice-like care should be offered to families who do choose to keep the patient at home. See IMAI-IMCI Palliative care: symptom management and end-of-life guideline module.³

Follow the recommendations in this Section.
- Manage pain, cough or difficult breathing and other symptoms. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- Nutrition and hydration.
  - Nutrition: Small and frequent meals are often best for a person at the end of life. It should be accepted that oral intake will reduce as the patient’s condition deteriorates, their appetite wanes and eating and drinking needs more efforts. The
focus of nutrition should be on patient comfort and not maintaining a normal nutritional intake as this will not change the natural illness trajectory. As patients become weaker, they often require assistance to eat. Nausea and vomiting, and any other conditions that interfere with nutritional support, should be treated. If a patient loses their ability to swallow safely, discuss the risk versus benefit of continued oral feeding with the patient and family. Compare the comfort that feeding brings and the risk of aspiration. The current evidence of the risks and benefits of artificial feeding and nutrition are not clear-cut and decisions should be made on an case-by-case basis. Artificial feeding should be discussed with the patient and family. In patients who are at the end of life, artificial feeding will not change this and it is important to communicate this to patients and families. If the burdens and risks to the patient outweigh the benefits then it will not usually be appropriate to start or continue artificial feeding.

- **Hydration:** Consider hydration as separate from nutrition, and again, the risks and benefits of artificial hydration should be discussed with the patient and family.

- **Continue regular medical visits.**
- **Continue ancillary medicines, such as those for depression and anxiety.**
- **Treat fever if the patient is uncomfortable.** Fever treatment is not always necessary at the end of life.
- **Continue preventive measures; oral care, prevention of bedsores, bathing, and prevention of muscle contractures are indicated in all patients.** Regular, scheduled movement of the bedridden patient is very important.
- **Continue infection control measures when needed.** For example, the patient who is taken off antituberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures are very important and should be continued.

### Bereavement care

Support for people who are bereaved is an important aspect of palliative care. This support may be provided at the district level, but it is more likely that the support will be provided at the community level.

- **It is important that the health worker recognizes the need for bereavement support and can refer people for support where necessary.**
- **After a person’s death, try to support the family with regard to their wishes for disposal of the body and funeral rites.**
- **Bereavement support is not only needed for the family but also for the patients prior to death.** The caregiver needs to give them the opportunity to talk about what is happening to them if they want to; but be careful not force this. The patient may need some practical help and support, e.g. helping them to make a will, planning for the care of their children, etc. Wherever possible, respect the patient’s wishes.
- **Support for the family may include:** acknowledging their loss and sharing memories as appropriate; linkage with other organizations that may provide support; visiting when needed; counselling on expected responses to grief; encouraging rituals as culturally and religiously appropriate and encouraging the family members to care for themselves.
- **It is important to recognize that the health worker may come into contact with many people who are dying and are bereaved.** It is important for the health worker to care for themselves and grieve as appropriate, while not letting their grief get in the way of care for the patient or family.

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For further information, please contact:
Infectious Hazards Management (IHM)
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WHO Regional Office for South-East Asia (SEARO)
https://www.who.int/southeastasia/outbreaks-and-emergencies/infectious-hazard-management