PRESENTING PROBLEMS IN INFECTIOUS DISEASES

- Infectious diseases present with myriad clinical manifestations.

FEVER:

- ‘Fever’ implies an elevated core body temperature > 38.0 °C, i.e. above the normal daily variation.
- Fever is a response to cytokines and acute phase proteins and is a common manifestation of infection, although it also occurs in other conditions.

Clinical assessment:

- The differential diagnosis is very broad and there is a long list of potential investigations, so any clues from the clinical features which help to focus the investigations are extremely valuable.

13.1 Fever in old age

- **Temperature measurement**: fever may be missed because oral temperatures are unreliable in older people. Rectal measurement may be needed but core temperature is increasingly measured using eardrum reflectance.
- **Associated acute confusion**: common with fever, especially in those with underlying cerebrovascular disease or other causes of dementia.
- **Prominent causes of PUO**: include tuberculosis and intra-abdominal abscesses, complicated urinary tract infection and infective endocarditis. Non-infective causes include polymyalgia rheumatica/temporal arteritis and tumours. A smaller fraction of cases remain undiagnosed.
- **Pitfalls in the elderly**: certain conditions such as cerebrovascular accident/thromboembolic disease can cause fever but every effort must be made to exclude concomitant infection.
- **Common infectious diseases in the very frail** (e.g. nursing home residents): include pneumonia, urinary infection, soft tissue infection and gastroenteritis.

Investigations:

- If the cause is not obvious, e.g. in a patient with purulent sputum or symptoms of urinary tract infection, then initial screening investigations should include:

- a full blood count (FBC) with differential, including eosinophil count
- urea and electrolytes, liver function tests (LFTs),blood glucose and muscle enzymes

- inflammatory markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- autoantibodies, including antinuclear antibodies(ANA)
- chest X-ray and electrocardiogram (ECG)
- urinalysis and urine culture
- blood culture (a minimum of 20 mL blood in three sets of blood culture bottles)
- throat swab for culture

- other specimens, as indicated by history and examination, e.g. wound swab; sputum culture; stool culture, microscopy for ova and parasites and *Clostridium difficile* toxin assay*;* if relevant, malaria films on 3 consecutive days or a malaria rapid diagnostic test (antigen detection by lateral flow immunochromatography).

Management:

- Fever and its associated systemic symptoms can be treated with paracetamol, and by tepid sponging to cool the skin.
- Replacement of salt and water is important in patients with drenching sweats.
- Further management is focused on the underlying cause.

Fever with localising symptoms or signs:

- In most patients, the potential site of infection is apparent after clinical evaluation, and the likelihood of infection may be reinforced by typical abnormalities on the initial screening investigations (e.g. neutrophilia and raised ESR and CRP in bacterial infections).

- Not all apparently localising symptoms are reliable, however; headache, breathlessness and diarrhoea can occur in sepsis without localised infection in the central nervous system (CNS), respiratory tract or gastrointestinal tract.

- Careful evaluation of the constellation of clinical features is vital (e.g. severe headache associated with photophobia, rash and neck stiffness suggests meningitis, whereas moderate headache with cough and rhinorrhoea is consistent with a viral upper respiratory tract infection).

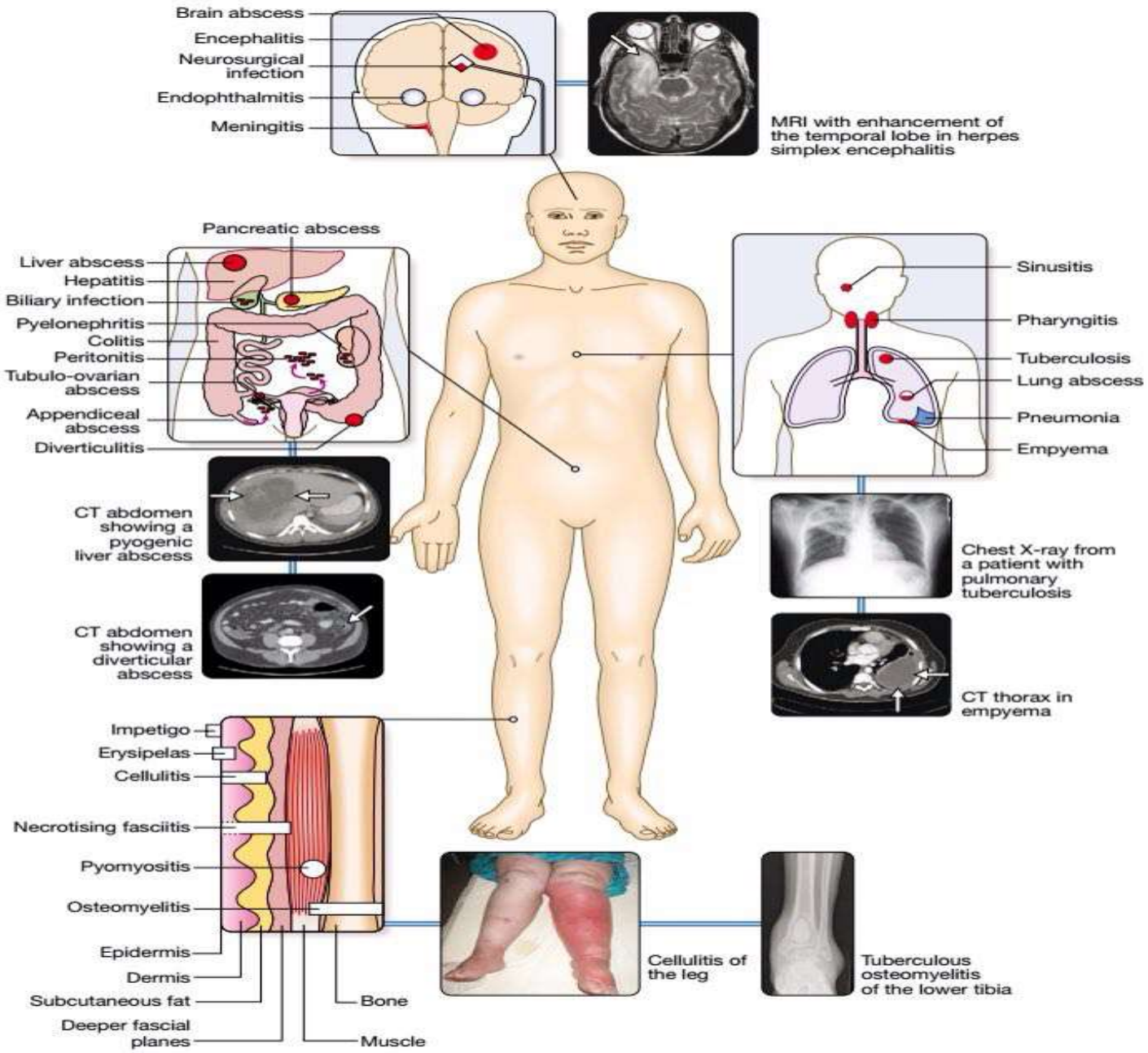


Fig. 13.1 Common infectious syndromes presenting with fever and localised features. Major causes are grouped by approximate anatomical location and include central nervous system infection; respiratory tract infections; abdominal, pelvic or urinary tract infections; and skin and soft tissue infections (SSTI) or osteomyelitis. For each site of infection particular syndromes and their common causes are described elsewhere in the book. The causative organisms vary, depending on host factors, which include whether the patient has lived or resided in a tropical country or particular geographical location, has acquired the infection in a health-care environment or is immunocompromised.

- Further investigation and management is specific to the cause, but may include empirical antimicrobial therapy pending confirmation of the microbiological diagnosis.

Pyrexia of unknown origin (PUO):

- PUO is defined as a temperature persistently above 38.0 °C for more than 3 weeks, without diagnosis despite initial investigation during 3 days of inpatient care or after more than two outpatient visits.
- Subsets of PUO are described by medical setting: HIV-related, immunedeficient or nosocomial.
- Up to one-third of cases of PUO remain undiagnosed.

13.2 Aetiology of pyrexia of unknown origin

Infections (~30%)

Specific locations
- Abscesses: hepatobiliary*, diverticular*, urinary tract* (including prostate), pulmonary, CNS
- Infections of oral cavity (including dental), head and neck (including sinuses)
- Bone and joint infections
- Infective endocarditis*

Specific organisms
- Tuberculosis (particularly extrapulmonary)*
- HIV-1 infection
- Other viral infections (cytomegalovirus (CMV), Epstein–Barr virus (EBV))
- Fungal infections (e.g. *Aspergillus* spp., *Candida* spp. or dimorphic fungi)
- Infections with fastidious organisms (e.g. *Bartonella* spp., *Tropheryma whipplei*)

Specific patient groups
- Imported infections
  - Malaria, dengue, rickettsial infections, *Brucella* spp., amoebic liver abscess, enteric fevers, *Leishmania* spp. (southern Europe, India, Africa and Latin America), *Burkholderia pseudomallei* (South-east Asia)
  - HIV and respiratory tract infections
- Nosocomial infections
  - Infections related to prosthetic materials and surgical procedures
- HIV-positive individuals
  - Acute retroviral syndrome
  - AIDS-defining infections (disseminated *Mycobacterium avium* complex (DMAC), *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP), CMV and others)

Malignancy (~20%)

Haematological malignancy
- Lymphoma*, leukaemia and myeloma

Solid tumours
- Renal, liver, colon, stomach, pancreas, kidney

Connective tissue disorders (~15%)

Older adults
- Temporal arteritis/polymyalgia rheumatica*

Younger adults
- Still's disease (juvenile rheumatoid arthritis)*
- Systemic lupus erythematosus (SLE)
- Vasculitic disorders (including polyarteritis nodosa, rheumatoid disease with vasculitis and Wegener's granulomatosis)
- Polymyositis
- Behçet's disease

Geographically restricted
- Rheumatic fever

Miscellaneous (~20%)

Cardiovascular
- Atrial myxoma, aortitis, aortic dissection

Respiratory
- Sarcoidosis, pulmonary embolism and other thromboembolic disease, extrinsic allergic alveolitis

Gastrointestinal
- Inflammatory bowel disease, granulomatous hepatitis, alcoholic liver disease, pancreatitis

Endocrine/metabolic
- Thyrotoxicosis, thyroiditis, hypothalamic lesions, phaeochromocytoma, adrenal insufficiency, hypertriglyceridaemia

Haematological
- Haemolytic anaemia, paroxysmal nocturnal haemoglobinuria, thrombotic thrombocytopenic purpura, myeloproliferative disorders, Castleman's disease, graft-versus-host disease (after allogeneic bone marrow transplantation)

Inherited
- Familial Mediterranean fever and periodic fever syndromes

Drug reactions*,
- e.g. Antibiotic fever, drug hypersensitivity reactions etc.

Factitious fever*

Idiopathic (~15%)

*Most common causes within each group.

Clinical assessment:

- Rare causes, such as periodic fever syndromes, should be considered in those with a positive family history.
- Children and younger adults are more likely to have infectious causes, in particular viral infections.

- Older adults are more likely to have certain infections and non-infectious causes.
- Detailed examination should be repeated at regular intervals to detect emerging features, such as rashes, signs of infective endocarditis or features of vasculitis.

- In men the prostate deserves careful consideration as a potential source of infection.
- Clinicians should be alert to the possibility of factitious fever, in which high temperature recordings are engineered by the patient.

13.3 Clues to the diagnosis of factitious fever

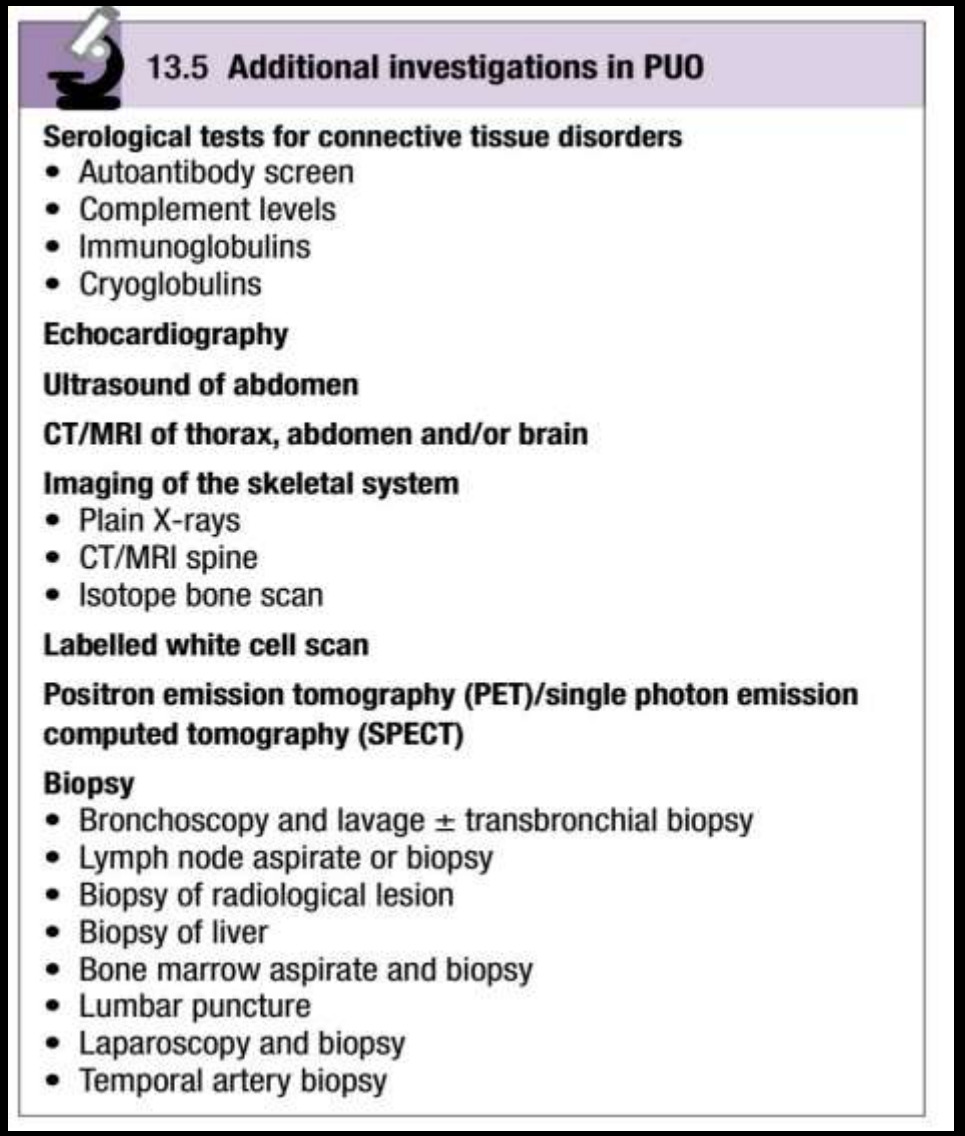
- A patient who looks well
- Bizarre temperature chart with absence of diurnal variation and/or temperature-related changes in pulse rate
- Temperature > 41°C
- Absence of sweating during defervescence
- Normal ESR and CRP despite high fever
- Evidence of self-injection or self-harm
- Normal temperature during supervised (observed) measurement and of freshly voided urine

Investigations:

- If initial investigation of fever is negative, a series of further microbiological and non-microbiological investigations should be considered.

These will usually include:

- induced sputum or other specimens for mycobacterial stains and culture
- serological tests
- imaging of the abdomen by ultrasonography or computed tomography (CT)
- echocardiography.



13.5 Additional investigations in PUO

Serological tests for connective tissue disorders
- Autoantibody screen
- Complement levels
- Immunoglobulins
- Cryoglobulins

Echocardiography

Ultrasound of abdomen

CT/MRI of thorax, abdomen and/or brain

Imaging of the skeletal system
- Plain X-rays
- CT/MRI spine
- Isotope bone scan

Labelled white cell scan

Positron emission tomography (PET)/single photon emission computed tomography (SPECT)

Biopsy
- Bronchoscopy and lavage ± transbronchial biopsy
- Lymph node aspirate or biopsy
- Biopsy of radiological lesion
- Biopsy of liver
- Bone marrow aspirate and biopsy
- Lumbar puncture
- Laparoscopy and biopsy
- Temporal artery biopsy

13.4 Microbiological investigation of PUO

Microscopy

- Blood for atypical lymphocytes (EBV, CMV, HIV-1, hepatitis viruses or *Toxoplasma gondii*), trypanosomiasis, malaria, *Borrelia* spp.
- Respiratory samples for mycobacteria, fungi
- Stool for ova, cysts and parasites
- Biopsy for light microscopy (bacteria, mycobacteria, fungi, *Leishmania* and other parasites) and/or electron microscopy (viruses, protozoa (e.g. microsporidia) and other fastidious organisms (e.g. *T. whipplei*))
- Urine for white or red blood cells, schistosome ova, mycobacteria (early morning urine × 3)

Culture

- Aspirates and biopsies (e.g. joint, deep abscess, debrided tissues)
- Blood, including prolonged culture and special media conditions
- Cerebrospinal fluid (CSF)
- Gastric aspirate for mycobacteria
- Stool
- Swabs
- Urine ± prostatic massage in older men

Antigen detection

- Blood
- CSF for cryptococcal antigen
- Nasopharyngeal aspirate/throat swab for respiratory viruses
- Urine, e.g. for *Legionella* antigen

Nucleic acid detection

- Blood for *Bartonella* spp. and viruses
- CSF for viruses and key bacteria (meningococcus, pneumococcus)
- Nasopharyngeal aspirate/throat swab for respiratory viruses
- Tissue specimens, e.g. for *Tropheryma whipplei*
- Urine, e.g. for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*
- Stool, e.g. for norovirus, rotavirus

Immunological tests

- Serology (antibody detection) for viruses, dimorphic fungi and some bacteria and protozoa
- Interferon-γ release assay for diagnosis of tuberculosis

Note This list does not apply to every patient with a PUO. Appropriate tests should be selected in a stepwise manner, according to specific predisposing factors, epidemiological exposures and local availability, and should be discussed with a microbiologist.

- Lesions identified on imaging should usually be biopsied to obtain material for culture, including for the diagnosis of tuberculosis, and histopathology, including special stains for pathogens associated with the clinical scenario.

- The chance of a successful diagnosis is greatest if procedures for obtaining and transporting the correct samples in the appropriate media are carefully planned in advance; this requires discussion between the clinical team, the radiologist or surgeon performing the procedure, and the local microbiologist and histopathologist.

- Liver biopsy may be justified, e.g. to identify idiopathic granulomatous hepatitis, if there are biochemical or radiological abnormalities.
- Bone marrow biopsies have a diagnostic yield of up to 15%.

- A biopsy is most useful in revealing haematological malignancy, myelodysplasia or tuberculosis, and may also identify brucellosis, typhoid fever or visceral leishmaniasis.
- Bone marrow should always be sent for culture as well as microscopy.
- Laparoscopy is occasionally undertaken with biopsy of abnormal tissues.

- Splenic aspiration in specialist centres is the diagnostic test of choice for suspected leishmaniasis.
- Temporal artery biopsy should be considered in patients over the age of 50 years, even in the absence of physical signs or a raised ESR.

- ‘Blind’ biopsy of other structures in the absence of localising signs, or laboratory or radiology results is unhelpful.

Prognosis:

- The overall mortality of PUO is 30–40%, mainly attributable to malignancy in older patients.
- If no cause is found, the long-term mortality is low and fever often settles spontaneously.

Fever in the injection drug-user:

- Intravenous injection of drugs of abuse is endemic in many parts of the world.
- Infective organisms are introduced by non-sterile (often shared) injection equipment, while host defences against infection are overcome by direct access to the normally sterile blood stream and by immune deficiencies in poorly nourished addicts.

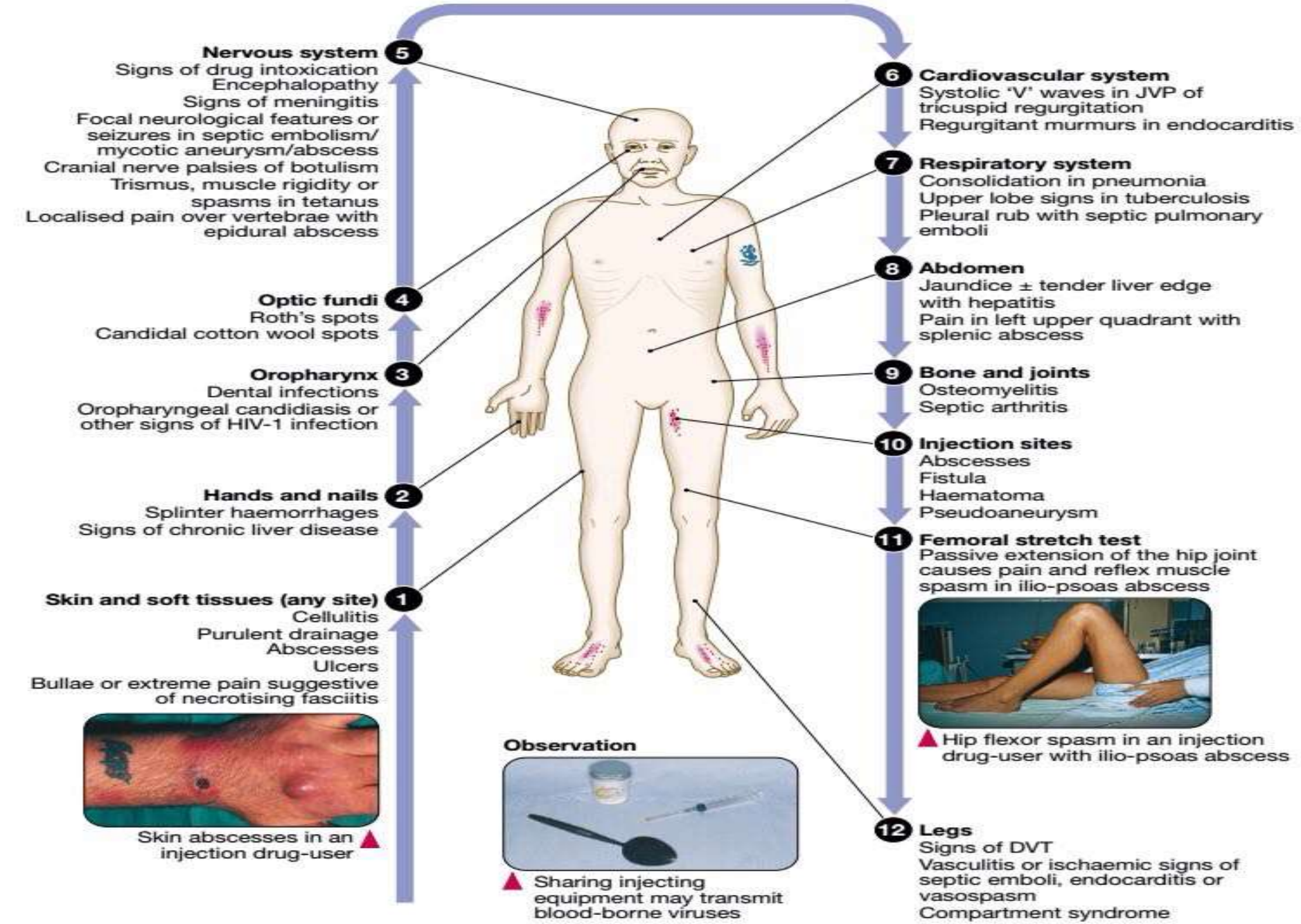


Fig. 13.2 Fever in the injection drug-user: key features of clinical examination. Full examination (p. 290) is required but features most common amongst injection drug-users are shown here.

- The risks increase with prolonged drug use and injection into large veins of the groin and neck because of progressive thrombosis of superficial peripheral veins.
- A varied and unusual constellation of infectious diseases is encountered in this group of patients.

- Although the differential diagnosis of fever is wide, the most common causes are soft tissue or respiratory infections.

Clinical assessment:

The history should include consideration of the following risk factors:

a. **Site of injection:** Femoral vein injection is associated with vascular complications such as deep venous thrombosis (50% of which are septic) and accidental arterial injection with false aneurysm formation or a compartment syndrome due to swelling within the fascial sheath.

- Local complications include ilio-psoas abscess, and septic arthritis of the hip joint or sacro-iliac joint.
- Injection of the jugular vein can be associated with cerebrovascular complications.

- Subcutaneous and intramuscular injection has been associated with infection by clostridial species, the spores of which contaminate heroin.

- *Clostridium novyi* causes a local lesion with significant toxin production leading to shock and multi-organ failure.
- Tetanus, wound botulism and gas gangrene also occur.

b. Technical details of injection: Sharing of needles and other injecting paraphernalia (including spoons and filters) greatly increases the risk of blood-borne virus infection.

- Some users lubricate their needles by licking them prior to injection, thus introducing mouth organisms such as anaerobic streptococci, *Fusobacterium* spp. and *Prevotella* spp.

- Contamination of commercially available lemon juice, used to dissolve heroin before injection, has been associated with blood-stream infection with *Candida* spp.

c. Substances injected: Injection of cocaine is associated with a variety of vascular events.

- Certain formulations of heroin have been associated with particular infections, e.g. wound botulism with black tar heroin.
- Drugs are often mixed with other substances, e.g. talc.

d. Blood-borne virus status: Results of previous hepatitis B virus (HBV), HCV and HIV tests or vaccinations for HAV/HBV should be recorded.

e. Surreptitious use of antimicrobials: Addicts may use antimicrobials to self-treat infections, masking initial blood culture results.

- It can be difficult to distinguish effects of infection from the effects of drugs themselves or the agitated state of drug withdrawal (excitement, tachycardia, sweating, marked myalgia, confusion).

- Stupor and delirium may result from drug administration but may also signal meningitis or encephalitis.
- Non-infected venous thromboembolism is also common in this group.

Investigations:

- The initial investigations are as for any fever, including a chest X-ray and blood cultures.
- Since blood sampling may be difficult, contamination is often a problem.

- Echocardiography to detect infective endocarditis should be performed in all injection drug-users: with bacteraemia due to *Staph. aureus* or other organisms associated with endocarditis; with thromboembolic phenomena; or with a new or previously undocumented murmur.

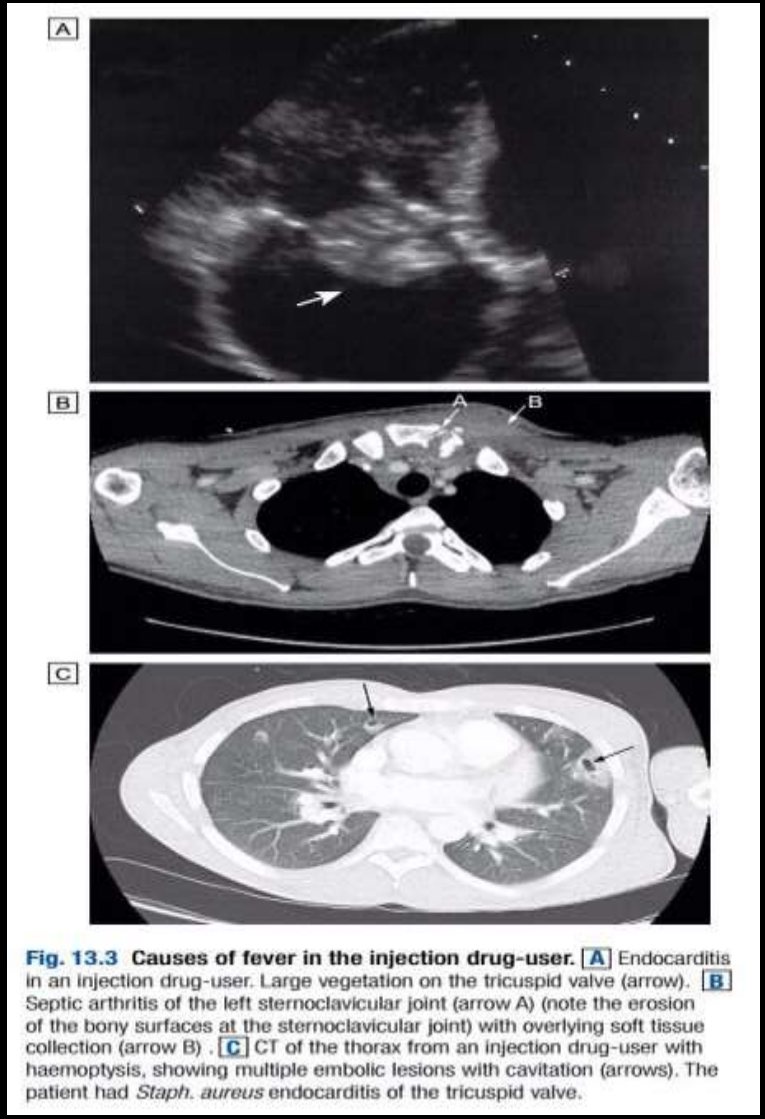


Fig. 13.3 Causes of fever in the injection drug-user. [A] Endocarditis in an injection drug-user. Large vegetation on the tricuspid valve (arrow). [B] Septic arthritis of the left sternoclavicular joint (arrow A) (note the erosion of the bony surfaces at the sternoclavicular joint) with overlying soft tissue collection (arrow B) . [C] CT of the thorax from an injection drug-user with haemoptysis, showing multiple embolic lesions with cavitation (arrows). The patient had *Staph. aureus* endocarditis of the tricuspid valve.

- Endovascular infection should also be suspected if lung abscesses or pneumatocoeles are detected radiologically.
- Additional imaging should be focused on sites of symptoms and signs.
- Any pathological fluid collections should be sampled either under radiological guidance or by surgical means.

- In patients with suspected compartment syndrome (leg swelling and pain with neurological and ischaemic features), serum creatine kinase and urine myoglobin are useful.

- Urinary toxicology may suggest a non-infectious cause of the presenting complaint.
- While being investigated, all injection drug-users should be offered testing for HBV, HCV and HIV-1.
- Microbiological results are crucial in guiding therapy.
- Injection drug-users may have more than one infection.

- Skin and soft tissue infections are most often due to *Staph. aureus* or streptococci, and sometimes to *Clostridium* spp. or anaerobes.
- Pulmonary infections are most often due to community-acquired pneumonia, pulmonary tuberculosis or septic pulmonary emboli.

- Endocarditis with septic emboli commonly involves *Staph. aureus* and viridans streptococci, but *Pseudomonas aeruginosa* and *Candida* spp. are also encountered.

Management:

- Empirical therapy of fever in the injection drug user includes an antistaphylococcal penicillin (e.g. flucloxacillin) or, if meticillin-resistant *Staph. aureus* (MRSA) is prevalent in the community, a glycopeptide.

- Once a particular pathogen is identified, specific therapy is commenced, with modification when antimicrobial susceptibility is available.
- In injection drug-users, right-sided endocarditis due to *Staph. aureus* is customarily treated with high-dose intravenous flucloxacillin.

- In left-sided *Staph. aureus* endocarditis, aminoglycoside therapy may be added.
- Right-sided endocarditis caused by MRSA is usually treated with 4 weeks of vancomycin plus gentamicin for the first week. Specialist advice should be sought.

- For localised infections of the skin and soft tissues, oral therapy with agents active against staphylococci, streptococci and anaerobes is appropriate (e.g. co-amoxiclav or clindamycin).

Fever in the immunocompromised host:

- Immunocompromised hosts include those with congenital immunodeficiency, HIV infection and iatrogenic immunosuppression induced by chemotherapy, transplantation or immunosuppressant medicines, including high-dose corticosteroids.

- Metabolic abnormalities such as under-nutrition or hyperglycaemia may also contribute.
- Multiple elements of the immune system are potentially compromised.

- A patient may have impaired neutrophil function from chemotherapy, impaired T cell and/or B cell responses due to underlying malignancy, T cell and phagocytosis defects due to corticosteroids, mucositis from chemotherapy and an impaired skin barrier due to insertion of a central venous catheter.

- Fever may result from infectious or from non-infectious causes, including drugs, vasculitis, neoplasm, organising pneumonitis, lymphoproliferative disease, graft-versus-host disease (in recipients of haematopoietic bone marrow transplants) and Sweet's syndrome (reddish nodules or plaques with fever and leucocytosis, in association with haematological malignancy).

Clinical assessment:

The following should be addressed in the history:

a. Identification of the immunosuppressant factors, and nature of the immune defect.

b. Any past infections and their treatment. Infections may recur and antimicrobial resistance may have been acquired in response to prior therapy.

c. Evidence of microbial colonisation, especially with antimicrobial-resistant organisms, in past surveillance cultures.

d. Exposure to infections, including opportunistic infections that would not cause disease in an immunocompetent host.

e. Prophylactic medicines and vaccinations administered.

- Examination should include inspection of the normal physical barriers provided by skin and mucosal surfaces, in particular central venous catheters, the mouth, sinuses, ears and perianal area (though avoid digital rectal examination).

- Disseminated infections can manifest as cutaneous lesions; the areas around finger and toenails should be closely inspected.

Investigations:

- Immunocompromised hosts often have decreased signs of inflammation.
- This manifests as attenuation of physical signs, such as neck stiffness with meningitis, or of radiological and laboratory abnormalities, such as leucocytosis.

- In patients with respiratory symptoms, a high-resolution chest CT scan should be considered in addition to chest X-ray.
- Abdominal imaging may also be warranted, particularly if there is right lower quadrant pain.

- Blood cultures through the central venous catheter, urine cultures, and stool cultures if diarrhoea is present may also be helpful.
- Nasopharyngeal aspirates are sometimes diagnostic, as immunocompromised hosts may shed respiratory viruses for prolonged periods.

- Skin lesions should be biopsied if nodules are present and investigation should include fungal stains.
- Useful molecular techniques include polymerase chain reaction (PCR) for CMV and *Aspergillus* spp.
- DNA, and antigen assays (e.g. cryptococcal antigen (CrAg) for *Cryptococcus neoformans*, and galactomannan for *Aspergillus* spp. in blood or *Legionella pneumophila* type 1 in urine).

- Antibody detection is rarely useful in immunocompromised patients.
- Patients with respiratory signs or symptoms should be considered for a bronchoscopy to obtain bronchoalveolar lavage fluid for investigation of pathogens, including *Pneumocystis jirovecii* (*carinii*) as well as bacteria, fungi and viruses.

Neutropenic fever:

- Neutropenic fever is strictly defined as a neutrophil count of less than 0.5×10^9/L and a single axillary temperature > 38.5°C or three recordings > 38.0°C over a 12-hour period, although the infection risk increases progressively as the neutrophil count drops below 1.0×10^9/L.

- Patients with neutropenia are particularly prone to bacterial or fungal infection.
- Gram-positive organisms are the most common pathogens, particularly in association with in-dwelling catheters.
- Empirical broad-spectrum antimicrobial therapy is commenced as soon as neutropenic fever occurs and cultures have been obtained.

- The most common regimens for neutropenic sepsis are broad-spectrum penicillins such as piperacillin-tazobactam i.v.

- Although aminoglycosides are commonly used in combination, this practice is not supported by trial data.

EBM 13.6 Treatment of neutropenic fever

'Broad spectrum β-lactam monotherapy is equivalent to β-lactam-aminoglycoside combination therapy for neutropenic fever in many settings.'

- If fever has not resolved after 3–5 days, empirical antifungal therapy (e.g. an amphotericin B preparation or caspofungin) is added.

- An alternative antifungal strategy, which is gaining favour, is to use azole prophylaxis in high-risk patients, and to employ sensitive markers of early fungal infection to guide treatment initiation (a ‘pre-emptive approach’).

Post-transplantation fever:

- Fever in transplant recipients may be due to infection, or to episodes of graft rejection in solid organ transplant recipients or graft-versus-host disease in bone marrow transplant recipients.

13.7 Infections in transplant recipients

Time post-transplantation	Infections
Solid organ recipients	
0–1 month	Bacterial or fungal infections related to the underlying condition or surgical complications
1–6 months	CMV, other opportunistic infections (e.g. PCP)
> 6 months	Bacterial pneumonia, other bacterial community-acquired infections, shingles, cryptococcal infection, post-transplant lymphoproliferative disorder (PTLD)
Bone marrow recipients	
Pre-engraftment (typically 0–4 weeks)	Bacterial and fungal infections (including moulds) or respiratory viruses
Post-engraftment	CMV, PCP, moulds, other opportunistic infections
Late (> 100 days)	Community-acquired bacterial infections, shingles, CMV, PTLD

- Infections in solid transplant recipients are grouped according to the time of onset.
- Those in the first month are related to the underlying condition or surgical complications.
- Those occurring 1–6 months after transplantation are characteristic of impaired T cell function.

- Risk factors for CMV infection have been identified and patients commonly receive either prophylaxis or intensive monitoring involving regular testing for CMV DNA by PCR and early initiation of anti-CMV therapy using intravenous ganciclovir or oral valganciclovir if tests become positive.

- For bone marrow transplant recipients, infections in the first four weeks are more common in patients receiving a myeloablative conditioning regimen.
- Later infections are more common if an allogeneic procedure is performed.

- Post-transplant lymphoproliferative disorder (PTLD) is an Epstein–Barr virus (EBV)-associated lymphoma that can complicate transplantation, particularly when primary EBV infection occurs after transplantation.

Positive blood culture:

- Blood-stream infection (BSI) or bacteraemia is a frequent presentation of infection.
- This can be community-acquired or may arise in hospital (‘nosocomial’), although with increasing outpatient treatment ‘community-acquired’ BSI is more precisely ‘community-onset’ BSI since it may arise after hospital-based interventions.

13.8 Common causes of blood-stream infection

Community-acquired

- *Staph. aureus* including MRSA
- *Strep. pneumoniae*
- Other streptococci
- *Escherichia coli*

Nosocomial

- *Staph. aureus* including MRSA
- Coagulase-negative staphylococci
- Enterococci including VRE
- Gram-negative bacteria
- *Candida* spp.

(MRSA = meticillin-resistant *Staph. aureus;* VRE = vancomycin-resistant enterococci)

- In immunocompromised hosts a wider range of microorganisms may be isolated, e.g. fungi in neutropenic hosts.
- Primary bacteraemia refers to cases in which the site of infection is unknown; this applies in approximately 10% of community-acquired cases and approximately 30% of nosocomial cases, and is more common in *Staph. aureus* bacteraemias.

- In community-acquired *Staph. aureus* bacteraemia, 20–30% of cases are associated with infectious endocarditis and up to 10% are due to osteomyelitis.
- Peripheral and central venous catheter-related infections are an important source of nosocomial BSI.
- BSI has an associated mortality of 15–40%, depending on the setting, host and microbial factors.

Clinical assessment:

- The history should determine the setting in which BSI has occurred.
- Host factors predisposing to infection include skin disease, diabetes mellitus, injection drug use, the presence of a central venous, urinary or haemodialysis catheter, and surgical procedures, especially involving implantation of prosthetic materials (in particular, endovascular prostheses).

- Physical examination should focus on signs of endocarditis, evidence of bone or joint infection (tenderness or restriction of movement), and abdominal or flank tenderness.
- Central venous catheters should be examined for erythema or purulence at the exit site.
- Particularly in cases with *Candida* spp. infection or suspected infectious endocarditis, fundoscopy after pupil dilatation should be performed.

Investigations:

- Positive blood cultures may be caused by contaminants.
- When isolated from only one bottle or from all bottles from one venesection, coagulase-negative staphylococci often represent contamination.
- Repeated isolation of this organism, however, should raise suspicion of infective endocarditis or, in a patient with any form of prosthetic material, prosthesis infection.

- Viridans streptococci occasionally contaminate blood cultures but, in view of their association with infective endocarditis, significant infection must always be excluded clinically.
- *Bacillus* spp. (‘aerobic spore bearers’) and *Clostridium* spp. often represent incidental transient bacteraemia or contamination, but certain species (e.g. *C. septicum) may be genuine* pathogens.

- Further investigations are influenced by the causative organism and setting. Initial screening tests are similar to those for fever and should include chest X-ray, urine culture and, in many cases, ultrasound or other imaging of the abdomen.
- Imaging should also include any areas of bone or joint pain and any prosthetic material, e.g. a prosthetic joint or an aortic graft.

- Echocardiography should be considered for patients with BSI who are at risk of endocarditis from underlying valvular heart disease, those with clinical features of endocarditis (including a heart murmur), those whose cultures reveal an organism that is a common cause of endocarditis (e.g. *Staph. aureus,* viridans streptococci or enterococci), and those in whom multiple blood cultures are positive for the same organism.

- The sensitivities of transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) for the detection of vegetations are 50–90% and > 95%, respectively.
- Therefore, if TTE is negative, TOE should be used.

- Certain rare causes of BSI have specific associations that warrant further investigation.
- Endocarditis caused by *Strep. bovis and infection caused by C. septicum are* both associated with colonic carcinoma and their isolation is considered to be an indication for colonoscopy.

Management:

- BSI requires antimicrobial therapy and attention to the source of infection, including surgical drainage if appropriate.
- Two weeks of therapy may be sufficient for *Staph. aureus* BSI from central and peripheral venous catheter infections when the source is identified and removed, for uncomplicated skin and soft tissue infections and for selected cases of uncomplicated right-sided infective endocarditis.
- Other *Staph. aureus* BSI is usually treated for 4–6 weeks.

Central venous catheter infections:

- Infections of central venous catheters typically involve the catheter lumen and are associated with fever, positive blood cultures and, in some cases, signs of purulence or exudate at the site of insertion.

- Infection is more common in temporary catheters inserted into the groin or jugular vein than those in the subclavian vein.
- Tunnelled catheters, e.g. Hickman catheters, may also develop tunnel site infections.
- Staphylococci account for 70–90% of catheter infections, with coagulase-negative staphylococci more common than *Staph. aureus.*

- Other causes include enterococci and Gram-negative bacilli.
- Unusual Gram-negative organisms, such as *Citrobacter freundii* and *Pseudomonas fluorescens, c*ause pseudo-outbreaks and raise the possibility of non-sterile infusion equipment or infusate.
- *Candida* spp. are a common cause of line infections, particularly in association with total parenteral nutrition.
- Non- tuberculous mycobacteria may cause tunnel infections.

Investigations and management:

- In bacteraemic patients with fever and no other obvious source of infection, a catheter infection is likely.
- Local evidence of erythema, purulence or thrombophlebitis supports the diagnosis.
- However, microbiological confirmation is essential.
- Catheter-related infection is suggested by higher colony counts or shorter time to positivity in blood cultures obtained through the catheter than in peripheral blood cultures.

- If the line is removed, a semi-quantitative culture of the tip should confirm the presence of 15 or more colony-forming units, but this is retrospective and does not detect luminal infection.

- For coagulase-negative staphylococcal line infections, the options are to remove the line or, in the case of tunnelled catheters, to treat empirically with a glycopeptide antibiotic, e.g. vancomycin, with or without the use of antibiotic-containing lock therapy to the catheter for approximately 14 days.

- For *Staph. aureus* infection, the chance of curing an infection with the catheter in situ is low, and the risks from infection are high.
- Therefore, unless the risks of catheter removal outweigh the benefits, treatment should involve catheter removal followed by 14 days of appropriate antimicrobial therapy; the same applies to infections with *Candida* spp. or *Bacillus* spp.

- Infection prevention is a key component of the management of vascular catheters.
- Measures include strict attention to hand hygiene, optimal siting, full aseptic technique on insertion and subsequent interventions, skin antisepsis with chlorhexidine and isopropyl alcohol, daily assessment of catheter sites (e.g. with visual infusion phlebitis (VIP) score), and daily consideration of the continuing requirement for catheterisation.
- The use of catheters impregnated with antimicrobials such as chlorhexidine or silver is advocated in some settings.

Sepsis:

- It describes patients with signs of the systemic inflammatory response syndrome (SIRS: two of temperature > 38 °C or < 36 °C, pulse rate > 90 beats per minute, respiratory rate > 20 per minute or PCO_2 < 4.3 kPa (32.5 mmHg), and white blood cell count > 12 or < 4×10^9/L and evidence of infection.

- Septic shock describes sepsis plus hypotension (systolic blood pressure < 90 mmHg systolic or a fall of > 40 mmHg from baseline that is not responsive to fluid challenge or due to another cause).
- It may be complicated by multi-organ failure and requires intensive care unit admission.

- Sepsis largely results from host responses to microbial lipopolysaccharide, peptidoglycans, lipoproteins or superantigens, and there are many infectious causes.

13.9 Causes of sepsis

Infection	Setting
Bacterial	
Staph. aureus, coagulase-negative staphylococci	Bacteraemia may be associated with endocarditis, intravascular cannula infection, or skin or bone foci
Strep. pneumoniae	Invasive pneumococcal disease, usually with pneumonia or meningitis
Other streptococci	Invasive streptococcal disease, especially necrotising fasciitis. *Viridans* streptococci in neutropenic host with severe mucositis
Staphylococcal or streptococcal toxic shock syndrome	Toxin-mediated, blood cultures negative; clues include erythrodermic rash and epidemiological setting
Enterococci	Most often with abdominal focus
Neisseria meningitidis	Sepsis in children or young adults with petechial rash and/or meningitis
E. coli, other Gram-negative bacteria	Urinary or biliary tract infection, or other abdominal infections
Pseudomonas aeruginosa, multidrug-resistant Gram-negative bacteraemia	Nosocomial infection
Yersinia pestis	In plague
Burkholderia pseudomallei	Endemic in areas of Thailand; more likely to involve patients with diabetes mellitus or immunocompromised
Capnocytophaga canimorsus	Associated with dog bites and asplenic individuals
C. difficile	Severe colitis, particularly in the elderly
Polymicrobial infection with Gram-negatives and anaerobes	Bowel perforation
Mycobacterium tuberculosis, *M. avium complex* (MAC)	HIV-positive or immunocompromised with miliary TB or disseminated MAC
Fungal	
Candida spp.	Line infection or post-operative complication, nosocomial or immunocompromised host
Histoplasma capsulatum, other dimorphic fungi	Immunocompromised host
Parasitic	
Falciparum malaria	Malaria with high-level parasitaemia and multi-organ failure or as a complication of bacterial superinfection
Babesia microti	Asplenic individual
Strongyloides stercoralis hyperinfection syndrome	Gram-negative infection complicating *Strongyloides* infection in immunocompromised host

- The results of blood cultures and known host factors allow an initial assessment of likely sources of infection which should be the target of initial investigations.
- Patients who are immunocompromised may have a sepsis syndrome in association with a broader range of pathogens which may be harder to culture, including mycobacteria and fungi.
- In any individual who has recently visited the tropics, malaria must also be considered.

Severe skin and soft tissue infections (SSTI):

- SSTIs are an important cause of sepsis.
- Cases can be classified according to the clinical features and microbiological findings.
- In some cases severe systemic features may be out of keeping with mild local features

13.10 Severe necrotising soft tissue infections

- Necrotising fasciitis (primarily confined to subcutaneous fascia and fat)
- Clostridial anaerobic cellulitis (confined to skin and subcutaneous tissue)
- Non-clostridial anaerobic cellulitis
- Progressive bacterial synergistic gangrene (*Staph. aureus* + micro-aerophilic streptococcus) ('Meleney's gangrene', primarily confined to skin)
- Pyomyositis (discrete abscesses within individual muscle groups)
- Clostridial myonecrosis (gas gangrene)
- Anaerobic streptococcal myonecrosis (non-clostridial infection mimicking gas gangrene)
- Group A streptococcal necrotising myositis

Necrotising fasciitis:

- In this condition, cutaneous involvement with erythema and oedema progresses to bullae or areas of necrosis.
- However, in contrast to cellulitis, the cutaneous features are often minimal while the pain is severe.
- The infection spreads quickly along the fascial plane.
- It is a medical emergency, which requires immediate débridement in addition to antimicrobial therapy.

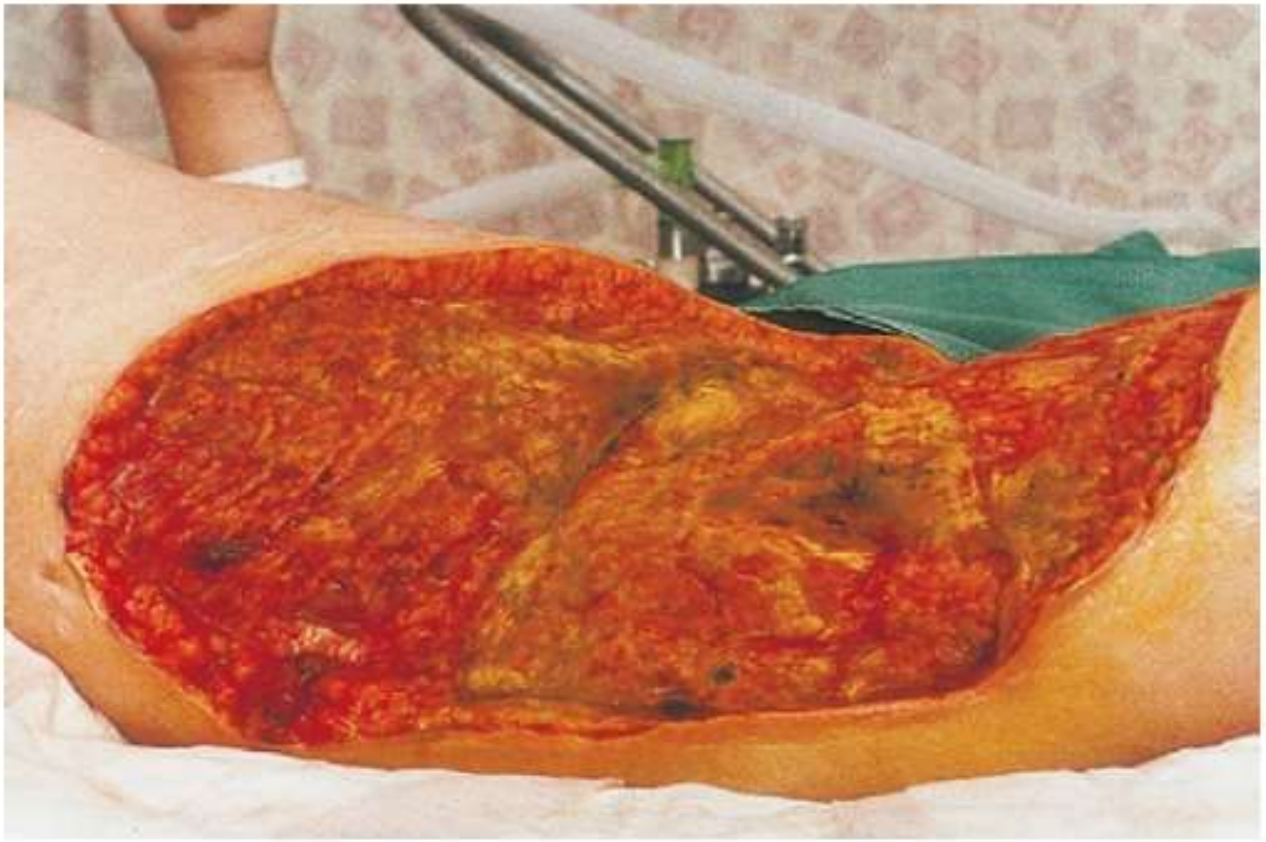


Fig. 13.4 Excision following necrotising fasciitis in an injection drug-user.

- Although the infection may be diagnosed by imaging studies, its rapid spread means that surgical inspection of the involved muscle groups is urgently required to facilitate prompt diagnosis and treatment.

- Type 1 necrotising fasciitis is a mixed infection with Gram-negative bacteria and anaerobes, often seen post-operatively in diabetic or immunocompromised hosts.
- Subcutaneous gas may be present.
- Type 2 necrotising fasciitis is caused by group A or other streptococci.
- Approximately 60% of cases are associated with streptococcal toxic shock syndrome.

- Empiric treatment is with broad-spectrum agents (e.g. piperacillin-tazobactam plus clindamycin plus ciprofloxacin; meropenem monotherapy; or third-generation cephalosporin plus metronidazole) and surgical débridement.
- Hyperbaric oxygen therapy may be considered for polymicrobial infection.
- Group A streptococcal infection is treated with benzylpenicillin plus clindamycin, and often immunoglobulin.

Gas gangrene:

- Although *Clostridium* spp. may colonise or contaminate wounds, no action is required unless there is evidence of spreading infection.
- In anaerobic cellulitis, usually due to *C. perfringens* or other strains infecting devitalised tissue following a wound, gas forms locally and extends along tissue planes, but bacteraemia and invasion of healthy tissue are not found.
- Prompt surgical débridement of devitalised tissue and therapy with penicillin or clindamycin usually result in an excellent outcome.

- Gas gangrene (clostridial myonecrosis) is defined as acute invasion of healthy living muscle undamaged by previous trauma, and is most commonly caused by *C. perfringens.*
- In at least 70% of cases it follows deep penetrating injury sufficient to create an anaerobic (ischaemic) environment and allow clostridial introduction and proliferation.

- Severe pain at the site of the injury progresses rapidly over 18–24 hours.
- Skin colour changes from pallor to bronze/purple discoloration and the skin is tense, swollen, oedematous and exquisitely tender.
- Gas in tissues may be obvious with crepitus on clinical examination, or visible on X-ray, CT or ultrasound.

- Signs of systemic toxicity develop rapidly, with high leucocytosis, multi-organ dysfunction, raised creatine kinase and evidence of disseminated intravascular coagulation and haemolysis.

- Antibiotic therapy with high-dose intravenous penicillin and clindamycin is recommended, coupled with aggressive surgical débridement of the affected tissues.
- Alternative agents include cephalosporins and metronidazole.
- Hyperbaric oxygen has a putative but controversial role.

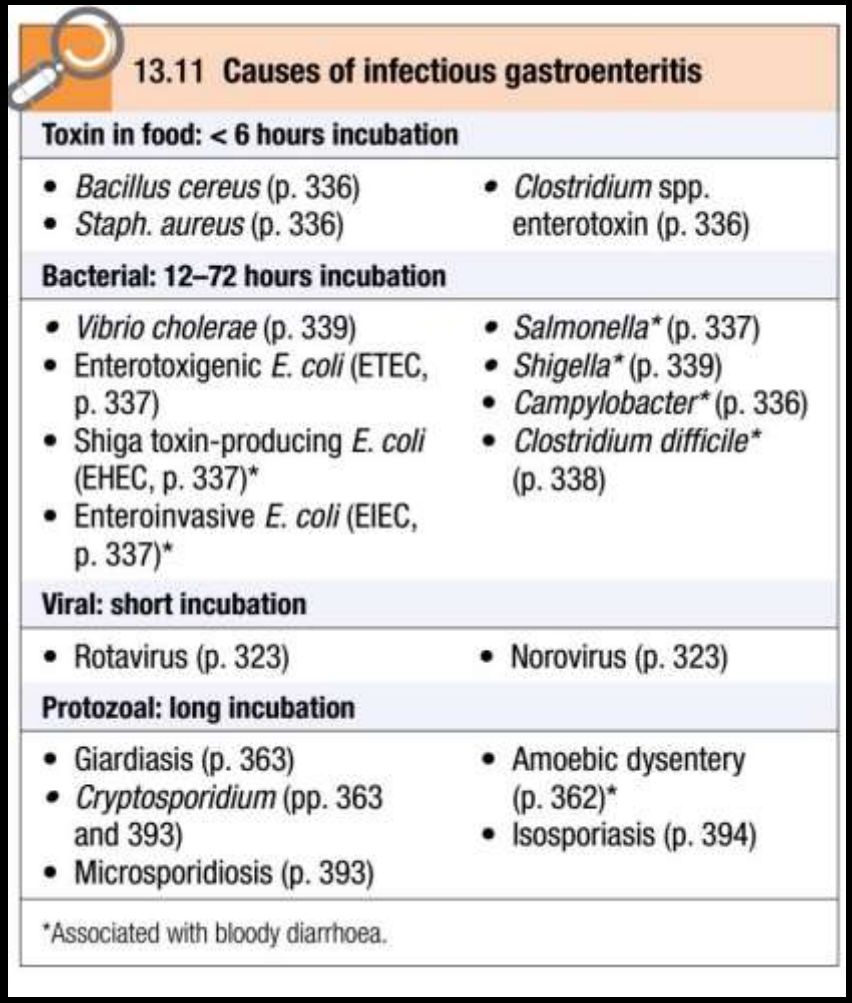
Other SSTIs:

- ‘Synergistic gangrene’ is a combined infection with anaerobes and other bacteria (*Staph. aureus* or Gram-negatives).
- When this affects the genital/perineal area it is known as ‘Fournier’s gangrene’.
- Severe gangrenous cellulitis in immunocompromised hosts may involve Gram-negative bacteria or fungi.

- *Entamoeba histolytica* can cause soft tissue necrosis following abdominal surgery in areas of the world where infection is common.
- Contact with shellfish in tropical areas and regions such as the Gulf of Mexico can lead to infection with *Vibrio vulnificus,* which causes soft tissue necrosis and bullae.
- Patients with chronic liver disease are particularly susceptible.

Acute diarrhoea and vomiting:

- Acute diarrhoea, sometimes with vomiting, is the predominant symptom in infective gastroenteritis.

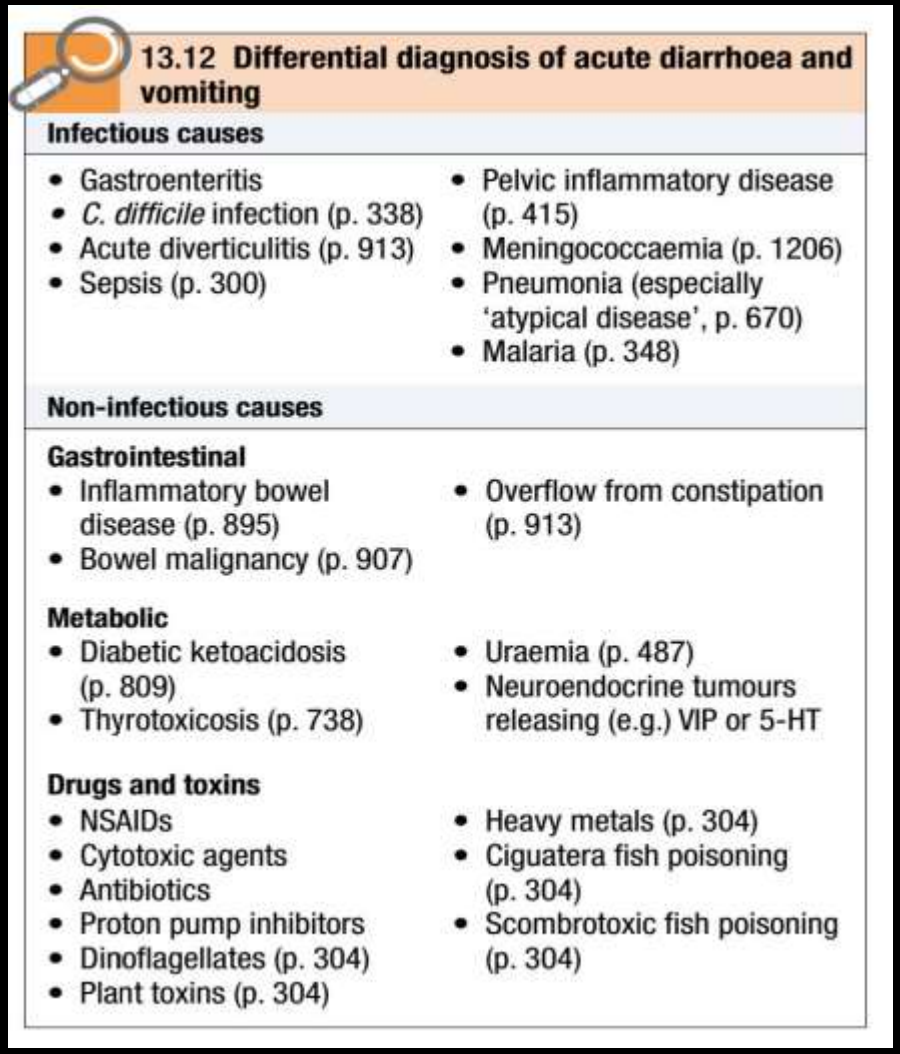


13.11 Causes of infectious gastroenteritis

Toxin in food: < 6 hours incubation	
• *Bacillus cereus* (p. 336) • *Staph. aureus* (p. 336)	• *Clostridium* spp. enterotoxin (p. 336)
Bacterial: 12–72 hours incubation	
• *Vibrio cholerae* (p. 339) • Enterotoxigenic *E. coli* (ETEC, p. 337) • Shiga toxin-producing *E. coli* (EHEC, p. 337)* • Enteroinvasive *E. coli* (EIEC, p. 337)*	• *Salmonella** (p. 337) • *Shigella** (p. 339) • *Campylobacter** (p. 336) • *Clostridium difficile** (p. 338)
Viral: short incubation	
• Rotavirus (p. 323)	• Norovirus (p. 323)
Protozoal: long incubation	
• Giardiasis (p. 363) • *Cryptosporidium* (pp. 363 and 393) • Microsporidiosis (p. 393)	• Amoebic dysentery (p. 362)* • Isosporiasis (p. 394)

*Associated with bloody diarrhoea.

- Acute diarrhoea may also be a symptom of other infectious and non-infectious diseases.
- Stress, whether psychological or physical, can also produce loose stools.



13.12 Differential diagnosis of acute diarrhoea and vomiting

Infectious causes

- Gastroenteritis
- *C. difficile* infection (p. 338)
- Acute diverticulitis (p. 913)
- Sepsis (p. 300)
- Pelvic inflammatory disease (p. 415)
- Meningococcaemia (p. 1206)
- Pneumonia (especially 'atypical disease', p. 670)
- Malaria (p. 348)

Non-infectious causes

Gastrointestinal

- Inflammatory bowel disease (p. 895)
- Bowel malignancy (p. 907)
- Overflow from constipation (p. 913)

Metabolic

- Diabetic ketoacidosis (p. 809)
- Thyrotoxicosis (p. 738)
- Uraemia (p. 487)
- Neuroendocrine tumours releasing (e.g.) VIP or 5-HT

Drugs and toxins

- NSAIDs
- Cytotoxic agents
- Antibiotics
- Proton pump inhibitors
- Dinoflagellates (p. 304)
- Plant toxins (p. 304)
- Heavy metals (p. 304)
- Ciguatera fish poisoning (p. 304)
- Scombrotoxic fish poisoning (p. 304)

- The World Health Organization (WHO) estimates that there are more than 1000 million cases of acute diarrhoea annually in developing countries, with 3–4 million deaths, most often in infants and young children.
- In developed countries diarrhoea remains an important problem and the elderly are most vulnerable.

13.13 Infectious diarrhoea in old age

- **Incidence**: not increased, but the impact is greater.
- **Mortality**: most deaths due to gastroenteritis in the developed world are in adults aged over 70 years. Most are presumed to be caused by dehydration leading to organ failure.
- ***C. difficile* infection (CDI):** old age is associated with CDI, especially in hospital and nursing home settings, usually following antibiotic exposure.

- The majority of episodes are due to infections spread by the faecal–oral route and transmitted either on fomites, on contaminated hands, or in food or water.
- Measures such as the provision of clean drinking water, appropriate disposal of human and animal sewage, and simple principles of food hygiene all limit gastroenteritis.

- The clinical features of food-borne gastroenteritis depend on the pathogenic mechanisms involved.
- Some organisms (*Bacillus cereus, Staph. aureus* and *Vibrio cholerae)* elute exotoxins, which exert their major effects on the stomach and small bowel, and produce vomiting and/or so-called ‘secretory’ diarrhoea, which is watery diarrhoea without blood or faecal leucocytes.

- In general, the time from ingestion to the onset of symptoms is short and, other than dehydration, little systemic upset occurs.
- Other organisms, such as *Shigella* spp., *Campylobacter* spp. and enterohaemorrhagic *E. coli (*EHEC*),* may directly invade the mucosa of the small bowel or produce cytotoxins that cause mucosal ulceration, typically affecting the terminal small bowel and colon.

- The incubation period is longer and more systemic upset occurs, with prolonged bloody diarrhoea. *Salmonella* spp. are capable of invading enterocytes, and of causing both a secretory response and invasive disease with systemic features.
- This is seen with *Salmonella typhi and S. paratyphi* (enteric fever), and, in the immunocompromised host, with non-typhoidal *Salmonella spp.*

Clinical assessment:

- The history should include questioning about foods ingested , the duration and frequency of diarrhoea, the presence of blood or steatorrhoea, abdominal pain and tenesmus, and whether family or community members have been affected.
- Fever and bloody diarrhoea suggest an invasive, colitic, dysenteric process.

13.14 Foods associated with infectious illness, including gastroenteritis

Raw seafood

- Norovirus
- *Vibrio* spp.
- Hepatitis A

Raw eggs

- *Salmonella* spp.

Undercooked meat or poultry

- *Salmonella* spp.
- *Campylobacter* spp.
- EHEC
- *C. perfringens*

Unpasteurised milk or juice

- *Salmonella* spp.
- *Campylobacter* spp.
- EHEC
- *Y. enterocolitica*

Unpasteurised soft cheeses

- *Salmonella* spp.
- *Campylobacter* spp.
- ETEC
- *Y. enterocolitica*
- *L. monocytogenes*

Home-made canned goods

- *C. botulinum*

Raw hot dogs, pâté

- *L. monocytogenes*

- Incubation periods of less than 18 hours suggest toxin-mediated food poisoning; a period longer than 5 days suggests diarrhoea caused by protozoa or helminths.
- Examination includes assessment of the degree of dehydration by skin turgor, with pulse and blood pressure measurement.
- The urine output and ongoing stool losses should be monitored.

Investigations:

- These include stool inspection for blood and microscopy for leucocytes, and also an examination for ova, cysts and parasites if the history indicates former tropical residence or travel.
- Stool culture should be performed, if possible.
- FBC and serum electrolytes indicate the degree of inflammation and dehydration.

- In a malarious area, a blood film for malaria parasites should be obtained.
- Blood and urine cultures and a chest X-ray may identify alternative sites of infection, particularly if the clinical examination is suggestive of a syndrome other than gastroenteritis.

Management:

- All patients with acute, potentially infective diarrhoea should be appropriately isolated to minimise person-to-person spread of infection.
- If the history suggests a food-borne source, public health measures must be implemented to identify the source and whether other linked cases exist.

Fluid replacement:

- Replacement of fluid losses in diarrhoeal illness is crucial and may be life-saving.
- Although normal daily fluid intake in an adult is only 1–2 L, there is considerable additional fluid movement in and out of the gut in secretions.
- Infective and toxic processes in the gut disturb or reverse resorption in the small intestine and colon, potentially resulting in substantial fluid loss.

- Cholera is the archetype of this process, in which 10–20 L of fluid may be lost in 24 hours.
- The fluid lost in diarrhoea is isotonic, so both water and electrolytes need to be replaced.
- Absorption of electrolytes from the gut is an active process requiring energy.
- Infected mucosa is capable of very rapid fluid and electrolyte transport if carbohydrate is available as an energy source.

- Oral rehydration solutions (ORS) therefore contain sugars, as well as water and electrolytes.
- ORS can be just as effective as intravenous replacement fluid, even in the management of cholera.
- In mild to moderate gastroenteritis, adults should be encouraged to drink fluids and, if possible, continue normal dietary food intake.

13.15 Composition of oral rehydration solution and other replacement fluids*

Fluid	Na	K	Cl	Energy
WHO	90	20	80	54
Dioralyte	60	20	60	71
Pepsi®	6.5	0.8	–	400
7UP®	7.5	0.2	–	320
Apple juice	0.4	26	–	480
Orange juice	0.2	49	–	400
Breast milk	22	36	28	670

*mmol/L for electrolyte and Kcal/L for energy components.

- If this is impossible, e.g. due to vomiting, intravenous fluid administration will be required.
- In very sick patients, or those with cardiac or renal disease, monitoring of urine output and central venous pressure may be necessary.

The volume of fluid replacement required should be estimated based on the following considerations:

a. Replacement of established deficit: After 48 hours of moderate diarrhoea (6–10 stools per 24 hours) the average adult will be 1–2 L depleted from diarrhoea alone. Associated vomiting will compound this. Adults with this symptomatology should therefore be given rapid replacement of 1–1.5 L, either orally (ORS) or by intravenous infusion (normal saline), within the first 2–4 hours of presentation.

- Longer symptomatology or more persistent/severe diarrhoea rapidly produces fluid losses comparable to diabetic ketoacidosis and is a metabolic emergency requiring active intervention.

b. Replacement of ongoing losses: The average adult's diarrhoeal stool accounts for a loss of 200 mL of isotonic fluid. Stool losses should be carefully charted and an estimate of ongoing replacement fluid calculated. Commercially available rehydration sachets are conveniently produced to provide 200 mL of ORS; one sachet per diarrhoea stool is an appropriate estimate of supplementary replacement requirements.

c. Replacement of normal daily requirement: The average adult has a daily requirement of 1–1.5 L of fluid in addition to the calculations above. This will be increased substantially in fever or a hot environment.

Antimicrobial agents:

- In non-specific gastroenteritis, antibiotics have been shown to shorten symptoms by only 1 day in an illness usually lasting 1–3 days.
- This benefit, when related to the potential for the development of antimicrobial resistance or side-effects, does not justify treatment, except if there is systemic involvement and a host with immunocompromise or significant comorbidity.

- Evidence suggests that, in EHEC infections, the use of antibiotics may make the complication of haemolytic uraemic syndrome (HUS) more likely due to increased toxin release.
- Antibiotics should therefore not be used routinely in bloody diarrhoea.

- Conversely, antibiotics are indicated in *Sh. Dysenteriae* infection and in invasive salmonellosis, in particular typhoid fever.
- Antibiotics may also be advantageous in cholera epidemics, reducing infectivity and controlling the spread of infection.

Antidiarrhoeal, antimotility and antisecretory agents:

- In general, these agents are not recommended in acute infective diarrhoea and their use may even be contraindicated.
- Loperamide, diphenoxylate and opiates are potentially dangerous in dysentery in childhood, causing intussusception.

- Antisecretory agents such as bismuth and chlorpromazine may be effective but can cause significant sedation.
- They do not reduce stool fluid losses, although the stools may appear more bulky.
- Adsorbents such as kaolin or charcoal have little effect.

Non-infectious causes of food poisoning:

- Whilst acute food poisoning and gastroenteritis are most frequently caused by bacteria or their toxins, a number of non-infectious causes must be considered in the differential diagnosis.

Plant toxins:

- Legumes and beans produce oxidants which are toxic to people with glucose-6-phosphate dehydrogenase (G6PD) deficiency .
- Consumption produces headache, nausea and fever, progressing to potentially severe haemolysis, haemoglobinuria and jaundice (favism).
- Red kidney beans, if incompletely cooked, cause acute abdominal pain and diarrhoea from their lectin content. Adequate cooking abolishes this.

- Alkaloids develop in potato tubers exposed to light, causing green discoloration.
- Ingestion induces acute vomiting and anticholinesterase-like activity.
- Fungi and mushrooms of the *Psilocybe* spp. produce hallucinogens.

- Many fungal species induce a combination of gastroenteritis and cholinergic symptoms of blurred vision, salivation, sweating and diarrhoea.
- *Amanita phalloides* (‘death cap’) causes acute abdominal cramps and diarrhoea, followed by inexorable hepatorenal failure, often fatal.

Chemical toxins:

a. Paralytic shellfish toxin:

- Saxitoxin from dinoflagellates, responsible for ‘red tides’, is concentrated in bivalve molluscs, e.g. mussels, clams, oysters, cockles and scallops.
- Consumption produces gastrointestinal symptoms within 30 minutes, followed by perioral paraesthesia and even respiratory paralysis.
- The UK water authorities ban the harvesting of molluscs at times of the year associated with excessive dinoflagellate numbers.

b. Ciguatera fish poisoning:

- Warm-water coral reef fish acquire ciguatoxin from dinoflagellates in their food chain.
- Consumption produces gastrointestinal symptoms 1–6 hours later, with associated paraesthesiae of the lips and extremities, distorted temperature sensation, myalgia and progressive flaccid paralysis.

- Autonomic dysfunction with hypotension may occur.
- In the South Pacific and Caribbean there are 50000 cases per year, with a case fatality of 0.1%.
- The gastrointestinal symptoms resolve rapidly but the neuropathic features may persist for months.

c. Scombrotoxic fish poisoning:

- Under poor storage conditions, histidine in scombroid fish—tuna, mackerel, bonito, skipjack and the canned dark meat of sardines—may be converted by bacteria to histamine and other chemicals.

- Consumption produces symptoms within minutes, with flushing, burning, sweating, urticaria, pruritus, headache, colic, nausea and vomiting, diarrhoea, bronchospasm and hypotension.
- Management is with salbutamol and antihistamines.
- Occasionally, intravenous fluid replacement is required

d. Heavy metals:

- Thallium and cadmium can cause acute vomiting and diarrhoea resembling staphylococcal enterotoxin poisoning.

Antibiotic-associated diarrhoea (AAD):

- AAD is a common complication of antibiotic therapy, especially with broad-spectrum agents.
- It is most common in the elderly but can occur at all ages.
- Although the specific mechanism is unknown in most AAD, *C. difficile* is implicated in 20–25% of cases and is the most common cause amongst patients with evidence of colitis.

- Infection is diagnosed by detection of *C. difficile* toxins and is usually treated with metronidazole or vancomycin.
- *C. perfringens* is a rarer cause which usually remains undiagnosed, and *Klebsiella oxytoca* is an occasional cause of antibiotic-associated haemorrhagic colitis

Infections acquired in the tropics:

- Recent decades have seen unprecedented increases in long-distance business and holiday travel, as well as extensive migration.
- Although certain diseases retain their relatively fixed geographical distribution, being dependent on specific vectors or weather conditions, many travel with their human hosts and some may then be transmitted to other people.

- This means that the pattern of infectious diseases seen in each country changes constantly and travel history is crucial.

- In general, the diversity of infectious diseases is greater in tropical than in temperate countries, and people in temperate countries have less immunity to many infections, so that the most common travel-associated infections are those which are acquired by residents of temperate countries during visits to the tropics.

- Most travel-associated infections can be prevented.
- Pre-travel advice is tailored to the destination and the traveller. It includes avoidance of insect bites (using at least 20% diethyltoluamide (DEET), sun protection (sunscreen with a sun protection factor (SPF) of at least 15), food and water hygiene (‘Boil it, cook it, peel it or forget it!’), how to respond to travellers’ diarrhoea (seek medical advice if bloody or lasts more than 48 hours) and, if relevant, safe sex (condom use).

13.16 How to assess health needs in travellers before departure*

- Destination
- Personal details, including previous travel experience
- Dates of trip
- Itinerary and purpose of trip
- Personal medical history, including pregnancy, medication and allergies (e.g. to eggs, vaccines, antibiotics)
- Past vaccinations

  Childhood schedule followed? Diphtheria, tetanus, pertussis, polio, *N. meningitidis* type C, *Haemophilus influenzae* B (HiB)

  Travel-related? Typhoid, yellow fever, hepatitis A, hepatitis B, meningococcal ACW135Y, rabies, Japanese B encephalitis, tick-borne encephalitis
- Malaria prophylaxis: questions influencing the choice of antimalarial drugs are destination, past experience with antimalarials, history of epilepsy or psychiatric illness

*Further information is available at www.fitfortravel.nhs.uk/

Fever in travellers returning from the tropics:

- Presentation with unexplained fever is common in returning travellers.
- Frequent final diagnoses in such patients are malaria, typhoid fever, viral hepatitis and dengue fever.
- Travellers returning from West Africa may have viral haemorrhagic fevers (VHF), such as Lassa fever, Crimean–Congo haemorrhagic fever, Marburg and Ebola.

- Those from South-east Asia may have avian influenza (H5N1), which may pose an infection control risk and require special isolation precautions to be taken.

Clinical assessment:

- Note that medicines purchased while travelling may not be reliable, e.g. for malaria prophylaxis.
- Consult reliable up-to-date sources about resistance to antimalarial drugs in the country in question.

13.17 How to obtain a history from travellers to the tropics with fever

Questions	Factors to ascertain
Countries visited and dates of travel	Relate travel to known outbreaks of infection or antimicrobial resistance
Determine the environment visited	Travel to rural environments, forests, rivers or lakes
Clarify where the person slept	Sleeping in huts, use of bed nets, sleeping on the ground
Establish what he/she was doing	Exposure to people with medical illness, animals, soil, lakes or rivers
History of insect bites	Type of insect responsible, circumstances (location, time of day etc.), preventive measures
Dietary history	Ingestion of uncooked foods, salads and vegetables, meats (especially if undercooked), shellfish, molluscs, unpasteurised dairy products, unbottled water and sites at which food prepared
Sexual history	History of sexual intercourse with commercial sex workers, local population
Malaria prophylaxis	Type of prophylaxis
Vaccination history	Receipt of pre-travel vaccines and appropriateness to area visited
History of any treatments received while abroad	Receipt of medicines, local remedies, blood transfusions or surgical procedures

- Vaccinations against yellow fever and hepatitis A and B are sufficiently effective to virtually rule out these infections.
- Oral and injectable typhoid vaccinations are 70–90% effective.

13.18 Specific exposures and causes of fever in the tropics

Exposure	Infection or disease
Mosquito bite	Malaria, dengue fever, Chikungunya, filariasis, tularaemia
Tsetse fly bite	African trypanosomiasis
Tick bite	Rickettsial infections, including typhus, Lyme disease, tularaemia, Crimean–Congo haemorrhagic fever, Kyasanur forest disease, babesiosis, tick-borne encephalitis
Louse bite	Typhus
Flea bite	Plague
Sandfly bite	Leishmaniasis, arbovirus infection
Reduviid bug	Chagas' disease
Animal contact	Q fever, brucellosis, anthrax, plague, tularaemia, viral haemorrhagic fevers, rabies
Fresh-water swimming	Schistosomiasis, leptospirosis, *Naegleria fowleri*
Exposure to soil	Inhalation: dimorphic fungi Inhalation or inoculation: *Burkholderia pseudomallei* Inoculation (most often when barefoot): hookworms, *Strongyloides stercoralis*
Raw or undercooked fruit and vegetables	Enteric bacterial infections, hepatitis A or E virus, *Fasciola hepatica*, *Toxocara* spp., *Echinococcus granulosus* (hydatid disease), *Entamoeba histolytica*
Undercooked pork	*Taenia solium* (cysticercosis)
Crustaceans or molluscs	Paragonimiasis, gnathostomiasis, *Angiostrongylus cantonensis* infection, hepatitis A virus, cholera
Unpasteurised dairy products	Brucellosis, salmonellosis, abdominal tuberculosis, listeriosis
Untreated water	Enteric bacterial infections, giardiasis, *Cryptosporidium* spp. (chronic in immunocompromised), hepatitis A or E virus

13.19 Incubation times and illnesses in travellers*

< 2 weeks

Non-specific fever

- Malaria
- Chikungunya
- Dengue
- Scrub typhus
- Spotted group rickettsiae
- Acute HIV
- Acute hepatitis C virus
- *Campylobacter*
- Salmonellosis
- Shigellosis
- East African trypanosomiasis
- Leptospirosis
- Relapsing fever
- Influenza
- Yellow fever

Fever and coagulopathy (usually thrombocytopenia)

- Malaria
- Viral haemorrhagic fever (VHF)
- Meningococcaemia
- Enteroviruses
- Leptospirosis and other bacterial pathogens associated with coagulopathy

Fever and central nervous system involvement

- Malaria
- Typhoid fever
- Rickettsial typhus (epidemic caused by *Rickettsia prowazekii*)
- Meningococcal meningitis
- Arboviral encephalitis
- East African trypanosomiasis
- Encephalitis or meningitis
- Angiostrongyliasis
- Rabies

Fever and pulmonary involvement

- Influenza
- Pneumonia due to atypical pathogens
- *Legionella* pneumonia
- Acute histoplasmosis
- Acute coccidioidomycosis
- Q fever
- Severe acute respiratory syndrome (SARS)

Fever and rash

- Viral exanthems (rubella, measles, varicella, mumps, human herpes virus 6 (HHV-6), enteroviruses)
- Chikungunya
- Dengue
- Spotted or typhus group rickettsiosis
- Typhoid fever
- Parvovirus B19

2–6 weeks

- Malaria
- Tuberculosis
- Hepatitis A, B, C and E viruses
- Visceral leishmaniasis
- Acute schistosomiasis
- Amoebic liver abscess
- Leptospirosis
- African trypanosomiasis
- Viral haemorrhagic fever (VHF)
- Q fever
- Acute American trypanosomiasis
- Viral causes of mononucleosis syndromes

> 6 weeks

- Non-*falciparum* malaria
- Tuberculosis
- Hepatitis B and E viruses
- Visceral leishmaniasis
- Filariasis
- Onchocerciasis
- Schistosomiasis
- Amoebic liver abscess
- Chronic mycoses
- African trypanosomiasis
- Rabies
- Typhoid fever

*Adapted from Traveller's Health Yellow Book, CDC Health Information for International Travel 2008.

- *Falciparum* malaria tends to present between 7 and 28 days after return from an endemic area.
- VHF, dengue and rickettsial infection can usually be excluded if more than 21 days have passed between return from the affected area and the onset of illness.

- In clinical examination, particular attention should be paid to the skin, throat, eyes, nail beds, lymph nodes, abdomen and heart.
- Patients may be unaware of tick bites or eschars.
- Body temperature should be measured at least twice daily.

Investigations and management:

- Initial investigations should start with thick and thin blood films for malaria parasites, FBC, urinalysis and chest X-ray if indicated.

13.20 Further investigations in the absence of localising signs in acute fever acquired in the tropics

Features on FBC	Further investigations
Neutrophil leucocytosis	
Bacterial sepsis	Blood culture
Leptospirosis	Culture of blood and urine, serology
Borreliosis (tick- or louse-borne relapsing fever)	Blood film
Amoebic liver abscess	Ultrasound
Normal white cell count and differential	
Typhoid fever	Blood, stool and culture
Typhus	Serology
Arboviral infection	Serology (PCR and viral culture)
Lymphocytosis	
Viral fevers	Serology
Infectious mononucleosis	Monospot test
Rickettsial fevers	Serology

- Management is directed at the underlying cause.
- In patients with suspected VHF, strict infection control measures with isolation and barrier nursing should be implemented to prevent any contact with the patient’s body fluids.
- The risk of VHF should be determined using epidemiological risk factors and clinical signs.

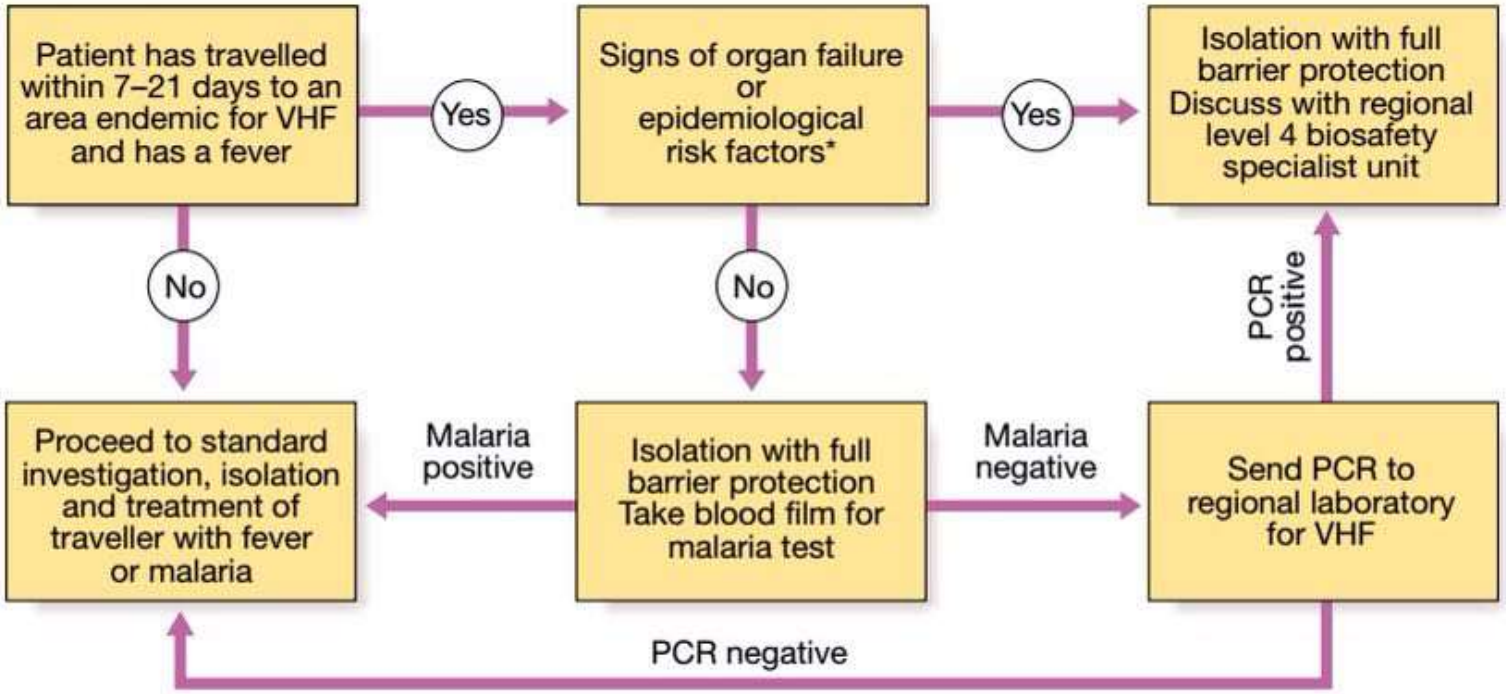


Fig. 13.5 Approach to the patient with suspected viral haemorrhagic fever (VHF). See pages 319–321. *Epidemiological risk factors: staying with a febrile individual, caring for a sick individual or contact with body fluids from a suspected human or animal case of VHF. (PCR = polymerase chain reaction).

Diarrhoea acquired in the tropics:

- Gastrointestinal illness is the most commonly reported imported infection, with *Salmonella* spp., *Campylobacter* spp. and *Cryptosporidium* spp. infections common worldwide, including in Europe.
- For typhoid, paratyphoid, *Shigella* spp. and *Entamoeba histolytica* (amoebiasis), the Indian subcontinent and sub-Saharan and southern Africa are the most commonly reported regions of travel.

13.21 Most common causes of travellers' diarrhoea

- Enterotoxigenic *E. coli* (ETEC)
- *Shigella* spp.
- *Campylobacter jejuni*
- *Salmonella* spp.
- *Plesiomonas shigelloides*
- Non-cholera *Vibrio* spp.
- *Aeromonas* spp.

- The benefits of treating travellers' diarrhoea with antimicrobials are marginal.

EBM 13.22 Antibiotics in travellers' diarrhoea

'Antibiotics reduce the duration of acute non-bloody diarrhoea in patients over 5 years old, but with a risk of side-effects.'

- The differential diagnosis of diarrhoea persisting for more than 14 days is wide.
- Parasitic and bacterial causes, tropical malabsorption, inflammatory bowel disease and neoplasia should all be considered.

Causes encountered particularly in the tropics are:

13.23 Causes of chronic diarrhoea in the tropics

- *Giardia lamblia*
- Strongyloidiasis
- Hypolactasia (primary and secondary)
- Enteropathic *E. coli*
- Tropical sprue
- Chronic calcific pancreatitis
- HIV enteropathy
- Intestinal flukes
- Chronic intestinal schistosomiasis

- The work-up should include tests for parasitic causes of chronic diarrhoea, e.g. examination of stool and duodenal aspirates for ova and parasites, and serological investigation.

- Tropical sprue is a malabsorption syndrome with no defined aetiology.
- It was typically associated with a long period of residence in the tropics or with overland travel but is now rarely seen.
- *Giardia lamblia* infection may progress to a malabsorption syndrome that mimics tropical sprue.
- If no cause is found, empirical treatment for *Giardia lamblia* infection with metronidazole is often helpful.

- HIV has now emerged as a major cause of chronic diarrhoea.
- This may be due to HIV enteropathy or infection with agents such as *Cryptosporidium* spp., *Isospora belli* or microsporidia.
- However, many other causes of chronic AIDS-associated diarrhoea seen in the developed world are less common in tropical settings, e.g. CMV or disseminated *Mycobacterium avium* complex infections.

Eosinophilia acquired in the tropics:

- Eosinophilia occurs in a variety of haematological, allergic and inflammatory conditions.
- It may also occur in HIV and human T cell lymphotropic virus (HTLV)-1 infection.
- However, eosinophils are important in the immune response to parasitic infections, in particular those parasites with a tissue migration phase.

- In the context of travel or residence in the tropics, a patient with an eosinophil count of > 0.4 × 10^9/L should be investigated for both non-parasitic and parasitic causes.

13.24 Parasite infections that cause eosinophilia

Infestation	Pathogen	Clinical syndrome with eosinophilia
Strongyloidiasis	*Strongyloides stercoralis*	Larva currens
Soil-transmitted helminthiases		
Hookworm	*Necator americanus*	Anaemia
	Ancylostoma duodenale	Anaemia
Ascariasis	*Ascaris lumbricoides*	Löffler's syndrome
Toxocariasis	*Toxocara canis*	Visceral larva migrans
Schistosomiasis	*Schistosoma haematobium*	Katayama fever
	S. mansoni, S. japonicum	Chronic infection
Filariases		
Loiasis	*Loa loa*	Skin nodules
Wuchereria bancrofti	*W. bancrofti*	Lymphangitis, lymphadenopathy orchitis, intermittent bouts of cellulitis, lymphoedema and elephantiasis
Brugia malayi	*B. malayi*	Brugian elephantiasis similar but typically less severe than that caused by *W. bancrofti*
Mansonella perstans	*M. perstans*	Asymptomatic infection, occasionally subconjunctival nodules
Onchocerciasis	*Onchocerca volvulus*	Visual disturbance, dermatitis
Other nematode infections	*Trichinella spiralis*	Myositis
Cestode infections	*Taenia saginata, T. solium*	Usually asymptomatic; eosinophilia associated with migratory phase
	Echinococcus granulosus	Lesions in liver or other organ; eosinophilia associated with leakage from cyst
Liver flukes	*Fasciola hepatica*	Hepatic symptoms; eosinophilia associated with migratory phase
	Clonorchis sinensis	As for fascioliasis
	Opisthorchis felineus	As for fascioliasis
Lung fluke	*Paragonimus westermani*	Lung lesions

- The response to parasite infections is often different when travellers to and residents of endemic areas are compared.
- Travellers often have recent and light infections associated with eosinophilia.
- Residents have often been infected for a long time, have evidence of chronic pathology and no longer have an eosinophilia.

Clinical assessment:

- Comparison of where the patient has travelled and the known endemic areas for diseases such as schistosomiasis, onchocerciasis and the filariases will indicate possible causes.
- Establish how long patients have spent in endemic areas and take a thorough history.

- Physical signs or symptoms that suggest a parasitic cause for eosinophilia include transient rashes (schistosomiasis or strongyloidiasis), fever (Katayama syndrome), pruritus (onchocerciasis) or migrating subcutaneous swellings (loiasis, gnathostomiasis).

- Paragonimiasis can give rise to haemoptysis and the migratory phase of intestinal nematodes or lymphatic filariasis to cough, wheezing and transient pulmonary infiltrates.

- Schistosomiasis induces transient respiratory symptoms with infiltrates in the acute stages and, when eggs reach the pulmonary vasculature in chronic infection, can result in shortness of breath with features of right heart failure due to pulmonary hypertension.

- Fever and hepatosplenomegaly are seen in schistosomiasis, *Fasciola hepatica* and toxocariasis (visceral larva migrans).

- Intestinal worms such as *Ascaris lumbricoides* and *Strongyloides stercoralis* can cause abdominal symptoms, including intestinal obstruction and diarrhoea.
- In the case of heavy infestation with ascaris this may be due to fat malabsorption and there may be associated nutritional deficits.

- *Schistosoma haematobium* can cause haematuria or haematospermia.
- *Toxocara* spp. can give rise to choroidal lesions with visual field defects.

- *Angiostrongylus cantonensis* and gnathostomiasis induce eosinophilic meningitis, and the hyperinfection syndrome caused by *Strongyloides stercoralis* in immunocompromised hosts induces meningitis due to Gram-negative bacteria.
- Myositis is a feature of trichinellosis and cysticercosis, while periorbital oedema is a feature of trichinellosis.

Investigations:

- To establish the diagnosis of a parasitic infestation, direct visualisation of adult worms, larvae or ova is required.
- Serum antibody detection may not distinguish between active and past infection and is often unhelpful in those born in endemic areas.
- Radiological investigations may provide circumstantial evidence of parasite infestation.

13.25 Initial investigation of eosinophilia

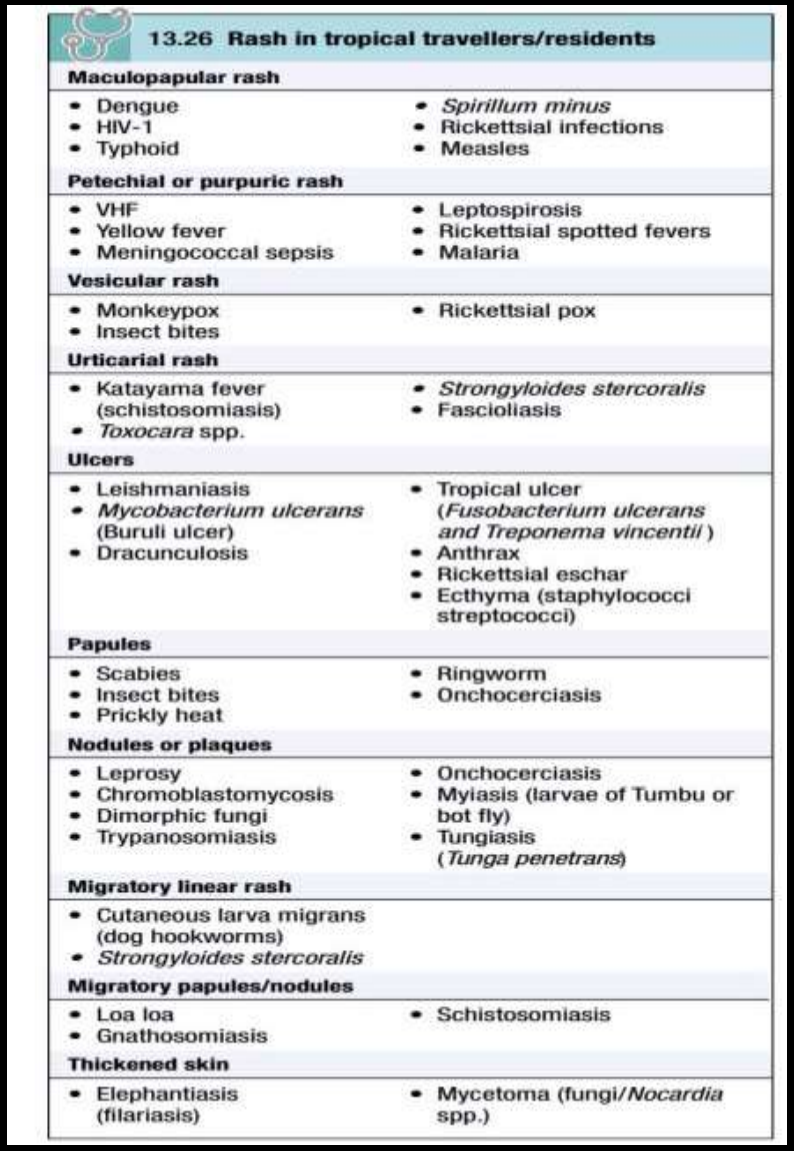
Investigation	Pathogens sought
Stool microscopy	Ova, cysts and parasites
Terminal urine	Ova of *Schistosoma haematobium*
Duodenal aspirate	Filariform larvae of *Strongyloides*, liver fluke ova
Day bloods	Microfilariae *Brugia malayi, Loa loa*
Night bloods	Microfilariae *Wuchereria bancrofti*
Skin snips	*Onchocerca volvulus*
Slit lamp examination	*Onchocerca volvulus*
Serology	Schistosomiasis, filariasis, strongyloidiasis, hydatid, trichinosis etc.

Management:

- A specific diagnosis guides therapy.
- In the absence of a specific diagnosis, many clinicians will give an empirical course of praziquantel if the individual has been potentially exposed to schistosomiasis, or with albendazole/ ivermectin if strongyloidiasis or intestinal nematodes are likely causes.

Skin conditions acquired in the tropics:

- Community-based studies in the tropics consistently show that skin infections (bacterial and fungal), scabies and eczema are the most common skin problems.



13.26 Rash in tropical travellers/residents

Maculopapular rash	
• Dengue • HIV-1 • Typhoid	• *Spirillum minus* • Rickettsial infections • Measles
Petechial or purpuric rash	
• VHF • Yellow fever • Meningococcal sepsis	• Leptospirosis • Rickettsial spotted fevers • Malaria
Vesicular rash	
• Monkeypox • Insect bites	• Rickettsial pox
Urticarial rash	
• Katayama fever (schistosomiasis) • *Toxocara* spp.	• *Strongyloides stercoralis* • Fascioliasis
Ulcers	
• Leishmaniasis • *Mycobacterium ulcerans* (Buruli ulcer) • Dracunculosis	• Tropical ulcer (*Fusobacterium ulcerans and Treponema vincentii*) • Anthrax • Rickettsial eschar • Ecthyma (staphylococci streptococci)
Papules	
• Scabies • Insect bites • Prickly heat	• Ringworm • Onchocerciasis
Nodules or plaques	
• Leprosy • Chromoblastomycosis • Dimorphic fungi • Trypanosomiasis	• Onchocerciasis • Myiasis (larvae of Tumbu or bot fly) • Tungiasis (*Tunga penetrans*)
Migratory linear rash	
• Cutaneous larva migrans (dog hookworms) • *Strongyloides stercoralis*	
Migratory papules/nodules	
• Loa loa • Gnathosomiasis	• Schistosomiasis
Thickened skin	
• Elephantiasis (filariasis)	• Mycetoma (fungi/*Nocardia* spp.)

- Cutaneous leishmaniasis and onchocerciasis have defined geographical distributions.
- In travellers, secondarily infected insect bites, pyoderma, cutaneous larva migrans and non-specific dermatitis are common.

- When investigating skin lesions, enquire about habitation, activities undertaken and regions visited.

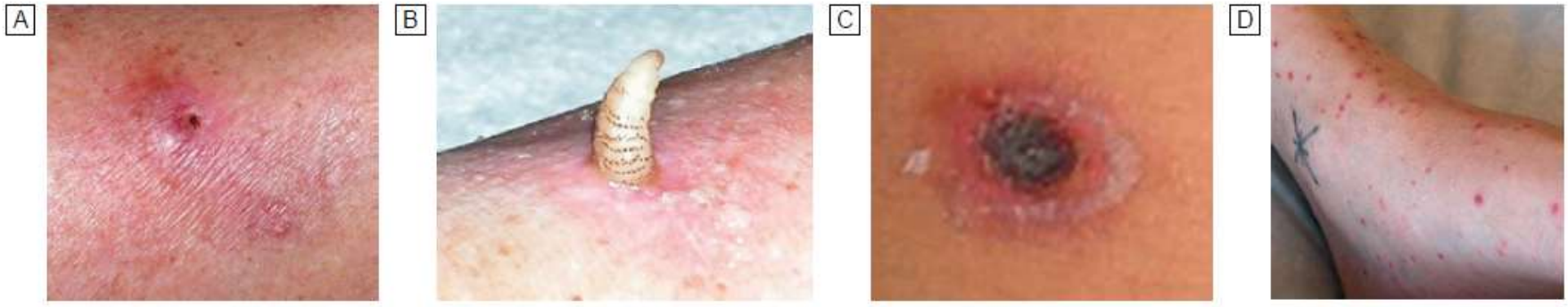


Fig. 13.6 Examples of skin lesions in patients with fever in the tropics. A Subcutaneous nodule due to botfly infection. B Emerging larva after treatment with petroleum jelly. C Eschar of scrub typhus. D Rat bite fever.

- Skin biopsies are helpful in diagnosing fungal or parasitic infections and persistent reactions to insect bites.
- Culture of biopsy material may be needed to diagnose bacterial, fungal, parasitic and mycobacterial infections.

Infections in pregnancy:

13.27 Infections during pregnancy

Infection	Consequence	Prevention and management
Rubella	Congenital malformation	Vaccination of non-immune mothers
Cytomegalovirus	Neonatal infection, congenital malformation	Limited prevention strategies
Varicella zoster virus	Neonatal infection, congenital malformation, severe infection in mother	VZ immune globulin (see Box 13.33, p. 314), or aciclovir if exposure > 4 days previously
Herpes simplex virus	Congenital or neonatal infection	Aciclovir and consideration of caesarean section for mothers who shed HSV from the genital tract at the time of delivery. Aciclovir for infected neonates
Hepatitis B virus	Chronic infection of neonate	Hepatitis B immune globulin and active vaccination of newborn
HIV	Chronic infection of neonate	Antiretrovirals to mother and infant and consideration of caesarean section if HIV viral load detectable. Avoidance of breastfeeding
Parvovirus B19	Congenital infection	Avoid contact with individuals with acute infection if pregnant
Measles	More severe infection in mother and neonate	Immunisation of mother
Syphilis	Congenital malformation	Serological testing in pregnancy with prompt treatment of infected mothers
Neisseria gonorrhoeae* and *Chlamydia trachomatis	Neonatal conjunctivitis (*ophthalmia neonatorum*)	Treatment of infection in mother and neonate
Listeriosis	Neonatal meningitis or bacteraemia, bacteraemia or PUO in mother	Avoidance of unpasteurised cheeses and other dietary sources
Brucellosis	Possibly increased incidence of fetal loss	Avoidance of unpasteurised dairy products
Group B streptococcal infection	Neonatal meningitis and sepsis. Sepsis in mother after delivery	Risk- or screening-based antimicrobial prophylaxis in labour (recommendations vary between countries)
Toxoplasmosis	Congenital malformation	Diagnosis and prompt treatment of cases, avoidance of undercooked meat while pregnant
Malaria	Fetal loss, intrauterine growth retardation, severe malaria in mother	Avoidance of insect bites. Intermittent preventative treatment during pregnancy to decrease incidence in high-risk countries

THE END