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CHAPTER

## 17 Multisystem diseases and infections

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### Abstract

Differential diagnosis of fevers?, Fever without localizing features?, Sepsis?, Cancer?, General rules of cancer management?, Rheumatoid arthritis?, Osteoarthritis?, Systemic lupus erythematosus?, Typhoid and paratyphoid fevers?, Rickettsioses?, Bartonella?, Ehrlichia?, Coxiella?, Relapsing fevers?, Leptospirosis?, Brucellosis?, Plague?, Melioidosis?, Anthrax?, African trypanosomiasis?, American trypanosomiasis?, Visceral leishmaniasis (kala-azar)?, Infectious mononucleosis?, Measles?, Arboviruses and zoonotic haemorrhagic fever viruses , Ebola and Marburg virus diseases, Crimean-Congo haemorrhagic fever, Rift Valley fever, Lassa fever, Hantavirus infections, Severe fever and thrombocytopenia, Zika virus, Japanese encephalitis , Dengue virus, Yellow fever, West Nile virus , Kyasanur Forest Disease, Chikungunya, Ross River fever, O'nyong nyong

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## Differential diagnosis of fevers

Fever is a common presentation of infection (Tables 17.1 and 17.2), and, less commonly, inflammatory conditions or malignancy.

General principles of fever include:

- Fever pattern and intensity does not reliably distinguish bacterial, viral, parasitic, fungal, or non-infectious causes of fever.
- Fever is often intermittent; it may be absent at any particular point in time including in the morning, or if antipyretics (e.g. paracetamol) have been taken.
- Patients on steroids, regular antipyretics, or who are immunocompromised or neonates (0–27d) may have little or no fever.
- Rigors (uncontrollable chills/shivering) are always highly significant—most commonly caused by malaria, bacterial sepsis, or severe viral infection (e.g. influenza, dengue, Lassa fever).
- Fever may trigger febrile convulsions in children aged 6mths–5yrs (should be a diagnosis of exclusion—see 🔄 p. 16).
- Drenching sweats, especially at night, are highly significant, but can occur with any cause of fever.
- Prolonged fever → weight loss due to ↓ appetite and catabolic state.

## History and examination

Perform a detailed history and physical examination, considering:

- What is the age of the patient?
- Where is the site of infection?
- Which are the likely infecting organisms?
- Is this presentation unusual? Has it become more common recently? Might an epidemic be occurring?
- Is the patient immunocompromised? If so, consider possible causes for both immunocompetent and immunocompromised individuals.
- Severe malnutrition and extremes of age are associated with poorer immune responses which may → more subtle features of infection.
- Serious infections such as bacterial sepsis and malaria may have non-specific ‘false localizing’ symptoms, such as headache, breathlessness, vomiting, or diarrhoea.
- Viral (adenovirus, influenza) and ‘atypical’ bacterial (mycoplasma pneumoniae, pertussis, syphilis, TB) may be indistinguishable from ‘classic’ bacterial infection, especially in infants and young children.
- Carefully investigate fever in infants <3mths old; exclude meningitis with LP (fever may be only clinical sign in early meningitis).
- In the presence of localizing features, investigations are targeted towards the presumed cause, including specimens (blood, urine, CSF, etc.) for microscopy and culture, if available.
- Empiric antimicrobial treatment may be started based on a clinical diagnosis and the likely infecting organisms. Consult local guidelines for choosing antibiotics, if available.
- Be aware of risk factors (e.g. HIV, malnutrition) that ↑ risk of both severe infection and death.

**Table 17.1** Common infections with localizing features

Infection syndrome	Common symptoms
Pneumonia	Breathlessness, cough, sputum, pleurisy
Pulmonary TB	Prolonged cough, haemoptysis
UTI	Urinary frequency, dysuria, haematuria, loin pain
Gastroenteritis	Vomiting and watery diarrhoea
Infective enteritis	Watery diarrhoea, central abdominal pain
Colitis/dysentery	Diarrhoea with blood and mucus, lower abdominal pain, tenesmus
Cellulitis	Red, hot skin
Septic arthritis	Painful, swollen joint
Osteomyelitis	Bone pain
Meningitis	Headache, confusion, neck stiffness
Streptococcal, EBV, diphtheria infection	Sore throat, exudate over tonsils/pharynx
TB lymphadenitis	Prominent cervical lymphadenopathy

**Table 17.2** Common paediatric infections by age

Age range	Common infections
Birth to 3mths	<ul style="list-style-type: none"><li>• Bacterial sepsis</li><li>• Pneumonia</li><li>• Meningitis</li><li>• UTI</li><li>• Skin/soft tissue infection</li><li>• Omphalitis</li><li>• Viral (RSV; influenza; enterovirus)</li><li>• Congenital infection (syphilis, CMV, <i>Toxoplasma</i>)</li><li>• Gastroenteritis</li></ul>
3mths–5yrs	<ul style="list-style-type: none"><li>• Sepsis</li><li>• Malaria</li><li>• Pneumonia</li><li>• Meningitis</li><li>• Gastroenteritis</li><li>• Septic arthritis</li><li>• Osteomyelitis</li><li>• Tuberculosis</li><li>• Viral (chickenpox; influenza; adenovirus; measles, mumps, roseola, parvovirus)</li></ul>
>5yrs	<ul style="list-style-type: none"><li>• Appendicitis</li></ul>
>10yrs	<ul style="list-style-type: none"><li>• Sepsis</li><li>• Meningitis</li><li>• Osteomyelitis/septic arthritis</li><li>• Cerebral abscess/subdural empyema</li></ul>

## Fever without localizing features

Fever without localizing features may be a challenging clinical problem. Investigations (Box 17.1) should include:

- Malaria test (thick and thin blood films; malaria RDT).
- FBC (incl. differential WBC and platelet count).
- Blood culture (where available).

## The importance of malaria

- Malaria is a common and important cause of fever in many settings.
- Fever is cyclical, so patient may be afebrile in a clinic.
- Asymptomatic parasitaemia is common in adults and older children in many endemic areas, due to development of partial immunity. Low-grade parasitaemia (or a +ve RDT) does not therefore prove that the fever is caused by malaria—always consider other diagnoses.
- In patients with persistent, unexplained fever, malaria testing should be repeated to exclude malaria (Chapter 2).
- Febrile patients with no visible malaria parasites (or a -ve RDT) should not routinely be treated for malaria. Exceptions may include severely ill patients unlikely to have acquired any immunity, whom it may be reasonable to treat while awaiting repeat testing.
- Artemisinins rapidly ↓ parasite counts—consider as cause of negative malaria film if prior treatment given at another health facility.
- Malaria is rare in young infants (<3mths) in endemic areas due to vertical transmission of maternal antibodies.

## Blood counts in a patient with fever

WBC and platelet count may give clues to the cause (Tables 17.3 and 17.4), although they must be considered in the context of a full and careful clinical assessment of the patient.

## Treatment of fever of unknown cause

Quite commonly, a definitive diagnosis cannot be made at the initial clinical assessment. Management then depends on the most likely diagnoses, how severely ill the patient is, and the available resources. Patients judged to be (or at risk of becoming) seriously unwell should be given 'best-guess' empirical antimicrobial therapy, using local guidelines if they exist. Consider admission to hospital if serious illness or concern. In time, diagnosis is likely to become apparent, particularly if patient is regularly reassessed.

## Persistent fever despite antimicrobial therapy

Depending on the infection site, severity, and type, fever may take hours to days to resolve. Common causes of prolonged fever include:

- Poor source control (e.g. presence of collection/abscess).
- Antimicrobial failure—infesting organism(s) not susceptible.
- Inadequate drug concentration at site of infection—consider dose, absorption, and penetration into special sites (e.g. CSF, abscesses).
- Non-adherence or inadequate provision of antibiotics.
- Non-infectious causes of fever (including drug fever).

**Table 17.3** Causes of a raised WBC (leukocytosis)—if total WBC ↑, look at the differential WBC count

Differential WBC	Common or important causes
Neutrophilia*	Bacterial infections (focal infections, sepsis, abscess, leptospirosis, borreliosis); amoebic liver abscess
Lymphocytosis	Infectious mononucleosis (EBV), pertussis, brucellosis, leukaemia
Eosinophilia	Invasive worm infections (e.g. schistosomiasis), TB

\* Bacterial infections in neonates may cause neutropenia. Neutropenia may also pre-exist in infants and young children, pre-disposing to bacterial infection (e.g. congenital neutropenia; neonatal alloimmune neutropenia).

**Table 17.4** Causes of fever with a normal WBC—if total WBC normal or low, look at the platelet count

Platelet count	Common or important causes
Normal	Viral infections (incl. the prodrome of acute viral hepatitis), typhoid, rickettsial infection Early bacterial infection
Low	Malaria, dengue, and other viral infections, HIV Bacterial sepsis (esp. Gram –ve infections)

### Box 17.1 Investigations for fever of unknown source in children <3mths

- FBC, CRP if available.
- Urine for urinalysis, microscopy/culture.
- Blood culture.
- LP (CSF for microscopy and culture).
- CXR (even in absence of clinical signs).
- Syphilis serology (e.g. VDRL) if any signs of congenital syphilis or maternal syphilis status not known.

## Sepsis

Sepsis is a syndrome of life-threatening organ dysfunction caused by infection. Bacterial infections are the commonest cause; other serious infections (e.g. falciparum malaria, Lassa fever) can cause an identical clinical syndrome. Some non-infectious insults may also → a similar clinical syndrome (e.g. pancreatitis, chemical toxins, burns, leukaemia). 2° bacterial sepsis may complicate other infections, such as malaria and severe viral infections (e.g. influenza).

## Clinical features

- Clinical features of sepsis reflect the focus of infection, the systemic inflammatory response, and organ dysfunction.
- Symptoms and signs vary considerably depending on the aetiology, focus, severity, and host factors, and may be subtle in very young children (see Box 17.2 for signs of possible serious bacterial infection), the elderly, and the immunocompromised.
- Septic shock occurs when severe sepsis leads to circulatory failure and metabolic abnormalities (e.g. ↑ lactate) despite adequate fluid resuscitation, and carries a case fatality risk of >40%.

## Sepsis definitions

Various definitions have been proposed, including presence of a systemic inflammatory response syndrome (SIRS) +/- organ dysfunction; and the Sepsis-3 definitions published by an international critical care task force.<sup>1</sup> All definitions require evidence of both infection and severe illness; all are imperfect. A pragmatic definition of sepsis is therefore 'bad (usually bacterial) infection'. Examples of severe illness ('badness') include acute confusion, hypoxia, respiratory distress, hypoperfusion, poor urine output, AKI, hepatic dysfunction, ↑ lactate, ↓ platelets, coagulopathy, etc.

## Management

Sepsis matters because early diagnosis and rapid treatment of bad infections saves lives. Key components of treatment are:

- *Prompt, appropriate antimicrobial therapy* (ideally give within 1h, after blood cultures; refer to local guidelines, if available).
- Fluid resuscitation, guided by serial clinical assessments +/- lactate.
- Blood cultures (+/- other cultures as clinically appropriate).
- Regular monitoring of vital signs and urine output.
- Supportive care as indicated (e.g. vasopressors, mechanical ventilation, haemofiltration, IV hydrocortisone).

## Box 17.2 Neonatal and infant sepsis

### Neonatal sepsis

(Also see ➡ Sick child p. 18.)

- *Early neonatal sepsis* (onset <72h of birth) is typically due to ascending infection of maternal colonizing bacteria or infection at time of delivery (e.g. group B streptococci, *Escherichia coli*).
- *Late neonatal sepsis* (onset >72h of age) is typically due to *Staphylococcus aureus* or Gram -ve bacteria acquired from the hospital or community environment.

### Sepsis in young infants

(Also see ➡ Sick child p. 18.)

- Sepsis in babies <3mths can be difficult to diagnose as clinical signs are non-specific.
- Severe infection (including bloodstream infection, pneumonia, and meningitis) may present with limited clinical signs.
- WHO recommends using signs of possible serious bacterial infection (PSBI) to identify infants at risk of serious infection, to guide community management and referral.

### PSBI criteria

- Temperature <35.5°C or >37.5°C.
- Lethargy (movement only when stimulated).
- Convulsions.
- Fast breathing (>60 breaths/min) or nasal flaring.
- Severe chest wall indrawing.
- Abdominal distension or refusal to feed.

## Cancer

Cancer is an increasingly important cause of mortality in resource-poor countries. The global burden of cancer is likely to ↑ markedly in the next 20 years and most of the ↑ will come from resource-poor countries (globally, 1 in 5 men and 1 in 6 women will develop cancer in their lifetime). Populations are expanding and ageing, tobacco consumption is ↑, diets and lifestyle are changing to a 'westernized' pattern, and prevention of certain viral-related cancers is possible. ~60% of global cancer occurs in resource-poor countries; prevention and screening programmes, stage at diagnosis, and accessibility of therapy all affect incidence of cancer and its mortality.

There is wide geographical variation in the prevalence of some cancers. Lung cancer is the most common cancer worldwide, followed by breast, colorectal, prostate, and stomach. Cervix uteri cancer (in low-resource countries esp. sub-Saharan Africa), liver, and oesophagus are also common.

Cancer requires early intervention for therapy to be effective. Bearing this in mind, basic rules include:



- Suspect cancer in any unexplained illness, esp. in the elderly.
- Attempt to make a histological or cytological diagnosis as soon as feasible.
- Once diagnosed, patients should start a planned regimen of treatment, including symptom control, within days, not weeks (Box 17.3). Tumours grow exponentially and there is no reason to delay.

## Signs and symptoms common to many forms of cancer

These may be due to a local effect of the tumour, to obstructive symptoms (e.g. biliary tract, urinary tract, airways, bowel, and lymphatics) and distant effects (e.g. paraneoplastic syndromes).

- *Pain*: due to direct effect of tumour (e.g. infiltration of nerves or compression), or metastatic spread to the bones or other organs. Any patient with unexplained persistent pain should be suspected of having malignant disease. Treatment may also → pain.
- *Weight loss*: due to involvement of GI tract (obstruction, metastatic liver involvement), anorexia, or general cachexia due to a catabolic state. This may be ↑ by treatment.
- *Tumour mass*: enables early diagnosis by biopsy (incisional or excisional); this may be part of the treatment.
- *Fever*: while normally caused by superimposed infection, fever itself may be a feature of cancers (e.g. lymphomas, renal carcinoma, and tumours metastasizing to the liver). Frequently occurs as drenching night sweats, without rigors.
- *Anaemia*: normocytic normochromic (sometimes hypochromic, microcytic if due to occult bleeding), malabsorption, or anaemia of chronic disease.
- *Hypercalcaemia*: occurs in 10–30% of cancers and is due to ↑ osteoclastic bone resorption associated with metastases to the skeleton and/or to paraneoplastic syndromes.

## Paraneoplastic syndromes

These occur in ~15% of tumours, may pre-date the actual cancer diagnosis, and are due to tumour-derived cytokines or hormones, or to a tumour-induced immune response cross-reacting with normal tissue. The range includes endocrine, neurological, dermatological, musculoskeletal, haematological, and occasionally renal and GI syndromes. Paraneoplastic symptoms often improve on therapy of the cancer but the prognosis is highly variable. Most neurological problems are due to metastases, and most endocrine problems are due to endocrine tumours themselves, not paraneoplastic syndromes.

### Box 17.3 WHO performance status

This is useful for grading the status of cancer patients and determining prognosis.

- 0 Able to carry out normal activity without restriction.
- 1 Restricted in physically strenuous activity, but walking about and able to carry out light work.
- 2 Walking about and capable of self-care, but unable to carry out any work; up and about >50% of waking hours.
- 3 Capable of self-care; confined to bed or chair >50% of waking hours.
- 4 Completely disabled; cannot carry out self-care; totally confined to bed or chair.
- 5 Death.

### Further reading

Website:  <http://www.inctr.org/about/develop.shtml>.

WorldCat

## General rules of cancer management

Whenever you see a patient with cancer, consider the following points:

### Could the patient have neutropenia?

Infection in a neutropenic patient often presents suddenly with sepsis, but without localizing features, and cultures are usually –ve. Neutropenia commonly follows chemotherapy. Bacterial flora from the mouth, digestive tract, respiratory tract, or skin are usually responsible, and indwelling lines and catheters may be the source; fungal infection is also possible. Any cancer patient who is feeling ‘run down’ and especially with a fever must have their WBC and differential count checked immediately and not be sent home. Such patients can deteriorate quickly and demise within hours.

### Could the patient have hypercalcaemia?

Unlike 1° parathyroid disease, the onset is rapid and there are none of the classical ‘stones, bones, or groans’. Instead, clinical features include: polyuria, thirst, confusion, fatigue, coma. Treatment of hypercalcaemia → marked improvement in the patient’s condition (Box 17.4).

### Is patient’s pain controlled?

See Box 17.5. It may be necessary to use morphine. The following regimen is useful:

- Give morphine 10mg 4hrly at 07.00, 11.00, hours, etc., until 23.00, at which point give a double dose so that the 03.00 dose can be missed out, offering the chance of a good night’s sleep.

- If pain breaks through, give an extra dose of morphine 10mg (even if the next 4hrly dose is only 10min away), continuing other doses as normal.
- As more breakthrough doses are required, ↑ regular 4hrly dose (e.g. to 20mg).
- If using long-acting morphine (e.g. MST<sup>®</sup> 80mg bd), take total daily dose (160mg) and divide by six doses to give size of the IV morphine dose to use for breakthroughs—here  $160/6 = \sim 25\text{mg}$ .

## Could the patient have early cord compression?

Ask:

- Can you walk?
- When was the last time you walked?
- Have you been incontinent of urine and/or faeces?
- Do a neurological exam including anal tone and sacral sensation, and check for a palpable bladder.
- Missing spinal cord compression may → patient spending their last few weeks or months in a miserable paraplegic state.

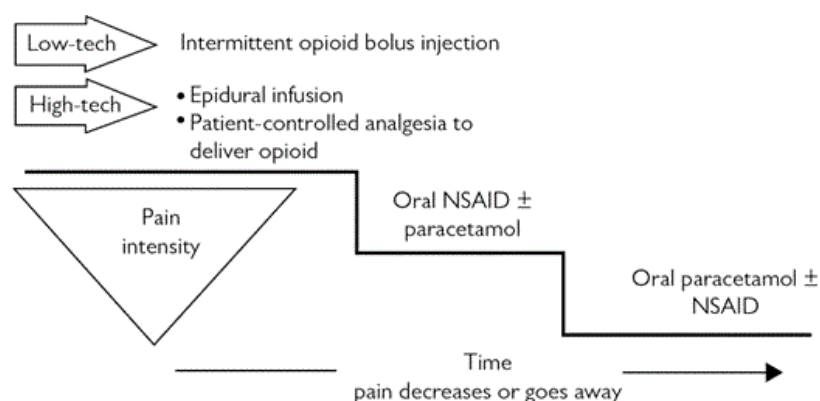
### Box 17.4 Hypercalcaemia

- Rehydrate with 0.9% saline IV (e.g. 4–6L in 24h depending on hydration status).
- Once rehydrated consider forced saline diuresis: continue 0.9% saline infusion and use IV or oral furosemide 40mg if fluid overload is a potential risk.
- IV bisphosphonate infusion (e.g. zoledronic acid, pamidronate) to ↓  $\text{Ca}^{2+}$  (max. effect at 4–7d). May need to be repeated, adjust dose with renal dysfunction. Other options exist if no response to bisphosphonates (e.g. denosumab, calcitonin). Dose varies according to serum  $\text{Ca}^{2+}$  level.
- Steroids may help in some conditions (e.g. sarcoidosis, malignancy).
- If possible, treat the underlying cause.

### Box 17.5 Management of acute pain in hospital

- Effective relief can be achieved with oral non-opioids and NSAIDs. Ibuprofen 400mg is very effective and is associated with fewer GI bleeds than some other NSAIDs. Also effective are paracetamol 1g and paracetamol combined with codeine.
- Initial management of moderate pain (e.g. in post-surgical patients) should ideally be an oral NSAID, such as ibuprofen, supplemented if necessary with paracetamol. In the elderly, paracetamol may be preferred, although it is less effective. There is no evidence that parenteral is more beneficial than oral administration.
- Opioids are the first-choice treatment for severe acute pain. Additional, often smaller doses can be given if the patient is still in pain and you are sure that all the previous dose has been delivered and absorbed. Repeat doses can be given 5min after IV injection, 1h after IM or SC injection, and 90min after an oral dose. The route of administration can be changed to achieve faster control if there is no response to the repeated dose.
- Titrate opioids against degree of pain relief. Inadequate pain control results from too little drug, too long dosing intervals, too little attention being paid to the patient, or too much reliance on rigid regimens.
- Morphine is the most appropriate opioid and it is popular among pain specialists. Its analgesia lasts a reliable 4h and is easier to titrate than opioids with a longer half-life. Set up a 4hrly regimen which prevents the occurrence of pain (see 'Is patient's pain controlled?').
- As the pain ↓, the patient can be switched to ibuprofen and paracetamol. Supplementation of morphine with an NSAID if appropriate, may allow ↓ morphine dose.
- Remember to manage possible constipation resulting from opioid use.
- See Fig. 17.1.

Fig. 17.1



Overview of the management of acute severe pain.

# Rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic, systemic inflammatory condition of unknown cause that primarily involves joints. It is associated with disability, accelerated atherosclerosis, and ↑ mortality. Lack of treatment and poor response to treatment → permanent joint destruction and deformity. Onset usually in the 3rd to 5th decade and RA affects women 2–3× more frequently than men.

## Clinical features

### Symptoms

Joint pain, swelling, and morning stiffness.

### Clinical signs

Usually chronic symmetrical joint swelling (often proximal interphalangeal (PIP), metacarpophalangeal (MCP), metatarsophalangeal (MTP), wrists, knees; affects the cervical but not the lumbar spine.

### Extra-articular disease

Anaemia of chronic disease, subcutaneous nodules (usually extensor), fatigue, pleuropericarditis, myocarditis, lymphadenopathy, nerve entrapment (e.g. carpal tunnel syndrome), mononeuritis multiplex, splenomegaly, episcleritis, scleritis, Sjögren's syndrome, interstitial lung disease, vasculitis, and coronary artery disease.

### Complications

Patients with long-standing RA and poor disease control may → irreversible joint damage and deformity, ↓ functional capacity, and atlanto-axial instability/subluxation. Premature death is mainly attributed to comorbid conditions such as atherosclerosis and infection.

## Diagnosis

Primarily by history and physical examination. There is no definitive test (Box 17.6). The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have proposed classification criteria for patients with at least one joint with definite clinical synovitis not better explained by other disease (Box 17.7).

### X-rays

Affected joints may show typical changes (soft tissue swelling, symmetric joint space narrowing, bone erosions, and deformities).

### Immunology

Rheumatoid factor (RhF) is +ve in ~80% (false +ve in 5% of healthy people, more often in old age, chronic infections, liver disease, fibrotic lung disease, and other rheumatic diseases). Anti-citrullinated peptide antibodies (ACPA) and RhF have similar sensitivity, but ACPA are more specific (95%).

## Management

- *Non-pharmacologic*: patient education, aerobic and resistance exercise, physical and occupational therapy, smoking cessation.
- *Pharmacologic*: conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) are critical to prevent permanent damage. Conventional DMARDs should be prescribed as early as possible and monitoring for drug toxicity is needed (Table 17.5); they are used alone or in combination for disease control. Most widely used are methotrexate, leflunomide, sulfasalazine, and antimalarials (chloroquine and hydroxychloroquine). A common combination is methotrexate + sulfasalazine + hydroxychloroquine. Biologic agents include anti-TNF drugs (infliximab, etanercept, adalimumab, golimumab, or certolizumab pegol), anti-CD-20 (rituximab), CTLA-4 Ig (abatacept), anti-IL-6 (tocilizumab), and anti-Janus kinase (tofacitinib—a new oral small molecule). All biologic agents and tofacitinib are extremely expensive. Rarely used DMARDs include gold salts, minocycline, cyclosporin and azathioprine. Treatment target is remission or minimal disease activity.
- *Oral NSAIDs*: they only provide symptomatic relief and do not affect outcome, and if used, should always be used with DMARDs.
- *Corticosteroids*: can be used orally in low doses (equivalent to <7.5mg of prednisolone/d) or as intra-articular injections. If steroids are used, it should be in low doses, in combination with a DMARD, and with a plan to slowly taper to lowest dose of steroid required.
- *Surgery*: for deformity, loss of function, and complications.

## Contraindications to drugs for RA

- *NSAIDs*: GI bleed, peptic ulcer; if past history of GI bleed or ulcer and NSAID required, combine with a PPI (e.g. omeprazole). Caution with hypertension, IHD.
- *Methotrexate*: pregnancy, elevated creatinine, alcohol use, liver disease, abnormal LFTs, HIV, HBV, HCV.
- *Sulfasalazine*: allergy to sulfas, G6PD deficiency.

**Box 17.7 2010 ACR/EULAR classification criteria for RA**

Classification is based on a score of at least 6 (of possible 10 points).

- Number and site of involved joints:
  - 2–10 large joints = 1 point.
  - 1–3 small joints = 2 points.
  - 4–10 small joints = 3 points.
  - >10 joints (at least 1 small joint) = 5 points.
- Serological abnormality (RhF or ACPA):
  - Low +ve RhF or ACPA = 2 points.
  - High +ve RhF or ACPA = 3 points.
- *Elevated acute phase reactant*: abnormal CRP or abnormal ESR = 1 point.
- Symptom duration 6wks = 1 point.

**Table 17.5** ACR recommendations for monitoring of drugs commonly used to treat RA

Drug (usual doses)	Monitoring
Methotrexate (15–25mg once a week)	FBC, LFTs, albumin, creatinine 2–4wks for the first 3mths or after dose increase, then every 8–12wks
Hydroxychloroquine (400mg od)	Fundoscopy and visual fields every 12mths
Sulfasalazine (max. 3g per day)	FBC 2–4wkly for for the first 3mths or after dose increase, then every 8–12wks

### Box 17.6 Differential diagnosis of RA

- *Acute viral polyarthritis*: caused by chikungunya, hepatitis B and C, rubella.
- *Parvovirus*: self-limited (weeks); history of rash, IgM viral antibodies.
- *Connective tissue diseases*: symmetric polyarthritis without joint deformities. Look for other multisystemic features (e.g. SLE).
- *Septic arthritis*: usually acute monoarthritis. Immediate joint aspirate (for Gram stain and culture) and antibiotics are required to prevent permanent joint damage.
- *Fibromyalgia*: diffuse pain without inflammation. Insomnia and fatigue are common features.
- *Reactive arthritis*: asymmetric oligoarthritis, sausage digits. Look for urethritis, conjunctivitis, and history of enteric infection.
- *Gout/pseudogout*: acute attacks. In gout, monoarthritis of the first MTP joint is common. Definitive diagnosis made by finding crystals in synovial fluid.
- Osteoarthritis (➡ [Osteoarthritis](#), p. 688).
- Paraneoplastic syndromes.
- HIV-associated arthritis.

## Osteoarthritis

Osteoarthritis (OA) is a chronic, non-inflammatory arthropathy that can be idiopathic or 2° to trauma or other conditions.

### Symptoms

Non-inflammatory joint pain (Box 17.8). The knees, hips, and distal interphalangeal (DIP) joints are most commonly affected. If unusual joints are involved (elbows, ankles, MCPs) look for 2° causes: previous trauma, haemochromatosis, Wilson's disease, or reconsider diagnosis (could be RA).

### Clinical signs

Bony swelling, crepitus.

### X-ray findings

Non-uniform joint space narrowing, osteophytes, and juxta-articular osteosclerosis.

### Diagnosis

By history and physical exam.



## Management

- Non-pharmacological: patient education (↓ weight if obese, exercise to strengthen muscles around affected joint), physical and occupational therapy.
- Analgesia: paracetamol +/- NSAID +/- codeine (avoid narcotics if possible).
- Intra-articular hyaluronans (limited evidence of efficacy).
- Intra-articular glucocorticoids.
- Topical NSAIDs.
- Duloxetine.
- Surgery including joint replacement.

### Box 17.8 Characteristics of joint pain and type of arthritis

Inflammatory, e.g. RA	Non-inflammatory, e.g. OA
• Pain ↓ with activity.	• Pain ↑ by activity.
• Worse in the morning.	• Worse at night.
• Morning stiffness >60min.	• Morning stiffness <30min.
• Systemic features: sometimes.	• Systemic features: absent.
• Soft swelling (effusion).	• Hard swelling ('bony').
• Sometimes erythema.	• No erythema.
• Sometimes warmth.	• No warmth.

## Systemic lupus erythematosus

Multisystem chronic inflammatory disease, characterized by facial rash, photosensitivity, alopecia, cytopenias, nephritis, serositis, non-erosive arthritis, CNS involvement, vasculitis, and fever. Aetiology unknown. Women affected 7–15× more often than men; peak incidence 15–40yrs of age. It is associated with premature mortality. Causes of death include infections and disease activity (particularly renal) in early phases of the disease, and atherosclerosis in the long term (➡ Connective tissue diseases, p. 560, for details on cutaneous lupus erythematosus). See Box 17.10 for markers of poor prognosis.

## Clinical features

- *General*: fever, fatigue, ↓ weight, Raynaud's phenomenon.
- *Joints*: arthralgia/arthritis (similar to RA, but usually non-erosive).
- *Mucocutaneous*: malar rash, photosensitivity, discoid lupus, purpura, alopecia, livedo reticularis, mouth ulcers.
- *Renal*: nephritic or nephrotic syndrome; renal failure.
- *Neurological*: cognitive defects, psychosis, seizures.
- *Serositis*: pleural and pericardial effusion.
- *Pulmonary*: pneumonitis, fibrosis, bronchiolitis, shrinking lung syndrome.
- *Cardiovascular*: hypertension, pericarditis, sterile (Libman–Sacks) endocarditis, myocarditis, coronary artery disease.
- *Blood*: normocytic anaemia, haemolysis (Coombs +ve), leukopenia, thrombocytopenia.
- *Thrombosis and miscarriage*: may be part of the antiphospholipid antibody syndrome.

## Laboratory tests

Several autoantibodies that react with the cell nucleus are a feature of SLE. Antinuclear antibodies (ANAs) are +ve in >98% of patients. However, ANAs are not specific; patients with other rheumatic conditions or chronic diseases, and 5% of normal subjects can have +ve ANAs. Anti-double-stranded DNA and particularly anti-Smith (anti-Sm) antibodies are more specific but less sensitive. Other autoantibodies sometimes present are anti-Ro, anti-La, anti-RNP, and antiphospholipid antibodies. Patients can have low complement levels.

## Diagnosis

The Systemic Lupus International Collaborating Clinics classification criteria for SLE are given in Box 17.9.

## Management of SLE

- *Education*: avoid sun, sunscreen, hat, long sleeves, smoking cessation, prevent atherosclerotic disease.
- *NSAIDs*: useful for musculoskeletal symptoms and serositis.
- *Antimalarials (chloroquine/hydroxychloroquine)*: effective for skin and musculoskeletal symptoms; prevent renal and CNS flares, ↓ risk of thrombosis.
- *Systemic corticosteroids*: prednisolone <0.5mg/kg for moderate disease; higher doses (1mg/kg) for severe or life-threatening disease, e.g. renal disease, pneumonitis, severe cytopenias, or CNS lupus. Consider high-dose IV methylprednisolone 1g boluses for severely ill patients.

### Box 17.9 The Systemic Lupus International Collaborating Clinics classification criteria

Four or more, at least one clinical and one immunologic criterion or biopsy proven lupus nephritis required:

#### Clinical

- Acute cutaneous lupus.
- Chronic cutaneous lupus.
- Non-scarring alopecia.
- Oral or nasal ulcers.
- Arthritis in two or more joints or pain in two more joints and morning stiffness for at least 30min.
- Serositis.
- Renal involvement: proteinuria ( $>0.5\text{g/d}$ ) or RBC casts.
- Neurological disorders: seizures, psychosis, mononeuritis multiplex\*, myelitis, peripheral or cranial neuropathy\*, or acute confusion\*.
- Haemolytic anaemia.
- Leukopenia\*.
- Lymphopenia.
- Thrombocytopenia.

#### Immunologic

- ANA.
- Anti-double-stranded DNA.
- Anti-Sm.
- Antiphospholipid.
- Low complement.
- Direct Coombs' test.

\* In the absence of other known causes.

- Corticosteroids should be tapered early according to response; combine with steroid-sparing agents to minimize steroid side effects.
- *Cyclophosphamide*: for severe SLE including proliferative lupus nephritis, vasculitis, CNS involvement, and alveolar haemorrhage.

- *Mycophenolate mofetil*: for lupus nephritis; may be as effective as cyclophosphamide with less adverse events.
- *Azathioprine*: as a steroid-sparing agent.
- *Methotrexate* or *leflunomide*: for arthritis.
- *Others*: chlorambucil, ciclosporin, and expensive biologic agents—rituximab (anti-CD20 antibody) and belimumab (antibody that binds to soluble B-lymphocyte stimulator).
- *Anticoagulation*: for the antiphospholipid syndrome.
- *Manage comorbidities*: such as hypertension, diabetes, osteoporosis, and heart disease.

### Box 17.10 Markers of poor prognosis in patients with SLE

- Diffuse proliferative renal disease.
- Hypertension.
- Male sex.
- Lower socioeconomic and education status.
- Black and Hispanic ethnicity.
- Antiphospholipid antibodies.
- Disease activity involving multiple organs.
- Renal failure.

### Further reading

Useful website:  <http://www.hopkins-arthritis.org/>.  
WorldCat

## Typhoid and paratyphoid fevers

Also called enteric fever, these conditions follow infection with *Salmonella enterica* (*S. enterica* serovar Typhi (typhoid); or *S. enterica* serovars Paratyphi A, B and occasionally C (paratyphoid)). Endemic and important causes of morbidity across developing world. Typhoid and paratyphoid A are most severe; paratyphoid B mildest, with paratyphoid C falling somewhere in between.

### Transmission

Via ingestion of food or water contaminated by infected human faeces (or occasionally, infected urine). Gastric acid is protective so ↓ acid production (e.g. due to PPIs) → ↑ susceptibility to infection. Faecal shedding occurs during acute illness, convalescence, and chronically from asymptomatic gall bladder infection.

## Pathophysiology

Following ingestion, bacteria survive gastric acid barrier, then penetrate ileal wall, probably through M-cells, and pass to mesenteric lymph nodes. Following 1° multiplication in mesenteric lymph nodes, bacteria then infect cells of the reticuloendothelial system where further multiplication occurs → 2° bacteraemia, infection of multiple organs, and clinical illness. If untreated, >10% die from overwhelming sepsis or 2° organ involvement, particularly encephalopathy, toxic myocarditis, GI haemorrhage, and/or perforation and peritonitis.

## Clinical features

Incubation period 10–20d; untreated illness typically lasts 4wks (may be longer in severe infections and shorter in mild cases).

- *1st week*: non-specific symptoms—malaise, headache, rising remitting fever, mild cough, constipation or mild diarrhoea, vomiting, abdominal pain.
- *2nd week*: patient becomes ‘toxic’ and apathetic; often mentally dull (e.g. slow response to questions) or occasionally psychotic (e.g. an agitated, febrile patient admitted to psychiatric ward); sustained high temperature with relative bradycardia; distended abdomen; enlarged liver and/or spleen; rose spots (2–4mm pink papules on central torso, fading on pressure) may transiently occur.
- *3rd week*: ↑ toxicity with persistent high temperature, delirium; weak with feeble pulse, tachypnoea +/– basal crepitations, profuse ‘pea soup’ diarrhoea. Look and listen for abdominal distension and absent bowel sounds. Neurological complications may occur (may rarely be the presenting complaint).
- *4th week*: if patient survives, fever, mental state, and abdominal distension gradually improve.
- Intestinal haemorrhage, perforation, and peritonitis may occur at any time, most commonly in weeks 2–4. If death occurs it is usually during weeks 2, 3, or 4.

## Diagnosis

Culture of bone marrow (~75% culture +ve) or blood (~50% culture +ve; concentration of bacteria in bone marrow ~10× greater than in blood). Positive stool/rectal swab cultures may indicate either acute infection, or carriage with the acute illness having another cause. The Widal and other serological tests have poor sensitivity and specificity (giving many false +ve and false –ve results) and are not recommended for diagnosis.

## Management

Early antibiotic treatment essential to prevent complications and death. Start treatment empirically if clinical suspicion strong—see Box 17.11.

- Consider dexamethasone: 3mg/kg IV stat, then 1mg/kg qds for 2d for patients with shock or ↓ consciousness. May ↓ mortality.
- Observe toxic patients carefully for signs of GI haemorrhage (manage conservatively with blood transfusion if required for significant blood loss) or peritonitis (treat with surgery).

## Relapse

5–10% of treated patients relapse after initial treatment, even if the organism is susceptible to the antimicrobials used. Relapses tend to occur within 1mth of end of treatment; are generally milder and shorter than 1° illness, but may be equally severe. Second and third relapses have been reported. Arrange follow-up if possible. Co-infection with schistosomes may result in chronic or recurrent fever, since bacteria survive within adult worms, protected from antimicrobials.

## Prevention

Good sanitation, clean water, and safe food are the most important preventative measures. Standard infection control precautions are indicated in the management of cases to prevent transmission.

Three vaccines are currently available (➡ Immunization, p. 858):

- Live attenuated oral vaccine (Ty21a) requires three doses over 5d with a booster every 5yrs. Not recommended for children <6yrs.
- Unconjugated Vi polysaccharide vaccine, given as a single dose IM; boosters every 3yrs. Not recommended for children <2yrs.
- Conjugated Vi polysaccharide vaccine, given as a single IM dose from age ≥6mths. Recommended for routine use in typhoid endemic countries and in high-risk groups.

Vaccines for paratyphoid are in development.

### Box 17.11 Treatment of typhoid

In most areas of the Americas, first- and second-line antimicrobials can be used. In many areas of Asia and Africa, infection with MDR strains (resistant to the first-line antimicrobials chloramphenicol, amoxicillin, trimethoprim–sulfamethoxazole) is common. Reduced susceptibility to fluoroquinolones (nalidixic acid resistance) and full resistance to fluoroquinolones also occur, particularly in Asia, as well as XDR strains with resistance to extended-spectrum cephalosporins.

#### First-line antimicrobials

- Chloramphenicol 1g oral qds for 14–21d.
- Amoxicillin 500mg oral tds for 14d.
- Trimethoprim–sulfamethoxazole 960mg oral bd for 14d.

#### Nalidixic acid susceptible MDR strains

- Ciprofloxacin 500–750mg oral bd for 7–10d.
- Ofloxacin 400mg oral bd for 7–10d.
- Ceftriaxone 50–80mg/kg IV od for 10–14d.
- Azithromycin 500mg oral od for 7d (not in severe disease).

#### Nalidixic acid/fluoroquinolone-resistant MDR strains

- Ceftriaxone 50–80mg/kg IV od for 10–14d.
- Azithromycin 500mg oral od for 7d (not in severe disease).

#### XDR strains resistant to extended-spectrum cephalosporins

- Azithromycin 500mg oral od for 7d (not in severe disease).
- Meropenem 1g IV every 8h for 10–14d.

#### In severe disease

- Consider adding dexamethasone 3mg/kg IV stat, then 1mg/kg qds for 2d.
- Antibiotics doses may be  $\uparrow 1.5\times$  initially and given IV.

### Public health note

- Typhoid fever vaccination may be offered to travellers (including those visiting friends and relatives) to destinations where risk of typhoid fever is high, especially if staying in endemic areas  $>1\text{mth}$  or visiting locations where antimicrobial resistant *S. enterica* serovar Typhi common.
- Routine immunization from age  $\geq 6\text{mths}$  is recommended by WHO in typhoid endemic areas and high-risk populations.

# Rickettsioses

Rickettsioses are zoonoses caused by small intracellular Gram –ve bacilli. Ticks, fleas, or mites act as vectors and/or reservoirs; the commonest is African tick bite fever.

## Spotted fever group

Usually transmitted by the bite of ixodid (hard) ticks. Dogs, rodents, and other animals are reservoirs. After 3–14d (usually 5–7d) of incubation, fever, headache, muscle pain, rash, local lymphadenopathy, and an inoculation eschar (small ulcer with black centre and red areola; see Colour Plate 22c) typically develop.

- *Rocky Mountain spotted fever (Rickettsia rickettsii, USA)*: often severe, mortality 13–25% in untreated cases. There is no eschar.
- *Boutonneuse fever or Mediterranean spotted fever (R. conorii, Africa, India, Europe, and the Middle East)*: usually less severe, but occasional fatal cases occur, esp. in elderly or when treatment has been delayed.
- *Rickettsialpox (R. akari, eastern USA and former Soviet Union)*: transmitted by mites. Rash vesicular—may be confused with chickenpox.
- *African tick bite fever (R. africae, sub-Saharan Africa)*: most common. More fully described in [African tick bite fever](#), p. 696; Table 17.6.
- *Flea-borne spotted fever/cat flea typhus (R. felis, worldwide)*: recently recognized illness with clinical picture similar to spotted fever group. Transmitted by cat flea.
- *Other types*: Queensland tick typhus, and North Asian tick fever.

## Typhus group

### Epidemic (louse-borne) typhus fever (*Rickettsia prowazekii*)

*R. prowazekii* is transmitted between humans by the human body louse in cold, unhygienic conditions, particularly during war and famine (Fig. 17.2). The disease is endemic in mountainous areas in eastern Africa, Mexico, Central and S America, and Asia.

- Rickettsiae are excreted in faeces of infected lice and inoculated into abrasions or bite wound by scratching.
- After 1–2wks' incubation, abrupt onset of fever, headache, prostration, myalgia, conjunctival injection, rales. No eschar. Macular rash appears on days 5–6. Fatality ranges from 10% to 40% (untreated) and with age.
- Brill–Zinsser disease is a milder recrudescent disease, which may occur years later in those who have not been adequately treated.
- In the eastern USA, flying squirrels have been the source of occasional human infections that tend to be milder than classical typhus.



## Endemic (flea-borne) typhus fever (*Rickettsia typhi*)

Transmitted from rats → humans by fleas. Found worldwide, esp. in warm, humid climates, where rats and humans coexist. *Rickettsiae* transmitted via flea faeces by scratching itchy flea bites. Illness similar to louse-borne typhus, but milder.

## Scrub typhus

Scrub typhus (*Orientia tsutsugamushi*) transmitted by the bite of trombiculid mites living in sharply delimited rural and suburban areas ('mite islands') in Central, E, and SE Asia, and northern Australia.

- Punched-out eschar develops in ~50% after 6–21d followed by severe acute febrile illness resembling typhus. Deafness and pneumonitis are common. Case fatality varies with infecting strain and ↑ age.
- Unlike other rickettsial illnesses, repeat infections may occur, since immunity does not cross-protect against heterologous strains.

## Diagnosis and management of rickettsial infection

### Diagnosis

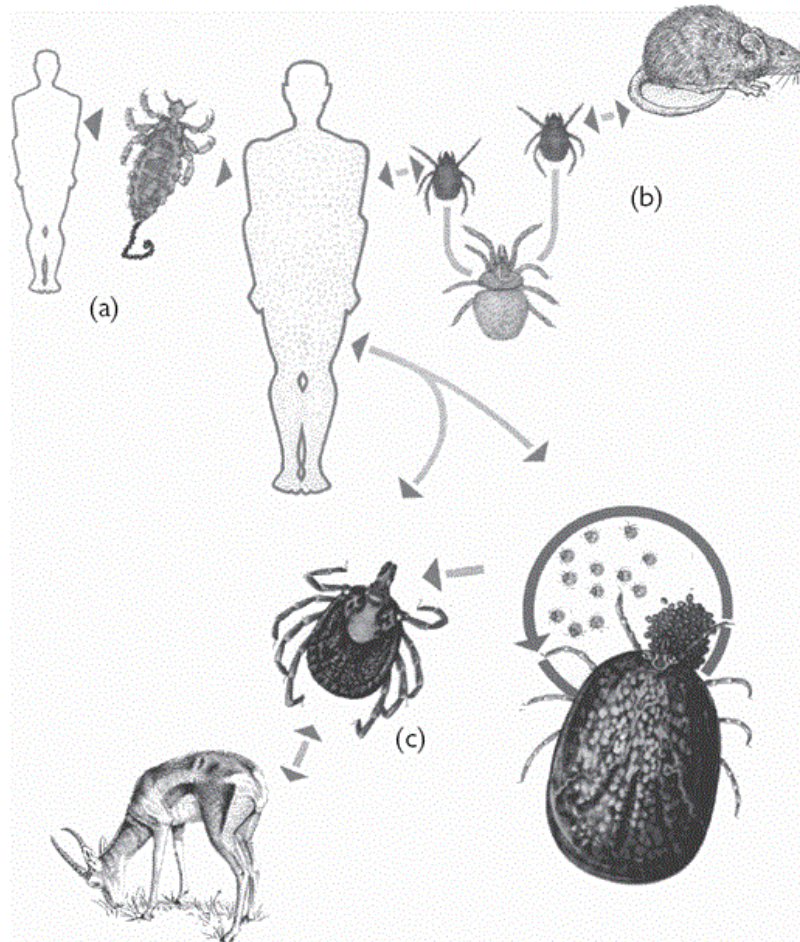
Often clinical in suitable epidemiological setting, if typical triad of fever, rash, and eschar are present (see Colour Plate 22c). Can be verified by serology—but typically only positive ~1–10d after onset of clinical illness. (preferably immunofluorescence; classical Weil–Felix test is obsolete); PCR on blood, swab from eschar or skin biopsy, or isolation of rickettsiae in cell culture from such samples early in infection, are possible, but not widely available.

### Management

Give antibiotics (in severe cases, drugs can be given IV):

- Doxycycline 100mg oral bd or 200mg od for 10–14d. Duration varies for different diseases. In some situations (e.g. louse-borne typhus), a single 200mg dose is sufficient.
- Alternative: chloramphenicol 500mg oral qds for 7–10d.
- Quinolones, like macrolides, are effective but are not optimal for moderate or severe spotted fever infections. IV quinolones are useful in severe cases when oral doxycycline cannot be used or when the diagnosis is not confirmed. They are not effective in scrub typhus.

**Fig. 17.2**



Life cycles of rickettsial infections. (a) *Epidemic (louse-borne) typhus*. Body louse, *Pediculus humanus* feeds on patient infected with *R. prowazekii*; new host is infected when louse faeces are inoculated into skin. (b) *Scrub typhus*: larvae of trombiculid mites are infected with *Orientia tsutsugamushi* from feeding on infected animal or trans-ovarially; humans accidentally infected when bitten. (c) *African tick bite fever*: infection with *R. africae* is prevalent in many animal species and sustained in *Amblyomma* ticks trans-ovarially and -stadially; humans accidentally infected when bitten.

Adapted from G. Piekarski, *Medical parasitology in plates*, 1962, with kind permission of Bayer.

### Paediatric note

Doxycycline is favoured for treatment of moderate to severe rickettsial infections in children and pregnant women. Milder infections in children and pregnant women can be treated with azithromycin 10mg/kg/d for 3d.

Severe infections often benefit from a few doses of doxycycline before changing to azithromycin.

# African tick bite fever

## Epidemiology

- Seroprevalence is  $\geq 70\%$  among adults living in endemic areas in southern Africa. Whereas reports on African tick bite fever in indigenous populations are scarce, a large number of cases are reported in travellers from Europe and elsewhere.
- Vectors are ixodid *Amblyomma* ticks, mainly *A. variegatum* (the tropical bont tick) and *A. hebraeum* (southern African bont tick; Fig. 17.3). Infection in ticks is maintained at very high levels (30% to  $>70\%$ ) by trans-ovarial transmission (from adult female  $\rightarrow$  offspring) and trans-stadial transmission (from larva  $\rightarrow$  nymph  $\rightarrow$  adult). Ticks are aggressive and actively seek mammalian hosts, crawling up the legs before attaching to thin, moist skin esp. in folds behind knees, groin, and buttocks.
- Patient has typically walked in long grass, e.g. in game reserve, within 10d preceding onset. Rainy season is time of greatest tick abundance, but infections may be acquired at any time of year.

## Clinical features

- Most patients present with abrupt onset of fever, nausea, fatigue, headache, and myalgia.
- Neck muscle myalgia is prominent, with subjective neck stiffness.
- Inoculation eschar is present in most cases but may be overlooked, particularly on dark skin, in hair, or on the perineum. Sometimes, non-typical eschars mimicking acne are seen (Fig. 17.4).
- Rash is typically a maculopapular erythema, becoming confluent in areas, with regional lymphadenopathy draining the site of eschar. Rash may be absent or there may occasionally be scattered vesicles. Reactive arthritis occasionally occurs.
- Severe illness with multisystem involvement including bleeding is noted in a small percentage of cases especially infections with *R. conorii*. Differentiation from Crimean–Congo haemorrhagic fever (CCHF) and other severe bacterial and viral infections must be considered.

## Diagnosis

In first 10d of illness,  $\uparrow$  CRP and moderate lymphopenia seen in most cases;  $\uparrow$  liver enzymes in  $\sim 40\%$  and  $\downarrow$  platelets in  $\sim 20\%$ . Diagnosis can be confirmed in most cases by +ve rickettsial serology, but usually only after the acute illness. Serology lacks sensitivity and specificity for *R. africae*. PCR of eschar swab often positive.

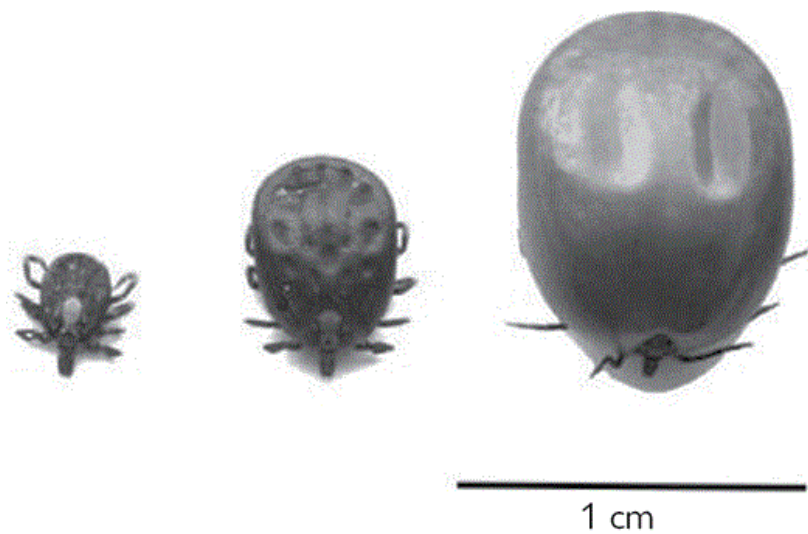
## Treatment

Give doxycycline 100mg oral bd for 7d or until 48h without fever; most cases improve in 48h. Azithromycin is an alternative for pregnant women and young children; in severe cases, start with doxycycline for a few doses then change to azithromycin.

**Table 17.6** Signs and symptoms in African tick bite fever

Characteristic	Frequency (%)
Fever	59–100
Headache	62–83
Myalgia	63–87
Neck muscle myalgia	81
Inoculation eschar	53–100
Multiple eschars	21–54
Regional lymphadenitis	43–100
Cutaneous rash	15–46
Maculopapular rash	15–26
Vesicular rash	0–21
Aphthous stomatitis	11

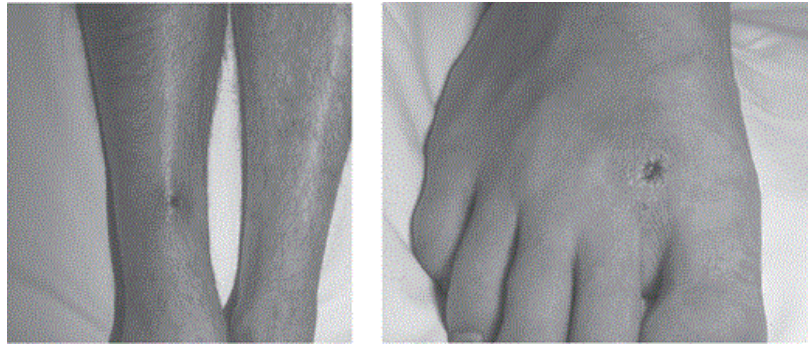
**Fig. 17.3**



*Amblyomma hebraeum* (vector of African tick bite fever): females at different feeding stages: unfed, partially fed, and fully engorged.

Image courtesy Alex Smith, University of Alberta, Canada.

**Fig. 17.4**



Eschars at the site of vector bites resulting in rickettsial infections. Left: eschar on shin, with surrounding halo of erythema and macular rash in patient with African tick bite fever (*R. africae*). Right: eschar of scrub typhus (*Orientia tsutsugamushi*) without a rash.

## Bartonella infections

Bartonellas are intracellular bacteria with tropism for erythrocytes and endothelial cells. Clinical features overlap.

- *Bartonella quintana* is transmitted by the human body louse among the homeless, those living in crowded, unhygienic conditions, and during war. It causes *trench fever*, chronic bacteraemia, and endocarditis in the immunocompetent, and *bacillary angiomatosis* (BA) in the immunocompromised esp. HIV/AIDS.
- *B. henselae* is transmitted among cats by the cat flea and to humans by cat scratch or bite. It causes *cat scratch disease* (uncommonly, bacteraemia and endocarditis in immunocompetent persons) as well as BA and *peliosis hepatis* in the immunocompromised.
- *B. bacilliformis* is unlike other bartonellas in being transmitted by sandflies in the Andes; it causes *Oroya fever* (especially in tourists and transient workers) and *verruca peruana* (especially among natives of the Peruvian Andes). See Box 17.12 for notes.
- Other, unusual species are occasionally associated with *endocarditis* (*B. elizabethae*, *B. vinsonii*) or *cat scratch disease* (*B. clarridgeiae*).

## Clinical features

- *Trench fever*: acute-onset fever ('5-day fever'), headache, dizziness, and shin pain. Most cases are self-limiting, but illness in some patients may be prolonged, and relapsing in others. A minority develops chronic infection (attacks of fever, chronic bacteraemia, endocarditis).
- *Cat scratch disease*: usually presents as a tender, self-limiting (2–3mths) regional lymphadenopathy without fever. Complications are rare: retinitis, encephalopathy, visceral forms.
- *Bacillary angiomatosis and peliosis hepatis*: due to vascular proliferative lesions, respectively, in the skin or liver/spleen, but can involve any organ. Typically occur in immunocompromised (HIV+ve) patients. Skin lesions are nodules or papules which may be red to purple, may ulcerate, or bleed (Fig. 17.5).
- *Endocarditis* mainly affects middle-aged patients, presenting with fever, emboli, and occasionally glomerulonephritis. Previously normal or damaged valves may be infected.

## Diagnosis

- *Serology*: extensive cross-reactions between *B. henselae* and *B. quintana*.
- PCR of lymph node aspirate, tissue biopsy, or blood.
- Culture from blood is possible, but technically difficult.
- For cat scratch disease and bacillary angiomatosis, organisms can be seen in tissue sections stained with Warthin–Starry silver stain (but not Gram or ZN stains).

## Management

- *Trench fever*: doxycycline 200mg po od for 4wks plus gentamicin 3mg/kg IV od for the first 2wks.
- *Cat scratch disease*: no therapy needed, unless extensive or complicated: azithromycin 500mg po on day 1 then 250mg po on days 2–5.
- *Bacillary angiomatosis* and *peliosis hepatis*: azithromycin 250mg po od or erythromycin 500mg po qds for 2–3mths or doxycycline.

### Box 17.12 *Bartonella bacilliformis*: Oroya fever and verruga peruana

#### Clinical features

- *Oroya fever*: has a variable incubation period (~2mths) followed by fever and severe anaemia, and in some cases, multiple organ failure. Death is frequently caused by opportunistic bacterial (esp. salmonellosis and *Staphylococcus aureus*), protozoal, or viral infections.
- *Verruga peruana*: may follow Oroya fever or occur independently; the classical presentation is that of recurrent crops of erythematous papules, nodules, or angioma-like skin lesions, caused by vascular endothelial proliferation. The verrucae dry up and slough, leaving no scars. Usually relatively benign, lesions may bleed or become 2° infected.

#### Diagnosis

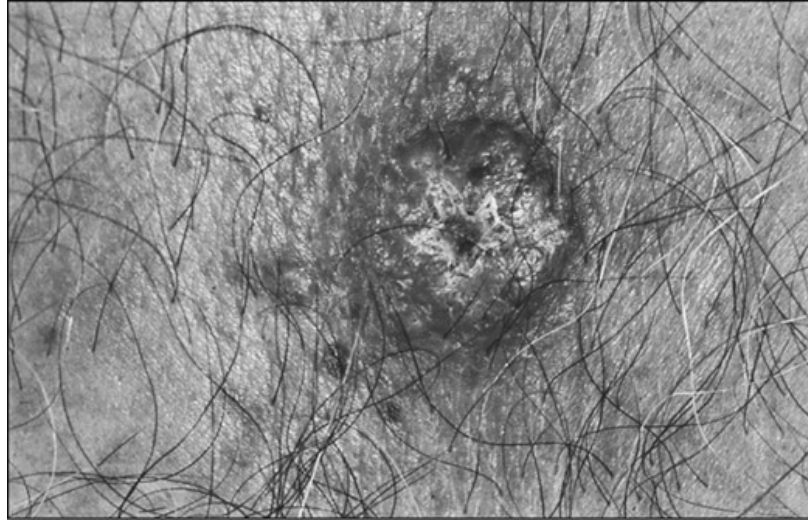
- History of travel and possible exposure.
- Serology; PCR of blood, in reference laboratories.
- Examine peripheral blood films for bacilli within or adherent to erythrocytes.

#### Management

- *Oroya fever*: ciprofloxacin 500mg po bd for 10d.
- *Verruga peruana*: rifampicin or streptomycin may ↓ size and pain of large lesions.



**Fig. 17.5**



Cutaneous lesion ~1cm diameter of bacillary angiomatosis (*Bartonella henselae*) in a patient with advanced HIV infection.

## **Ehrlichia infections**

Human ehrlichioses are tick-borne zoonoses caused by intracellular bacilli. The organisms are found in vacuoles within leukocytes where they divide to form a cluster (morula). *Ehrlichia chaffeensis* infects monocytes while *E. ewingii* and *Anaplasma phagocytophilum* infect neutrophils.

- *E. chaffeensis* and *E. ewingii* are transmitted to humans by the *Amblyomma americanum* tick from a variety of mammals, esp. deer and dogs; occurs in the southern USA.
- *A. phagocytophilum* is transmitted to humans by *Ixodes* spp. ticks from mammals, esp. ruminants and rodents; occurs in the USA and Europe.

## **Clinical features**

*Ehrlichiosis* presents with an acute flu-like illness, which may be accompanied by rash, vomiting, and meningoencephalitis. Leukopenia, thrombocytopenia, and ↑ liver enzymes levels are common. Illness caused by *E. chaffeensis* is generally more severe, with ~3% mortality. *E. ewingii* generally causes disease in immunocompromised patients.

## **Diagnosis**

- Serology or PCR, in reference laboratories.
- Examination of Giemsa-stained peripheral blood films for morulae within neutrophils or monocytes.

## **Management**

Doxycycline 100mg bd po or IV for 7–10d.

### Paediatric note

Rifampicin can be used for ehrlichiosis in pregnancy or in children; neither erythromycin nor azithromycin are thought to be effective.

### Public health note

*Control or avoidance of the vectors:* delousing of clothing and body with powder; preventive measures against tick bites.

- *Lice:* apply residual insecticide powder (e.g. 1% permethrin, 30–50mg/adult) to clothes and persons in situations favouring infestation; reapply regularly. Provide facilities for bathing and washing clothes and bedclothes. In epidemic situations, apply residual insecticide to all contacts or the entire community.
- *Ticks:* look for and remove attached or crawling ticks after exposures. De-tick dogs and use canine-appropriate acaricides. Use tick repellents and protective clothing to avoid contact.
- *Fleas:* for bubonic plague control, apply residual insecticides to rat burrows or harbourages. Wait until flea populations have been reduced before instituting rodent control measures (to avoid human exposure to fleas).

Cat scratches and bites should be thoroughly cleaned and cat fleas controlled to prevent cat scratch disease.

## Coxiella infections

*Coxiella burnetii* is an intracellular coccobacillus that causes *Q fever*. It infects a wide variety of animals (esp. cattle, sheep, and goats), and ticks. Animals shed *C. burnetii* in milk, faeces, urine, and particularly birth by-products. Hides and wool may be contaminated with tick faeces containing concentrated organisms. Humans acquire infection through inhalation of infected aerosols (which may be air-borne over considerable distances), ingestion of unpasteurized dairy products, or contact with contaminated clothing. Person-to-person spread is rare.

### Clinical features

Q fever may be asymptomatic or present as an acute flu-like illness with varying severity of hepatitis and pneumonia. Aseptic meningitis or encephalitis is more common in some areas. Culture –ve endocarditis is an important chronic presentation, usually on a previous damaged or prosthetic valve. *C. burnetii* can recur in pregnancy → abortion. It may also cause a chronic fatigue-like syndrome.



## Diagnosis

- *Acute Q fever*: serology on acute and convalescent samples. Phase II antibodies higher than phase I.
- *Chronic Q fever*: phase I antibodies higher than phase II.
- PCR, immunostaining or EM of liver biopsy or heart valve in reference laboratories.

## Management

Doxycycline 100mg oral bd for 7–10d. *C. burnetii* endocarditis requires 18mths of doxycycline plus hydroxychloroquine.

### Paediatric note

- Co-trimoxazole or azithromycin are used for the treatment of Q fever in children.
- Erythromycin 10–15mg/kg qds for 7–10d may also be used to treat Q fever in children.

### Public health note

Persons at risk of Q fever (abattoir workers, farmers, researchers) should be educated on sources of infection and safe disposal of infected materials (esp. birth products). Milk should be pasteurized. Q fever vaccine is available for those at high risk in some countries.

## Relapsing fevers

These are acute febrile illnesses caused by *Borrelia* spirochaetes. Untreated infections relapse repeatedly with afebrile intervals of 5–9d. As well as clothes/body lice and ticks (Fig. 17.6) *Borrelia* are, rarely, transmitted by blood transfusion, needle sticks, and transplacentally.

### Louse-borne relapsing fever (LBRF)

#### Transmission

Epidemic louse-borne relapsing fever, caused by *B. recurrentis*, is transmitted by human clothes/body lice (*Pediculus humanus corporis*) (Fig. 17.6). Lice are infected by feeding on human blood. They transmit *B. recurrentis* to a new human host not by bites, but by inoculation of infected louse faeces through broken skin or intact mucosae, by scratching. Humans are sole host and reservoir.

## Epidemiology

LBRF is now confined to Northeast Africa. In the cold, rainy season when people wear more clothes and crowd together for warmth, conditions encourage louse infestation and transmission. Historically, LBRF caused massive pandemics in Africa, the Middle East, and Europe (1903–1936, 50 million cases with 5 million deaths; 1943–1946 10 million cases), exacerbated by wars, crowding, floods, famines, and forced migration.

Since 2015, almost 100 cases of LBRF have been identified in young, mainly male, refugees from the Horn of Africa arriving in several European countries.

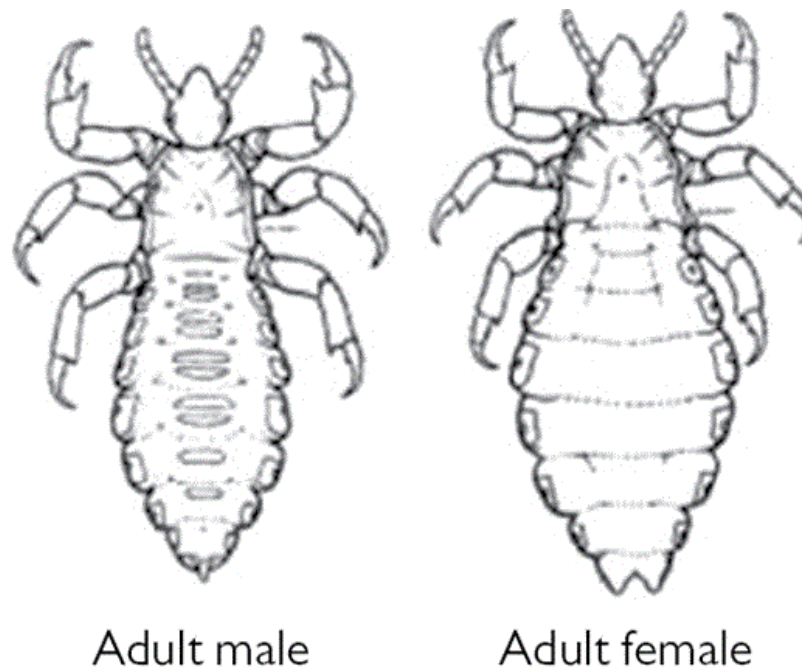
## Clinical features

- Incubation is 4–18d (average 7d).
- Symptoms start with sudden high fever, chills/rigors, headache, confusion, myalgias, arthralgias, fatigue, dizziness, cough, anorexia, nightmares, and prostration.
- Examination reveals bleeding (epistaxes, subconjunctival haemorrhages, petechiae), tender splenomegaly and hepatomegaly, jaundice, and chest signs.
- The first attack ends dramatically with a febrile crisis, either spontaneously on about the 5th day if untreated or with a Jarisch–Herxheimer reaction (Box 17.13) precipitated by antibiotic treatment.
- Inadequately treated patients may suffer their first relapse about 1wk later. Subsequent attacks tend to be less severe.

## Complications

Pregnant women have high risk of abortion. Death is due to myocarditis, liver failure, severe bleeding due to thrombocytopenia, DIC, and hepatic dysfunction; ruptured spleen, splenic infarctions, and bacterial superinfection (dysentery, salmonellosis, typhoid, typhus, malaria, TB). During the Jarisch–Herxheimer reaction, patients may die from hyperpyrexia, shock, or pulmonary oedema. Untreated case fatalities ~40% occur during epidemics; treatment can reduce this to <5%.

Fig. 17.6



Human body lice (*Pediculus humanus corporis*), the vector of LBRF and epidemic typhus. Adult lice are 2.3–3.6mm long. Body lice live and lay eggs on clothing and move to the skin to feed. Lice spread by close contact, esp. with crowding/poor hygiene. Animals do not play a role in the transmission of human lice.

Source: Drawing by J H Grundy, courtesy of D A Warrell.

### Box 17.13 Jarisch–Herxheimer reactions in spirochaete infections

Acute inflammatory exacerbation of symptoms and pathology following treatment is most frequent (33–100%) and severe in LBRF, although it also occurs in TBRF, Lyme disease, leptospirosis, syphilis, and other spirochaetal infections.

Within a few hours of treatment, patient becomes restless, then develops violent rigors with soaring temperature, respiratory, and pulse rates, high BP, and associated vomiting, diarrhoea, coughing, and delirium.

This is followed by the flush phase during which there is profuse sweating and vasodilatation, sometimes complicated by hypovolaemic shock or acute pulmonary oedema from myocarditis.

#### Treatment

For severe Jarisch–Herxheimer reactions precipitated by antibiotics:

- Control pyrexia by physical cooling.
- Prevent hypovolaemia with IV fluids.
- Nurse in bed for 48–72h to prevent fatal postural hypotension.

Treat acute pulmonary oedema and myocarditis with IV digoxin. No effective antibiotic regimen has yet been shown to cause fewer Jarisch–Herxheimer reactions, but in highly vulnerable patients, initiate treatment with IM procaine penicillin and give doxycycline the next day.

## Tick-borne relapsing fever (TBRF)

Endemic TBRF is caused by >15 *Borrelia* spp. and transmitted by soft ticks (*Ornithodoros*), and in the case of *B. miyamotoi*, by hard ticks (*Ixodes*) (Fig. 17.7). TBRF is widely distributed in tropical and temperate countries esp. Africa, but not Australasia and Pacific islands.

### Transmission

Ticks are infected by feeding on animal or human blood or acquire spirochaetes congenitally (trans-ovarially). They transmit *Borrelia* to animals or humans during a blood meal. They are reservoirs as well as vectors. Peri-domestic rodents are the main vertebrate reservoir. Ecology and species of *Borrelia* and tick vary geographically. Only classic E African TBRF (*B. duttonii*) is anthroponotic (not a zoonosis). Risk of infection is associated with sleeping in tick- and rodent-friendly huts. Tick bites are painless. They feed for only a few hours at night and then drop off, so exposure is usually unsuspected.

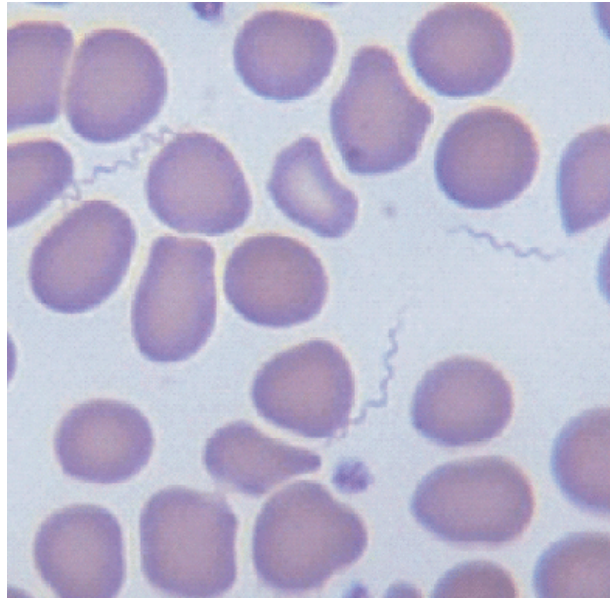
### Clinical features

After incubation of 2–18d, symptoms resemble LBRF, usually milder and briefer, although ARDS and severe Jarisch–Herxheimer reactions have been reported.

- Fever, epistaxis, abdominal pain, diarrhoea, and cough.
- Splenomegaly and splenic infarction are common; hepatomegaly and jaundice are unusual.
- Transient neurological problems in 5–10%: paraesthesiae, cranial nerve palsies (esp. VII), visual symptoms, hemiparesis or paraparesis, lymphocytic meningitis.
- Erythematous and petechial rashes may appear.
- Fever may recur up to 13 times, separated by a few days–3wks in untreated patients.
- Miscarriage in up to 1/3 of pregnant cases.

### Diagnosis of the relapsing fevers

LBRF is easily diagnosed by finding spirochaetes (sometimes in vast numbers, e.g. >500,000/mm<sup>3</sup>) in Giemsa-stained blood films (Fig. 17.8 and  Colour plate 24). However, in TBRF, spirochaetaemia may be scanty and intermittent, making microscopy insensitive. PCR of blood is accurate; serology is unhelpful.



*Borrelia recurrentis* spirochaetes in blood film.

Reproduced with permission from <http://library.med.utah.edu/WebPath/COW/COW077.html>

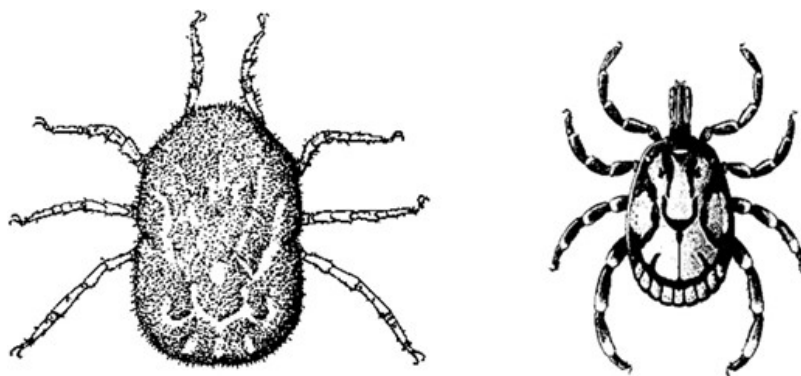
## Management of tick- and louse-borne relapsing fever

Single-dose antibiotic therapy is curative for LBRF:

- Adults: doxycycline 100mg or tetracycline 500mg, oral (for sick patients, tetracycline 250mg IV) stat.
- Pregnant women or children: erythromycin adult 500mg, children 10mg/kg oral (for sick patients, erythromycin IV) stat or
- For mixed infections with louse-borne typhus (adults): doxycycline 100–200mg oral stat.
- Benzylpenicillin and chloramphenicol are also effective.

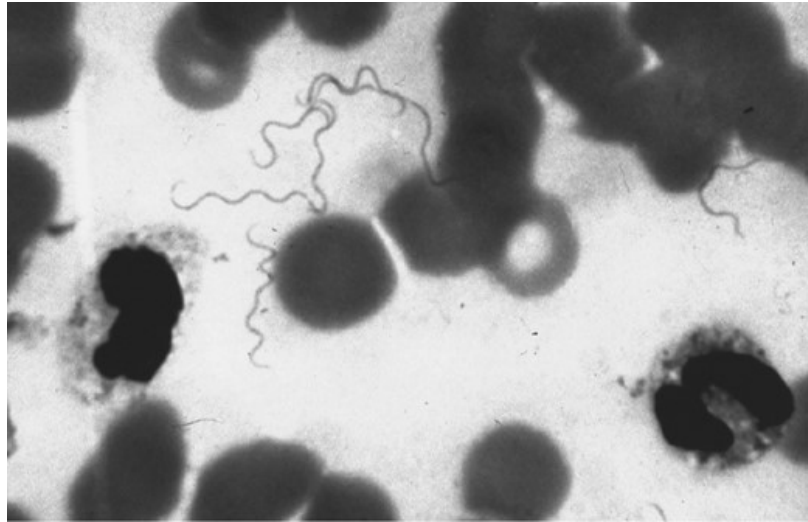
For TBRF, 10d courses of the same drugs are required. For treatment of Jarisch–Herxheimer reactions, see Box 17.13.

**Fig. 17.7**



Left: soft tick (genus *Ornithodoros*) vector of tick-borne relapsing fever. Right: hard tick (genus *Ixodes*) vector of *B. miyamotoi*, Lyme disease, rickettsial infections, and tick-borne encephalitis.

**Fig. 17.8**



Blood film showing several *B. duttonii* spirochaetes in a patient with untreated TBRF.

#### **Public health note: control of relapsing fever**

- *LBRF*: washing clothes in hot water (>60°C) for >10min kills clothes lice and their eggs. Isolating infested clothing away from wearers for 7–10d starves lice to death. Insecticides are also effective. Patients should be bathed with soap. Head lice should be removed by washing or shaving, although their role in LBRF is unproven. These measures are essential to control an epidemic.
- *TBRF*: kill or deter ticks with residual insecticides in dwellings, repellents (DEET), improved house construction, rodent control.

## **Leptospirosis**

A zoonosis caused by *Leptospira* spirochaetes. Leptospire are excreted in urine of wild and domestic animals into water sources and can survive for days in warm, damp conditions esp. fresh water and damp soil. Exposure can → self-limiting or serious, sometimes fatal, disease.

## Epidemiology and transmission

- Global distribution, esp. tropics (incidence  $\geq 10/100,000$  population; seroprevalence  $\sim 5\text{--}10\%$ ).
- *Leptospira* spp. can be divided into 25 serogroups and  $>250$  serovars; or by genotyping into  $>17$  genomospecies. Not all are pathogenic.
- The commonest source of infection is rats; wild and domestic animals (e.g. cattle, pigs, dogs) are also reservoirs of infection and can excrete large numbers of leptospires in urine for long periods.
- Leptospires enter the body through cuts or abrasions of skin or mucous membranes after immersion in contaminated water (pools, canals, rivers), or through close animal contact.
- Risk groups are those in contact with contaminated water or infected animals during occupational or recreational activities, e.g. farmers, sewage or abattoir workers, military personnel, humanitarian workers, adventure travellers (trekking or water-based activities). Epidemics may occur after heavy rains or flooding.
- Human-to-human transmission, incl. congenital infection is rare.

## Clinical features

Following infection, leptospiraemia spreads spirochaetes to multiple organs. Incubation period is  $\sim 10$  d (range 5–14 d). Disease severity correlates with leptospire burden. Leptospirosis pathogenesis remains poorly understood but involves small vessel endothelial cell injury. Clinical manifestations reflect organ dysfunction resulting from direct effects of leptospires and/or host immune responses to infection. There are three clinical categories:

- *Subclinical infection*: common in endemic areas.
- *Self-limiting infection*: infection is followed 1–2 wks later by sudden-onset fever, headache, severe myalgia (characteristically affecting calves and lower back), N&V, and conjunctival suffusion or haemorrhage. Cough is common.
- *Severe disease*: multisystem illness with high fever, jaundice, renal failure, and respiratory failure, which may be complicated by pulmonary haemorrhage and haemoptysis (Weil's disease). Illness may be biphasic with  $\sim 2$  d remission after the first 4–7 d, followed by a second immunopathological phase when the patient's condition worsens with persistent high fever, meningoencephalitis, myocarditis, widespread haemorrhage, renal failure, jaundice, and shock.

Case fatality ranges from  $\sim 2\%$  in uncomplicated disease to  $\geq 19\%$  in jaundiced patients, and  $\uparrow$  with advancing age. Maternal infection may  $\rightarrow$  fetal loss.

## Diagnosis

The differential diagnosis of uncomplicated disease is wide (e.g. malaria, dengue, rickettsial infection, community-acquired pneumonia). Bloods may show  $\uparrow$  WBC (neutrophilia)  $\pm$   $\downarrow$  platelets,  $\uparrow$  CK. Renal and hepatic impairment are common, typically with  $\uparrow$  bilirubin but only modestly  $\uparrow$  ALT/AST. Urine frequently contains blood, protein, and WBCs. CSF findings are those of aseptic meningitis.

## Culture

Slow-growing leptospires can be isolated from blood or CSF (days 7–10d of illness) or urine (weeks 2–3). However, culture is not sensitive and too slow to make the diagnosis during the acute phase.

## Serology

Antibodies are usually detectable from day 5–7 of the illness, although seroconversion may be delayed. The microscopic agglutination test (MAT) performed on paired sera is the standard diagnostic test. Rapid tests are available but generally of low sensitivity.

## PCR

Quantitative PCR on serum or urine, if available, is reliable early in the course of the illness.

## Management

Antibiotic therapy provides greatest benefit early in the illness.

Supportive treatment includes cardiovascular support for sepsis; early renal replacement therapy; and ventilatory support if indicated.

- *Mild disease*: doxycycline 100mg bd for 7d, started <3d after onset of symptoms, will hasten recovery. Alternatives are azithromycin 1g, followed by 500mg at 24h and 48h; or amoxicillin 25–50mg/kg/d in three divided doses for 7d.
- *Moderate or severe disease*: benzylpenicillin 1.2–2.4g IV qds for 5–7d (even if patient has been ill for several days). Alternatives for severe disease: ampicillin 1g IV qds or cefotaxime 1–2g IV every 12h or ceftriaxone 1–2g IV od.

## Complications

The Jarisch–Herxheimer reaction may occur after starting antibiotics in some patients (➡ p. 705).

### Public health note: control of leptospirosis

- ↓ *exposure*: education of high-risk groups, personal protective equipment (PPE).
- ↓ *animal transmission*: control of rodent populations and vaccination of domestic animals.
- *Prophylaxis*: doxycycline 200mg weekly has been shown to ↓ clinical disease (but not infection) in populations with very high risk of exposure over a limited time.

*Immunization*: commercial vaccines with limited protective efficacy against certain serotypes have been produced for use in humans but are not widely available.



# Brucellosis

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A zoonosis of worldwide distribution caused by the Gram –ve bacillus, *Brucella*. There are ~500,000 human cases/yr. Responsible species are: *Brucella melitensis* (sheep, goats, camels), *B. abortus* (cattle, buffalo, yaks, camels), *B. suis* (pigs, hares, rodents, caribou, reindeer), *B. ovis* (sheep), and *B. canis* (dogs). *B. melitensis* is the commonest. The organism lives and multiplies within phagocytes in the reticuloendothelial system. The cellular immune response, in particular the interferon- $\gamma$  pathway, is important in pathogenesis.

## Transmission

Infected animals shed large numbers of bacilli in milk, urine, and products of conception. Humans infected either by:

- Sporadic cases occur by direct contact with infected animals (entry is through breaks in skin or inhalation of aerosols in stables, abattoirs, and laboratories).
- Sporadic cases and outbreaks occur by ingestion of unpasteurized milk, soft cheese (Fig. 17.9), yoghurt, butter, and ice-cream.

## Clinical features

Variable incubation period (usually 2–4wks, may be months), followed by acute or insidious onset of fever (may be rigors), and non-specific constitutional symptoms (sweating, anorexia, malaise, headache, back pain). Lymphadenopathy and hepatosplenomegaly may be present. Complications can affect virtually any organ system, including:

- Osteoarticular (spondylitis, peripheral arthritis, sacroiliitis).
- Reproductive (epididymo-orchitis, spontaneous abortion).
- Hepatitis, peritonitis.
- CNS (meningitis, encephalitis, abscess).
- Endocarditis (responsible for most mortality).

## Diagnosis

The serum agglutination test is most widely used (single titre >1:160 or rising titre), but cross-reacts with other Gram –ves. ELISA (IgG, IgM, IgA) has  $\uparrow$  sensitivity and specificity. Rapid (dipstick-type) serological tests are commercially available. PCR is promising. Culture from blood or tissue is confirmatory, but is relatively insensitive and requires prolonged incubation. When cultured, it is readily transmitted to laboratory staff via aerosols produced by laboratory procedures.

## Management

### Optimal treatment

6wks of doxycycline 100mg oral bd plus 6wks of rifampicin 300mg oral bd plus an aminoglycoside for first 2–3wks: either streptomycin 15mg/kg IM daily or gentamicin 5mg/kg IM od.

## Alternative

Doxycycline plus rifampicin (as above-described) for 6wks, but relapse rate higher in regimens that do not include an aminoglycoside. Ciprofloxacin/ofloxacin may be added as an alternative third agent. Rifampicin plus co-trimoxazole are useful in pregnancy. HIV+ve individuals respond to the same regimens used for HIV-ve individuals.

**Fig. 17.9**



Unpasteurized goat cheese, Canta valley, Peru. Unpasteurized cheese may transmit brucellosis.

Source: Image courtesy of D A Warrell.

### **Paediatric note: paediatric doses**

Children aged >9yrs may be treated as adults. For younger children, combine two of the following:

- Rifampicin 15mg/kg (max. 600mg) oral od for 6wks.
- Co-trimoxazole: sulfamethoxazole 20mg/kg + trimethoprim 4mg/kg (max. 800 + 160mg) oral bd for 6wks.
- Gentamicin 2.5mg/kg IV or IM tds for first 2wks.

### Public health note: prevention and control

- Pasteurize (or boil) milk products.
- PPE (masks, gloves, etc.) for those at occupational risk, e.g. vets.
- Screen livestock by serology or by testing cow's milk and eliminate infected animals.
- Vaccinate animals in high-prevalence areas using live attenuated vaccine (no human vaccine is available; vaccine strains may cause disease in humans if accidentally inoculated and post-exposure prophylaxis with doxycycline for 3wks should be given).
- Identify source of outbreaks (usually milk or milk products from infected herd); recall all affected products.
- Laboratory exposures: give prophylactic rifampicin + doxycycline (or doxycycline alone) for 3–6wks.

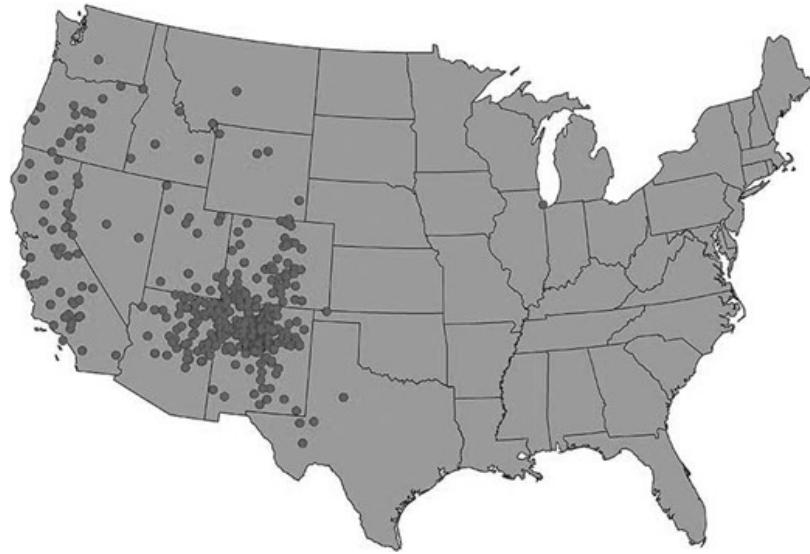
## Plague

An acute febrile illness caused by the Gram –ve coccobacillus *Yersinia pestis*, plague can be rapidly fatal unless treatment is started promptly. Early empiric antibiotic therapy is therefore essential when clinical suspicion is high.

Plague has had a profound effect on the course of human history, mainly through the impact of three pandemics. Although another pandemic is unlikely, plague remains a threat due to high case fatality rates and the potential for epidemic spread (Fig. 17.10).

The plague bacterium cycles among rodents and their fleas in focal areas of Africa, Asia, and the Americas (incl. the western USA). Since 2010, >95% of cases reported to the WHO have been from Madagascar, the Democratic Republic of Congo (DRC), Uganda, and Tanzania. Humans are incidental hosts and can be infected in a variety of ways.

**Fig. 17.10**



Cases of plague by country, 2013 - 2018. CDC, Atlanta, GA, USA.

## Transmission

Bubonic and 1° septicaemic plague occur following the bite of infected fleas or through direct contact with infectious tissues. Peri-domestic rodents (e.g. *Rattus rattus*, *R. norvegicus*) amplify and bring the infection closer to humans during an epizootic. Although many flea species can transmit the bacterium, *Xenopsylla cheopis* is the important vector. Pneumonic plague is the only clinical form that can be directly transmitted from person to person: transmission occurs through respiratory droplets rather than aerosols, typically when the source patient is very ill.

## Clinical features

### Bubonic plague

The commonest clinical presentation. The first specific sign is local lymphadenitis in the nodes draining the site of inoculation (e.g. flea bite). After 2–7d (always <15d), a ‘bubo’ forms in these nodes. There is typically a short prodrome of fever, malaise, headache, and, in some cases, a dull ache in the affected nodes for up to 24h before the bubo appears. The enlarged nodes are extremely painful and swollen, and the mass is non-fluctuant and immobile. The overlying skin may be warm, red, oedematous, and adherent (Fig. 17.11). Mortality is ~50% without treatment.

### Pneumonic plague

Pneumonic plague occurs following haematogenous spread of *Y. pestis* to the lungs; either as a complication of untreated bubonic or septicaemic plague, or after direct inhalation of bacteria in droplets coughed from a patient or animal with pneumonic plague.

Intense headache, malaise, fever, and vomiting → rapidly evolving dyspnoea, chest pain, cough, haemoptysis, and prostration. There are often scanty chest signs despite multifocal consolidation or bronchopneumonia on CXR. Respiratory involvement needs to be distinguished from ARDS, which may occur in bubonic and septicaemic plague. Rapid deterioration and death from fulminant pneumonia, sepsis,

and multiorgan/respiratory failure is common even with treatment, and without treatment pneumonic plague is usually fatal.

### Septicaemic plague

*Yersinia* sepsis may occur as 1° septicaemia, or as a complication of untreated bubonic or pneumonic plague. GI symptoms (vomiting, diarrhoea, abdominal pain) and skin purpura may be prominent, and it may rapidly → multiorgan failure and death.

### Other presentations

Rarer clinical presentations include meningitis, pharyngitis, and cutaneous infections.

**Fig. 17.11**



Enlarged inguinal lymph node (bubo) in child with bubonic plague.

CDC, Atlanta, GA, USA.

### Diagnosis

Consider as a cause of acute febrile illness in a person recently in a plague endemic area. Diagnosis confirmed by aspiration of a bubo for smear (bipolar coccobacilli on Giemsa or Gram stain) and culture; blood for smear and culture; and acute and convalescent serology. If available, antigen detection directly on primary clinical samples (i.e. bubo aspirate) may → rapid diagnosis.

### Management

Recommendations are given in Table 17.7. Start empiric IV therapy immediately plague is suspected. Once the patient improves consider IV to oral switch, to complete a 10–14d course. Most experience is with streptomycin. Some regimens shown might be avoided in children and pregnant women in other circumstances, but the life-threatening nature of plague justifies their use.

**Table 17.7** Recommended antibiotic treatment regimens

Antibiotic	Adults	Children
Streptomycin	1g IM bd	15mg/kg IM bd (max. 2g/d)
Gentamicin	5mg/kg IV/IM od (max. 500mg)	2.5mg/kg IV/IM tds
Ciprofloxacin	400mg IV bd or tds or 500–750mg po bd	15mg/kg (max. 400mg) IV bd or 20mg/kg (max. 500mg) po bd
Levofloxacin	500mg IV/po od (750mg may be used if clinically indicated)	8mg/kg (max. 250mg) IV/po od
Doxycycline	100mg IV/po bd	2.2mg/kg (max. 100mg) IV/po bd
Chloramphenicol	25mg/kg (max. 750mg) IV/oral qds	25mg/kg (max. 750mg) IV/oral qds

### Public health note: prevention and control of plague

- Rodent control measures (e.g. remove rodent food and habitats from vicinity of households).
- Flea control (must occur before rodent control during outbreaks).
- Notify local health authorities of all suspected cases.
- Conduct case finding in affected and nearby households.
- Isolate pneumonic plague patients; use respiratory droplet precautions until  $\geq 48$ h after starting antibiotics and clinically improving.
- Consider prophylaxis for close contacts of pneumonic plague (e.g. 1° caregivers, medical staff, those within 2–3m of patient); use doxycycline 100mg bd or ciprofloxacin 500mg bd for 7d.
- Vaccination currently not generally available.

## Melioidosis

A disease caused by Gram –ve bacteria *Burkholderia pseudomallei* that is endemic in S and SE Asia, northern Australia, the Caribbean, and increasingly reported from elsewhere including areas of Africa and S America. It is a major cause of septicaemia in NE Thailand. The bacteria are present in mud and surface water (e.g. rice paddies), and infection occurs following inoculation, inhalation or ingestion. The time from exposure to illness ranges from 1d to >60yrs, but most cases are acute infection from recently acquired bacteria. Overall case fatality is 43% in NE Thailand (20–30% in children) and 14% in Australia, with ~89,000 deaths per year worldwide from melioidosis. *Glanders* is a similar disease of horses caused by *Burkholderia mallei*, with very rare cases in humans. Diagnose and treat as for melioidosis.

## Clinical features

These are very variable, and range from fulminant sepsis and rapid death to a chronic illness characterized by fever, weight loss, and wasting. The most frequent clinical picture is a septicaemic illness, often with bacterial dissemination → pneumonia (50%) and/or abscess formation, most commonly in the liver and spleen (30%) . Infection may occur in bone, joints, skin, soft tissue, parotid gland, testis, prostate, and CNS (Fig. 17.12). Severe sepsis and its complications are the usual cause of death if it occurs.

## Diagnosis

- Consider melioidosis in febrile patients with a history of one or more of:
  - Residency in an endemic region or relevant travel history.
  - Any contact with soil or water containing *B. pseudomallei*.
  - Risk factors for melioidosis, e.g. diabetes mellitus or renal disease.
- Diagnostic confirmation relies on culture. *B. pseudomallei* colonization is extremely rare and isolation of even a single colony from any clinical sample can be diagnostic.
- Culture blood, urine, throat swab, and respiratory secretions from suspected patients, together with pus and wound swabs where relevant. Site of culture positivity may not necessarily relate to clinical features (e.g. urine may be +ve without features of UTI).
- *B. pseudomallei* is a hazard group 3 biological agent and requires safe handling during culture, so tell your diagnostic laboratory if you suspect melioidosis.
- *B. pseudomallei* grows on most routine culture media, but as an oxidase +ve Gram –ve rod may be disregarded as an environmental pseudomonad, so be alert to the diagnosis in the right clinical and epidemiological setting. *B. cepacia* agar is often available in Western laboratories (it is used to culture sputum from cystic fibrosis patients) and is a good selective agar for *B. pseudomallei*.
- *B. pseudomallei* can be identified using biochemical tests and susceptibility pattern (resistant to gentamicin and colistin, susceptible to amoxicillin–clavulanate), commercial kits, or automated systems.
- Consider sero–diagnosis in cases of suspected melioidosis who are culture –ve, but interpret with caution. It is common for the healthy population living in regions where infection is endemic to be seropositive, and serology may be falsely –ve in definite cases.

## Management

- Start appropriate antibiotics as soon as possible—immediately after culture, or even before culture if sampling is going to be delayed.
- Treatment is divided into IV and oral phases and is required for at least 12wks. Recommendations are given in Box 17.14.
- Use imaging (where available) to detect abscesses in the liver, spleen, and elsewhere. Drain collections of pus wherever feasible.
- Fever clearance is often slow (median 9d), and is not an indication for a change of antimicrobials unless associated with clinical deterioration.
- If blood culture is +ve at presentation then repeat again at 1wk; if still +ve, this is a poor prognostic sign. Review antimicrobial therapy and re-image for pus collections.
- There is no clinical benefit in repeating cultures from other sites. Sputum and draining abscess cultures can be culture +ve for several weeks, but this is not associated with ↑ mortality in a patient who is otherwise responding to treatment.
- Infection is not thought to be easily transmitted from person to person, but infection control measures may be recommended.
- Recurrent melioidosis is common (6% in 1st year and 13% by 10yrs) and is usually due to relapse following failure to eradicate the infecting organism.

**Fig. 17.12**



Thai child with melioidosis leading to a parotid abscess, which is discharging pus, and a left VIIth nerve lesion.

Source: Image courtesy of S Looareesuwan and D A Warrell.



**Box 17.14 Antimicrobial therapy for melioidosis****Initial parenteral therapy**

Give IV therapy for at least 10d and extend to 4–8wks for deep-seated infection incl. complicated pneumonia, deep-seated infection incl. prostatic abscesses, neurological melioidosis, osteomyelitis and septic arthritis.

- *First line:* ceftazidime 50mg/kg per dose (up to 2g) every 6–8h, or meropenem 25mg/kg per dose (up to 1g) every 8h.
- *Second line:* amoxicillin/clavulanate 20/5mg/kg every 4h; this gives equivalent mortality to first-line drugs, but more treatment failure.

**Oral eradication therapy**

Duration of oral therapy, a minimum of 3mths after the end of parenteral therapy.

**Adults**

Trimethoprim/sulfamethoxazole using a weight-based dosing schedule:

- If <40kg give 2 × 480mg tablets bd.
- If 40–60kg give 3 × 480mg tablets bd.
- If >60kg give 4 × 480mg tablets bd.

**Children <8yrs and pregnant women**

*Children:* amoxicillin/clavulanate 20/5mg/kg oral tds.

- For adults <60kg, amoxicillin/clavulanate 1000/250mg oral tds.
- For adults >60kg, amoxicillin/clavulanate 1500/375mg oral tds.

**Anthrax**

Anthrax is a zoonosis from infection with the spores of the Gram +ve rod *Bacillus anthracis*. Anthrax is a disease of grazing animals (sheep, cattle, goats) in parts of Asia, Africa, S and Central America, southern Europe, Caribbean, and Middle East. The hardy spores remain viable in soil or on animal products for many years.

**Transmission**

Anthrax is primarily an occupational disease of workers who process hides, hair, bone products, and wool and those who handle infected animals (veterinarians, wildlife workers). Spores may be dispersed by wind, water, scavengers, or transport of animal products. Outbreaks can follow ingestion of contaminated meat. Anthrax spores are resistant and can be aerosolized, so they have been used as agents of bioterrorism.

## Clinical presentation

### Cutaneous anthrax

Accounts for 95% of naturally occurring cases. Spores are inoculated into the skin through abrasions or cuts. A short incubation period (typically 1–5d) → an itchy papule → a vesicle, ulcer, and finally → a painless black eschar (Fig. 17.13) with extensive local oedema and surrounding purple vesicles. This heals spontaneously in 1–3wks; however, bacteraemic spread and overwhelming septicaemia may occur. Neck lesions may → airway obstruction (consider early tracheostomy).

### Inhalational anthrax

Usually occurs 1–4d following exposure, but may be delayed for up to 43d. A biphasic illness, it presents with symptoms of a viral URTI followed by sudden onset of haemorrhagic mediastinitis with fever, hypoxia, dyspnoea, and shock. Treatment in the late stages is usually unsuccessful, with mortality up to 90%.

### Gastrointestinal anthrax

Follows ingestion of contaminated meat. Severe abdominal pain, bloody diarrhoea, massive ascites, and sepsis occur. Mortality is >50%.

### Other forms

Incl. meningitis (which may complicate any of the other forms) and oropharyngeal anthrax. A newly recognized form is injection anthrax, associated with skin-popping (injection into subcutaneous and muscle tissues) of heroin contaminated with spores of *B. anthracis*. An outbreak in Scotland resulted in 47 cases with 13 deaths.

## Diagnosis

Rapid diagnosis is by demonstrating Gram +ve bacilli in smears from fluid from under the eschar, or other site-of-disease samples (or using newer methods such as PCR, direct immunofluorescence). Culture blood, LNs, and CSF as appropriate (Box 17.15).

## Management

- Early, high-dose antibiotic therapy is vital: give benzylpenicillin 2.4g IV 4hrly for 10d. Naturally (or genetically modified) penicillin-resistant mutants can occur, so until culture and sensitivity available, add ciprofloxacin 400mg IV bd followed by 500mg oral bd. Doxycycline 100mg bd is an alternative.
- Passive immunity: monoclonal antibodies (raxibacumab and obiltoxaximab) have been made available by the Centers for Disease Control and Prevention (CDC), Atlanta, USA, for the treatment of inhalational anthrax, in combination with appropriate antibiotics. They can also be used in prophylaxis, should other treatments be unavailable or inappropriate. Human anthrax immunoglobulin can also be given to provide passive immunity to those exposed to inhalational anthrax. It is used in combination with antibiotics.
- Surgical debridement of the black, necrotic eschar is unnecessary. Eschars become sterile in <2d. However, in injection anthrax prompt widespread debridement of the affected subcutaneous tissue is mandatory.
- *Infection control*: little risk of patient-to-patient transmission; use standard barrier precautions with gloves, gowns/aprons.

## Duration of antibiotic therapy

- *Cutaneous*: 7–10d.
- *Inhalational*: at least 14d after symptoms abate.
- *GI*: at least 14d after symptoms abate.

## Post-exposure prophylaxis

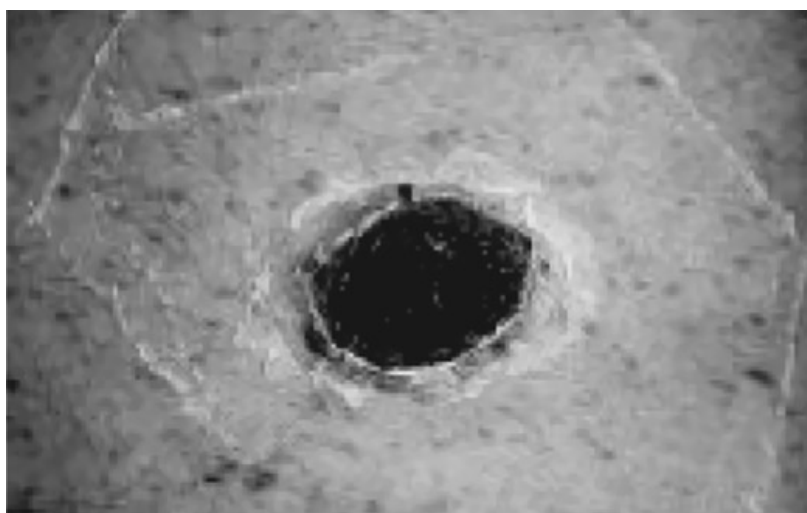
Should be considered following possible deliberate aerosol release—ciprofloxacin 500mg oral bd, or doxycycline 100mg bd, for 60d.

**Box 17.15 Differential diagnosis of eschar****Infective causes**

- Staphylococcal skin infection.
- Tularaemia.
- Scrub typhus.
- Rickettsial spotted fevers.
- Rat bite fever.
- Ecthyma gangrenosum.

**Non-infective causes**

- Spider bites.
- Vasculitides.

**Fig. 17.13**

Typical eschar of cutaneous anthrax.

**Paediatric note: paediatric doses for anthrax**

- Ciprofloxacin 10–15mg/kg (max. 400mg) IV bd followed by 10–15mg/kg (max. 500mg) oral bd.
- If penicillin susceptible, use IV benzylpenicillin 150mg/kg daily in four divided doses.
- For children >12yrs, use adult doses.

### Public health note: prevention of anthrax

- Disinfection: spores are resistant to desiccation, heat, UV light, gamma irradiation, and many disinfectants. For disinfection of discharge from lesions or soiled materials use hypochlorite, hydrogen peroxide, peracetic acid, or glutaraldehyde. Burn or autoclave contaminated material, where possible.
- Vaccination: immunize high-risk persons with cell-free, supernatant-derived vaccine. Regular boosters required.
- Veterinary public health measures: infected carcasses should be incinerated at site, do not bury or transport if possible; immunize all domestic animals at risk, with annual re-immunization.
- Control occupational exposure: control dust; ventilate work areas; wear protective clothing; disinfect wool, hides, and bone prior to processing.

## African trypanosomiasis

Human African trypanosomiasis (HAT) or ‘sleeping sickness’, is a protozoan disease confined to sub-Saharan Africa (Fig. 17.14), caused by *Trypanosoma brucei* spp. Two forms of HAT exist, *T.b. gambiense* and *T.b. rhodesiense*, both transmitted by tsetse flies (genus *Glossina*) (Fig. 17.15), but epidemiological (Table 17.8) and clinical features (Table 17.9) differ.

### Epidemiology

Incidence of *T.b. gambiense* HAT has been decreasing since 2000 (2131 cases in 2016). *T.b. rhodesiense* HAT is sporadic ( $\leq 100$  cases/year), but likely underdiagnosed in some areas. Uganda is the only country with both forms, albeit in different geographical areas.

**Table 17.8** Summary epidemiology and transmission of HAT

	<b><i>T.b. gambiense</i></b>	<b><i>T.b. rhodesiense</i></b>
Geography (Fig. 17.14)	Central and W Africa	E and southern Africa (Malawi, Zambia, Zimbabwe, Uganda, Tanzania, Kenya)
Transmission areas	Waterholes, rivers	Savannah, recently cleared bush
Reservoir	Humans	Game animals, cattle
Disease pattern	Endemic	Sporadic (occasional epidemics)

**Table 17.9** Summary clinical features of HAT

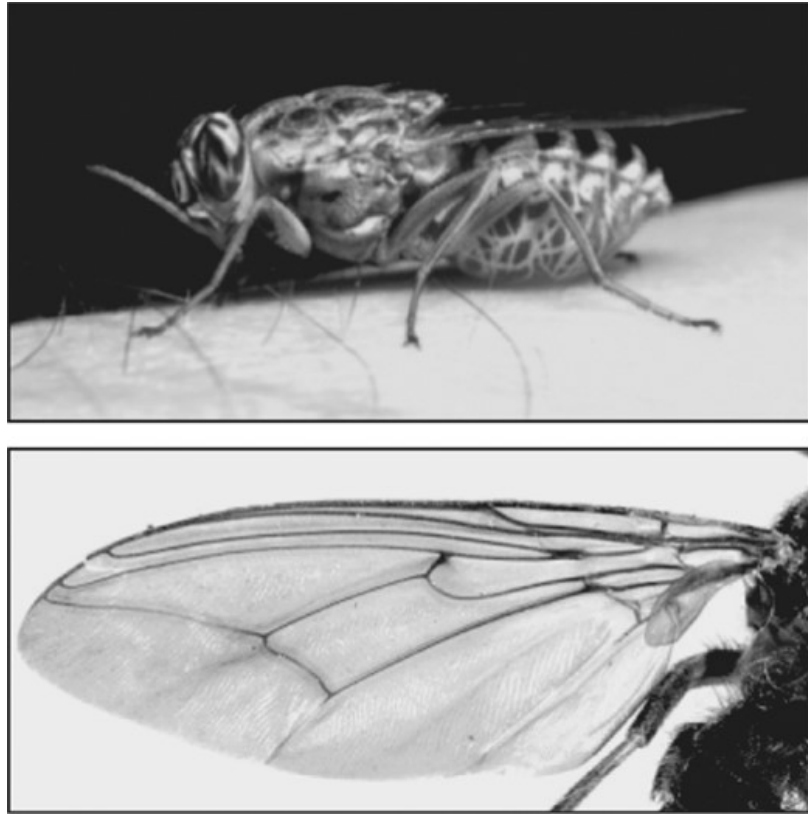
	<b>T.b. gambiense</b>	<b>T.b. rhodesiense</b>
Clinical time course	Chronic, insidious (after asymptomatic phase)	Acute, sometimes fulminant
Inoculation site	Rarely chancre	Often chancre
Symptoms	<i>Early:</i> non-specific fevers, pruritus, arthralgia <i>Late:</i> CNS symptoms	Fever, malaise, headache, myalgia, arthralgia, cardiac symptoms <i>Late:</i> CNS symptoms
Signs	<i>Early:</i> LNs <i>Late:</i> CNS signs	<i>Early:</i> rash, LNs, acute myocarditis, dysrhythmia, heart failure <i>Late:</i> DIC, multiorgan failure, CNS signs
Outcomes untreated	Fatal (months–years)	Fatal <1–3mths

**Fig. 17.14**



Distribution of human African trypanosomiasis. The area southeast of the line = *T.b. rhodesiense* and northwest of the line = *T.b. gambiense*.

**Fig. 17.15**

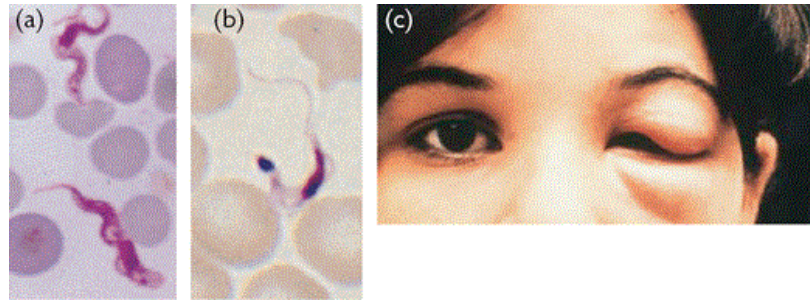


Female tsetse fly (*Glossina morsitans*) engorged with blood after feeding. All *Glossina* flies can be identified by the pattern of 'cells' on their wings. Between the fourth and fifth veins of the wing is the 'hatchet cell'—looks like a butcher's cleaver.

## Clinical features

*T.b. gambiense* HAT is a chronic illness, but *T.b. rhodesiense* HAT is an acute, sometimes fulminant disease. Both forms usually fatal if untreated. An infective tsetse bite → a local inflammatory reaction → an itchy, tender subcutaneous swelling (chancre) (*T.b. rhodesiense*) → regional lymphadenopathy (both types). Invasion of bloodstream and lymphoreticular system follows —the haemolymphatic (early) stage. Trypanosomes then invade CNS, → meningo-encephalitic (late) stage of the disease. Trypanosomes escape host immunological responses by changing surface antigens (antigenic variation; see 🔄 Table 17.10, p. 729; see Colour Plate 9a).

## Plate 9



Trypanosomes. (a) *Trypanosoma b. rhodesiense* (Giemsa); (b) *Trypanosoma cruzi* (Leishman stain); (c) Romaña's sign (unilateral oedema and conjunctivitis at the portal of entry in acute Chagas' disease). (c)

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### Gambian trypanosomiasis

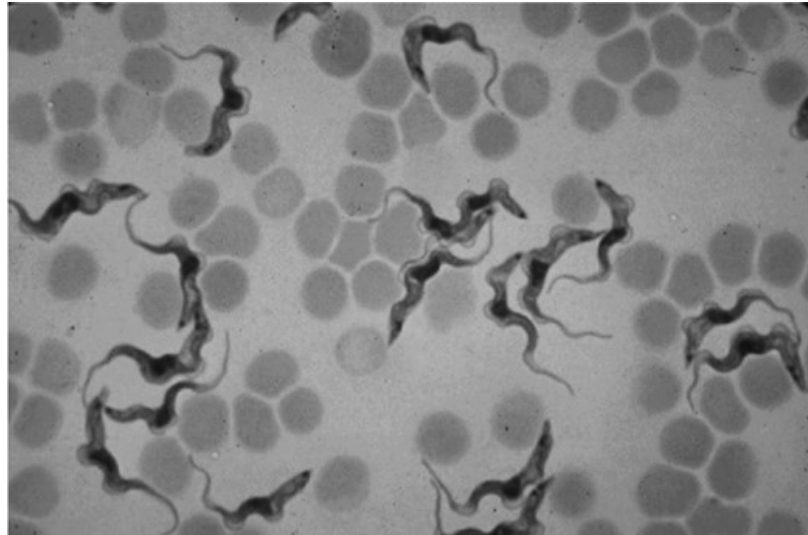
After asymptomatic phase (months–years), the early stage is characterized by irregular fevers, fatigue, arthralgia, myalgia, pruritus, headache. Lymphadenopathy, often in post-cervical triangle (Winterbottom's sign), is common; LNs are soft and non-tender; splenomegaly is rare. CNS symptoms incl. headache, change in personality, apathy, forgetfulness; psychosis (abnormal behaviour, agitation, delusions). CNS signs incl. pyramidal (focal motor weakness), extra-pyramidal (resting tremor common), and cerebellar (ataxia). Late features incl. daytime somnolence, coma, and seizures. Patients die of starvation, intercurrent bacterial infection, or convulsions.

### Rhodesian trypanosomiasis

1° chancre at bite site, subsides in 2–3wks. After 1–3wks, acute severe illness with high fever, chills, malaise, severe headache, weight loss, myalgia, arthralgia. Erythematous rash (macular, papular or circinate) may occur. Disease often runs a fulminant course with multiple-organ failure and early death. CNS involvement (meningo-encephalitis) progresses rapidly and is fatal if untreated. Myocarditis causing atrial or ventricular dysrhythmia, or heart failure, may precede meningo-encephalitis.



**Fig. 17.16**



Trypomastigote forms of *T.b. rhodesiense* on a peripheral thin blood smear. See Colour Plate 9a.

## Diagnosis

Screening for Gambian HAT is by card agglutination trypanosome test (CATT), a sensitive, practical serological test. No serologic test exists for Rhodesian HAT. Direct microscopic observation of trypanosomes in LN aspirates, blood (Giemsa-stained thick smear, quantitative buffy coat, haematocrit, or mini-anion exchange centrifugation techniques) or CSF (single centrifugation) confirms diagnosis. Sensitivity of blood examination is greater in *T.b. rhodesiense* due to larger numbers of circulating trypanosomes (Fig. 17.16).

Staging disease by LP is mandatory. Findings in the CSF that indicate trypanosomal meningo-encephalitis:

- Trypanosomes.
- ↑ leukocytes (>5 per mm<sup>3</sup>) and/or
- ↑ total or specific (anti-trypanosomal) IgM.

## Treatment

- Depends on stage of disease and if Gambian or Rhodesian. *Note:* following renewed agreement between pharmaceutical industry and WHO, drugs for HAT are being donated to WHO.
- A new oral drug, fexinidazole has been shown to be effective and safe for treatment of early- and late-stage Gambian HAT safe and effective and is an oral treatment for Gambian HAT and is registered now for use in a number of countries for first-line therapy. This drug is in clinical trials (2019–) for the treatment of both stages of Rhodesian HAT.

## Gambian HAT

- Early stage: pentamidine isetionate 4mg/kg IM od for 7d.
- Late stage (first choice): eflornithine 200mg/kg IV bid for 7d, diluted in normal saline and infused over 2h, and nifurtimox 5mg/kg oral tds for 10d.
- Late stage (*alternative if nifurtimox not available or contraindicated*): eflornithine 100mg/kg IV qds for 14d.
- Late stage (*alternative only if eflornithine not available or for treatment of relapse after eflornithine-based regimen*): melarsoprol 2.2mg/kg/d slow IV injection, with prednisolone 1mg/kg oral od for 10 consecutive days. Use a glass syringe, or draw up and inject with a plastic syringe as soon as possible, since melarsoprol binds to plastic; very irritant, avoid extravasation (risk soft tissue necrosis). Melarsoprol is more toxic than eflornithine-based regimen and associated with up to 30% treatment failure in parts of Angola, Uganda, Central African Republic, DRC, and Sudan.

## Rhodesian HAT

- Early stage: suramin 5mg/kg by slow IV injection on day 1 (test dose), followed by 20mg/kg on days 3, 10, 17, 24, and 31. In Rhodesian HAT, because of the possibility of introducing circulating trypanosomes into the CSF by the LP needle itself, it is recommended to clear the blood of visible trypanosomes with suramin prior to performing the LP.
- Late stage: melarsoprol sequential regimen (i.e. three cycles of three daily injections of 3.6mg/kg with resting period of 7–10d between each cycle) or 2.2mg/kg/d for 10 consecutive days (recently showed a similar efficacy and toxicity profile), plus prednisone 1mg/kg oral od (commence prior to melarsoprol to reduce occurrence of melarsoprol-induced encephalopathy). Eflornithine is thought to be ineffective.

See Box 17.16 for adverse effects of drugs.

**Box 17.16 Adverse effects of drugs used for HAT**

- Eflornithine: leukopenia, anaemia, thrombocytopenia, soft tissue infections, and convulsions.
- Nifurtimox: anorexia, nausea, vomiting, insomnia, mood change, psychosis, convulsions.
- Melarsoprol: encephalopathic syndrome (see later in box), polyneuropathy, severe (sometimes bloody) diarrhoea, and rash.
- Pentamidine isetionate: hypoglycaemia (frequent), hypotension, sterile abscess, and pancreatitis (rare).
- Suramin: anaphylactic shock, rash, fever, neurological, haematological, and/or renal toxicity, peripheral neuropathy.

**Melarsoprol-induced encephalopathic syndrome (ES)**

Occurs in 5–15% of treated patients, producing status epilepticus and coma. Mortality is ~50%. May be partially prevented by oral prednisolone 1mg/kg oral od in Gambian HAT. Onset of fever, tachycardia, headache, tremor, and conjunctival suffusion during melarsoprol treatment should be considered as a warning. Melarsoprol treatment should be stopped immediately; it can be restarted once symptoms subside. Some authorities recommend the use of high-dose dexamethasone IV (e.g. 30mg loading dose followed by 15mg every 6h for adults) for treatment of ES or impending ES.

**Paediatric health note**

HAT in neonates and infants can be due to mother-to-child transmission or early exposure to tsetse fly bites. Delayed diagnosis is common in young children due to non-specific symptoms and signs. Chronic neurodevelopmental disorders are common sequelae of late-stage HAT. Treatment regimens are similar to adults.

**Public health note: prevention and control of HAT**

- *Screening*: Gambian HAT control programmes rely on active case finding through systematic serologic screening by CATT of communities, and treatment of all those infected (humans are the only significant reservoir). In areas of low prevalence of Gambian HAT, integration of disease management within existing health structures is a challenge.
- *Vector control*: by tsetse fly trapping is cumbersome but effective, particularly in Rhodesian HAT control programmes.
- In outbreaks of Rhodesian HAT, a combined programme of vector control, treatment of infected cattle, and active detection and treatment of human cases should be implemented.

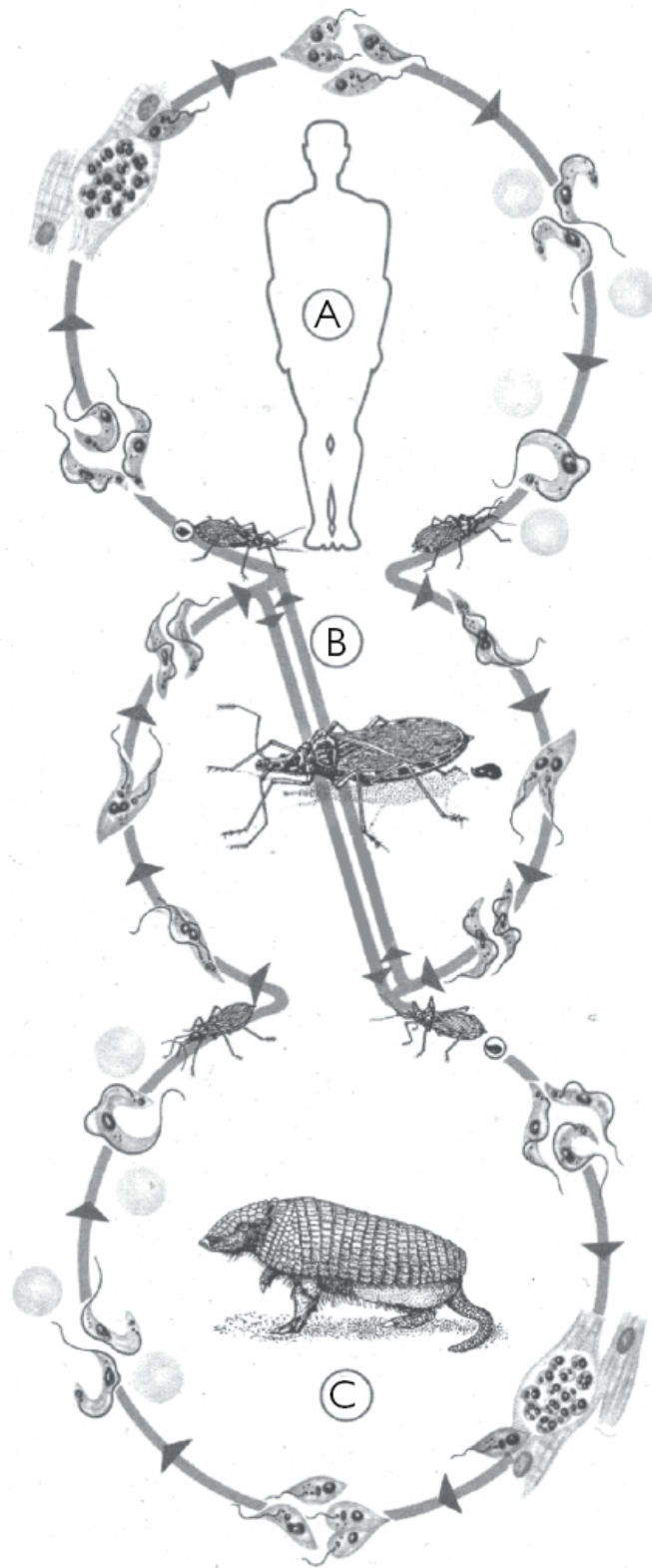
*Challenges*: improved diagnostic tools and drugs and simplified diagnosis–treatment algorithms are urgently needed.

## American trypanosomiasis

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American trypanosomiasis or Chagas' disease (CD) is endemic in Latin America, caused by the protozoa *Trypanosoma cruzi*, and transmitted by triatomine bugs of the reduviid family (see Fig. 17.17 and Colour Plate 9b.)

Fig. 17.17



Life cycle of *T. cruzi*. Reduviid bug (B) transmits infection via faeces when taking blood meals from animal reservoirs such as the armadillo (C) or humans (A).

## Pathogenesis

Parasites invade mesenchymal tissues (esp. heart muscle) where they persist as amastigotes with only intermittent parasitaemia, making direct detection difficult. In ~70% of adults, an adequate immune response controls infection, producing a benign chronic phase ('indeterminate form'). Persistent infection and failure to modulate the inflammatory immune response cause chronic cardiomyopathy in ~30%. GI CD is thought to result from damage to intramural autonomic ganglia during the acute phase and subsequent unmasking by age-related neural attrition.

## Epidemiology and transmission

~6 million people are infected by *T. cruzi* in endemic countries of Latin America. ~1.2 million individuals have chronic Chagas cardiomyopathy. Social determinants of CD: poor housing → house infestation → risk of CD. Risk of acquiring CD while travelling is very low, but travellers should avoid poor-quality housing, and use insecticide-treated nets if sleeping in an infested house is unavoidable.

### Transmission routes

- Vector transmission: via triatomine bugs (a subfamily of the Reduviidae). >140 species have been identified; five species that routinely infest or invade human dwellings are responsible for most human infections. Parasites from insect faeces enter via human nose and mouth mucous membranes, conjunctivae, or damaged skin—esp. where the insect bite is scratched and rubbed → ~30,000 new CD cases/yr.
- Transplacental transmission: ~9000 cases/yr.
- Ingestion of accidentally infected food or beverage: incl. fruit juice, occasional outbreaks of disease.
- Blood transfusion, organ transplantation: <1% blood donations are infected; blood bank screening is conducted in all endemic countries of Latin America, the USA, and Spain.
- Occupational exposure in laboratory workers.

### Reservoirs

- Domestic and wild mammals are reservoirs for the parasite.

### Distribution

- In the Americas, the epidemiology can be divided into two groups according to whether or not there is significant domestic and peri-domestic vector-borne transmission (Table 17.10). However, these patterns have been altered by 15–25yrs of intensive domestic and peri-domestic insecticide application under regional control programmes.
- With migration, CD has become a globalized disease, and individuals infected in the endemic area may be diagnosed years later in other countries. Non-endemic countries (Canada, Spain, France, Switzerland, Italy, Japan, etc.), receive migrants infected with *T. cruzi*, requiring diagnosis and treatment. In the USA, ~300,000 Latin American immigrants are infected with *T. cruzi*, and 30,000–45,000 have clinical CD. The southern USA also has local sylvatic cycles with infected vectors and animals, incl. domestic dogs; the number of locally acquired human infections is unknown. See Fig. 17.18.

**Fig. 17.18**



Distribution of American trypanosomiasis. *T. cruzi* infections of animals occur over a much wider range than Chagas' disease in man.

## Clinical features

CD is classified into acute and chronic phases. During the chronic phase, an infected individual may be asymptomatic and have no evidence of end-organ damage (the indeterminate form) or have cardiomyopathy, GI disease, or both.

### Acute

The acute phase lasts 6–8wks following infection. Infection may be subclinical, with non-specific symptoms. Local inflammation at bite site → chagoma and lymphadenopathy. If inoculation occurs via the conjunctiva, unilateral eyelid oedema may occur (Romaña's sign, see 🔄 Colour plate 9c). This characteristic feature usually lasts ~1mth (c.f. bacterial conjunctivitis which usually only persists max. ~10d).

Fever occurs after an incubation period of ~2wks post infection, coinciding with parasitaemia. Rarely, the acute phase can include a maculopapular or petechial rash. There may be oedema, esp. of the face. Other features incl. hepatosplenomegaly, cardiac dysrhythmia, or failure, and rarely, meningo-encephalitis which is potentially fatal. Most congenital infections are asymptomatic. ~20–30% of infected infants present with LBW and/or hepatosplenomegaly. A few infants have more severe signs, e.g. jaundice, respiratory distress syndrome, and/or meningoencephalitis, with high risk of death.

## Chronic *T. cruzi* infection

Diagnosis relies on positive anti-*T. cruzi* IgG serology. Parasitological and molecular tests may or may not be positive; there is usually no obvious evidence of organ damage (cardiac or GI). Normal ECG, CXR, and bowel imaging. Rigorous and sophisticated testing may detect mild changes, but no established evidence of prognostic value.

Chronic end-organ damage affects ~30% of those infected, often after decades of asymptomatic infection. Chagas cardiomyopathy occurs in all endemic areas with ↓ frequency and ↓ severity in areas under effective vector control. GI CD is much less common than cardiomyopathy, and seen almost exclusively in southern Brazil, Bolivia, Argentina, Chile, Uruguay, and Paraguay.

## Cardiac

Pathology incl. conduction system deficits, esp. right bundle branch block (RBBB) and/or left anterior hemiblock, frequent ventricular arrhythmias, LV aneurysm, thromboembolism, progressive dilated cardiomyopathy, and cardiac failure in late stages. Some patients with chronic Chagas cardiomyopathy have normal LV function with only arrhythmias and conduction disorders. Ventricular arrhythmias and LV dysfunction → poor prognosis. Chest pain (usually atypical angina) is common. Dilated ventricles +/- aneurysm → mural thrombi → systemic, pulmonary, and cerebral emboli. Heart failure is exacerbated by AF; prognosis worsens as cardiac disease progresses:

- Stage 1: asymptomatic, normal ECG or non-specific findings; normal LV function on echocardiography.
- Stage II: asymptomatic or mild symptoms, characteristic ECG abnormalities (RBBB + left anterior hemiblock, first- or second-degree AV block), segmental wall motion abnormalities but no ↓ LV function on echocardiography.
- Stage III: New York Heart Association (NYHA) class I/II, more advanced abnormalities on ECG, mild to moderate ventricular dysfunction.
- Stage IV: NYHA class III/IV, atrial flutter/fibrillation, severe global ventricular dysfunction (e.g. LV ejection fraction <30%), complex ventricular arrhythmias.

## Gastrointestinal

Dysphagia, regurgitation of food, chronic constipation, abdominal pain. Dysregulation of peristalsis and oesophageal sphincter relaxation, → oesophagitis, mega-oesophagus, megacolon. Complications incl. large bowel obstruction or volvulus.

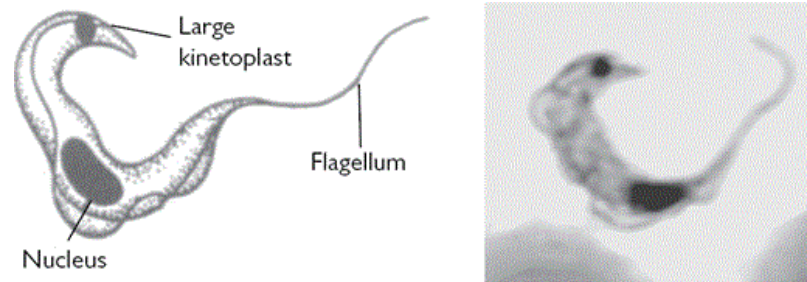
Some patients have both cardiac and GI disease.

## Diagnosis

In acute phase, parasites may be detectable in fresh preparations of buffy coat or stained peripheral blood specimensx (see Fig. 17.19). Serology (>2 tests) for anti-*T. cruzi* IgG +ve is the main diagnostic tool in chronic infection. Parasites may sometimes also be detected directly in wet mount or Giemsa-stained blood films (🔍 Colour plate 9b) or CSF precipitate (CSF only positive in acute or reactivation disease); parasite DNA may be detected by PCR. Seropositive individuals should be evaluated for symptoms and signs of cardiac and GI disease.



**Fig. 17.19**



*T. cruzi* as seen in a blood film.

## Management

### Acute phase

Give either:

- *Benznidazole* 5–7mg/kg/d (children 10mg/kg/d): orally in two divided doses for 60d; max. recommended daily dose is 300mg. For adults >60kg, calculate the total dose and extend treatment period >60d. Common side effect is urticarial dermatitis (30% in 1st week of treatment), with good response to antihistamines or corticosteroids. If fever, adenopathy, or exfoliative dermatitis occurs, discontinue treatment. Other adverse effects incl. polyneuropathy (usually towards end of treatment) with pain and/or tingling in the legs, anorexia); or
- *Nifurtimox* 8–10mg/kg: oral in three divided doses (children 15mg/kg oral in four divided doses) for 90d; side effects: anorexia (common), abdominal pain, nausea, vomiting and weight loss; peripheral neuropathy, CNS side effects incl. insomnia, irritability, depression.

### Chronic phase

Benznidazole is used, but the efficacy difficult to assess because serology takes years to decades to become negative. Trials in children 6–12yrs of age show >60% efficacy based on serology, but adult data are mixed. In the benznidazole arms of recent adult clinical trials, quantitative PCR quickly becomes negative in 85–90% of those who complete 60d treatment and remains negative during >12mth follow-up. Negative PCR is a good indicator that the parasite load has fallen below detectable levels, but does not prove parasitological cure.

- *Symptomatic treatment*: for complications, e.g. CCF, arrhythmias (➡ Cardiac arrhythmias, p. 332), AV block, and sick-sinus syndrome or anticoagulation for systemic emboli.
- *Pacemakers*: implanted in patients with severe bradyarrhythmias.
- *Surgery*: may be required for mega-oesophagus or megacolon.
- *Heart transplantation*: in severe heart patients (CD is the third major cause of heart transplantation in Brazil).

**Table 17.10** Grouping of countries by American trypanosomiasis transmission cycle

<b>Countries</b>	Argentina, Belize <sup>2</sup> , Bolivia, Brazil <sup>1</sup> (outside of the Amazon), Chile <sup>1</sup> , Colombia, Costa Rica, Ecuador, Honduras <sup>2</sup> , Mexico, Paraguay, Peru, Uruguay <sup>1</sup> , Venezuela, El Salvador <sup>2</sup> , Guatemala <sup>2</sup> , Nicaragua <sup>2</sup> , Panama	Amazon Basin, Caribbean islands <sup>3</sup> , USA, French Guiana, Guyana, Haiti, Jamaica, Suriname
<b>Transmission cycles</b>	Domestic, peri-domestic, Sylvaic	Sylvatic

- 1
- T. cruzi* transmission by *T. infestans* certified as interrupted throughout Brazil, Chile, Uruguay.
- 2
- T. cruzi* transmission by *R. prolixus* certified as interrupted throughout Belize, El Salvador, Guatemala, Honduras, Nicaragua.
- 3
- Documented in Trinidad, presumed in other islands.

**Paediatric note: congenital *T. cruzi* infection**

Transmission from infected mother to newborn children varies from 1% to 12% (median 5–6%) in different Latin American countries and should be evaluated in seropositive mothers. Congenital infection is confirmed by identification of parasites or parasite DNA in the infant’s blood and/or detection of infant anti-*T. cruzi* IgG 8–9mths after birth (assuming vector and other modes of transmission excluded). Congenital CD is considered acute and requires trypanocidal treatment. Notification is mandatory.

**Public health note: prevention and control of Chagas’ disease**

- Limit exposure to the vector: improved housing, residual insecticide spraying of houses.
- Promote the use of insecticide-treated bed nets.
- Screen donors of blood for transfusion and organ transplantation.

CD is a clear example of public policy success, with five separate large-scale vector control programmes with modern pyrethroid insecticides being implemented in last few decades in different Latin American countries. Mandatory notification of acute cases for intense epidemiological surveillance. Micro-epidemics of acute cases due to oral transmission through contaminated food, such as sugar cane juice, or açai (*Euterpe oleracea*) fruit juice or sauce, have been described, especially in Amazon Region and in South Brazil.

# Visceral leishmaniasis (kala-azar)

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## Introduction

Visceral leishmaniasis (VL), or kala-azar, is a severe systemic protozoan disease caused by zoonotic *Leishmania infantum* (in S America and the Mediterranean Basin; also known as *L. chagasi* in Latin America) or anthroponotic *L. donovani* (in S Asia and E Africa), transmitted to humans by nocturnal sandfly bites (Fig. 17.20). VL is endemic in areas of South America, the Mediterranean basin, Asia, and Africa (Fig. 17.21). Large deadly epidemics of *L. donovani* VL may occur in non-immune or malnourished populations. Generalized infection of macrophages → the classical clinical picture of persistent fever, splenomegaly, and anaemia and to progressive immunosuppression. VL can be confirmed by serology, including rK39 antigen-based RDTs, by microscopic examination of spleen, bone marrow or LN aspirates, or by PCR. Liposomal amphotericin B is the preferred treatment, except for *L. donovani* in E Africa where the combination of pentavalent antimonials and paromomycin is used. Treatment of VL is usually effective except in HIV co-infected or other immunosuppressed patients, who are prone to frequent relapses.

## Pathogenesis

Promastigotes (flagellate forms) are present in infected sandflies' saliva; they enter human macrophages, where they transform into amastigotes (rounded forms) that proliferate, killing the host cell, infecting other cells, and spreading to the whole reticuloendothelial system (spleen, bone marrow, liver, LNs) and other tissues. Infection is often subclinical, when controlled by an efficient cell-mediated immune response. When the immune response is ineffective, clinical VL develops. Latent infections can reactivate during immunosuppression.

## Transmission

Transmission is by the nocturnal bite of female *Phlebotomus* and *Lutzomyia* sandflies (Fig 17.20). Dogs are the major reservoir of *L. infantum* in the Mediterranean basin and Brazil, where the zoonotic form of VL primarily—but not exclusively—affects children and immunosuppressed individuals (see Fig. 17.21). Humans are the main reservoir of *L. donovani*, a more virulent *Leishmania* species that can affect all age groups. Patients with post-kala-azar dermal leishmaniasis (PKDL) are medium-term reservoirs of *L. donovani*. Transmission by blood transfusion or organ transplantation, and from mother to child (congenital VL), occasionally occur. (Fig 17.22).

## Clinical features

Following an incubation period of several weeks or months, patients present with persistent fever, accompanied by night sweats, headaches, cough, epistaxis, and abdominal pain/distension due to the enlarged spleen. Enlarged 2–3cm lymph nodes (esp. inguinal) are commonly noticed in E Africa. Darkened skin is noticed in <20% of patients in Asia—means 'black disease' in Hindi. Weight loss, cachexia, anaemia, and fatigue gradually worsen. Epistaxis is characteristic. In the absence of treatment, death occurs, usually from superimposed infections like pneumonia, sepsis, tuberculosis, measles, or malaria; or from major bleeding; or from anaemic heart failure.

## Main differential diagnosis

Malaria, disseminated TB, brucellosis, enteric fever.

## Diagnosis

Several diagnostic confirmatory tools have been validated in clinical suspect patients, e.g. with  $\geq 2$ wk fever and splenomegaly:

- *Serology*: ELISA and IFA tests have good diagnostic performance but are not designed for field use. The semi-quantitative direct agglutination test (DAT) has high sensitivity and specificity in all endemic areas. Rapid diagnostic tests (RDTs) detecting antibodies against recombinant K39 antigen allow for decentralized diagnosis. Whereas the specificity of rK39 RDTs is high ( $>90\%$ ) in all endemic areas, their sensitivity varies with the geographic location, being rather insensitive ( $<85\%$ ) in E Africa.
- *Parasitology/PCR*: microscopic examination of Giemsa-stained smears of spleen aspirate is  $\geq 95\%$  sensitive but the procedure requires expertise. Sensitivity is lower (60–80%) with aspirates from LN or bone marrow. Sensitivity is markedly improved by culture or PCR.

## Management

VL treatment is both supportive (e.g. nutrition, blood transfusions, antibiotics) and specific (anti-leishmanials). Superimposed bacterial infections should be treated with a low index of suspicion. The choice of antileishmanial drugs and regimen depends on the geographical area, presence of immunosuppression (Box 17.17), and availability of drugs:

### L. infantum endemic areas

- Liposomal amphotericin B (LAmB): 18–21mg/kg total dose divided in 2–7 daily infusions.
- Alternative: IM or IV pentavalent antimonials (Sbv) 20mg/kg/d for 30d; there is no upper limit on the daily dose; meglumine antimoniate and sodium stibogluconate are equivalent.

### L. donovani in South Asia

- LAmB: 10mg/kg single dose or 15mg/kg total dose divided in three daily infusions.
- Alternative: oral miltefosine (dosage adjusted to body weight) + IM paromomycin 15mg/kg/d for 10d.

### L. donovani in East Africa

- IM or IV pentavalent antimonials (Sbv) 20mg/kg/d + IM paromomycin 15mg/kg/d for 17d.
- Alternative: LAmB 30–40mg/kg total dose divided in 6–10 daily infusions; used as preferred treatment for patients at  $\uparrow$  risk of death with Sbv: age  $<2$  yrs or  $\geq 45$  years, severe malnutrition (BMI  $<13$ kg/m<sup>2</sup>), severe anaemia (Hb  $<6$ g/dL), jaundice, concomitant HIV or TB.

Main drug-specific side effects:

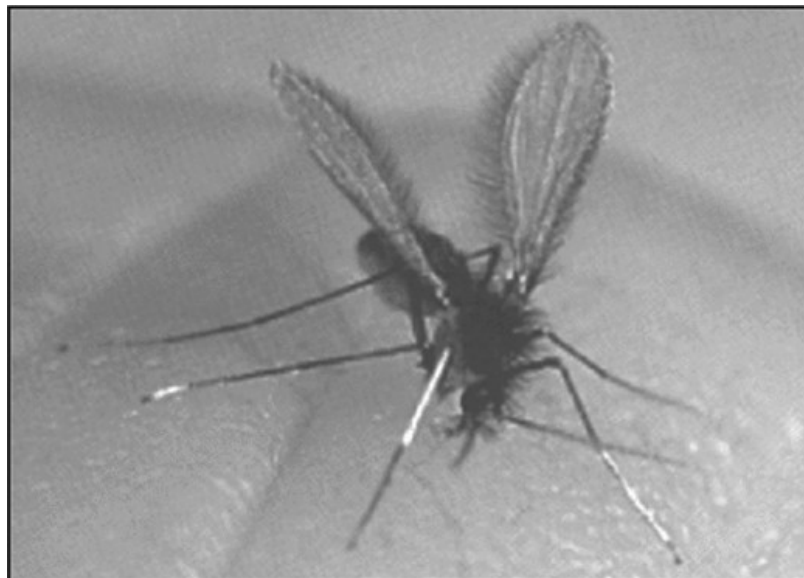
- LAmB: (mild) infusion-related reactions, renal toxicity, hypokalaemia.
- Sbv: arthralgias, pancreatitis, cardiac arrhythmias (may be fatal).
- Paromomycin: pain at injection site, (mild) renal toxicity, ototoxicity.
- Miltefosine: (mild) vomiting, renal or hepatic toxicity, teratogenicity (effective contraception during and  $\geq 5$  mths after treatment).

Clinical improvement should be evident in 7–10d. Response can be monitored by ↓ fever, ↑ Hb, and ↑ spleen size. A parasitological response is shown by a negative test-of-cure (splenic, bone marrow, or LN aspirate). Clinical follow-up for 6–12mths is important to detect relapses, which should be <5%.

### Box 17.17 VL–HIV co-infection

- Co-infections have been reported in all VL endemic areas, but are particularly prevalent in northern Ethiopia.
- HIV and VL have a synergistic effect to ↓ cellular immunity, → fewer subclinical and more overt infections and an accelerated progression of HIV disease.
- The VL clinical features in HIV+ve patients are similar to non-HIV patients but some HIV+ve patients present with atypical features, e.g. skin, pulmonary, or intestinal involvement.
- There is ↓ sensitivity of most serological tests (the DAT being spared), but ↑ sensitivity of parasitology and PCR (due to ↑ parasite load).
- Pentavalent antimonials are contraindicated due to significant (up to 25%) risk of death; patients should be treated with LAmB 40mg/kg total dose. Clinical trials are underway to assess the efficacy and safety of LAmB combined with miltefosine.
- Relapses are frequent and are only partially prevented/delayed by 2° prophylaxis with IM or IV pentamidine isethionate 4mg/kg once a month and early introduction of ART.

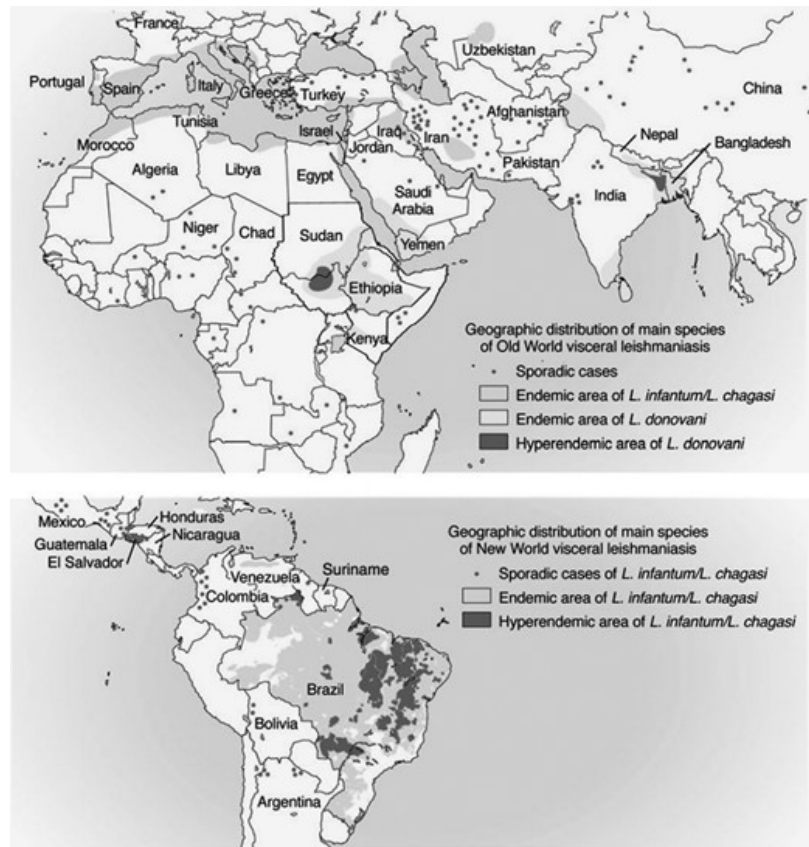
Fig. 17.20



The female phlebotomine sandfly is about half the size of a mosquito and feeds nocturnally. Several species transmit visceral or cutaneous leishmaniasis.

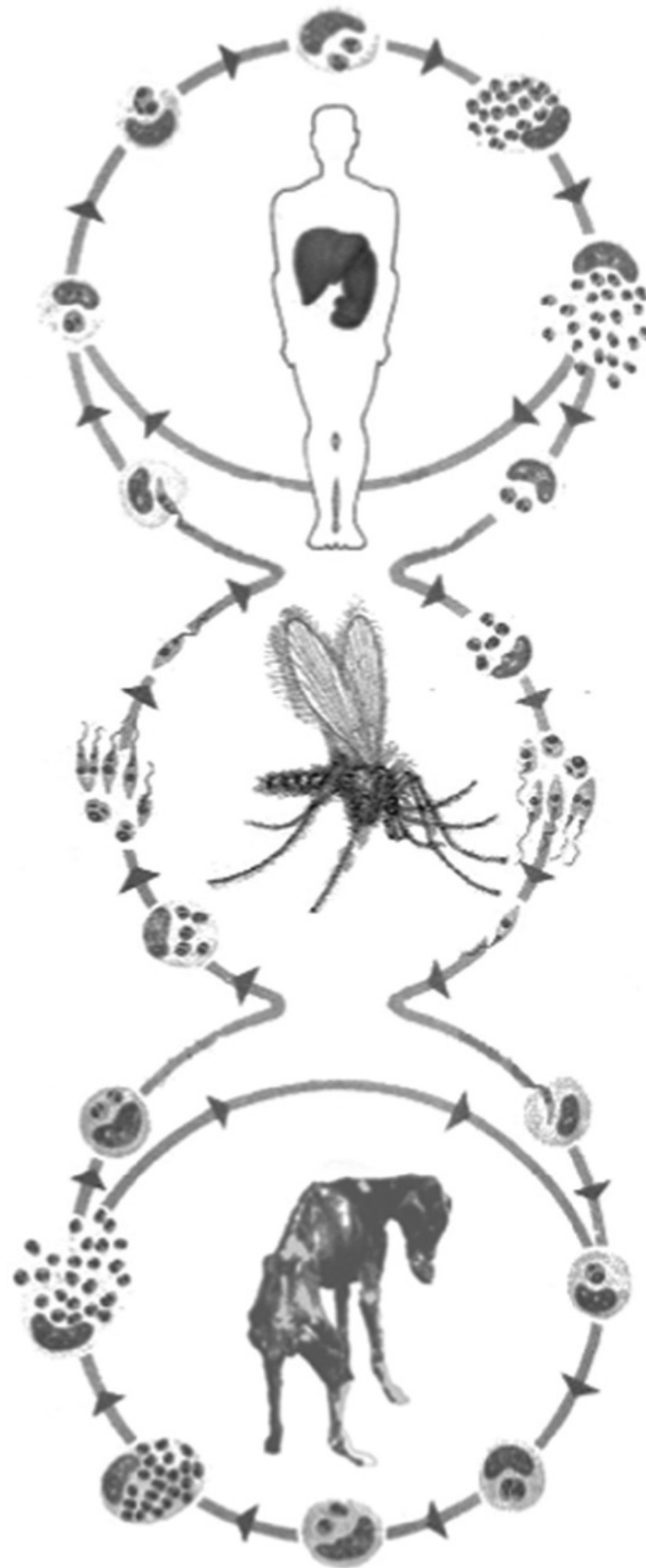
Reproduced with permission from Centers for Disease Control and Prevention's Public Health Image Library (PHIL), ID: #10277. Image is in the public domain.

**Fig. 17.21**



Geographic distribution of visceral leishmaniasis.

Fig. 17.22



Life cycle of visceral leishmaniasis.

Adapted from Piekarski, G, Medical Parasitology in Plates, 1962, with kind permission of Bayer Pharmaceuticals.

### Public health note

- Commercial vaccines are available to prevent VL in dogs but none are yet available for humans.
- In areas of zoonotic VL, deltamethrin-impregnated dog collars ↓ transmission of *L. infantum*.
- In the *L. donovani* S Asian focus, the governments of India, Nepal, and Bangladesh are implementing an elimination programme aiming at ↓ the VL annual incidence to <1/10,000 at subdistrict level. Activities are based on early detection and treatment of cases and vector control by indoor residual spraying.
- In the *L. donovani* E African focus, transmission to humans mainly occurs outdoors. While the use of insecticide-treated bed nets and peri-domestic spraying may have some limited effect on transmission, VL cannot be controlled effectively in this region and recurrent epidemics occur, which are magnified by civil unrest and population displacements.

## Infectious mononucleosis

Infectious mononucleosis (glandular fever) is classically caused by 1° infection with EBV infection. A glandular fever-like illness is also caused by acute HIV, CMV, and *Toxoplasma gondii* infection.

### Transmission

EBV (human herpesvirus 4) is usually transmitted orally via saliva. It establishes infection in the oropharynx and circulating B cells. Latent EBV infection persists, and intermittent viral shedding occurs spontaneously and esp. during febrile illnesses, e.g. malaria. In resource-poor regions, >90% children are infected with EBV by 5yrs, but show little clinical illness. The clinical picture of infectious mononucleosis is common in adolescence/adults, of whom ~50% develop clinical illness when infected.

### Clinical features

#### Symptoms/signs

Classically fever, pharyngitis, lymphadenopathy, and fatigue. The grey necrotic slough on tonsils needs to be distinguished from diphtheria. Splenomegaly/hepatosplenomegaly, hepatitis, thrombocytopenia, palatal petechiae, and morbilliform rash may occur (rash more common following ampicillin or amoxicillin administration).

#### Complications

Splenic rupture (spontaneously or after minor trauma) is uncommon but may be fatal. Upper airway obstruction may occur due to tonsillar and adenoidal enlargement. Encephalitis, hepatitis, myocarditis, pericarditis, pneumonitis, haemolytic anaemia, and nephritis are rare.

Latent EBV is implicated in some malignancies, including:

- Burkitt's lymphoma, common in equatorial Africa and Papua New Guinea; linked to intense malaria transmission.



- Nasopharyngeal carcinoma, esp. in SE Asia, China, and parts of N and E Africa; linked to environmental/dietary factors.
- Hodgkin's lymphoma.
- B-cell lymphoproliferative disease in the immunocompromised.
- Oral hairy leukoplakia, CNS and other lymphomas in HIV.

## Diagnosis

- Lymphocytosis, atypical lymphocytes, mild ↓ platelets, ↑ transaminases.
- IgM heterophil antibody tests (Paul Bunnell, Monospot) commonly used (limited value in children <4yrs). Presence of IgM antibody against EBV viral capsid antigens (VCA) in absence of IgG antibody against EBV nuclear antigen 1 (EBNA) confirms acute infection.

## Management

- *Supportive*: hydration, analgesia, +/- mild NSAIDs.
- Avoid contact sports for at least 4wks after symptom onset (splenic rupture rarely reported after 4wks).
- Consider corticosteroids for impending airway obstruction.
- Avoid amoxicillin in infectious mononucleosis as it precipitates a morbilliform rash in 70–90% of patients.
- Aciclovir is of no proven clinical benefit and is not recommended.

## Measles

Measles is a highly contagious viral (paramyxovirus) disease, which is vaccine preventable, and can cause severe disease and death, particularly in children.

## Epidemiology

Measles immunization prevented ~20.3 million deaths between 2000 and 2015 (a 79% reduction in annual deaths) but still caused >130,000 deaths in 2015. All WHO Regions have the goal of measles elimination goals by 2020; the Americas successfully interrupted endemic transmission in September 2016. Only eight of the 24 known measles virus genotypes have been detected since 2009. Unless 95% immunity is achieved in each birth cohort, measles will continue to discover immunity gaps and cause outbreaks.

## Transmission

- Only humans are infected, mainly by respiratory droplets and small particle aerosols that can remain airborne for 2h. Direct contact with respiratory secretions is another route.
- A measles case is infectious from 4d before to 4d after onset of the rash.
- On average, 9–18 non-immune people can be infected by a single measles case.
- Incubation period from exposure to onset of febrile symptoms is 10d (14d to onset of rash) but may be as long as 23d.

## Clinical features

Measles should be considered in the differential diagnosis of any patient with fever and erythematous rash.

### Fever

Fever  $>38^{\circ}\text{C}$  accompanied by at least one of the three Cs: cough, coryza, or conjunctivitis, with fever persisting after the appearance of rash.

### Rash

Distinctive, erythematous, non-vesicular maculopapular rash appears on day 3 or 4 of fever. As well as having rash, patient looks ill, miserable, and the three Cs are common. Rash begins on face and behind ears, within 24–36h the rash spreads down trunk → extremities (palms and soles rarely often involved). Begins to fade after 3–5d, initially to a purplish hue and then brown/black lesions with desquamation esp. in malnourished children. Koplik spots (grey-white spots surrounded by erythema on the buccal mucosa) may appear 24–48h before rash onset, but are often missed.

## Diagnosis

Measles should be suspected in all cases of:

- Fever.
- Generalized maculopapular rash.
- Especially if at least one of:
  - Cough.
  - Coryza.
  - Conjunctivitis.
- Particularly where there is no prior history of confirmed measles disease or two appropriately timed doses of measles vaccination.

## Laboratory confirmation

As measles elimination is approached, it is important to attempt to confirm all sporadic suspected measles cases and chains of transmission, by serology or detection of viral RNA by PCR. An epidemiologically confirmed measles case is a suspected measles case, although not laboratory confirmed, with onset of rash 7–23d after contact with a laboratory- or epidemiologically confirmed measles case.

- Serology: measles-specific IgM (unreliable during first 72h after rash onset) or fourfold ↑ in measles IgG antibody titres between acute and convalescent specimens. An adequate specimen for antibody detection is ≥0.5mL of sera or ≥3 fully filled circles of dried blood on a filter paper, or oral fluid collected <28d after rash onset.
- PCR: from throat or nasopharyngeal swabs or urine samples; PCR is +ve from 1st day of rash up to 14d.
- Virus isolation: measles virus can be isolated from nasopharynx or conjunctival swabs, respiratory secretions, and urine.

## Complications of measles

Measles complications occur commonly but particularly in immunocompromised (HIV+ve), malnourished (protein-calorie and vitamin A deficiency), pregnant women, and young children (<5yrs), with up to 20% case fatality in those aged <1yr.

Measles causes local tissue damage and ↓ cellular immunity; this predisposes to infection and persists for ~6–8wks after the acute illness. Pneumonia and diarrhoea are the most common complications and account for ↑ case fatality.

### Respiratory tract infection

- Respiratory symptoms are characteristic of measles and assumed to be 1° viral pneumonitis.
- Giant cell pneumonia and 2° bacterial pneumonia (*Staph. aureus*, *Strep. pyogenes*, *Strep. pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *Pseudomonas* spp.) are the leading causes of measles-associated deaths.
- Otitis media, with attendant hearing loss, may also follow 1° measles infection.

### Gastrointestinal complications

Diarrhoea can occur within a few days of rash onset, and → ↑ case fatality and ↑ malnutrition.

### Neurological complications

Encephalitis occurs in 1/1000 cases and 25% of affected children have neurodevelopmental sequelae, with a 15% case fatality.

- Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disease occurring 2wks after rash. Presents with fever, seizures, and other neurological symptoms.
- Measles inclusion body encephalitis (MIBE) is progressive measles virus infection of the brain in patients with ↓ cellular immunity with neurological deterioration and death within months of acute infection.

- Sub-acute sclerosing panencephalitis (SSPE) is a fatal, neurodegenerative disease which occurs in 1/10,000 to 1/100,000 cases, 5–10yrs after the primary illness.
- *Eye complications*: keratoconjunctivitis may → blindness, esp. in children who are vitamin A deficient.
- Other common complications: incl. malnutrition, mouth ulceration, premature delivery, and spontaneous abortion.

## Management

There is no specific antiviral treatment, so management includes: supportive care, identification and management of complications, and preventing spread through careful infection control measures (Box 17.18).

- Ensure adequate nutrition, hydration, and support, incl. education about complications.
- Give vitamin A (dose and regimen, ➡ Vitamin A deficiency, p. 658): this corrects vitamin A deficiency, ↓ severity of illness, and ↓ case fatality.

If specific symptoms/signs or conditions are present:

- Give symptomatic relief from high fever with paracetamol.
- Treat eye infection (cornea cloudy or pus draining from eyes) with topical antibiotics.
- Manage diarrhoea/dysentery and dehydration as on ➡ General management of dehydration, p. 236.
- Broad-spectrum antibiotics for treatment of pneumonia.

### Box 17.18 Prevention of measles

- Give first dose of measles-containing vaccine (MCV) at 9–12mths of age.
- MCV can be given as early as 6mths of age, e.g. during outbreaks, for internally displaced populations and refugees, HIV-infected children, and children at high risk of contracting measles, e.g. travel into outbreak-affected area. This is an additional MCV dose, and does not replace the 9–12mth dose.
- HIV-infected children should be revaccinated against measles following immune reconstitution with ART.
- Second MCV vaccine dose should be administered to all children in the 2nd year of life. This will → life-long protection in most people.
- Identify children who have missed out on immunization at school entry.
- Measles outbreaks can be devastating in refugee settings. Urgent measles immunization to unimmunized displaced people is a public health priority.
- Measles vaccine is a live attenuated virus vaccine with an excellent safety record. It is contraindicated in pregnancy. It should be given routinely to asymptomatic, HIV-infected children, adolescents, and young adults. Those with severe clinical symptoms of HIV infection are contraindicated for vaccination.
- Measles surveillance is a public health priority, allowing prompt recognition and investigation of outbreaks and immunity gaps in certain age-groups or subpopulations.

## Arboviruses and zoonotic haemorrhagic fever viruses

Arboviruses are transmitted to humans by an arthropod vector, e.g. mosquito, tick, fly, flea, or midge. The majority are zoonoses. Most arboviruses can cause a mild self-limiting fever, or a febrile syndrome with myalgia, arthralgia, rash, encephalitis, or meningoencephalitis. Disease can however be severe and some arboviral infections, such as CCHF, Rift Valley fever (RVF), dengue, and yellow fever, can be accompanied by haemorrhagic symptoms. Similarly, infection with Lassa, Ebola, and Marburg viruses, which are zoonotic but not arboviruses, can also cause bleeding. The term ‘viral haemorrhagic fevers (HFs)’ has been used for a diverse group of viral infections where bleeding may be observed, but is misleading since haemorrhage occurs only in a minority (see Fig. 17.19).

Ebola, Marburg, Lassa, and some arboviruses (e.g. CCHF virus) are biosafety level 4 (BSL-4) category viruses due to the high case fatality rate and the potential for human-to-human transmission. Interhuman transmission can occur through contact with bodily fluids, usually via caring for infected individuals without appropriate infection prevention and control (IPC) measures. These viruses are associated with a high risk of nosocomial infection, with healthcare workers and laboratory workers at particular risk. Stringent IPC procedures must be used when dealing with suspected HF cases and their body fluids (see ‘Public health note’). Early symptoms are often non-specific, so clinical suspicion is often low outside of an outbreak. A high index of suspicion is needed in endemic areas, and it is essential that IPC precautions are adhered to in all healthcare facilities.

In an endemic area, any patient with fever and bleeding should be considered to have HF until proven otherwise. Bleeding can be subtle. Patients should be carefully examined for bleeding gums, conjunctival bleeding, oozing from venepuncture sites, and petechiae. History taking, depending on the virus, should focus on exposure to animals, tick bites, illness among contacts, travel history, visits to natural healers, burial attendances and contact with corpses. For viruses such as Ebola and Marburg, where inter-human transmission is the main mechanism of spread, an index case often infects household contacts and relatives. A cluster of illness among family members should raise alarm bells. Pregnant patients can present with complications of pregnancy (e.g. bleeding, premature rupture of membranes, fetal death), sometimes without fever. A high index of suspicion is therefore needed in pregnant patients. In non-endemic areas it is important to consider recent travel to endemic areas.

Table 17.11 outlines the geographical distribution, vector, mode of transmission, and biosafety level (BSL) for arboviruses and zoonotic HF viruses.

**Table 17.11** Classification of arbovirus infections and zoonotic haemorrhagic fever viruses

Family, disease	Geographic distribution	Vector/mode of transmission	Natural host	BSL
<b>Flaviviruses</b>				
Japanese encephalitis	Asia, Western Pacific	<i>Culex</i> mosquito	Birds, (pigs amplifying host)	3
St. Louis encephalitis	Americas	<i>Culex</i> mosquito	Birds	3
Murray Valley encephalitis	Australia, Papua New Guinea	Mosquito, mainly <i>Culex</i>	Birds	3
Yellow fever	Africa, South and Central America	<i>Aedes</i> and jungle mosquitoes, anthroponotic <sup>^</sup>	Primates	3
Dengue (DEN 1–4)	Africa, the Americas, the Eastern Mediterranean, SE Asia, the Western Pacific	<i>Aedes</i> mosquito, anthroponotic <sup>^</sup> , human blood, breast milk	Humans (and non-human primates)	3
Kyasanur Forest disease	S Asia	<i>Ixodid</i> (hard) ticks	Small forest mammals	3
Kunjin	Australia, Indonesia, Asia	<i>Culex</i> mosquito	Birds	3
West Nile	Africa, Europe, Asia, Middle East, N and Central America	<i>Culex</i> mosquito	Birds	3
Tick-borne encephalitis	Russia, Asia, Europe, Scandinavia	<i>Ixodid</i> (hard) ticks, non-pasteurized milk, human blood, breast milk	Small mammals	3
<b>Alphaviruses</b>				
Chikungunya	Africa, Americas, Asia, Europe	<i>Aedes</i> mosquito, anthroponotic <sup>^</sup>	Humans, primates	3
O'nyong'nyong	Africa	<i>Anopheline</i> mosquito	Humans (other unknown)	2
Venezuelan equine encephalitis	S and Central America	Mosquito	Horses	3
Eastern equine encephalitis	N and S America, the Caribbean	<i>Aedes</i> , <i>Culex</i> , and <i>Coquillettidia</i> mosquitoes	Horses	3
Western equine encephalitis	N and S America	<i>Culex</i> and <i>Culiseta</i> mosquitoes	Horses	3
Ross River fever	Australia, S Pacific	<i>Culex</i> and <i>Aedes</i> mosquitoes	Kangaroos, wallabies, other mammals	2
<b>Coltiviruses</b>				
Colorado tick fever	Western USA, Canada	Wood tick	Rodents and small mammals	2
<b>Bunyaviruses</b>				
Rift Valley fever	Africa, Middle East	Mosquito (mostly <i>Aedes</i> ), animal blood/tissue	Domesticated livestock	3

La Crosse encephalitis	USA, Canada	<i>Aedes triseriatus</i> mosquito	Small forest mammals	3
Haemorrhagic fever with renal syndrome and Hantavirus cardiopulmonary syndrome*	Far East, Europe	Rodent bite/urine/faeces	Rural rodents	2/3
Crimean–Congo haemorrhagic fever	Eastern Europe, Asia, Africa	<i>Ixodid</i> (hard) ticks, animal blood, human body fluids	Small wild mammals, domestic livestock	4
Severe fever with thrombocytopenia syndrome	China, Japan, Korea	<i>Haemaphysalis longicornis</i> ticks	Domestic livestock	3
Toscana virus and other sandfly fever viruses	Southern Europe, Africa, Asia, the Americas	Phlebotomine sandfly	Unknown	2
<b>Arenaviruses</b>				
Lassa fever	Western Africa	Rodent urine/faeces, human body fluids	<i>Mastomys</i> rodent	4
South American HF <sup>**</sup>	South America	Rodent saliva/urine, human body fluids	Rodents	4
<b>Filoviruses</b>				
Ebola and Marburg	Sub-Saharan Africa	Human body fluids, animal blood/tissue	Unknown	4

BSL, biosafety level.

<sup>^</sup> Anthroponotic: human–vector–human transmission.

<sup>\*</sup> Hantaan, Seoul, Dobrava, and Puumala viruses.

<sup>\*\*</sup> Argentine, Bolivian, Venezuelan and Brazilian HF, caused by Junin, Machupo/Chapare, Guanarito, and Sabia viruses, respectively.



## Public health note

Always adhere to IPC procedures when dealing with patients with febrile illness. For viruses that can be spread via contact with bodily fluids (e.g. Ebola, Marburg, Lassa, Junin, Machupo, CCHF) consult local experts, WHO, or CDC immediately to advise on infection control and diagnosis. See the following list for general guide. More detailed infection control advice is available at: <http://www.cdc.gov/vhf/ebola/clinicians/evd/infection-control.html>.

### Infection control precautions

- Isolate patient immediately.
- Set up at least two areas or wards: one for patients meeting case definition for suspect cases; and one for confirmed patients. High-risk patients, i.e. 'probable' cases, should be isolated in a separate area if space and resources allow.
- Wear PPE in isolation areas and when in contact with patients, their clothing, belongings, or body fluids.
- Use two sets of gloves, a coverall that passes ASTM F1671 (13.8 kPa) or ISO 16604 ( $\geq 14$  kPa), apron, boots, eyewear, hood, and a mask (FFP3 or N95). PPE must completely cover clothes, skin, and mucous membranes.
- Reinforce and monitor the use of universal precautions in non-isolation areas of the health facility.
- Putting on (donning) and taking off (doffing) PPE should always be supervised by a colleague. There are different procedures for doffing PPE; whichever is chosen, use the same systematic method to avoid errors during doffing; ensure this is standardized through the use of Standard Operating Procedures (SOPs).
- Use extra precautions with pregnant patients during delivery (e.g. elbow-length gloves, delivery from side of patient).
- Always enter the isolation area with a 'buddy' for safety reasons.
- 0.5% hypochlorite solutions should be used when cleaning gloves between patients, but gloves should be dried before patient contact. 0.05% hypochlorite solution should be used for hand hygiene.
- Handle needles and other sharp instruments safely. Never recap needles. Dispose of needles, syringes, and other sharp instruments in puncture-resistant containers. Never re-use needles.
- Report all instances of PPE breaches to the person responsible for occupational health in your organization. All organizations should have SOPs in place to manage PPE breaches.
- In the case of a needlestick injury or mucous membrane exposure, seek expert advice regarding post-exposure prophylaxis (e.g. CDC, Public Health England, or WHO).
- Avoid sharing equipment between patients. Designate equipment for each patient, if supplies allow. If sharing equipment is unavoidable, make sure it is not reused by another patient until it has been cleaned, disinfected, and sterilized properly.
- Disinfect all spills, equipment, and supplies safely. Use disinfectant sprayers and 0.5%

hypochlorite solutions.

- Dispose of all contaminated waste, including human remains, by incineration or burial in a safe, secure way (including safe burial of corpses).
- Set up a triage system at the entrance of healthcare facilities. Patients meeting the case definition should be isolated until they test negative for the disease.
- Determine case's places of residence and activities over last 3wks; search for unreported or undiagnosed cases.
- Establish surveillance for individuals at risk—all close contacts <3wks since onset of illness, and healthcare workers and laboratory staff that have come in contact with patients or specimens without full PPE. Surveillance comprises body temperature measurement twice-daily until 3wks after last possible exposure.
- If a contact develops a fever >38°C or otherwise meets the case definition, they should be hospitalized immediately in isolation.
- Provide appropriate information to families and the community about the prevention of infection and the care patients will receive in healthcare facilities. There may be fear/suspicion of healthcare facilities and organizations during outbreaks; early involvement of social scientists, anthropologist and health promotion specialists is recommended to engage and inform communities.

## Ebola and Marburg virus diseases

Ebola and Marburg viruses are BSL-4 filoviruses. Although both may cause a viral haemorrhagic fever (VHF) syndrome, most patients do not bleed so the terms Ebola virus disease (EVD) and Marburg virus disease (MVD) are favoured.

There are six species of Ebola virus: Zaire, Sudan, Bundibugyo, Tai Forest, Bombali, and Reston. Mortality is 40–90%, depending on the species, size of the outbreak, and level of healthcare. The majority of outbreaks have been caused by the Zaire strain. Reston and Bombali are not known to cause symptomatic infection in humans.

There is one species of Marburg virus, and <500 confirmed cases of MVD since 1967. The mortality of MVD is ~50%.

## Epidemiology and transmission

Bats are thought to be the reservoir for EVD and MVD. Primates and other mammals may also be infected. Outbreaks usually start after infected animals are handled or consumed, with 2° cases among relatives and HCWs caring for sick individuals, through contact with body fluids; or through contact with corpses at burials. Nosocomial infections are frequent early in outbreaks, before identification of the viruses and systematic use of PPE. Vertical transmission can occur, as can sexual transmission and transmission via breastmilk.

Outbreaks of EVD have occurred in Central and W Africa—the majority in the DRC and Uganda. A large outbreak of EVD occurred in Sierra Leone, Liberia, and Guinea in 2014–2016, with >29,000 patients affected

and 11,000 deaths.

Outbreaks of MVD have to date been smaller and less frequent than EVD, and have mostly occurred in the DRC, Uganda, and Angola.

## Clinical features

The clinical features of 'VHF' syndromes are summarized in Table 17.12, p. 750. EVD and MVD result in similar symptoms. The incubation period is 2–21d. Almost all patients experience fever. Headache, myalgia, vomiting, diarrhoea, and abdominal pain are common. Vomiting and diarrhoea usually start within 6d of symptom onset. Diarrhoea may be severe and → dehydration and shock. A rash can occur but can be difficult to detect on dark skin. Confusion may occur due to dehydration, hypoglycaemia, and renal failure. A few patients will develop meningoencephalitis. Chest pain may result from oesophagitis, myocarditis, or pericarditis. Conjunctivitis occurs in some.

Bleeding is seen in some patients, with petechiae, bruising, mucosal bleeding, and bleeding from puncture sites. A minority of patients will develop frank haemorrhage, usually late in illness. Vascular leak may occur → peripheral oedema and respiratory distress, often complicated by hypoalbuminemia.

Pregnant patients can present with 'atypical symptoms', such as abdominal pain, back pain, or premature rupture of membranes without fever or other typical signs. Pregnancy is associated with higher mortality, and miscarriage and stillbirth are common.

Patients either recover or die around the 2nd week of illness. Death is usually a result of renal failure, respiratory failure, encephalitis, bleeding, or shock.

## Diagnosis

Virus may be detected in body fluids (usually blood) by nucleic acid testing (NAT; e.g. reverse transcription-PCR). NATs are usually positive from 3d after symptom onset; repeat testing may be needed in patients with <3d symptoms. Rapid antigen tests are available.

Laboratory findings, like the clinical features, are non-specific; they include leukopenia, thrombocytopenia, ↑ serum transaminase, as well as renal and coagulation abnormalities. Other laboratory findings incl. hypoalbuminaemia, hypoglycaemia, and ↑ amylase levels. Platelet levels rarely drop below 50,000/mm<sup>3</sup>. Transaminases are often in the hundreds and can peak in the thousands. Electrolyte disturbances are common due to vomiting and diarrhoea.

## Management

Several 1st line antiviral agents are under investigation. A number of mABs have been registered for treatment.

Patients with mild diarrhoea can be managed with ORS. Large volume diarrhoea may require up to 8L or more of IV fluids per day. Fluid management can be challenging due to vascular leak and should be guided by regular clinical assessments; consider urethral catheter to monitor urine output. Overhydration can → respiratory failure.

Treat fever with paracetamol, nausea/vomiting with antiemetics, and pain with analgesics, including opiates for severe pain. Avoid NSAIDs due to risk of renal failure. The role of antidiarrhoeal agents is unclear.

Invasive haemodynamic monitoring, respiratory support, and renal replacement therapy are appropriate if indicated and possible. These procedures should only be performed by clinicians who have been specifically trained in how to do so in PPE. In general, non-invasive ventilation should be avoided due to the risk of aerosol production.

The management of bleeding should be guided by clotting results. In the absence of coagulation tests, whole blood clotting time can be used (☞ Snake bite, p. 828), but patients should be closely monitored for signs of pulmonary oedema.

Test all patients for malaria co-infection. 2° bacterial infection may be a late complication—treat suspected sepsis with antibiotics, e.g. IV ceftriaxone.

Test all women of child-bearing age for pregnancy. Complications of pregnancy are common, and obstetric advice should be sought.

## Convalescence

EVD may be followed by prolonged convalescence, during which symptoms include fatigue, myalgia, arthralgia, insomnia, headache, and memory impairment. Severe complications incl. uveitis, hearing loss, and depression. These can develop within weeks or months of recovery. Patients should be followed up after discharge to monitor for these complications. Advise patients to use barrier contraception for at least 6mths after infection to prevent sexual transmission, due to the risk of persistent virus in genital fluids.

## Crimean–Congo haemorrhagic fever

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Crimean–Congo haemorrhagic fever (CCHF) is caused by CCHF virus, a BSL-4 bunyavirus. The reservoir is domestic livestock. Transmission to humans occurs by ticks, and by contact with body fluids of infected animals. Nosocomial and vertical transmission also occur.

Most cases occur in south-eastern Europe and western Asia, but CCHF is also reported in several African countries. Seasonal peaks usually occur in May–September.

The incubation period is usually 1–3d (up to 13d), following a tick bite. Patients may or may not report tick exposure. Clinical illness ranges from mildly symptomatic to frank bleeding and organ failure. Most patients have fever; myalgia, N&V are common. Patients either recover after ~7d or → to severe disease. Mortality is ~10%, but varies between countries.

## Diagnosis

Diagnosis is primarily by NATs, which are most sensitive. Due to variations in the strain of the virus, maximal sensitivity is provided by a combination of NAT and serology.

## Treatment

Treatment is mainly supportive. Some centres use ribavirin although its effectiveness is unclear. Invasive ventilation, vasopressors, and renal replacement therapy are appropriate if these can be safely performed. Give platelet transfusions to keep platelets  $>50,000/\text{mm}^3$  if active bleeding ( $>20,000/\text{mm}^3$  in absence of bleeding).

## Rift Valley fever

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Rift Valley fever (RVF) is caused by a bunyavirus. Transmission occurs via bites from infected mosquitoes or contact with body fluids of infected mammals. Outbreaks are most common in East and West Africa, esp. after heavy rains when ↑ mosquito numbers → infection of domesticated animals. Spill over into the human population mainly occurs via handling of infected animals.

Symptoms are non-specific. Fever, myalgia, headache, and GI symptoms are common (Table 17.12).

### Diagnosis

Diagnosis is by NAT (e.g. reverse transcription-PCR) and serology.

### Treatment

Treatment is supportive. Overall mortality is usually <1%, but has reached ~25% in hospitalized cases in some smaller outbreaks.

**Table 17.12** Clinical features of viral haemorrhagic fever syndromes

Disease	Incubation (days)	Case infection ratio	Case fatality rate	Features of severe disease
<b>Arenaviridae</b>				
South American HFs	7–14	>50%	15–30%	Overt bleeding and shock; CNS involvement (dysarthria, intention tremor) common
Lassa fever	5–16	Mild infection common	2–15%	Prostration and shock; fewer haemorrhagic or neurological manifestations cf. S American HF
<b>Bunyaviridae</b>				
Rift Valley fever	2–5	1%	50%	Bleeding, shock, anuria, jaundice; encephalitis and retinal vasculitis occur but are distinct from HF syndrome
Crimean–Congo HF	1–13	20–100%	15–30%	Most severe bleeding and bruising of all the HFs
HF with renal syndrome (Hantavirus)	9–35	>75%	5–15%	Febrile stage followed by shock and renal failure; bleeding at all stages
<b>Filoviridae</b>				
Marburg or Ebola virus disease	3–16	High	25–90%	Most severe of HFs; marked prostration; maculopapular rash common
<b>Flaviviridae</b>				
Dengue	➡ p. 756			
Yellow fever	➡ p. 761			
Kyasanur Forest disease	3–8	Variable	0.5–9%	Typical biphasic illness — fever and haemorrhage followed by CNS involvement

## Lassa fever

### Epidemiology and transmission

Lassa fever is caused by an arenavirus which is endemic in W Africa. Lassa virus is a BSL-4 virus. The animal reservoir for Lassa virus is the multimammate rat *Mastomys natalensis*.

Transmission to humans occurs via contact with infected rodent urine and faeces, or consumption of infected rodents. Person-to-person transmission can occur through contact with body fluids but is relatively rare outside hospital settings.

Annual seasonal outbreaks of Lassa fever occur throughout W Africa, with peaks in January–March. Incidence is highest in Nigeria, Sierra Leone, Liberia, and Guinea, with cases reported in Benin, Ghana, Mali, Côte d'Ivoire, and Burkina Faso. Serological studies from the 1980s suggested that there may be hundreds of thousands of infections per year, most being asymptomatic or mildly symptomatic.

In hospitalized patients, mortality averages 30%. Pregnancy is associated with ↑ mortality.

## Clinical features

The incubation period is 5d to ~3wks. Although Lassa virus can cause a VHF syndrome, most patients do not bleed.

Most infected individuals have mild symptoms, consisting of low-grade fever, malaise, and headache. In patients presenting to hospital, vomiting, diarrhoea, myalgia, chest pain, and abdominal pain are common. Abdominal pain can mimic an acute abdomen, and HCWs have been infected during surgery. Some patients develop pharyngitis with associated cervical lymphadenopathy.

Severe infection can → vascular leak → facial swelling, pulmonary oedema, and shock. Facial swelling, pharyngitis, or unexplained bleeding in a Lassa endemic zone, esp. during the Lassa season, should raise concern. Meningoencephalitis occurs in a few patients and can be the main presenting syndrome.

## Diagnosis

Diagnosis is by detection of virus in blood by NAT. A rapid antigen test is also available. Laboratory findings are non-specific. Renal failure and hepatitis are common and associated with a worse prognosis. Thrombocytopenia can occur but platelet levels rarely drop below  $100,000/\text{mm}^3$ . Coagulation abnormalities are not usually seen in Lassa fever, and bleeding is thought to be 2° to platelet dysfunction.

## Management

Treatment consists of IV ribavirin, the only antiviral agent currently available, and supportive care.

Give a loading dose of 33mg/kg ribavirin; followed by 16mg/kg qds for 4d; then 8mg/kg tds for 6d. The standard course of treatment is 10d. Treatment should not routinely continue beyond this, as severe anaemia can develop. Response to treatment should be guided by clinical improvement and not by NAT testing as the NAT may remain positive for weeks despite clinical improvement.

Supportive care is as for EVD and MVD (➡ [Ebola and Marburg virus diseases](#), p. 746). Optimal management of bleeding is unknown. Patients should be followed up for post-infection sequelae incl. hearing loss.

## Hantavirus infections

Hantaviruses are bunyaviruses whose distribution includes Asia, Europe, and N and S America. There are >20 species, not all of which cause infections in humans.

Patients often report encounters with dead or live rodents (usually mice); infection occurs via contact with urine or faeces of infected rodents, primarily through aerosol inhalation. Many outbreaks are seasonal, depending on the species of virus and country.

They generally cause two clinical syndromes: haemorrhagic fever with renal syndrome (HFRS), and hantavirus cardiopulmonary syndrome (HCPS). Both have ↑ vascular permeability. The incubation period is ~2wks (range 1–6wks).

## Diagnosis

Diagnosis is best confirmed by serology, as viral RNA becomes undetectable by NAT within a few days.

## Hantavirus cardiopulmonary syndrome

HCPS is confined to the Americas. It begins with fever, chills, and myalgias (often severe); N&V commonly develop over the next 2–8d. Diarrhoea, headache and marked abdominal pain can occur. Early thrombocytopenia is common, often accompanied by a left-sided granulocyte shift which is a clue to the diagnosis. After the initial phase, vascular leak and hypoalbuminaemia may → pulmonary oedema with cough and respiratory distress and ↑ haematocrit. The next 2–7d → recovery or death due to coagulopathy, haemorrhage (depending on the virus species) and shock.

### Treatment

Treatment is supportive. Manage hypotension with inotropes and vasopressors, and cautious IV fluids due to the risk of pulmonary oedema. Mortality is up to 40% even with advanced support.

## Haemorrhagic fever with renal syndrome

HFRS occurs mainly in Asia and Europe; cases have occurred in N America. Classically it causes fever, hypotension, bleeding, and renal failure. The clinical course is variable and some patients have mild symptoms. Nausea, vomiting, and abdominal pain are common. Pharyngeal and conjunctival congestion can occur with some viral species.

### Treatment

Ribavirin has shown some efficacy. Supportive treatment includes renal replacement therapy, which has been shown to ↓ mortality.

## Severe fever and thrombocytopenia

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Caused by the severe fever and thrombocytopenia virus, a bunyavirus in central and eastern China, western Japan, South Korea. Transmission is via ticks; livestock are the probable natural reservoir. Human-to-human transmission incl. nosocomial infection may occur through contact with body fluids.

The incubation period is 7–14d. Most patients have fever, myalgia, arthralgia, and headache. Vomiting and diarrhoea is common.

## Diagnosis

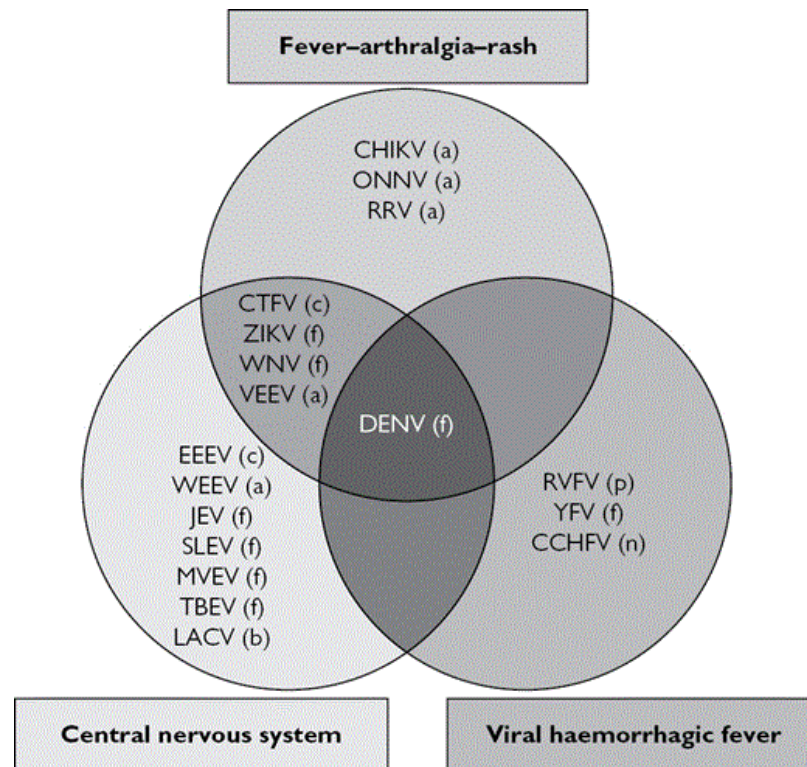
Diagnosis is by NAT. Laboratory findings include leukopenia, ↓ platelets, hepatitis, and coagulation abnormalities. Mortality is ~15%.

### Treatment

Treatment is supportive.



**Fig. 17.23**



Summary of arbovirus syndromes. (a) alphavirus, (c) coltivirus, (f) flavivirus, (b) bunyavirus, (n) nairovirus and (p) phlebovirus. CCHF, Crimean–Congo haemorrhagic fever; CHIKV, chikungunya; CTFV, Colorado tick fever; DEN, dengue; EEEV, Eastern equine encephalitis; JEV, Japanese encephalitis; LACV, La Crosse virus; MVEV, Murray Valley encephalitis; ONNV, O’nyong’nyong virus; RRV, Ross River fever; RVFV, Rift Valley fever; SLEV, St. Louis encephalitis; TBEV, tick-borne encephalitis; VEEV, Venezuelan encephalitis; WEEV, Western equine encephalitis; WNV, West Nile fever; YFV, yellow fever; ZIKV, Zika virus.

Adapted with permission from Solomon T in Beeching N, Gill G, eds., *Lecture notes: tropical medicine* (New York: Wiley; 2014), p. 274.

## Zika virus

Zika virus (ZIKV) is a mosquito-borne flavivirus first described in humans in Uganda and Tanzania in 1952. Transmission is mainly by *Aedes aegypti* mosquitoes. Since 2007, transmission/outbreaks have been reported widely in tropical and subtropical regions in Africa, the Americas, Asia, and the Pacific. Transmission also occurs vertically during pregnancy, via sexual contact, blood transfusion, and organ transplantation.

## Clinical features

Incubation is 3–14d. Most infections are asymptomatic. Symptoms incl. mild fever, rash, conjunctivitis, myalgia, arthralgia, malaise, and headache for 2–7d. Rarer neurological complications incl. GBS, neuropathy, and myelitis.

Both asymptomatic and symptomatic infection during pregnancy may → congenital Zika syndrome with microcephaly and/or other abnormalities (limb contractures, spasticity, eye abnormalities, and hearing loss), preterm birth, or miscarriage.

## Diagnosis

Diagnostic testing is recommended for symptomatic individuals and asymptomatic pregnant women with risk exposure. WHO recommends NATs using blood and/or urine if <7d of illness onset (viremia falls rapidly after 7d). Serology is useful if >7d since symptom onset; antibody cross-reactivity with other flaviviruses may occur.

## Management

Care is supportive. Follow latest national guidelines for following up confirmed infection or risk exposure during pregnancy.

## Prevention

- Mosquito bite avoidance measures are advised.
- WHO recommends that pregnant women avoid travel to areas with ZIKV transmission, particularly during outbreaks; and that travellers returning from affected areas use barrier contraception for 2mths (women) or 3mths (men) after last possible exposure.
- There is no vaccine available currently.

## Japanese encephalitis

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Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus first described in Japan in 1871. JEV is endemic in 24 countries in SE Asia and the Western Pacific, where it is the most common cause of viral encephalitis, with ~68,000 cases annually.

JEV mainly affects children, since many adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected. JEV is mainly transmitted to humans by *Culex* mosquitoes (e.g. *Culex tritaeniorhynchus*).

Transmission may occur all-year around in tropical regions, but ↑ after the rains due to ↑ mosquito populations. Major outbreaks occur every 2–15yrs.

## Clinical symptoms

The incubation period is 4–14d. Most infections are asymptomatic or mild (fever and headache). In children, abdominal pain and vomiting may be the main initial symptoms. ~1 in 250 infections → severe disease characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, and spastic paralysis. Mortality among those with encephalitis is up to 30% and the risk of permanent neurologic or psychiatric sequelae is 30–50%.

## Diagnosis

Suspect JE in any individual with encephalitis who lives in, or has travelled to, a JEV endemic area within the previous 14 d. WHO recommends testing for JEV-specific IgM antibody in a CSF or serum, using an IgM-capture ELISA. Testing of a CSF sample gives less false +ve results from previous infection or immunization. IgM antibodies are usually detectable 3–8d after onset and persist for 30–90d, occasionally longer. Positive IgM antibodies may reflect past infection or immunization, and cross-reactivity with other flaviviruses may occur. If positive confirm with neutralizing antibody testing. If negative, repeat on a convalescent sample.

## Management

There is no specific treatment besides supportive care.

## Prevention

- Effective vaccines are available (🌀 Japanese encephalitis vaccines, p. 854). WHO recommends routine immunization in areas of JEV transmission risk.
- JEV is a very low-risk disease for most travellers to endemic countries. Vaccination is therefore only recommended for those spending extensive time in JEV endemic areas, depending on areas visited, activities, season, and other risk factors.
- Mosquito bite prevention measures.
- Vector control.

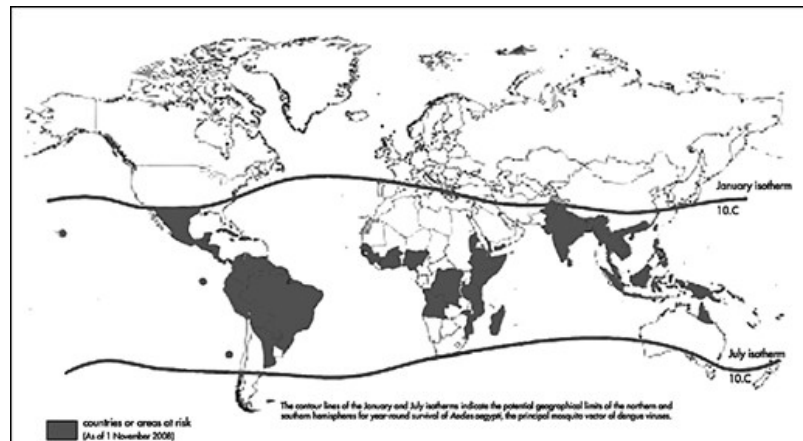
## Dengue virus

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Dengue virus (DENV) is a *flavivirus* transmitted from infected humans by *Aedes* mosquitoes, mainly *Ae. aegypti* or *Ae. albopictus*—domestic mosquitoes that breed in human-made containers. These also spread Zika and chikungunya viruses and co-infection can occur. The three arboviral diseases produce similar clinical symptoms during the first days of illness, but there are clinical differences (Fig. 17.23) which, together with region and travel history, can help guide diagnosis.

DENV is the most commonly diagnosed arbovirus worldwide. It is common in >100 countries, with ~390 million people infected each year. Transmission is most intense in Southeast Asia. There has also been ↑↑ transmission in the Indian subcontinent, the Americas, and the Western hemisphere in recent years (Fig. 17.24).

**Fig. 17.24**



Countries/areas at risk of dengue transmission, 2008 (shaded areas). Lines represent January and July isotherms, which indicate potential geographical limits of northern and southern hemispheres for year-round survival of *Aedes aegypti*, principal mosquito vector of dengue viruses.

Adapted from *Dengue: Guidelines for diagnosis, treatment, prevention and control*, p. 3, Figure 1.1 © WHO 2008. All rights reserved.

## Transmission

There are four dengue serotypes (DEN-1, DEN-2, DEN-3, DEN-4). 'Asian' genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections.

Recovery from infection → lifelong immunity against that serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes ↑ the risk of developing severe dengue, due to antibody-dependent enhancement.

Transmission is mainly human–vector–human → urban outbreaks. Transmission may also occur during pregnancy, and via breast milk, blood transfusion, organ transplant, and needlestick injury.

## Clinical features

The incubation period is 3–15d. Infection can be asymptomatic, or cause clinical dengue fever (DF) which can progress to severe dengue. WHO recommend distinguishing DF without warning signs, DF with warning signs and severe DF (Fig. 17.25). The early clinical features are indistinguishable between severe and non-severe dengue cases. Careful monitoring for warning signs and other clinical parameters is crucial to recognize progression to severe disease.

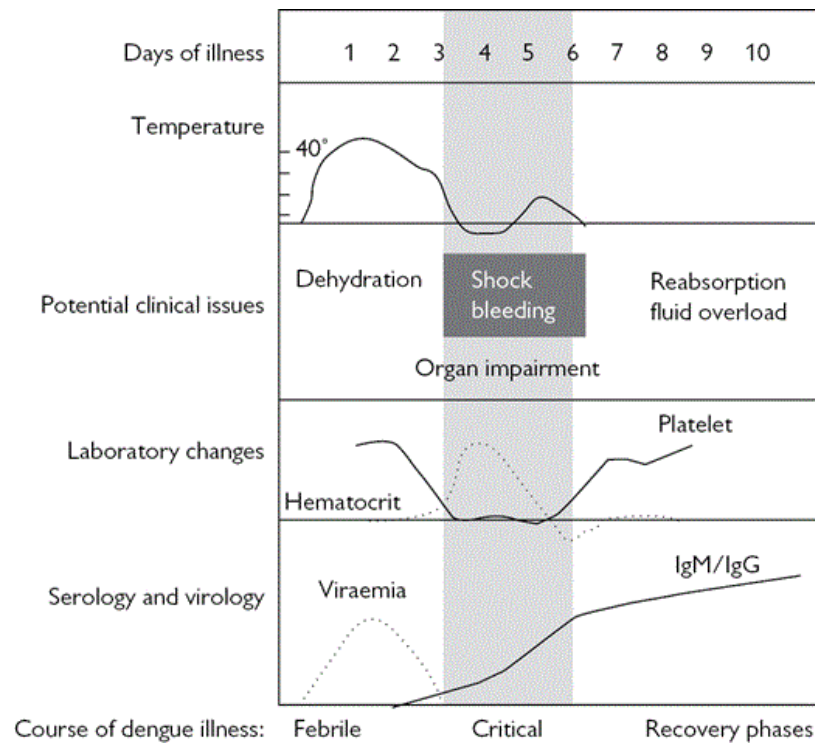
Suspect DF if high fever accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, and headache. Anorexia and N&V are common. Pharyngitis and conjunctival injection may occur.

A probable case is defined by WHO as fever in a patient that lives in or has travelled to dengue endemic area within the previous 15d, accompanied by two of the following: nausea, vomiting, rash, aches and pains, a positive tourniquet test (Box 17.19), leukopenia, or any warning sign of severe dengue (Fig. 17.25).

Most cases recover after 2–7d; a small % progress to severe disease, mostly characterized by plasma leakage +/- haemorrhage (see later in topic). DENV can occasionally → encephalitis.

Mortality from severe dengue is high without treatment, but may be reduced to 1–5% with appropriate supportive care.

**Fig. 17.25**



The course of dengue illness.

Reproduced with permission from Yip, WCL, *Medical Progress*, 7 (13), pp. 201–9, Dengue haemorrhagic fever: Current approaches to management, 1980.

### Box 17.19 Tourniquet test

The Tourniquet test is a measure of capillary fragility.

- Inflate a BP cuff to half way between the patient's systolic and diastolic BP for 5min.
- Then deflate the cuff and wait for 2min.
- Count the petechiae in the antecubital fossa.
- The test is positive if there are  $\geq 10$  petechiae in a  $2.5\text{cm}^2$  area.

The tourniquet test has variable sensitivity and specificity. In dengue, it is most sensitive around the time the fever ceases. It is less sensitive in patients with shock. Using a cut off of  $\geq 20$  petechiae/ $2.5\text{cm}^2$   $\uparrow$  specificity but  $\downarrow$  sensitivity (J).

[http://www.cdc.gov/dengue/training/cme/ccm/Tourniquet%20Test\\_F.pdf](http://www.cdc.gov/dengue/training/cme/ccm/Tourniquet%20Test_F.pdf)).

### Warning signs of severe dengue

occur 3–7d after symptom onset, usually around the time the fever ceases. Warning signs incl. abdominal pain or tenderness, persistent vomiting, mucosal bleeding, lethargy, restlessness, liver enlargement  $>2\text{cm}$ , fluid accumulation, and  $\uparrow$  haematocrit ( $2^\circ$  to  $\uparrow$  capillary permeability) accompanied by rapidly  $\downarrow$  platelets. Warning signs are a medical emergency requiring strict observation and medical intervention. Some patients  $\rightarrow$  critical phase of plasma leakage while still febrile.

## Severe dengue

is defined by one or more of the following:

- Plasma leakage that may → shock and/or fluid accumulation, with or without respiratory distress.
- Severe bleeding.
- Severe organ impairment (Fig. 17.26).

As vascular permeability progresses, hypovolaemia worsens → shock.

## Laboratory diagnosis

Laboratory diagnosis in symptomatic patients is by serum NAT or NS1 antigen test and IgM antibody during the 1st 7d of illness. NS1 tests detect the non-structural protein NS1 of DENV. Rapid diagnostic tests are available. Performing both NAT/NS1 and IgM antibody tests provides optimum sensitivity, and usually allows diagnosis with a single sample. If both tests are negative and the diagnosis is still suspected, test for IgM antibodies on a convalescent sample taken >7d after illness onset. IgM antibodies are usually present for ≥3mths; cross-reactivity with other *flaviviruses* may occur.

## Management

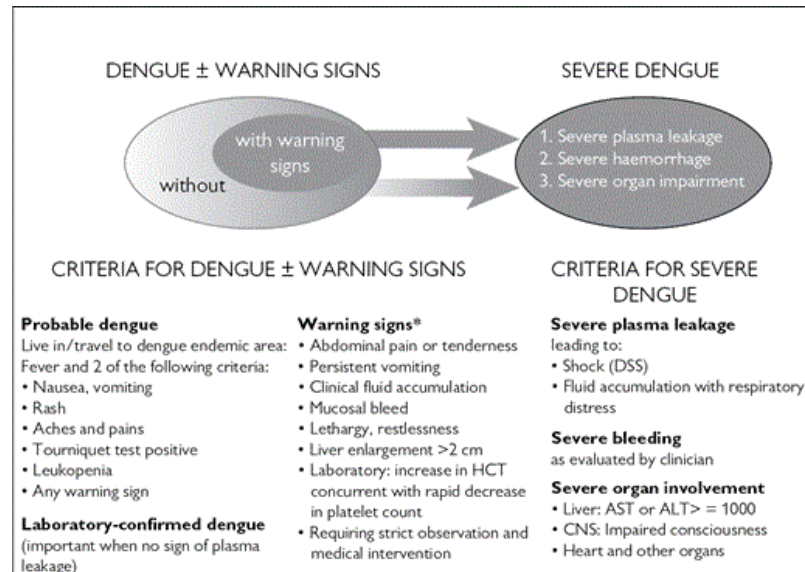
Management is supportive. Avoid NSAIDs and aspirin due to risk of bleeding. Severe dengue requires urgent medical care with prompt restoration of circulating volume. The vascular leak typically resolves within 24–48h, and careful monitoring is required to avoid fluid overload. Pulmonary oedema 2° to fluid overload can contribute to mortality. For more information see WHO guideline: <https://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf>.

### Box 17.20 Prevention

- Vector control measures.
- Bite prevention measures. Those with acute dengue should protect themselves from mosquito bites for 12d post symptom onset to prevent human–vector–human transmission to others.
- The first dengue vaccine, Dengvaxia® (CYD-TDV, Sanofi Pasteur) was licensed in 2015 and approved for 9–45yr-olds in endemic areas in 20 countries. The live attenuated vaccine is efficacious and safe in those who have had a previous DENV infection, but carries ↑ risk of severe dengue in those who experience their first natural dengue infection after vaccination. WHO currently recommend prevaccination screening, reserving vaccination for people with confirmed previous dengue infection in endemic areas. The vaccine is not recommended for use in travellers to endemic areas. (For updates, see: <http://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue>.)



**Fig. 17.26**



WHO suggested dengue case definition and levels of severity.

Reproduced with permission from *Dengue: Guidelines for diagnosis, treatment, prevention and control*, p. 11, Figure 1.4 © WHO 2008. All rights reserved.

## Yellow fever

Yellow fever (YF) is caused by a mosquito-borne *flavivirus*. 'Yellow' refers to jaundice, which is not always present. There are ~200,000 YF cases → ~30,000 deaths/yr worldwide, most in sub-Saharan Africa, with far fewer in Central and S America (Fig. 17.27). Although YF has never been reported in Asia, the region is potentially at risk because conditions exist for transmission. Direct human-to-human transmission has not been reported.

## Transmission

Jungle (sylvatic) YF → asymptomatic infection of non-human primates that maintain the reservoir of infection in tropical rain forest. Sporadic infection in humans occurs when they are bitten by infected mosquitoes in these forests. Localized outbreaks may occur in humid savannah regions of Africa where mosquitoes infect both monkeys and humans (intermediate/savannah YF).

If a viraemic person enters an urban environment, *Aedes aegypti* mosquitoes can spread the virus from human to human with the potential for explosive urban epidemics in unvaccinated populations. The urban cycle is rare in S America, where most infections are in persons living or working in tropical rainforest areas (Fig. 17.28).

## Clinical features

Infection may be subclinical. The incubation period is 3–6d. Characteristic features are fever, chills, headache, backache, nausea, vomiting, myalgia, and conjunctival injection. This ‘acute phase’ usually resolves spontaneously within 3–4d. However, in ~15% of patients, a ‘toxic phase’ develops within 24h of the initial remission of fever, with jaundice, abdominal pain, diarrhoea, and renal failure. Thrombocytopenia and coagulopathy can → frank bleeding from gums, nose, eyes, and GI tract. There may be relative bradycardia (Faget’s sign). Up to 50% of cases with severe disease will die within 2wks.

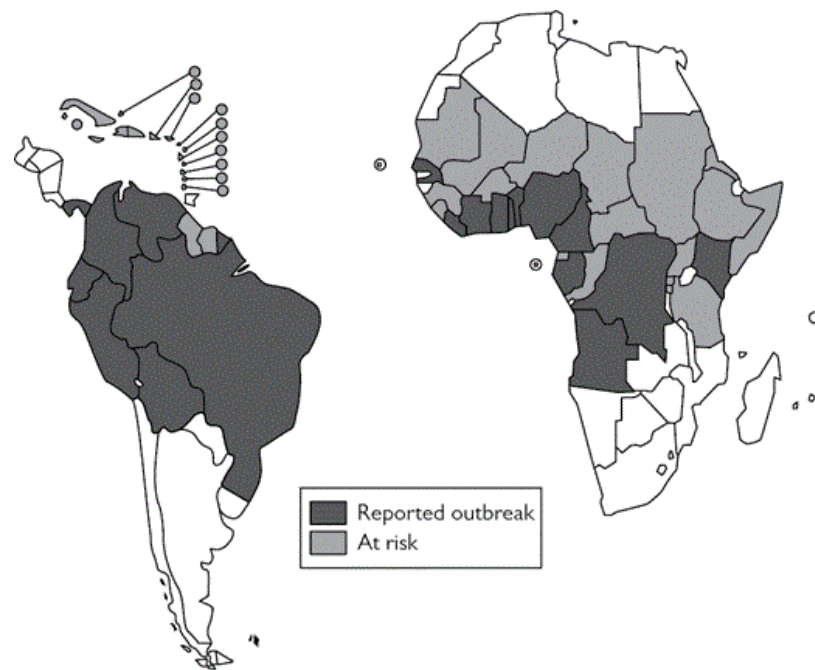
## Diagnosis

Diagnosis is usually made by detection of IgM by capture ELISA or by detection of virus in blood by NAT in the first few days of illness. Virus can be detected in postmortem liver tissue.

## Management

Treatment is supportive. Organ support is appropriate if available. Blood product support including FFP should be used for bleeding.

**Fig. 17.27**

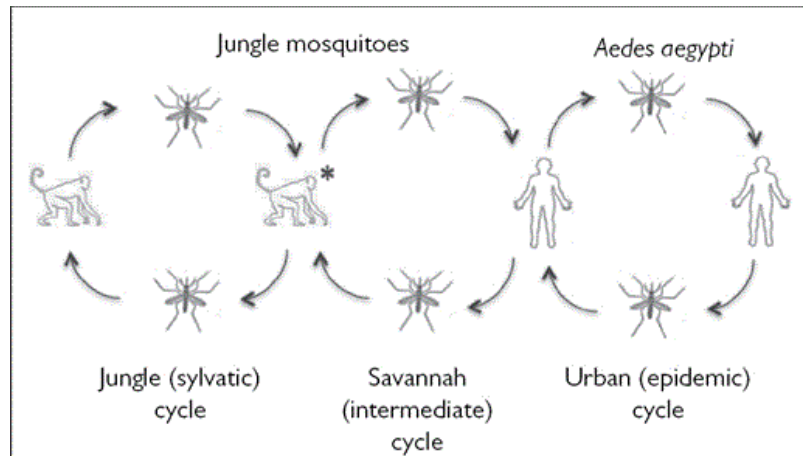


Countries at risk from YF (shaded) and reported cases from 1985–2004 (dark shading).

Adapted with permission from the WHO dengue guidelines for diagnosis, treatment, prevention and control (2009).



**Fig. 17.28**



Transmission cycle of YF virus in Africa (savannah YF does not occur in South America, and the urban cycle is rare).

\*Humans entering jungle environments can be incidentally infected at this point.

## Public health note

### Prevention

- Immunization is the most effective preventive strategy. YF vaccine is generally safe, affordable, and highly effective, though there is a small risk of severe adverse events, particularly in the elderly (➡ Yellow fever vaccine, p. 854).
- Vector control can be effective but is difficult to sustain.

### Management of a yellow fever (urban) outbreak

- Notify WHO of any confirmed YF case (required under international health regulations).
- Implement infection control measures.
- Mass immunization: if resources limited, target children aged 9mths–14yrs.
- Vector control focused on *Aedes* breeding sites. Refill and cover domestic water containers. Remove receptacles that collect water, e.g. discarded tires, tins, and jars.
- In a large urban outbreak, consider widespread insecticide spraying.
- Local surveillance: collect specimens for laboratory diagnosis from any new suspected cases (postmortem if necessary).

### Longer-term prevention measures

- Include YF vaccine in routine childhood EPI schedule (can give at 9mths with measles vaccine).
- Provide health education messages: domestic water containers should be covered with a lid or screen; waste items that can collect standing water should be buried or disposed of in a safe manner.

## West Nile virus

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West Nile virus (WNV) is a flavivirus first identified in Africa in 1937, and now present in Africa, Europe, the Middle East, the Americas, Australia, and W Asia. Transmission by *Culex* mosquitoes maintains the virus in birds (the main reservoir). Humans are accidental hosts usually infected by *C. pipiens* mosquitoes. Transmission may also occur via blood transfusion, organ donation, and vertically during pregnancy and via breast milk.

### Clinical features

The incubation period is 3–14d. ~80% of infections are asymptomatic. Symptoms of West Nile fever incl. headache, myalgia, joint pains, vomiting, diarrhoea, rash. Most patients make a complete recovery, but fatigue can last for months. <1% develop neuro-invasive disease with encephalitis, meningitis, or myelitis. Symptoms of severe disease include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness and paralysis. Risk groups for severe disease are people >50yrs or immunocompromised. Mortality is 3–15% in severe disease, highest in those >75yrs old.

### Diagnosis

NATs for viral RNA can be performed on serum, CSF, or tissue specimens collected early in the illness; a -ve result does not rule out WNV infection. WNV-specific IgM antibodies are usually detectable by 8d after illness onset, and persist for 30–90d (occasionally longer); positive IgM antibodies may reflect a past infection, and cross reactivity with other flaviviruses may occur.

### Management

Management is supportive. Prolonged ventilatory support may be required for neuro-invasive disease. Monitor closely for signs of ↑ ICP.

### Prevention

- Vector control.
- Prevent risk of transmission through blood transfusions—follow blood donation restriction guidelines during outbreaks/exposure.
- There is no licensed vaccine for humans.

## Kyasanur Forest disease

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Kyasanur Forest disease virus is a tick-borne flavivirus endemic in S India. Fever and headache are common. It can → bleeding. Treatment is supportive. A vaccine exists.

# Chikungunya

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Chikungunya virus (CHIKV) is a mosquito-borne alphavirus, mainly transmitted to human via *Aedes aegypti* and *Ae. albopictus* mosquitoes. The name 'chikungunya' derives from a word in the Kimakonde language, meaning 'to become contorted', and describes the stooped appearance of sufferers with arthralgia. CHIKV has a wide geographical range including sub-Saharan Africa, India, Indian Ocean islands and much of SE Asia. In recent decades the mosquito vector has spread and was reported in Europe in 2007, where localized travel-imported outbreaks have since been reported during the summer season, through human-vector-human transmission.

## Clinical features

The illness begins abruptly 3–12d after the bite of an infected mosquito. The most common symptoms are fever and polyarthralgia, which usually symmetrically involve the hands and feet. Other symptoms resemble DF, incl. headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, and a maculopapular rash. Laboratory findings incl. lymphopenia, ↓ platelets, ↑ creatinine, and ↑ hepatic transaminases.

Documented complications incl. myocarditis, hepatitis, and haemorrhagic, ocular, and neurological manifestations. Confirmed cases of meningoencephalitis have occasionally been reported in neonates and the elderly.

Mortality is low (0.02%), but recurrent, symmetric, often debilitating joint pain can persist for months or years in up to 30–40% of cases.

## Diagnosis

Clinical symptoms and travel history suggest the diagnosis. Often misdiagnosed as DF due to similar presentation. Diagnosis may be confirmed by NAT for CHIKV RNA (present in serum up to 8d after symptom onset) and/or serology for anti-CHIKV IgM (normally present from the end of the first week, peaks 3–5wks after the onset of illness and persist for about 2mths). Testing samples taken in the 1st week of illness with both NAT and serology maximizes sensitivity.

## Management

Treatment is symptomatic. Avoid aspirin and other NSAIDs unless dengue infection excluded.

## Prevention

- Vector control.
- Mosquito bite prevention measures.
- Confirmed cases should protect themselves from mosquito bites to reduce risk of transmission (human-vector-human) to others.
- There is no vaccine available.

## Ross River fever

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Caused by Ross River virus (RRV), an *alphavirus* endemic in Australia and islands of the western South Pacific. Ross River fever frequently occurs in tropical coastal regions with salt marsh habitats, the natural habitat for the main mosquito vector species. Infection is most common following the rainy season and the flooding of salt marshes. However, cases can occur in more arid regions after rains, when desiccation-resistant mosquito eggs, within which the virus persists, hatch.

Incubation is usually 3–9d (up to 21d). Subclinical infection is common. Common symptoms are fever, myalgia; a symmetrical polyarthritides involving small and large joints; and a maculopapular rash. Arthralgia can persist for months. Diagnosis is usually by serology for RRV-specific IgM. Treatment is with NSAIDs.

## O'nyong'nyong

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O'nyong'nyong (ONNV) is a mosquito-borne alphavirus related to CHIKV that is found in Central and E Africa and transmitted by anopheline mosquitoes. The clinical picture resembles CHIKV infection, with self-limiting fever, headache, rash, and joint pain. In contrast to CHIKV, ONNV is reported to cause lymphadenopathy more often and affected joints do not show effusions. It is non-fatal.

## Notes

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- 1 Singer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). J Am Med Assoc 2016;315:801–10 [10.1001/jama.2016.0287](https://doi.org/10.1001/jama.2016.0287)<sup>↗</sup>.