01-11 Infectious disease

11 Infectious disease

 Clinical examination of patients with infectious disease Insets (splinter haemorrhages) Courtesy of Dr Nick Beeching, Royal Liverpool University Hospital; (Roth’s spots) Courtesy of Prof. Ian Rennie, Royal Hallamshire Hospital, Sheffield.

Figs A–C opposite Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield. Heart and lungs Tachycardia, hypotension Murmurs or prosthetic heart sounds Pericardial rub Signs of consolidation Pleural or pericardial effusion Skin Generalised erythema Rash (see opposite) IV injection track marks Surgical scars Prosthetic devices, e.g. central venous catheters Tattoos Oropharynx Dental caries Tonsillar enlargement or exudate Candidiasis Hands and nails Finger clubbing Splinter haemorrhages Janeway lesions Signs of chronic liver disease Vasculitis lesions Head and neck Lymphadenopathy Parotidomegaly Abnormal tympanic membranes Chest X-ray consolidation in pneumonia Roth’s spots in endocarditis Testicular swelling in adult mumps Musculoskeletal Joint swelling, erythema or tenderness Localised tender spine suggestive of epidural abscesses or discitis Draining sinus of chronic osteomyelitis Eyes Conjunctival petechiae Painful red eye in uveitis Loss of red reflex in endophthalmitis Roth’s spots in infective endocarditis Haemorrhages and exudates of cytomegalovirus retinitis Choroidal lesions of tuberculosis Streptococcal tonsillitis Splinter haemorrhages in endocarditis Abdomen Hepatosplenomegaly Ascites Renal angle tenderness Localised tenderness or guarding with decreased bowel sounds,

e.g. in left iliac fossa with diverticulitis Mass lesions Surgical drains Neurological Neck stiffness Photophobia Delirium Focal neurological signs Genitalia and rectum Ulceration or discharge Testicular swelling or nodules Inguinal lymphadenopathy Prostatic tenderness Rectal fluctuance Observation • Temperature • Sweating • Weight loss • Respiratory distress • Altered consciousness • Pallor • Jaundice

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1 Skin lesions in infectious diseases Streptococcal toxic shock syndrome. A Meningococcal sepsis. B Shingles. C Erythema nodosum. D • Diffuse erythema, e.g. A • Migrating erythema, e.g. enlarging rash of erythema migrans in Lyme disease (see Fig. 11.21, p. 256) • Purpuric or petechial rashes, e.g. B • Macular or papular rashes, e.g. primary infection with HIV (see Box 12.8, p. 312) • Vesicular or blistering rash, e.g. C • Erythema multiforme (see Fig. 29.53 and Box 29.32, pp. 1264 and 1265) • Nodules or plaques, e.g. Kaposi's sarcoma (p. 315) • Erythema nodosum (D and Box 29.33, p. 1265) *Always consider non-infectious aetiologies in the differential diagnosis. (HBV/HCV = hepatitis B/C virus; HIV-1 = human immunodeficiency virus-1; TB = tuberculosis) Presenting complaint • Diverse manifestations of infectious disease make accurate assessment of features and duration critical; e.g. fever and cough lasting 2 days imply an acute respiratory tract infection but suggest TB if they last 2 months Review of systems • Must be comprehensive Past medical history • Define the 'host' and likelihood of infection(s) • Include surgical and dental procedures involving prosthetic materials • Document previous infections Medication history • Include non-prescription drugs, use of antimicrobials and immunosuppressants • Identify medicines that interact with antimicrobials or that may cause fever Allergy history • Esp. to antimicrobials, noting allergic manifestation (e.g. rash versus anaphylaxis) Family and contact history • Note infections and their duration • Sensitively explore exposure to key infections, e.g. TB and HIV Travel history • Include countries visited and where previously resident (relevant to exposure and likely vaccination history, e.g. likelihood of BCG vaccination in childhood) Occupation • e.g. Anthrax in leather tannery workers Recreational pursuits • e.g. Leptospirosis in canoeists and windsurfers Animal exposures • Include pets, e.g. dogs/hydatid disease Dietary history • Consider under-cooked meats, shellfish, unpasteurised dairy products or well water • Establish who else was exposed, e.g. to food-borne pathogens History of intravenous drug injection or receipt of blood products • Risks for blood-borne viruses, e.g. HIV-1, HBV and HCV Sexual history • Explore in a confidential manner (Ch. 13); remember that the most common mode of HIV-1 transmission is heterosexual (Ch. 12) Vaccination history and use of prophylactic medicines • Consider occupation- or age-related vaccines • In a traveller or infection-predisposed patient, establish adherence to prophylaxis History-taking in suspected infectious disease* Documentation of fever • 'Feeling hot' or sweaty does not necessarily signify fever – diagnosed only when a body temperature of over 38.0°C is recorded • Axillary and aural measurement is less accurate than oral or rectal • Outpatients may be trained to keep a temperature chart Rigors • Shivering (followed by excessive sweating) occurs with a rapid rise in body temperature from any cause Night sweats • Associated with particular infections (e.g. TB, infective endocarditis); sweating from any cause is worse at night Excessive sweating • Alcohol, anxiety, thyrotoxicosis, diabetes mellitus, acromegaly, lymphoma and excessive environmental heat all cause sweating without temperature elevation Recurrent fever • There are various causes, e.g. Borrelia recurrentis, bacterial abscess Accompanying features • Severe headache and photophobia, although characteristic of meningitis, may accompany other infections. • Delirium during fever is more common in young children or the elderly • Myalgia may

occur with viral infections, such as influenza, and with sepsis including meningococcal sepsis • Shock may accompany severe infections and sepsis (p. 196) Fever

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diseases in the very frail (e.g. nursing home residents): pneumonia, urinary tract infection, soft tissue infection and gastroenteritis. The principles of infection and its investigation and therapy are described in Chapter 6. This chapter and the following ones on human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and sexually transmitted infection (STI) describe the approach to patients with potential infectious disease, the individual infections and the resulting syndromes. Presenting problems in infectious diseases Infectious diseases present with myriad clinical manifestations. Many of these are described in other chapters or below. Fever 'Fever' implies an elevated core body temperature of more than 38.0°C (p. 138). Fever is a response to cytokines and acute phase proteins (pp. 65 and 70), and occurs in infections and in non-infectious conditions. Clinical assessment The differential diagnosis is very broad so clinical features are used to guide the most appropriate investigations. The systematic approach described on page 216 should be followed. Box 11.1 describes the assessment of elderly patients. Investigations If the clinical features do not suggest a specific infection, then initial 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) • a test for antibodies to HIV-1 (p. 310) • autoantibodies, including antinuclear antibodies (ANA) • chest X-ray and electrocardiogram (ECG) • urinalysis and urine culture • blood culture (p. 106) • throat swab for culture or polymerase chain reaction (PCR)

• induced sputum or other specimens for mycobacterial stains and culture • serological tests, including an HIV test, and ferritin estimation • imaging of the abdomen by ultrasonography or computed tomography (CT) • echocardiography. Lesions identified on imaging should usually be biopsied in order to seek evidence of relevant pathogens by culture, histopathology or nucleic acid detection. Particularly in patients who have received prior antimicrobials, 16S rRNA analysis (Box 6.2, p. 101) may aid diagnosis if a microorganism is not cultured. The chance of a successful diagnosis is greatest if procedures for obtaining (p. 527) or features of vasculitis). In men, the prostate should be considered 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 (Box 11.3). Investigations If initial investigation of fever is negative, further microbiological and non-microbiological investigations should be considered (Boxes 11.4 and 11.5). As with initial investigation of fever described above, the selection and prioritisation of tests will be influenced by the geographical location of potential exposure to pathogens (Box 11.4). These will usually include: Fig. 11.1 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 (SSTIs) 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 in or visited a tropical country or particular geographical location, has acquired the infection in a health-care environment or is immunocompromised. Insets (cellulitis of the leg) Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield; (pulmonary tuberculosis) Courtesy of Dr Ann Chapman, Royal Hallamshire Hospital, Sheffield; (empyema, pyogenic liver abscess, diverticular abscess, tuberculous osteomyelitis) Courtesy of Dr Robert Peck, Royal Hallamshire Hospital, Sheffield. Meningitis

Endophthalmitis Encephalitis Brain abscess Neurosurgical infection MRI with enhancement of the temporal lobe in herpes simplex encephalitis Chest X-ray from a patient with pulmonary tuberculosis CT thorax in empyema Cellulitis of the leg Tuberculous osteomyelitis of the lower tibia CT abdomen showing a pyogenic liver abscess CT abdomen showing a diverticular abscess Liver abscess Pancreatic abscess Hepatitis Biliary infection Pyelonephritis Diverticulitis Peritonitis Tubulo-ovarian abscess Appendiceal abscess Cellulitis Impetigo Erysipelas Subcutaneous fat Deeper fascial planes Necrotising fasciitis Muscle Epidermis Dermis Pyomyositis Bone Osteomyelitis Colitis Sinusitis Pharyngitis Tuberculosis Pneumonia Empyema Lung abscess

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Wegener’s granulomatosis) • Polymyositis • Behçet’s disease • Rheumatic fever (in regions where still endemic, e.g. Asia, Oceania and parts of Africa) 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 haematopoietic stem cell 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. 11.2 Aetiology of pyrexia of unknown origin (PUO)

11.5 Additional investigations in PUO • Serological tests for connective tissue disorders: Autoantibody screen Complement levels Immunoglobulins Cryoglobulins • Ferritin • 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 Location-independent investigations Microscopy • Blood for atypical lymphocytes (EBV, CMV, HIV-1, hepatitis viruses or Toxoplasma gondii) • Respiratory samples for mycobacteria and fungi • Stool for ova, cysts and parasites • Biopsy for light microscopy (bacteria, mycobacteria, fungi) and/or electron microscopy (viruses, protozoa (e.g. microsporidia) and other fastidious organisms (e.g. Tropheryma whipplei)) • Urine for white or red blood cells and mycobacteria (early morning urine × 3) Culture • Aspirates and biopsies (e.g. joint, deep abscess, debrided tissues) • Blood, including prolonged culture and special media conditions • Sputum for mycobacteria • CSF • Gastric aspirate for mycobacteria • Stool • Swabs • Urine ± prostatic massage in older men Antigen detection • Blood, e.g. HIV p24 antigen, cryptococcal antigen, Aspergillus galactomannan ELISA and for Aspergillus and other causes of invasive, fungal infection (1,3)-β-D-glucan • CSF for cryptococcal antigen • Bronchoalveolar lavage fluid for Aspergillus galactomannan • Nasopharyngeal aspirate/throat swab for respiratory viruses, e.g. IAV or RSV • Urine, e.g. for Legionella antigen Nucleic acid detection • Blood for Bartonella spp. and viruses • CSF for viruses and key bacteria (meningococcus, pneumococcus, Listeria monocytogenes) • Nasopharyngeal aspirate/throat swab for respiratory viruses • Sputum for Mycobacterium tuberculosis (MTB) and rifampicin (RIF) resistance with geneXpert MTB/RIF cartridge-based nucleic acid amplification test • Bronchoalveolar lavage fluid, e.g. for respiratory viruses • Tissue specimens, e.g. for T. whipplei • Urine, e.g. for Chlamydia trachomatis, Neisseria gonorrhoeae • Stool, e.g. for norovirus, rotavirus Immunological tests • Serology (antibody detection) for viruses, including HIV-1, and some bacteria • Interferon-gamma release assay for diagnosis of exposure to tuberculosis (but note this will not distinguish latent from active disease and can only be used to trigger further investigations of active disease) Geographically restricted tests2 Microscopy • Blood for trypanosomiasis, malaria and Borrelia spp. • Stool for geographically restricted ova, cysts and parasites • Biopsy for light microscopy (dimorphic fungi, Leishmania spp.

and other parasites) • Urine for red blood cells and schistosome ova Antigen detection • Blood, e.g. dengue virus NS1 antigen, Histoplasma antigen (restricted availability) and malaria antigen (e.g. HRP-2 for Plasmodium falciparum or parasite-specific LDH for P. falciparum and P. vivax) Nucleic acid detection • Blood for causes of viral haemorrhagic fever • CSF for geographically restricted viruses, e.g. Japanese encephalitis virus • Nasopharyngeal aspirate/throat swab or bronchoalveolar lavage fluid for geographically restricted respiratory viruses, e.g. MERS-CoV Immunological tests • Serology (antibody detection) for viruses, dimorphic fungi and protozoa (CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein–Barr virus; ELISA = enzyme-linked immunosorbent assay; HIV-1 = human immunodeficiency virus-1; HRP-2 = histidine-rich protein 2; IAV = influenza A virus; LDH = lactate dehydrogenase; MERS-CoV = Middle East respiratory syndrome coronavirus; NS1 = non-structural 1; RSV = respiratory syncytial virus) 1This list does not apply to every patient with a pyrexia of unknown origin. 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. 2Addition of these tests should be guided by the location of presentation or travel history. 11.4 Microbiological investigation of pyrexia of unknown origin1

222 • INFECTIOUS DISEASE large veins of the groin and neck necessitated by progressive thrombosis of superficial peripheral veins. The most common causes of fever are soft tissue or respiratory infections. Clinical assessment The history should address the following risk factors: • 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 sacroiliac joint. Injection of the jugular vein can be associated with cerebrovascular complications. Subcutaneous and intramuscular injection has been related to infection by clostridial species, the spores of which contaminate heroin. Clostridium novyi suspected visceral 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 No cause is found in approximately 10% of PUO cases, but as long as there is no significant weight loss or signs of another disease, the long-term mortality is low. Fever in the injection drug-user Intravenous injection of recreational drugs is widespread in many parts of the world (p. 1184). Infective organisms are introduced by non-sterile (often shared) injection equipment (Fig. 11.2). The risks increase with prolonged drug use and injection into Fig. 11.2 Fever in the injection drug-user: key features of clinical examination. Full examination (p. 216) is required but features most common amongst injection drug-users are shown here. (DVT = deep venous thrombosis; JVP = jugular venous pulse) Hands and nails Splinter haemorrhages Signs of chronic liver disease Oropharynx Dental infections Oropharyngeal candidiasis or other signs of HIV-1 infection Skin and soft tissues (any site) Cellulitis Purulent drainage Abscesses Ulcers Bullae or extreme pain suggestive of necrotising fasciitis Optic fundi Roth’s spots Candidal cotton wool spots Nervous system Signs of drug intoxication Encephalopathy Signs of meningitis Focal neurological features or seizures in septic embolism/ mycotic aneurysm/abscess Cranial nerve palsies of botulism Trismus, muscle rigidity or spasms in tetanus Localised pain over vertebrae with epidural abscess Cardiovascular system Systolic ‘V’ waves in JVP of tricuspid regurgitation (p. XXX) Regurgitant murmurs in endocarditis Respiratory system Consolidation in pneumonia Upper lobe signs in tuberculosis Pleural rub with septic pulmonary emboli Abdomen Jaundice ± tender liver edge with hepatitis Pain in left upper quadrant with splenic abscess Bone and joints Osteomyelitis

Septic arthritis Injection sites Abscesses Fistula Haematoma Pseudoaneurysm Femoral stretch test Passive extension of the hip joint causes pain and reflex muscle spasm in ilio-psoas abscess Legs Signs of DVT Vasculitis or ischaemic signs of septic emboli, endocarditis or vasospasm Compartment syndrome Hip flexor spasm in an injection drug-user with ilio-psoas abscess Skin abscesses in an injection drug-user Sharing injecting equipment may transmit blood-borne viruses Observation

glycopeptide (e.g. vancomycin) or lipopeptide (e.g.daptomycin). Once microbiological results are available, therapy can be narrowed to focus on the microorganism identified. In injection drug-users, meticillin-sensitive Staph. aureus is customarily treated with high-dose intravenous flucloxacillin, with shorter durations for uncomplicated right-sided endocarditis. 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. flucloxacillin plus co-amoxiclav or clindamycin). Non-adherence to prescribed antimicrobial regimens leads to a high rate of complications. Fever in the immunocompromised host Immunocompromised hosts include those with congenital immunodeficiency (p. 77), HIV infection (Ch. 12) and iatrogenic causes a local lesion with significant toxin production, leading to shock and multi-organ failure. Tetanus, wound botulism, anthrax and gas gangrene also occur. • Technical details of injection. Sharing of needles and other injecting paraphernalia (including spoons and filters) increases the risk of blood-borne virus infection (e.g. HIV-1, hepatitis B or C virus). Some users lubricate their needles by licking them prior to injection, thus introducing mouth organisms (e.g. 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. • Substances injected. Injection of cocaine is associated with a variety of vascular complications. Certain formulations of heroin have been linked with particular infections, e.g. wound botulism with black tar heroin. Drugs are often mixed with other substances, e.g. talc. • Blood-borne virus status. Results of previous HIV-1 and hepatitis virus tests or vaccinations for hepatitis viruses should be recorded. • Surreptitious use of antimicrobials. Addicts may use antimicrobials to self-treat infections, masking initial blood culture results. Key findings on clinical examination are shown in Figure 11.2. It can be difficult to distinguish the effects of infection from the effects of drugs or drug withdrawal (excitement, tachycardia, sweating, marked myalgia, delirium). Stupor and delirium may result from drug administration but may also indicate meningitis or encephalitis. Non-infected venous thromboembolism is also common in this group. Investigations The initial investigations are as for any fever (see above), 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 Staphylococcus aureus or other organisms associated with endocarditis (Fig. 11.3A); thromboembolic phenomena; or a new or previously undocumented murmur. Endovascular infection should also be suspected if lung abscesses or pneumatoceles are detected radiologically. Infected thrombus at injection sites, such as the groin, is common, and may lead to abscess formation. Additional imaging should be focused on sites of injection or of localising symptoms and signs (Fig. 11.3B). Any pathological fluid collections should be sampled. Urinary toxicology tests may suggest a non-infectious cause of the presenting complaint. While

being investigated, all injection drug-users should be offered testing for infection with hepatitis B and C virus and HIV-1. 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 the common pathogens causing community-acquired pneumonia, tuberculosis or septic emboli (Fig. 11.3C). 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 meticillinresistant Staph. aureus (MRSA) is prevalent in the community, a Fig. 11.3 Causes of fever in injection drug-users. A Endocarditis: 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 Tricuspid valve endocarditis caused by Staphylococcus aureus. Thoracic CT scan shows multiple embolic lesions with cavitation (arrows). The patient presented with haemoptysis. C, Courtesy of Dr Julia Greig, Royal Hallamshire Hospital, Sheffield. A B A B C

224 • INFECTIOUS DISEASE Neutropenic fever Neutropenic fever is defined as a neutrophil count of less than 0.5 × 109/L (p. 925) and a single axillary temperature above 38.5°C or three recordings above 38.0°C over a 12-hour period, although the infection risk increases progressively as the neutrophil count drops below 1.0 × 109/L. Patients with neutropenia are particularly prone to bacterial and 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 IV. The routine addition of aminoglycosides to these agents is not supported by trial data. If fever has not resolved after 3–5 days, empirical antifungal therapy (e.g. caspofungin) is added (p. 125). An alternative antifungal strategy is to use azole prophylaxis in high-risk patients and markers of early fungal infection, such as galactomannan and/or fungal PCR, to guide initiation of antifungal treatment (a ‘pre-emptive approach’). Post-transplantation fever Fever in transplant recipients may be due to infection, episodes of graft rejection in solid organ transplant recipients, or graftversus-host disease following HSCT (p. 936). Infections in solid organ transplant recipients are grouped according to the time of onset (Box 11.6). Those in the first month are mostly 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; 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. Following HSCT, infections in the first 4 weeks are more common in patients receiving a myeloablative-conditioning immunosuppression induced by chemotherapy (p. 1330), transplantation (p. 88) or immunosuppressant medicines, including high-dose glucocorticoids. 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 glucocorticoids, mucositis from chemotherapy and an impaired skin barrier due to insertion of a central venous catheter. Fever may result from infectious or non-infectious causes, including drugs, vasculitis, neoplasm, lymphoproliferative disease, graft-versus-

host disease (in recipients of haematopoietic stem cell transplants (HSCT); p. 936), organising pneumonitis or 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: • Identification of the immunosuppressant factors and nature of the immune defect. • Any past infections and their treatment. Infections may recur and antimicrobial resistance may have been acquired in response to prior therapy. • Exposure to infections, including opportunistic infections that would not cause disease in an immunocompetent host. • Prophylactic medicines and vaccinations administered. Examination should include inspection of the normal physical barriers provided by skin and mucosal surfaces and, in particular, central venous catheters, the mouth, sinuses, ears and perianal area (digital rectal examination should be avoided). Disseminated infections can manifest as cutaneous lesions. The areas around fingernails and toenails should also be inspected closely. Investigations Initial screening tests are as described above (p. 218). Immunocompromised hosts often have decreased inflammatory responses leading to attenuation of physical signs, such as neck stiffness with meningitis, radiological features and laboratory findings, such as leucocytosis. Chest CT scan should be considered in addition to chest X-ray when respiratory symptoms occur. Abdominal imaging may also be warranted, particularly if there is right lower quadrant pain, which may indicate typhlitis (inflammation of the caecum) in neutropenic patients. Blood cultures from a central venous catheter, urine cultures, and stool cultures if diarrhoea is present are also recommended. 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 PCR for cytomegalovirus (CMV) and Aspergillus spp. DNA, and antigen assays (e.g. cryptococcal antigen (CrAg) for Cryptococcus neoformans, galactomannan for Aspergillus spp. in blood, and (1,3)-β-D-glucan for Aspergillus spp. and other causes of invasive fungal infection (though this will not identify mucoraceous moulds) 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 bronchoalveolar lavage to detect Pneumocystis jirovecii, other fungi, bacteria and viruses. 11.6 Infections in transplant recipients Time post transplantation Infections Solid organ transplant 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. Pneumocystis jirovecii pneumonia)

> 6 months Bacterial pneumonia, other bacterial community-acquired infections, shingles, cryptococcal infection, PTLD Myeloablative haematopoietic stem cell transplant recipients Pre-engraftment (typically 0–4 weeks) Bacterial and fungal infections, respiratory viruses or HSV reactivation Post-engraftment: Early (< 100 days) CMV, Pneumocystis jirovecii pneumonia, moulds or other opportunistic infections Late (> 100 days) Community-acquired bacterial infections, shingles, CMV, PTLD (CMV = cytomegalovirus; HSV = herpes simplex virus; PTLD = post-transplant lymphoproliferative disorder)

bacteraemia or blood culture contamination but, in view of their association with infective endocarditis, significant infection must always be excluded. Bacillus spp. (‘aerobic spore bearers’) and Clostridium spp. often represent incidental transient bacteraemia or contamination, but certain species (e.g. C. septicum) are more likely to be genuine pathogens. Further investigations are influenced by the causative organism and setting. Initial screening tests are similar to those for fever (p. 218) 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 those patients with BSI who have valvular heart disease or clinical features of endocarditis (p. 527), those whose cultures reveal an organism that is a common cause of endocarditis (e.g. Staph. aureus, viridans streptococci or enterococci), those in whom multiple blood cultures are positive for the same organism, and those with a rapid positive result on culture. The sensitivities of transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE) for the detection of vegetations are 50–90% and over 95%, respectively. Therefore, if TTE is negative, TOE should be performed. Certain rare causes of BSI have specific associations that warrant further investigation. Endocarditis caused by Streptococcus gallolyticus subsp. gallolyticus (formerly Strep. bovis biotype I) and BSI with C. septicum are both associated with colonic carcinoma and their isolation is 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 uncomplicated right-sided infective endocarditis. Other Staph. aureus BSIs are 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 in 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, 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 (p. 106). Catheter-related infection is suggested by higher colony counts regimen (Box 11.6). 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) is a frequent presentation of infection. This can be community-acquired or hospital-acquired (‘nosocomial’). The most common causes are shown in Box 11.7. In immunocompromised hosts, a wider range of microorganisms may be isolated, e.g. fungi in neutropenic hosts. Primary BSI describes the situation in which there is no known extravascular source of infection (e.g. pneumonia or urinary tract infection), and is more common in Staph. aureus BSI. 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 catheters 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 those involving the implantation of prosthetic materials (in particular, endovascular prostheses). Physical examination should focus on signs of endocarditis (p. 527), 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 cause transient non-significant 11.7 Common causes of blood-stream infection Community-acquired • Escherichia coli • Staphylococcus aureus, including MRSA • Streptococcus pneumoniae • Other streptococci Nosocomial • Staph. aureus, including MRSA • Coagulase-negative staphylococci • Enterococci, including VRE • Gram-negative bacteria • Candida spp. (MRSA = meticillin-resistant Staphylococcus aureus; VRE = vancomycin-resistant enterococci)

226 • INFECTIOUS DISEASE Sepsis Sepsis is discussed on page 196 and there are many causes (Box 11.8). The results of blood cultures and pre-existing host factors guide initial investigations. Patients who are immunocompromised may have a broader range of causal pathogens that may be harder to culture, including mycobacteria and fungi. In many regions, malaria and dengue must also be excluded. Severe skin and soft tissue infections Skin and soft tissue infections (SSTIs) are an important cause of sepsis. Cases can be classified as in Box 11.9, according to the clinical features and microbiological findings. In some cases, severe systemic features may be out of keeping with mild local features. Necrotising fasciitis In necrotising fasciitis, cutaneous erythema and oedema progress to bullae or areas of necrosis. Unlike in cellulitis, pain may be disproportionately intense in relation to the visible cutaneous features or may spread beyond the zone of erythema. The infection spreads quickly along the fascial plane. 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 (p. 253). Type 3 infection 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 may 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 and provide 5–7 days' therapy or, particularly 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 involves catheter removal, followed by 14 days of antimicrobial therapy; the same applies to infections with Pseudomonas aeruginosa, Candida

spp., atypical mycobacteria or Bacillus spp. Infections complicated by endocarditis, thrombophlebitis, metastatic infection or tunnel infection also require catheter removal. 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; see Box 11.37, p. 251), 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. 11.8 Causes of sepsis Infection Setting Bacterial Staphylococcus aureus, coagulase-negative staphylococci Bacteraemia may be associated with endocarditis, intravascular cannula infection, or skin or bone foci Streptococcus pneumoniae Invasive pneumococcal disease, usually with pneumonia or meningitis; asplenia 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 Escherichia coli, other Gram-negative bacteria Urinary or biliary tract infection, or other abdominal infections Pseudomonas aeruginosa, multidrug-resistant Gram-negative bacteraemia Nosocomial infection Salmonella Typhi or Paratyphi In countries with a high incidence of enteric fever 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 Clostridium difficile Severe colitis, particularly in the elderly Polymicrobial infection with Gram-negatives and anaerobes Bowel perforation, bowel ischaemia Mycobacterium tuberculosis, M. avium complex (MAC) HIV-positive or immunocompromised with miliary tuberculosis 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

infection. Infection may be limited to tissue that is already damaged (anaerobic cellulitis) or may involve healthy muscle (gas gangrene). In anaerobic cellulitis, usually due to C. perfringens or other clostridia infecting devitalised tissue following a wound, gas forms locally and extends along tissue planes but bacteraemia does not occur. Prompt surgical débridement of devitalised tissue and therapy with penicillin or clindamycin is usually effective. 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 polymicrobial 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 sea water or shellfish consumption in tropical to subtropical regions worldwide, such as the Gulf of Mexico, can lead to infection with Vibrio vulnificus. This infection causes soft tissue necrosis and bullae, and may lead to necrotising fasciitis. Patients with chronic liver disease are particularly susceptible to this infection and can develop sepsis. Acute diarrhoea and vomiting Acute diarrhoea (p. 783), sometimes with vomiting, is the predominant symptom in infective gastroenteritis (Box 11.10). Acute diarrhoea may also be a symptom of other infectious and non-infectious diseases (Box 11.11). Stress, whether psychological or physical, can also produce loose stools. The World Health Organisation (WHO) estimates that there are more than 1.7 billion cases of acute diarrhoea annually globally, with 760 000 deaths in children under 5. In developed countries, diarrhoea remains an important problem, with the elderly being most vulnerable (Box 11.12). 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 the application of simple principles of food hygiene can all limit gastroenteritis. The clinical features of food-borne gastroenteritis vary. Some organisms (Bacillus cereus, Staph. aureus and Vibrio cholerae) elute exotoxins that cause vomiting and/or so-called ‘secretory’ diarrhoea (watery diarrhoea without blood or faecal leucocytes, involves organisms such as Aeromonas hydrophila and Vibrio vulnificus, which is found in tropical to subtropical regions and is associated with marine exposure. Type 4 is caused by fungi such as mucoraceous moulds and may also vary geographically in incidence with recent reports of increased cases in India and other regions. Necrotising fasciitis is a medical emergency, requiring immediate surgical débridement with inspection of the involved muscle groups, in addition to antimicrobial therapy (Fig. 11.4). Empirical treatment is with broad-spectrum agents (e.g. piperacillin– tazobactam plus clindamycin; meropenem with clindamycin). Ceftazidime or ciprofloxacin with doxycycline may be used where marine exposure is a factor, and antifungals for suspected fungal necrotising fasciitis, but it is important to combine these with effective coverage against streptococcal infection. MRSAassociated necrotising fasciitis has emerged in some regions and in these places appropriate therapy for MRSA, such as a glycopeptide or linezolid, should be added to the empirical regimen until microbiological results allow narrowing of the antimicrobial spectrum. Hyperbaric oxygen therapy may be considered for polymicrobial infection. Group A streptococcal infection is treated with benzylpenicillin plus clindamycin, and often immunoglobulin, though to date clinical trials have not provided clear evidence of the benefit of immunoglobulin. Gas gangrene Although Clostridium spp. may colonise or contaminate wounds, no action is required unless there is evidence of spreading Fig. 11.4 Excision following necrotising fasciitis in an injection drug-user. 11.9 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 (Staphylococcus 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

228 • INFECTIOUS DISEASE reflecting small bowel dysfunction). 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 Escherichia 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 Salmonella Paratyphi (enteric fever), but may occasionally be seen with other non-typhoidal Salmonella spp., particularly in the immunocompromised host and the elderly. Clinical assessment The history should address foods ingested (Box 11.13), duration and frequency of diarrhoea, presence of blood or steatorrhoea, abdominal pain and tenesmus, and whether other people have been affected. Fever and bloody diarrhoea suggest an invasive, colitic, dysenteric process. An incubation period of less than 18 hours suggests toxin-mediated food poisoning, and longer than 5 days suggests diarrhoea caused by protozoa or helminths. Person-to-person spread suggests certain infections, such as shigellosis or cholera. Examination includes assessment of the degree of dehydration. Assessment for early signs of hypotension, such as thirst, headache, altered skin turgor, dry mucous membranes and postural hypotension, is important, particularly in tropical regions where dehydration progresses rapidly. Signs of more marked dehydration include supine hypotension and tachycardia, decreased urinary output, delirium and sunken eyes. The blood pressure, pulse rate, urine output and ongoing stool losses should be monitored closely. 11.13 Foods associated with infectious illness, including gastroenteritis Raw seafood • Norovirus • Vibrio spp. • Hepatitis A Raw eggs • Salmonella serovars Undercooked meat or poultry • Salmonella serovars • Campylobacter spp. • EHEC • Hepatitis E (pork products) • Clostridium perfringens Unpasteurised milk or juice • Salmonella serovars. • Campylobacter spp. • EHEC • Yersinia enterocolitica Unpasteurised soft cheeses • Salmonella serovars • Campylobacter spp. • ETEC • Yersinia enterocolitica • Listeria monocytogenes Home-made canned goods • Clostridium botulinum Raw hot dogs, pâté • Listeria monocytogenes (EHEC = enterohaemorrhagic Escherichia coli; ETEC = enterotoxigenic E. coli) 11.12 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. Most are presumed to be caused by dehydration leading to organ failure. • Clostridium difficile infection (CDI): more common, especially in hospital and nursing home settings, usually following antibiotic exposure. 11.11 Differential diagnosis of acute diarrhoea and vomiting Infectious causes • Gastroenteritis • Clostridium difficile infection (p. 264) • Acute diverticulitis (p. 833) • Sepsis (p. 196) • Pelvic inflammatory disease (p. 336) • Meningococcaemia (p. 1119) • Pneumonia (especially ‘atypical disease’, p. 582) • Malaria (p. 273) Non-infectious causes Gastrointestinal • Inflammatory bowel disease (p. 813) • Bowel malignancy (p. 827) • Overflow from constipation (p. 834) • Enteral tube feeding Metabolic • Diabetic ketoacidosis (p. 735) • Thyrotoxicosis (p. 635) • Uraemia (p. 414) • Neuro-endocrine tumours releasing (e.g.) VIP or 5-HT Drugs and toxins • NSAIDs • Cytotoxic agents • Antibiotics • Proton pump inhibitors • Dinoflagellates (p. 149) • Plant toxins (p. 150) • Heavy metals • Ciguatera fish poisoning (p. 149) • Scombrotoxic fish poisoning (p. 150) (5-HT = 5-

hydroxytryptamine, serotonin; NSAIDs = non-steroidal antiinflammatory drugs; VIP = vasoactive intestinal peptide) 11.10 Causes of infectious gastroenteritis Toxin in food: < 6 hrs incubation • Bacillus cereus (p. 262) • Staphylococcus aureus (p. 262) • Clostridium spp. enterotoxin (p. 262) Bacterial: 12–72 hrs incubation • Enterotoxigenic Escherichia coli (ETEC, p. 263) • Shiga toxin-producing E. coli (EHEC, p. 263)* • Enteroinvasive E. coli (EIEC, p. 263)* • Vibrio cholerae (p. 264) • Salmonella (p. 262) • Shigella * (p. 265) • Campylobacter * (p. 262) • Clostridium difficile * (p. 264) Viral: short incubation • Rotavirus (p. 249) • Norovirus (p. 249) Protozoal: long incubation • Giardiasis (p. 287) • Cryptosporidiosis (pp. 287 and 317) • Microsporidiosis (p. 317) • Amoebic dysentery (p. 286)* • Cystoisosporiasis (p. 233) *Associated with bloody diarrhoea.

infection, particularly if the clinical features suggest 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 to establish whether other linked cases exist (p. 114). 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 (see Fig. 21.7, p. 769). Altered gut resorption with diarrhoea can result in substantial fluid loss; for example, 10–20 L of fluid may be lost in 24 hours in cholera. 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 (Box 11.14). 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. If this is impossible – due to vomiting, for example – 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: • Replacement of established deficit. After 48 hours of moderate diarrhoea (6–10 stools per 24 hrs), the average adult will be 2–4 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. The severity of diarrhoea may be assessed by reference to the Bristol stool form scale (Bristol stool chart), which allows an objective assessment of stool consistency by providing a verbal and visual reference scale (Fig. 11.5). The Bristol stool form scale was developed in the 1990s to monitor patients with irritable bowel syndrome, but its main use (at least in UK hospitals) is to monitor hospital inpatients with loose stool to assist in decisions on stool sampling and infection prevention precautions, especially in relation to C. difficile. Investigations These include stool inspection for blood and microscopy for leucocytes, and also an examination for ova, cysts and parasites if the history indicates residence or travel to areas where these infections are prevalent. Stool culture should be performed and C. difficile toxin sought. FBC and serum electrolytes indicate the degree of

inflammation and dehydration. Where cholera is prevalent, examination of a wet film with dark-field microscopy for darting motility may provide a diagnosis. 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 Fig. 11.5 Bristol stool chart. The stool is given a ‘score’ of 1–7 by reference to the verbal and visual description. This is recorded on a chart (usually known as a ‘Bristol stool chart’) or in a patient monitoring database. Adapted from Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32:920–924. Type 6 Fluffy pieces with ragged edges, a mushy stool Type 7 Watery, no solid pieces Entirely liquid Type 5 Soft blobs with clear-cut edges (passed easily) Type 4 Like a sausage or snake, smooth and soft Type 3 Like a sausage but with cracks on its surface Type 2 Sausage-shaped but lumpy Type 1 Separate hard lumps, like nuts (hard to pass) 11.14 Composition of oral rehydration solution and other replacement fluids* Fluid Na K Cl Energy WHO

Dioralyte

Pepsi 6.5 0.8 –

7UP 7.5 0.2 –

Apple juice 0.4

–

Orange juice 0.2

–

Breast milk

(WHO = World Health Organisation) *Values given in mmol/L for electrolyte and kcal/L for energy components.

 that the pattern of infectious diseases seen in each country changes constantly, and travel history and information on countries previously lived in, particularly during childhood, are crucial. In general, the diversity of infectious diseases is greater in tropical than in temperate countries, and people in temperate countries have immunity to a narrower range of infections, reflecting less exposure in childhood and less ongoing boosting of immunity later in life, so that the most common travel-associated infections are those that are acquired by residents of temperate countries during visits to the tropics. In addition, those who have lived in tropical areas may lose immunity when they move to temperate countries and become susceptible when visiting their homeland. Most travel-associated infections can be prevented. Pretravel advice is tailored to the destination and the traveller (Box 11.15). 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 if it lasts more than 48 hrs) and, if relevant, safe sex (condom use). Fever acquired in the tropics Presentation with unexplained fever is common in travellers who are visiting or have recently travelled to tropical areas. Fever may also

occur in those living in tropical regions if they have not developed immunity to the endemic pathogen or if this immunity is compromised by factors such as pregnancy. Frequent final diagnoses in such patients are malaria, typhoid fever, viral hepatitis and dengue fever. Travellers to affected areas may have viral haemorrhagic fevers (VHFs) such as Ebola, Lassa, Crimean–Congo and Marburg (see Box 11.36, p. 245), avian influenza (H5N1) or Middle East respiratory syndrome (MERS), which require special isolation precautions. Clinical assessment The approach to unexplained fever is as described above and key questions relating to infections acquired in tropical regions are listed in Box 11.16. Medicines purchased in some countries may have reduced efficacy, e.g. for malaria prophylaxis. Consult reliable up-to-date sources about resistance to antimalarial drugs *Further information is available at fitfortravel.nhs.uk. 11.15 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, Neisseria meningitidis types B/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 • 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. • 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, routine use of antimicrobials does not improve outcome and may lead to antimicrobial resistance or side-effects. They are usually used where there is systemic involvement, 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; p. 408) more likely due to increased toxin release. Antibiotics should therefore not be used in this condition. Conversely, antibiotics are indicated in Shigella 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 These agents are not usually recommended in acute infective diarrhoea. Loperamide, diphenoxylate and opiates are potentially dangerous in dysentery in childhood, causing intussusception. Antisecretory agents, such as bismuth and chlorpromazine, may make the stools appear more bulky but do not reduce stool fluid losses and may cause significant sedation. Adsorbents, such as kaolin or charcoal, have little effect. Non-infectious causes of food poisoning While acute food poisoning and gastroenteritis are most frequently caused by infections, non-infectious causes must also be considered in the differential diagnosis. These are discussed on page 149. Antimicrobial-associated diarrhoea Antimicrobial-associated diarrhoea (AAD) is a common complication of antimicrobial therapy, especially with broadspectrum agents. It is most common in the elderly but can occur at all ages. Although the specific mechanism is unknown in most cases of AAD, C. difficile (p. 264) is implicated in 20–25% of cases and is the most common cause among patients with evidence of colitis. C. perfringens is a rarer cause that usually remains undiagnosed, and Klebsiella oxytoca may also cause antibiotic-associated haemorrhagic colitis. Infections acquired in the tropics Recent

decades have seen unprecedented increases in longdistance 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

11.16 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 and 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 under-cooked), 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 or travellers from other countries 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 in the country visited. Vaccinations against yellow fever and hepatitis A and B are sufficiently effective to virtually exclude these infections. Oral and injectable typhoid vaccinations are 70–90% effective. The differential diagnosis is guided by the clinical scenario, presence of specific exposures (Box 11.17) and incubation period (Box 11.18). Falciparum malaria tends to present between 7 and 28 days after exposure in an endemic area. VHF, dengue and rickettsial infection can usually be excluded if more than 21 days have passed between leaving the area and onset of illness. Fig. 11.6 Approach to the patient with suspected viral haemorrhagic fever (VHF). See page 245. *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) No Yes Signs of organ failure or epidemiological risk factors* Isolation with full barrier protection Discuss with regional level 4 biosafety specialist unit PCR positive Proceed to standard investigation, isolation and treatment of traveller with fever or malaria Malaria positive Malaria negative PCR negative No Yes Patient has travelled within 7–21 days to an area endemic for VHF and has a fever Isolation with full barrier protection Take blood film for malaria test Send PCR to regional laboratory for VHF 11.17 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 under-cooked fruit and vegetables Enteric bacterial infections, hepatitis A or E virus, Fasciola hepatica, Toxocara spp., Echinococcus granulosus (hydatid disease), Entamoeba histolytica Under-cooked 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

232 • INFECTIOUS DISEASE Investigations and management Initial investigations should start with blood films for malaria parasites, FBC, urinalysis and chest X-ray if indicated. Box 11.19 lists diagnoses and investigations to consider in unexplained acute fever. Management is directed at the underlying cause. In patients with suspected VHF (p. 245), strict infection control measures with isolation and barrier nursing are implemented to prevent contact with the patient's body fluids. The risk of VHF should be determined using epidemiological risk factors and clinical signs (Fig. 11.6), and further management undertaken as described on page 246. Diarrhoea acquired in the tropics Gastrointestinal illness is the most common infection amongst visitors to the tropics, with Salmonella spp., Campylobacter spp. and Cryptosporidium spp. infections prevalent worldwide (Box 11.20). Shigella spp. and Entamoeba histolytica (amoebiasis) are usually encountered in visitors to or residents of the Indian subcontinent or sub-Saharan and southern Africa. The approach to patients with acute diarrhoea is described on page 227. The benefits of treating travellers' diarrhoea with antimicrobials are marginal, with slight reductions in stool Clinical examination is summarised on page 216. 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 (p. 270). Body temperature should be measured at least twice daily. 11.19 Investigation of tropically acquired acute fever without localising signs Features on full blood count 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 Malaria (may have low platelets or anaemia) Blood film, antigen test Typhoid fever Blood and stool culture Typhus Serology Lymphocytosis Viral fevers, including VHF Serology, PCR Infectious mononucleosis Monospot test, serology Malaria Blood film, antigen test Rickettsial fevers Serology Atypical lymphocytes Dengue and other VHF Serology, antigen, PCR Infectious mononucleosis-like syndromes Serology, PCR HIV (acute retroviral syndrome) Serology, antigen Hepatitis viruses Serology, antigen, PCR Parasitic, malaria, trypanosomiasis Blood film, antigen test, PCR (PCR = polymerase chain reaction; VHF = viral haemorrhagic fever) 11.20 Most common causes of travellers' diarrhoea • Enterotoxigenic E. coli (ETEC) • Shigella spp. • Campylobacter jejuni • Salmonella serovars • Plesiomonas shigelloides • Non-cholera Vibrio spp. • Aeromonas spp. 11.18 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 • 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 • Other causes of encephalitis or meningitis • Angiostrongyliasis • Rabies Fever and pulmonary involvement • Influenza • Pneumonia, including Legionella pneumonia • Acute histoplasmosis • Acute coccidioidomycosis • Q fever • SARS Fever and rash • Viral exanthems (rubella, measles, varicella, mumps, HHV-6, enteroviruses • Chikungunya • Dengue • Spotted or typhus group rickettsiosis • Typhoid fever • Parvovirus B19 • HIV-1 2–6 weeks • Malaria • Tuberculosis • Hepatitis A, B, C and E viruses • Visceral leishmaniasis • Acute schistosomiasis •

Amoebic liver abscess • Leptospirosis • African trypanosomiasis • VHF • Q fever • Acute American trypanosomiasis • Viral causes of mononucleosis syndromes

> 6 weeks • Non-falciparum malaria • Tuberculosis • Hepatitis B and E viruses • HIV-1 • Visceral leishmaniasis • Filariasis • Onchocerciasis • Schistosomiasis • Amoebic liver abscess • Chronic mycoses • African trypanosomiasis • Rabies • Typhoid fever (HHV-6 = human herpesvirus-6; SARS = severe acute respiratory syndrome; VHF = viral haemorrhagic fever) Adapted from Traveller's Health Yellow Book, CDC Health Information for International Travel 2008.

11.21 Causes of chronic diarrhoea acquired in the tropics • Giardia lamblia • Strongyloidiasis • Enteropathic Escherichia coli • HIV enteropathy • Intestinal flukes • Tropical sprue • Chronic intestinal schistosomiasis • Chronic calcific pancreatitis • Hypolactasia (primary and secondary) 11.22 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 Gnathostoma spinigerum Pruritus, migratory nodules, eosinophilic meningitis 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 frequency and likelihood of cure at 72 hours offset by increased side-effects. The differential diagnosis of diarrhoea persisting for more than 14 days is wide (see Box 21.18, p. 784). Parasitic and bacterial causes, tropical malabsorption, inflammatory bowel disease and neoplasia should all be considered. Box 11.21 lists causes encountered particularly in visitors to or residents of the tropics. The workup should include tests for parasitic causes of chronic diarrhoea, such as examination of stool and duodenal aspirates for ova and parasites, and serological investigation. Tropical sprue is a malabsorption syndrome (p. 807) 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-1 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., Cystoisospora belli (syn. Isospora belli) or microsporidia (p. 316). 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 discussed on page 927. It may also arise in HIV-1 and human T-cell lymphotropic virus (HTLV)-1 infection. However, eosinophils are important in the immune response to parasitic infections, in particular those involving parasites with a tissue migration phase. In the context of travel to or residence in the tropics, a patient with an eosinophil count of more than 0.4 × 109/L should be investigated for both non-parasitic (see Box 23.9, p. 926) and parasitic causes (Box 11.22). 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 eosinophilia. Clinical assessment A history of travel to known endemic areas for schistosomiasis, onchocerciasis and the filariases will indicate possible causes. Assessment should establish how long patients have spent in endemic areas and the history should address all the elements in Box 11.16. Physical signs or symptoms that suggest a parasitic cause for eosinophilia include transient rashes (schistosomiasis or strongyloidiasis), fever (Katayama syndrome; p. 295), pruritus (onchocerciasis) or migrating subcutaneous swellings (loiasis, gnathostomiasis) (see Box 11.22). Paragonimiasis can give rise to haemoptysis, and the migratory phase of intestinal nematodes or lymphatic filariasis may cause cough, wheezing and transient pulmonary infiltrates. Schistosomiasis, strongyloidiasis and gnathostomiasis induce transient respiratory symptoms with infiltrates in the acute stages and, when eggs reach the pulmonary vasculature in chronic schistosomiasis infection, can

 Skin biopsies are helpful in diagnosing aetiology. Culture of biopsy material may be needed to diagnose bacterial, fungal, parasitic and mycobacterial infections. Infections in adolescence Particular issues of relevance in adolescent patients are shown in Box 11.25. Infections in pregnancy Box 11.26 shows some of the infections encountered in pregnancy. result in shortness of breath with features of right heart failure due to pulmonary hypertension. Fever and hepatosplenomegaly are seen in schistosomiasis, Fasciola hepatica infection 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 S. stercoralis in immunocompromised hosts induces meningitis due to Gramnegative bacteria. Myositis is a feature of trichinosis (trichinellosis) and cysticercosis, while periorbital oedema is found in trichinosis. Investigations The diagnosis of a parasitic infestation requires direct visualisation of adult worms, larvae or ova. 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. Box 11.23 describes initial investigations for eosinophilia. 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 potentially been 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

(Box 11.24). Scabies and eczema are discussed on pages 1241 and 1244. Cutaneous leishmaniasis and onchocerciasis have defined geographical distributions (pp. 284 and 292). In travellers, secondarily infected insect bites, pyoderma, cutaneous larva migrans and non-specific dermatitis are common. During the investigation of skin lesions, enquiry should be made about habitation, activities undertaken and regions visited (see Box 11.16). Examples of skin lesions in tropical disease are shown in Figure 11.7. 11.23 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, gnathostomiasis etc. 11.24 Rash in tropical travellers/residents Maculopapular rash • Dengue • HIV-1 • Typhoid • Spirillum minus • Rickettsial infections • Measles Petechial or purpuric rash • Viral haemorrhagic fevers • 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 • Anthrax • Rickettsial eschar • Tropical ulcer (Fusobacterium ulcerans and Treponema vincentii) • Ecthyma (staphylococci, streptococci) Papules • Scabies • Insect bites • Prickly heat • Ringworm • Onchocerciasis Nodules or plaques • Leprosy • Chromoblastomycosis • Dimorphic fungi • Trypanosomiasis • Onchocerciasis • Myiasis (larvae of tumbu fly or botfly) • Tungiasis (Tunga penetrans) Migratory linear rash • Cutaneous larva migrans (CLM; dog hookworms) • Strongyloides stercoralis (larva currens, more rapid than CLM) Migratory papules/nodules • Loa loa • Gnathostomiasis • Schistosomiasis Thickened skin • Mycetoma (actinomycetoma/ eumycetoma) • Elephantiasis (filariasis)

Fig. 11.7 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. A, B and D, Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield. C, Courtesy of Dr Rattanaphone Phetsouvanh, Mahosot Hospital, Vientiane, PDR Laos. A B C D 11.25 Key issues in infectious diseases in adolescence • Common infectious syndromes: infectious mononucleosis, bacterial pharyngitis, whooping cough, pneumonia, staphylococcal skin/soft tissue infections, urinary tract infections, acute gastroenteritis. • Life-threatening infections: meningococcal infection (sepsis and/ or meningitis). • Sexually transmitted infections: human papillomavirus (HPV), HIV-1, hepatitis B virus and chlamydia. These may reflect either voluntary sexual activity or sexual coercion/abuse. • Travel-related infections: diarrhoea, malaria etc. are relatively common. • Infections in susceptible groups: patients with cystic fibrosis, congenital immunodeficiency, acute leukaemia and other adolescent malignancies are vulnerable to specific groups of infections. • Infections requiring prolonged antimicrobial use: adherence to chronic therapy is challenging, for both oral (antituberculous or antiretroviral) and systemic (osteomyelitis, septic arthritis or post-operative infections) treatments. Outpatient antimicrobial therapy is preferred to minimise hospitalisation. • Vaccination: engagement with age-specific vaccine programmes should be ensured, e.g. HPV, childhood booster vaccines and meningococcal vaccine. • Risk reduction: education relating to sexual health and alcohol and recreational drug usage is important. 11.26 Infections in pregnancy Infection Consequence Prevention and management

Rubella Congenital malformation Childhood vaccination and vaccination of non-immune mothers post-delivery Cytomegalovirus Neonatal infection, congenital malformation Limited prevention strategies Zika virus Congenital malformation Avoidance of travel, delay in pregnancy if infected Varicella zoster virus Neonatal infection, congenital malformation, severe infection in mother VZ immunoglobulin (see Box 11.31) Herpes simplex virus (HSV) Congenital or neonatal infection Aciclovir and consideration of caesarean section for mothers who shed HSV from genital tract at time of delivery. Aciclovir for infected neonates Hepatitis B virus Chronic infection of neonate Hepatitis B immunoglobulin and active vaccination of newborn Hepatitis E virus Fulminant hepatitis, pre-term delivery, fetal loss Maintenance of standard food hygiene practices HIV-1 Chronic infection of neonate Antiretroviral drugs for mother and infant and consideration of caesarean section if HIV-1 viral load detectable. Avoidance of breastfeeding Parvovirus B19 Congenital infection Avoidance of individuals with acute infection if pregnant Measles More severe infection in mother and neonate, fetal loss Childhood vaccination, human normal immunoglobulin in non-immune pregnant contacts and vaccination post-delivery Dengue Neonatal dengue if mother has infection < 5 weeks prior to delivery Vector (mosquito) control Syphilis Congenital malformation Serological testing in pregnancy with prompt treatment of infected mothers Neisseria gonorrhoeae and Chlamydia trachomatis Neonatal conjunctivitis (ophthalmia neonatorum, p. 340) Treatment of infection in mother and neonate Listeriosis Neonatal meningitis or bacteraemia, bacteraemia or pyrexia of unknown origin 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 under-cooked 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

236 • INFECTIOUS DISEASE Viral infections Systemic viral infections with exanthem Childhood exanthems are characterised by fever and widespread rash. Maternal antibody usually gives protection for the first 6–12 months of life. Comprehensive immunisation programmes have dramatically reduced the number of paediatric infections but incomplete uptake results in infections in later life. Measles The WHO has set the objective of eradicating measles globally using the live attenuated vaccine. However, vaccination of more than 95% of the population is required to prevent outbreaks. Natural illness produces life-long immunity. Clinical features Infection is by respiratory droplets with an incubation period of 6–19 days. A prodromal illness occurs, 1–3 days before the rash, with upper respiratory symptoms, conjunctivitis and the presence of the pathognomonic Koplik’s spots: small white spots surrounded by erythema on the buccal mucosa (Fig. 11.8A). As natural antibody develops, the maculopapular rash appears, spreading from the face to the extremities (Fig. 11.8B). Generalised lymphadenopathy and diarrhoea are common. Complications are more common in older children and adults, and include otitis media, bacterial pneumonia, transient hepatitis, pancreatitis and clinical encephalitis (approximately 0.1% of cases). A rare late complication is subacute sclerosing panencephalitis (SSPE), which occurs up to 7 years after infection. Diagnosis is clinical (although this has become unreliable in areas where measles is no longer common) and by detection of antibody (serum immunoglobulin M (IgM), seroconversion or salivary IgM). Measles is a serious disease in the malnourished, vitamindeficient or immunocompromised, in whom the typical rash may be missing and persistent infection with a

giant cell pneumonitis or encephalitis may occur. In tuberculosis infection, measles suppresses cell-mediated immunity and may exacerbate disease; for this reason, measles vaccination should be deferred until after commencing antituberculous treatment. Measles does not cause congenital malformation but may be more severe in pregnant women. Mortality clusters at the extremes of age, averaging 1 : 1000 in developed countries and up to 1 : 4 in developing countries. Death usually results from a bacterial superinfection, occurring as a complication of measles: most often pneumonia, diarrhoeal disease or noma/cancrum oris, a gangrenous stomatitis. Death may also result from complications of measles encephalitis. Management and prevention Normal immunoglobulin attenuates the disease in the immunocompromised (regardless of vaccination status) and in non-immune pregnant women, but must be given within 6 days of exposure. Vaccination can be used in outbreaks and vitamin A may improve the outcome in uncomplicated disease. Antibiotic therapy is reserved for bacterial complications. All children aged 12–15 months should receive measles vaccination (as combined measles, mumps and rubella (MMR), a live attenuated vaccine), and a further MMR dose at age 4 years. Rubella (German measles) Rubella causes exanthem in the non-immunised. Clinical features Rubella is spread by respiratory droplet, with infectivity from up to 10 days before to 2 weeks after the onset of the rash. The incubation period is 15–20 days. In childhood, most cases are subclinical, although clinical features may include fever, maculopapular rash spreading from the face, and lymphadenopathy. Complications are rare but include thrombocytopenia and hepatitis. Encephalitis and haemorrhage are occasionally reported. In adults, arthritis involving hands or knees is relatively common, especially in women. If transplacental infection takes place in the first trimester or later, persistence of the virus is likely and severe congenital disease may result (Box 11.27). Even if normal at birth, the infant has an increased incidence of other diseases developing later, e.g. diabetes mellitus. Diagnosis Laboratory confirmation of rubella is required if there has been contact with a pregnant woman. This is achieved either by detection of rubella IgM in serum or by IgG seroconversion. In the exposed pregnant woman, absence of rubella-specific IgG confirms the potential for congenital infection. Prevention All children should be immunised with MMR vaccine. Congenital rubella syndrome may be controlled by testing women of childbearing age for rubella antibodies and offering vaccination if seronegative. Antenatal rubella screening was offered to pregnant mothers in the UK for many years for this reason. However, this Fig. 11.8 Measles. A Koplik’s spots (arrows) seen on buccal mucosa in the early stages of clinical measles. B Typical measles rash. A B

Persistent viraemia in immunocompromised hosts may require immunoglobulin therapy to clear the virus. Pregnant women should avoid contact with cases of parvovirus B19 infection; if they are exposed, serology should be performed to establish whether they are non-immune. Passive prophylaxis with normal immunoglobulin has been suggested for non-immune pregnant women exposed to infection but there are limited data to support this recommendation. The pregnancy should be closely monitored by ultrasound scanning, so that hydrops fetalis can be treated by fetal transfusion. practice ceased in 2016 because: rubella is so rare in the UK as to be considered eliminated; pre-pregnancy MMR vaccination is considered to be a more effective method of protecting pregnant women; and the screening test may give inaccurate results, causing unnecessary stress to pregnant women. Parvovirus B19 Parvovirus B19 causes exanthem and other clinical syndromes. Some 50% of children and 60–90% of adults are seropositive. Most infections are spread by the respiratory route, although spread via contaminated blood is also possible. The

virus has particular tropism for red cell precursors. Clinical features Many infections are subclinical. Clinical manifestations result after an incubation period of 14–21 days (Box 11.28). The classic exanthem (erythema infectiosum) is preceded by a prodromal fever and coryzal symptoms. A ‘slapped cheek’ rash is characteristic but the rash is very variable (Fig. 11.9). In adults, polyarthropathy is common. Infected individuals have a transient block in erythropoiesis for a few days, which is of no clinical consequence, except in individuals with increased red cell turnover due to haemoglobinopathy or haemolytic anaemia. These individuals develop an acute anaemia that may be severe (transient aplastic crisis; p. 968). Erythropoiesis usually recovers spontaneously after 10–14 days. Immunocompromised individuals, including those with congenital immunodeficiency or AIDS, can develop a more sustained block in erythropoiesis in response to the chronic viraemia that results from their inability to clear the infection. Infection during the first two trimesters of pregnancy can result in intrauterine infection and impact on fetal bone marrow; it causes 10–15% of non-immune (non-Rhesus-related) hydrops fetalis, a rare complication of pregnancy. Diagnosis IgM to parvovirus B19 suggests recent infection but may persist for months and false positives occur. Seroconversion to IgG positivity confirms infection but in isolation a positive IgG is of little diagnostic utility. Detection of parvovirus B19 DNA in blood is particularly useful in immunocompromised patients. Giant pronormoblasts or haemophagocytosis may be demonstrable in the bone marrow. Management Infection is usually self-limiting. Symptomatic relief for arthritic symptoms may be required. Severe anaemia requires transfusion. 11.27 Rubella infection: risk of congenital malformation Stage of gestation Likelihood of malformations 1–2 months 65–85% chance of illness, multiple defects/ spontaneous abortion 3 months 30–35% chance of illness, usually a single congenital defect (most frequently deafness, cataract, glaucoma, mental retardation or congenital heart disease, especially pulmonary stenosis or patent ductus arteriosus) 4 months 10% risk of congenital defects, most commonly deafness

> 20 weeks Occasional deafness 11.28 Clinical features of parvovirus B19 infection Affected age group Clinical manifestations Fifth disease (erythema infectiosum) Small children Three clinical stages: a ‘slapped cheek’ appearance, followed by a maculopapular rash progressing to a reticulate eruption on the body and limbs, then a final stage of resolution. Often the child is quite well throughout Gloves and socks syndrome Young adults Fever and an acral purpuric eruption with a clear margin at the wrists and ankles. Mucosal involvement also occurs Arthropathies Adults and occasionally children Symmetrical small-joint polyarthropathy. In children it tends to involve the larger joints in an asymmetrical distribution Impaired erythropoiesis Adults, those with haematological disease, the immunosuppressed Mild anaemia; in an individual with an underlying haematological abnormality it can precipitate transient aplastic crisis, or in the immunocompromised a more sustained but often milder pure red cell aplasia Hydrops fetalis Transplacental fetal infection Asymptomatic or symptomatic maternal infection that can cause fetal anaemia with an aplastic crisis, leading to non-immune hydrops fetalis and spontaneous abortion Fig. 11.9 Slapped cheek syndrome. The typical facial rash of parvovirus B19 infection.

238 • INFECTIOUS DISEASE HHV-7 is very closely related to HHV-6 and is believed to be responsible for a proportion of cases of exanthem subitum. Like HHV-6, HHV-7 causes an almost universal infection in childhood, with subsequent latent infection and occasional infection in the immunocompromised host. Clinical features Exanthem subitum is also known as roseola infantum or sixth disease (Box 11.29). A high fever is followed by a maculopapular rash as the fever resolves. Fever and/or febrile convulsions may also occur without a rash. Rarely, older children or adults may develop an infectious mononucleosis-like illness, hepatitis or rash. In the immunocompromised, infection is rare but can cause fever, rash, hepatitis, pneumonitis, cytopenia or encephalitis. Diagnosis and management Exanthem subitum is usually a clinical diagnosis but can be confirmed by antibody and/or DNA detection. The disease is self-limiting. Treatment with ganciclovir or foscarnet is used in immunocompromised hosts infected with HHV-6. Chickenpox (varicella) Varicella zoster virus (VZV) is a dermotropic and neurotropic virus that produces primary infection, usually in childhood, which may reactivate in later life. VZV is spread by aerosol and direct contact. It is highly infectious to non-immune individuals. Disease in children is usually well tolerated. Manifestations are more severe in adults, pregnant women and the immunocompromised. Clinical features The incubation period is 11–20 days, after which a vesicular eruption begins (Fig. 11.10), often on mucosal surfaces first, followed by rapid dissemination in a centripetal distribution (most dense on trunk and sparse on limbs). New lesions occur every 2–4 days and each crop is associated with fever. The rash progresses from small pink macules to vesicles and pustules within 24 hours. Infectivity lasts from up to 4 days (but usually 48 hours) before the lesions appear until the last vesicles crust over. Due to intense itching, secondary bacterial infection from scratching is the most common complication of primary chickenpox. Self-limiting cerebellar ataxia and encephalitis are rare complications. Adults, pregnant women and the immunocompromised are at increased risk of visceral involvement, which presents as pneumonitis, hepatitis or encephalitis. Pneumonitis can be fatal and is more likely to occur in smokers. Maternal infection in Human herpesvirus 6 and 7 Human herpesvirus 6 (HHV-6) is a lymphotropic virus that causes a childhood viral exanthem (exanthem subitum), rare cases of an infectious mononucleosis-like syndrome and infection in the immunocompromised host. Infection is almost universal, with approximately 95% of children acquiring this virus by 2 years of age. Transmission is via saliva. 11.29 Herpesvirus infections Virus Infection Herpes simplex virus (HSV) HSV-1 (p. 247) Herpes labialis (‘cold sores’) Stomatitis, pharyngitis Corneal ulceration Finger infections (‘whitlows’) Eczema herpeticum Encephalitis HSV-2 (p. 247) Genital ulceration and neonatal infection (acquired during vaginal delivery) Acute meningitis or transverse myelitis; rarely, encephalitis Varicella zoster virus (VZV) Chickenpox (varicella) Shingles (herpes zoster) Cytomegalovirus (CMV) (p. 242) Congenital infection Infectious mononucleosis (heterophile antibody-negative) Hepatitis Disease in immunocompromised patients: retinitis, encephalitis, pneumonitis, hepatitis, enteritis Fever with abnormalities in haematological parameters Epstein–Barr virus (EBV) (p. 241) Infectious mononucleosis Burkitt’s and other lymphomas Nasopharyngeal carcinoma Oral hairy leucoplakia (AIDS patients) Other lymphomas, post-transplant lymphoproliferative disorder (p. 225) Human herpesvirus 6 and 7 (HHV-6, HHV-7) Exanthem subitum Disease in immunocompromised patients Human herpesvirus 8 (HHV-8) (p. 248) Kaposi’s sarcoma, primary effusion lymphoma, multicentric Castleman’s disease Fig. 11.10 Varicella zoster virus infection. A Chickenpox. B Shingles in a thoracic dermatome. B A

ipsilateral loss of taste and buccal ulceration, plus a rash in the external auditory canal. This may be mistaken for Bell's palsy (p. 1082). Bowel and bladder dysfunction occur with sacral nerve root involvement. The virus occasionally causes cranial nerve palsy, myelitis or encephalitis. Granulomatous cerebral angiitis is a cerebrovascular complication that leads to a stroke-like syndrome in association with shingles, especially in an ophthalmic distribution. Post-herpetic neuralgia causes troublesome persistence of pain for 1–6 months or longer, following healing of the rash. It is more common with advanced age. early pregnancy carries a 3% risk of neonatal damage with developmental abnormalities of eyes, CNS and limbs. Chickenpox within 5 days of delivery leads to severe neonatal varicella with visceral involvement and haemorrhage. Diagnosis Diagnosis is primarily clinical, by recognition of the rash. If necessary, this can be confirmed by detection of antigen (direct immunofluorescence) or DNA (PCR) of aspirated vesicular fluid. Serology is used to identify seronegative individuals at risk of infection. Management and prevention The benefits of antivirals for uncomplicated primary VZV infection in children are marginal, shortening the duration of rash by only 1 day, and treatment is not normally required. Antivirals are, however, used for uncomplicated chickenpox in adults when the patient presents within 24–48 hours of onset of vesicles, in all patients with complications, and in those who are immunocompromised, including pregnant women, regardless of duration of vesicles (Box 11.30). More severe disease, particularly in immunocompromised hosts, requires initial parenteral therapy. Immunocompromised patients may have prolonged viral shedding and may require prolonged treatment until all lesions crust over. Human VZ immunoglobulin (VZIG) is used to attenuate infection in people who have had significant contact with VZV, are susceptible to infection (i.e. have no history of chickenpox or shingles and are seronegative for VZV IgG) and are at risk of severe disease (e.g. immunocompromised or pregnant) (Box 11.31). Ideally, VZIG should be given within 7 days of exposure, but it may attenuate disease even if given up to 10 days afterwards. Susceptible contacts who develop severe chickenpox after receiving VZIG should be treated with aciclovir. A live, attenuated VZV vaccine is available and in routine use in the USA and other countries, but in the UK its use has been restricted to non-immune health-care workers and household contacts of immunocompromised individuals. Children receive one dose after 1 year of age and a second dose at 4–6 years of age; seronegative adults receive two doses at least 1 month apart. The vaccine may also be used prior to planned iatrogenic immunosuppression, e.g. before transplant and for the elderly aged over 70 to prevent shingles. Shingles (herpes zoster) After initial infection, VZV persists in latent form in the dorsal root ganglion of sensory nerves and can reactivate in later life. Clinical features Burning discomfort occurs in the affected dermatome following reactivation and discrete vesicles appear 3–4 days later. This is associated with a brief viraemia, which can produce distant satellite 'chickenpox' lesions. Occasionally, paraesthesia occurs without rash ('zoster sine herpete'). Severe disease, a prolonged duration of rash, multiple dermatomal involvement or recurrence suggests underlying immune deficiency, including HIV. Chickenpox may be contracted from a case of shingles but not vice versa. Although thoracic dermatomes are most commonly involved (Fig. 11.10B), the ophthalmic division of the trigeminal nerve is also frequently affected; vesicles may appear on the cornea and lead to ulceration. This condition can lead to blindness and urgent ophthalmology review is required. Geniculate ganglion involvement causes the Ramsay Hunt syndrome of facial palsy, 11.30 Therapy for herpes simplex and varicella zoster virus infection Disease state Treatment options Primary genital HSV Famciclovir 250 mg 3 times daily for 7–10 days Valaciclovir 1 g twice daily for 7–10 days Oral aciclovir 200 mg 5 times daily or 400 mg 3 times daily for 7–10 days Severe and preventing oral intake Aciclovir 5 mg/kg 3 times daily IV until patient can tolerate oral therapy Recurrent genital HSV-1 or 2 Oral aciclovir 200 mg 5 times daily

or 400 mg 3 times daily for 5 days Famciclovir 125 mg twice daily for 5 days Valaciclovir 500 mg twice daily for 3–5 days or 2 g twice daily for 1 day. Shorter durations increasingly favoured Primary or recurrent oral HSV Usually no treatment If required, usually short duration, e.g. valaciclovir 2 g twice daily for 1 day Mucocutaneous HSV infection in immunocompromised host Aciclovir 5 mg/kg 3 times daily IV for 7–10 days Oral aciclovir 400 mg 4 times daily for 7–10 days Famciclovir 500 mg 3 times daily for 7–10 days Valaciclovir 1 g twice daily for 7–10 days Chickenpox in adult or child Oral aciclovir 800 mg 5 times daily for 5 days Famciclovir 500 mg 3 times daily for 5 days Valaciclovir 1 g 3 times daily for 5 days Immunocompromised host/pregnant woman Aciclovir 5 mg/kg 3 times daily IV until patient is improving, then complete therapy with oral therapy until all lesions are crusting over Shingles Treatment and doses as for chickenpox but duration typically 7–10 days Visceral involvement (non-CNS) in HSV Aciclovir IV 5 mg/kg 3 times daily for 14 days Visceral involvement (non-CNS) in VZV Aciclovir IV 5 mg/kg 3 times daily for 7 days Severe complications (encephalitis, disseminated infection) Aciclovir IV 10 mg/kg 3 times daily (up to 20 mg/kg in neonates) for 14–21 days HSV disease suppression Aciclovir 400 mg twice daily Famciclovir 250 mg twice daily Valaciclovir 500 mg daily (CNS = central nervous system; HSV = herpes simplex virus; VZV = varicella zoster virus)

240 • INFECTIOUS DISEASE time have led to outbreaks in young adults. Infection is spread by respiratory droplets. Clinical features The median incubation period is 19 days, with a range of 15–24 days. Classical tender parotid enlargement, which is bilateral in 75%, follows a prodrome of pyrexia and headache (Fig. 11.11). Meningitis complicates up to 10% of cases. The CSF reveals a lymphocytic pleocytosis or, less commonly, neutrophils. Rare complications include encephalitis, transient hearing loss, labyrinthitis, electrocardiographic abnormalities, pancreatitis and arthritis. Approximately 25% of post-pubertal males with mumps develop epididymo-orchitis but, although testicular atrophy occurs, sterility is unlikely. Oophoritis is less common. Abortion may occur if infection takes place in the first trimester of pregnancy. Complications may occur in the absence of parotitis. Diagnosis The diagnosis is usually clinical. In atypical presentations without parotitis, serology for mumps-specific IgM or IgG seroconversion (fourfold rise in IgG convalescent titre) confirms the diagnosis. Virus can also be cultured from urine in the first week of infection or detected by PCR in urine, saliva or CSF. Management and prevention Treatment is with analgesia. There is no evidence that glucocorticoids are of value for orchitis. Mumps vaccine is one of the components of the combined MMR vaccine. Influenza Influenza is an acute systemic viral infection that primarily affects the respiratory tract and carries a significant mortality. It is caused by influenza A virus or, in milder form, influenza B virus. Infection is seasonal, and variation in the haemagglutinin (H) and neuraminidase (N) glycoproteins on the surface of the virus leads to disease of variable intensity each year. Minor changes in haemagglutinin are known as ‘genetic drift’, whereas a switch in the haemagglutinin or neuraminidase antigen is termed ‘genetic shift’. Nomenclature of influenza strains is based on these glycoproteins, e.g. H1N1, H3N2 etc. Genetic shift results in the circulation of a new influenza strain within a community to Management Early therapy with aciclovir or related agents has been shown to reduce both early- and late-onset pain, especially in patients over 65 years. Post-herpetic neuralgia requires aggressive analgesia, along with agents such as amitriptyline 25–100 mg daily, gabapentin (commencing at 300 mg daily and building slowly to 300 mg twice daily or more) or pregabalin (commencing at 75 mg twice daily and building up to 100 mg or 200 mg 3 times daily if tolerated). Capsaicin cream (0.075%) may be helpful. Although controversial, glucocorticoids have not been demonstrated to reduce post-herpetic neuralgia to date. Enteroviral exanthems Coxsackie or echovirus infections can lead to a

maculopapular eruption or roseola-like rash that occurs after fever falls. Enteroviral infections are discussed further under viral infections of the skin (see below). Systemic viral infections without exanthem Other systemic viral infections present with features other than a rash suggestive of exanthem. Rashes may occur in these conditions but differ from those seen in exanthems or are not the primary presenting feature. Mumps Mumps is a systemic viral infection characterised by swelling of the parotid glands. Infection is endemic worldwide and peaks at 5–9 years of age. Vaccination has reduced the incidence in children but incomplete coverage and waning immunity with Fig. 11.11 Typical unilateral mumps. A Note the loss of angle of the jaw on the affected (right) side. B Comparison showing normal (left) side. B A 11.31 Indications for varicella zoster immunoglobulin (VZIG) in adults An adult should satisfy all three of the following conditions:

1. Significant contact Contact with chickenpox (any time from 48 hrs before the rash until crusting of lesions) or zoster (exposed, disseminated or, with immunocompromised contacts, localised zoster; between development of the rash until crusting) defined as: • Prolonged household contact, sharing a room for ≥ 15 mins or face-to-face contact (includes direct contact with zoster lesions) • Hospital contact with chickenpox in another patient, health-care worker or visitor • Intimate contact (e.g. touching) with person with shingles lesions • Newborn whose mother develops chickenpox no more than 5 days before delivery or 2 days after delivery
2. Susceptible contact • Individual with no history of chickenpox, ideally confirmed by negative test for VZV IgG
3. Predisposition to severe chickenpox • Immunocompromised due to disease (e.g. acute leukaemia, HIV, other primary or secondary immunodeficiency) • Medically immunosuppressed (e.g. following solid organ transplant; current or recent (< 6 months) cytotoxic chemotherapy or radiotherapy; current or recent (< 3 months) high-dose glucocorticoids; haematopoietic stem cell transplant) • Pregnant (any stage) • Infants: newborn whose mother has had chickenpox as above; premature infants < 28 weeks

in the Indian subcontinent in 2014–16. Symptoms included more gastrointestinal symptoms than with seasonal influenza, respiratory failure and seizures or encephalitis. Severe disease was a feature of infants, adults less than 50 years, those with chronic lung or neurological disease, obese patients and pregnant women, but with time the clinical features have become indistinguishable from those of seasonal influenza. Infectious mononucleosis and Epstein–Barr virus Infectious mononucleosis (IM) is a clinical syndrome characterised by pharyngitis, cervical lymphadenopathy, fever and lymphocytosis (known colloquially as glandular fever). It is most often caused by Epstein–Barr virus (EBV) but other infections can produce a similar clinical syndrome (Box 11.32). EBV is a gamma herpesvirus. In developing countries, subclinical infection in childhood is virtually universal. In developed countries, primary infection may be delayed until adolescence or early adult life. Under these circumstances, about 50% of infections result in typical IM. The virus is usually acquired from asymptomatic excreters via saliva, either by droplet infection or environmental contamination in childhood, or by kissing among adolescents and adults. EBV is not highly contagious and isolation of cases is unnecessary. Clinical features EBV infection has a prolonged but undetermined incubation period, followed in some cases by a prodrome of fever, headache and malaise. This is followed by IM with severe pharyngitis, which may include tonsillar

exudates and non-tender anterior and posterior cervical lymphadenopathy. Palatal petechiae, periorbital oedema, splenomegaly, inguinal or axillary lymphadenopathy, and macular, petechial or erythema multiforme rashes may occur. In most cases, fever resolves over 2 weeks, and fatigue and other abnormalities settle over a further few weeks. Complications are listed in Box 11.33. Death is rare but can occur due to respiratory obstruction, haemorrhage from splenic rupture, thrombocytopenia or encephalitis. The diagnosis of EBV infection outside the usual age in adolescence and young adulthood is more challenging. In children under 10 years the illness is mild and short-lived, but in adults over 30 years of age it can be severe and prolonged. In both groups, pharyngeal symptoms are often absent. EBV may present with jaundice, as a PUO or with a complication. Long-term complications of EBV infection Lymphoma complicates EBV infection in immunocompromised hosts, and some forms of Hodgkin lymphoma are EBV-associated (p. 961). The endemic form of Burkitt's lymphoma complicates EBV infection in areas of sub-Saharan Africa where falciparum malaria is endemic. Nasopharyngeal carcinoma is a geographically restricted tumour seen in China and Alaska that is associated with EBV infection. X-linked lymphoproliferative (Duncan's) syndrome is a familial lymphoproliferative disorder that follows primary EBV infection in boys without any other history of immunodeficiency; which few people are immune, potentially initiating an influenza epidemic or pandemic in which there is a high attack rate and there may be increased disease severity. Clinical features After an incubation period of 1–3 days, uncomplicated disease leads to fever, malaise and cough. Viral pneumonia may occur, although pulmonary complications are most often due to superinfection with Strep. pneumoniae, Staph. aureus or other bacteria. Rare extrapulmonary manifestations include myositis, myocarditis, pericarditis and neurological complications (Reye's syndrome in children, encephalitis or transverse myelitis). Mortality is greatest in the elderly, those with medical comorbidities and pregnant women. Polymorphisms in the gene encoding an antiviral protein, interferon-induced transmembrane protein 3 (IFITM3), are associated with more severe influenza. Diagnosis Acute infection is diagnosed by viral antigen or RNA detection in a nasopharyngeal sample. The disease may also be diagnosed retrospectively by serology. Management and prevention Management involves early microbiological identification of cases and good infection control, with an emphasis on hand hygiene and preventing dissemination of infection by coughing and sneezing. Administration of neuraminidase inhibitor, oral oseltamivir (75 mg twice daily) or inhaled zanamivir (10 mg twice daily) for 5 days, can reduce the severity of symptoms if started within 48 hours of symptom onset (or possibly later in immunocompromised individuals). These agents have superseded routine use of amantadine and rimantadine. Antiviral drugs can also be used as prophylaxis in high-risk individuals during the 'flu' season. Resistance can emerge to all of these agents and so updated local advice should be followed with regard to the sensitivity to antivirals of the circulating strain. Prevention relies on seasonal vaccination of the elderly, children 2–7 years of age and individuals with chronic medical illnesses that place them at increased risk of the complications of influenza, such as chronic cardiopulmonary diseases or immune compromise, as well as their health-care workers. The vaccine composition changes each year to cover the 'predicted' seasonal strains but vaccination may fail when a new pandemic strain emerges. Avian influenza Avian influenza is caused by transmission of avian influenza A viruses to humans. Avian viruses, such as H5N1, possess alternative haemagglutinin antigens to seasonal influenza strains. Most cases have had contact with sick poultry, predominantly in South-east Asia, and person-to-person spread has been limited to date. Infections with H5N1 viruses have been severe, with enteric features and respiratory failure. Treatment depends on the resistance pattern but often involves oseltamivir. Vaccination against seasonal 'flu' does not adequately protect against avian influenza. There is a

concern that adaptation of an avian strain to allow effective person-to-person transmission is likely to lead to a global pandemic of life-threatening influenza. Swine influenza Re-assortment of swine, avian and human influenza strains can occur in pigs and lead to outbreaks of swine ‘flu’ in humans, as occurred in 2009, when an outbreak of H1N1pdm2009 influenza spread around the world from Mexico. Cases were still occurring 11.32 Causes of infectious mononucleosis syndrome • Epstein–Barr virus infection • Cytomegalovirus • Human herpesvirus-6 or 7 • HIV-1 primary infection (p. 311) • Toxoplasmosis

242 • INFECTIOUS DISEASE of test serum to agglutinate sheep and horse red blood cells, respectively.). Sometimes antibody production is delayed, so an initially negative test should be repeated. However, many children and 10% of adolescents with IM do not produce heterophile antibody at any stage. Specific EBV serology confirms the diagnosis. Acute infection is characterised by IgM antibodies against the viral capsid, antibodies to EBV early antigen and the initial absence of antibodies to EBV nuclear antigen (anti-EBNA). Seroconversion of anti-EBNA at approximately 1 month after the initial illness may confirm the diagnosis in retrospect. CNS infections may be diagnosed by detection of viral DNA in CSF. Management Treatment is largely symptomatic. If a throat culture yields a β-haemolytic streptococcus, penicillin should be given. Administration of ampicillin or amoxicillin in this condition commonly causes an itchy macular rash and should be avoided (Fig. 11.12B). When pharyngeal oedema is severe, a short course of glucocorticoids, e.g. prednisolone 30 mg daily for 5 days, may help. Current antiviral drugs are not active against EBV. Return to work or school is governed by physical fitness rather than laboratory tests; contact sports should be avoided until splenomegaly has resolved because of the danger of splenic rupture. Unfortunately, about 10% of patients with IM suffer a chronic relapsing syndrome. Cytomegalovirus Cytomegalovirus (CMV), like EBV, circulates readily among children. A second period of virus acquisition occurs among teenagers and young adults, peaking between the ages of 25 and 35 years, rather later than with EBV infection. CMV infection is persistent, and is characterised by subclinical cycles of active virus replication and by persistent low-level virus shedding. Most post-childhood infections are therefore acquired from asymptomatic excreters who shed virus in saliva, urine, semen and genital secretions. Sexual transmission and oral spread are common among adults but infection may also be acquired by women caring for children with asymptomatic infections. Clinical features Most post-childhood CMV infections are subclinical, although some young adults develop an IM-like syndrome and some have a prolonged influenza-like illness lasting 2 weeks or more. Physical signs resemble those of IM but in CMV infections hepatomegaly is it is due to mutation of the SAP gene, causing failure of T-cell and NK-cell activation and inability to contain EBV infection. Investigations Atypical lymphocytes are common in EBV infection but also occur in other causes of IM, acute retroviral syndrome with HIV infection, viral hepatitis, mumps and rubella (Fig. 11.12A). They are also a feature of dengue, malaria and other geographically restricted infections (see Box 11.19). A ‘heterophile’ antibody is present during the acute illness and convalescence, which is detected by the Paul–Bunnell or ‘Monospot’ test. (A heterophile antibody is an antibody that has affinity for antigens other than the specific one, in this case animal immunoglobulins; the Paul–Bunnell and Monospot tests exploit this feature by detecting the ability Fig. 11.12 Features of infectious mononucleosis. A Atypical lymphocytes in peripheral blood. B Skin reaction to ampicillin. A B 11.33 Complications of Epstein–Barr virus infection Common • Severe pharyngeal oedema • Antibiotic-induced rash (80–90% with ampicillin) • Hepatitis (80%) • Prolonged post-viral fatigue (10%) • Jaundice (< 10%) Uncommon Neurological • Cranial nerve palsies • Polyneuritis • Transverse myelitis • Meningoencephalitis Haematological •

Haemolytic anaemia • Thrombocytopenia Renal • Abnormalities on urinalysis • Interstitial nephritis Cardiac • Myocarditis • ECG abnormalities • Pericarditis Rare • Ruptured spleen • Respiratory obstruction • Agranulocytosis • X-linked lymphoproliferative syndrome EBV-associated malignancy • Nasopharyngeal carcinoma • Burkitt's lymphoma • Hodgkin lymphoma (certain subtypes only) • Primary CNS lymphoma • Lymphoproliferative disease in immunocompromised

in standing water; collections of water in containers, water-based air coolers and tyre dumps are a good environment for the vector in large cities. Aedes albopictus is a vector in some South-east Asian countries. There are four serotypes of dengue virus, all producing a similar clinical syndrome; type-specific immunity is life-long but immunity against the other serotypes lasts only a few months. Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) occur in individuals who are immune to one dengue virus serotype and are then infected with another. Prior immunity results in increased uptake of virus by cells expressing the antibody Fc receptor and increased T-cell activation with resultant cytokine release, causing capillary leak and disseminated intravascular coagulation (DIC; p. 978). Previously, dengue was seen in small children and DHF/DSS in children 2–15 years old, but these conditions are now being seen in children less than 2 years old, and most frequently in those 16–45 years of age or older, in whom severe organ dysfunction is more common. Other epidemiological changes include the spread of dengue into rural communities and greater case fatality in women. Clinical features Many cases of dengue infection are asymptomatic in children. Clinical disease presents with undifferentiated fever termed dengue-like illness. When dengue infection occurs with characteristic symptoms or signs it is termed 'dengue' (Box 11.34). A rash frequently follows the initial febrile phase as the fever settles. Laboratory features include leucopenia, neutropenia, more common, while lymphadenopathy, splenomegaly, pharyngitis and tonsillitis occur less often. Jaundice is uncommon and usually mild. Complications include meningoencephalitis, Guillain–Barré syndrome, autoimmune haemolytic anaemia, thrombocytopenia, myocarditis and skin eruptions, such as ampicillin-induced rash. Immunocompromised patients can develop hepatitis, oesophagitis, colitis, pneumonitis, retinitis, encephalitis and polyradiculitis. Women who develop a primary CMV infection during pregnancy have about a 40% chance of passing CMV to the fetus, causing congenital infection and disease at any stage of gestation. Features include petechial rashes, hepatosplenomegaly and jaundice; 10% of infected infants will have long-term CNS sequelae, such as microcephaly, cerebral calcifications, chorioretinitis and deafness. Infections in the newborn usually are asymptomatic or have features of an IM-like illness, although some studies suggest that subtle sequelae affecting hearing or mental development may occur. Investigations Atypical lymphocytosis is not as prominent as in EBV infection and heterophile antibody tests are usually negative. LFTs are often abnormal, with an alkaline phosphatase level raised out of proportion to transaminases. Serological diagnosis depends on the detection of CMV-specific IgM antibody plus a fourfold rise or seroconversion of IgG. In the immunocompromised, antibody detection is unreliable and detection of CMV in an involved organ by PCR, antigen detection, culture or histopathology establishes the diagnosis. Detection of CMV in the blood may be useful in transplant populations but not in HIV-positive individuals, since in HIV infection CMV reactivates at regular intervals, but these episodes do not correlate well with episodes of clinical disease. Detection of CMV in urine is not helpful in diagnosing infection, except in neonates, since CMV is intermittently shed in the urine throughout life following infection. Management Only symptomatic treatment is required in the

immunocompetent patient. Immunocompromised individuals are treated with ganciclovir 5 mg/kg IV twice daily or with oral valganciclovir 900 mg twice daily for at least 14 days. Foscarnet or cidofovir is also used in CMV treatment of immunocompromised patients who are resistant to or intolerant of ganciclovir-based therapy. They can be given intravitreally if required. Dengue Dengue is a febrile illness caused by a flavivirus transmitted by mosquitoes. It is endemic in Asia, the Pacific, Africa and the Americas (Fig. 11.13). Approximately 400 million infections and 100 million clinically apparent infections occur annually, and dengue is the most rapidly spreading mosquito-borne viral illness. The principal vector is the mosquito Aedes aegypti, which breeds Fig. 11.13 Endemic zones of yellow fever and dengue. Dengue Yellow fever Dengue + yellow fever 11.34 Clinical features of dengue fever Incubation period • 2–7 days Prodrome • 2 days of malaise and headache Acute onset • Fever, backache, arthralgias, headache, generalised pains ('break-bone fever'), pain on eye movement, lacrimation, scleral injection, anorexia, nausea, vomiting, pharyngitis, upper respiratory tract symptoms, relative bradycardia, prostration, depression, hyperaesthesia, dysgeusia, lymphadenopathy Fever • Continuous or 'saddle-back', with break on 4th or 5th day and then recrudescence; usually lasts 7–8 days Rash • Initial flushing faint macular rash in first 1–2 days. Maculopapular, scarlet morbilliform blanching rash from days 3–5 on trunk, spreading centrifugally and sparing palms and soles; onset often with fever defervescence. May desquamate on resolution or give rise to petechiae on extensor surfaces Convalescence • Slow and may be associated with prolonged fatigue syndrome, arthralgia or depression Complications • Dengue haemorrhagic fever and disseminated intravascular coagulation • Dengue shock syndrome • Severe organ involvement • Vertical transmission if infection within 5 weeks of delivery

 effusions and ascites. This may progress to metabolic acidosis and multi-organ failure, including acute respiratory distress syndrome (ARDS; p. 198). Minor (petechiae, ecchymoses, epistaxis) or major (gastrointestinal or vaginal) haemorrhage, a feature of DHF, may occur. Cerebrovascular bleeding may be a complication of severe dengue. Diagnosis In endemic areas, mild dengue must be distinguished from other viral infections. The diagnosis can be confirmed by seroconversion of IgM or a fourfold rise in IgG antibody titres. Serological tests may detect cross-reacting antibodies from infection or vaccination against other flaviviruses, including yellow fever virus, Japanese encephalitis virus and West Nile virus. Isolation of dengue virus or detection of dengue virus RNA by PCR (p. 106) in blood or CSF is available in specialist laboratories. Commercial enzymelinked immunosorbent assay (ELISA) kits to detect the NS1 viral antigen, although less sensitive than PCR, are available in many endemic areas. Management and prevention Treatment is supportive, emphasising fluid replacement and appropriate management of shock and organ dysfunction, which is a major determinant of morbidity and mortality. With intensive care support, mortality rates are 1% or less. Aspirin should be avoided due to bleeding risk. Glucocorticoids have not been shown to help. No existing antivirals are effective. Breeding places of Aedes mosquitoes should be abolished and the adults destroyed by insecticides. A recently licensed vaccine is available. Yellow fever Yellow fever is a haemorrhagic fever of the tropics, caused by a flavivirus. It is a zoonosis of monkeys in West and Central African, and South and Central American tropical rainforests, where it may cause devastating epidemics (Fig. 11.13). Transmission is by tree-top mosquitoes, Aedes africanus (Africa) and Haemagogus spp. (America). The infection is introduced to humans either by infected mosquitoes when trees are felled, or by monkeys raiding human settlements. In towns, yellow fever may be transmitted between humans by Aedes aegypti, which breeds efficiently in small collections of water. The distribution of this mosquito is far wider than that of yellow fever, and more widespread infection is a continued

threat. Yellow fever causes approximately 200 000 infections each year, mainly in sub-Saharan Africa, and the number is increasing. Overall mortality is around 15%, although this varies widely. Humans are infectious during the viraemic phase, which starts 3–6 days after the bite of the infected mosquito and lasts for 4–5 days. Clinical features After an incubation period of 3–6 days, yellow fever is often a mild febrile illness lasting less than 1 week, with headache, myalgia, conjunctival erythema and bradycardia. This is followed by fever resolution (defervescence) but, in some cases, fever recurs after a few hours to days. In more severe disease, fever recrudescence is associated with lower back pain, abdominal pain and somnolence, prominent nausea and vomiting, bradycardia and jaundice. Liver damage and DIC lead to bleeding with petechiae, mucosal haemorrhages and gastrointestinal bleeding. Shock, hepatic failure, renal failure, seizures and coma may ensue. thrombocytopenia and elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST). Many symptomatic infections run an uncomplicated course but complications or a protracted convalescence may ensue. Warning signs justify intense medical management and monitoring for progression to severe dengue. Atypical clinical features of dengue are increasingly common, especially in infants or older patients (Box 11.35). These, along with DHF or DSS, are recognised as features of severe dengue in the 2015 case definition. The period 3–7 days after onset of fever is termed the ‘critical’ phase, during which signs of DHF or DSS may develop. In mild forms, petechiae occur in the arm when a blood pressure cuff is inflated to a point between systolic and diastolic blood pressure and left for 5 minutes (the positive ‘tourniquet test’) – a non-specific test of capillary fragility and thrombocytopenia. As the extent of capillary leak increases, DSS develops, with a raised haematocrit, tachycardia and hypotension, pleural Adapted from https://wwwn.cdc.gov/nndss/conditions/dengue-virus-infections/ case-definition/2015/ 11.35 WHO case definitions of dengue, 2015 Probable dengue fever • Exposure in an endemic area • Fever • Two of: Nausea/vomiting Rash Aches/pains Positive tourniquet test Leucopenia Any warning sign Laboratory confirmation important Needs regular medical observation and instruction in the warning signs If there are no warning signs, need for hospitalisation is influenced by age, comorbidities, pregnancy and social factors Dengue with warning signs • Probable dengue plus one of: Abdominal pain or tenderness Persistent vomiting Signs of fluid accumulation, e.g. pleural effusion or ascites Mucosal bleed Hepatomegaly > 2 cm Rapid increase in haematocrit with fall in platelet count Needs medical intervention, e.g. intravenous fluid Severe dengue • Severe plasma leakage leading to: Shock (dengue shock syndrome) Fluid accumulation with respiratory distress • Severe haemorrhagic manifestations, e.g. gastrointestinal haemorrhage • Severe organ involvement (atypical features): Liver AST or ALT ≥ 1000 U/L CNS: impaired consciousness, meningoencephalitis, seizures Cardiomyopathy, conduction defects, arrhythmias Other organs, e.g. acute kidney injury, pancreatitis, acute lung injury, disseminated intravascular coagulopathy, rhabdomyolysis Needs emergency medical treatment and specialist care with intensive care input (ALT = alanine aminotransferase; AST = aspartate aminotransferase)

11.36 Viral haemorrhagic fevers Disease Reservoir Transmission Incubation period Geography Mortality rate Clinical features of severe disease1 Lassa fever Multimammate rats (Mastomys natalensis) Urine from rat Body fluids from patients 6–21 days West Africa 15% Haemorrhage, shock, encephalopathy, ARDS (responds to ribavirin), deafness in survivors Ebola fever Fruit bats (Pteropodidae family) and bush meat Body fluids from patients Handling infected primates 2–21 days Central Africa Outbreaks as far north as Sudan 25–90% Haemorrhage and/or diarrhoea,

hepatic failure and acute kidney injury Marburg fever Undefined Body fluids from patients Handling infected primates 3–9 days Central Africa Outbreak in Angola 25–90% Haemorrhage, diarrhoea, encephalopathy, orchitis Yellow fever Monkeys Mosquitoes 3–6 days See Figure 11.13 ~15% Hepatic failure, acute kidney injury, haemorrhage Dengue Humans Aedes aegypti 2–7 days See Figure 11.13 < 10%2 Haemorrhage, shock Crimean–Congo haemorrhagic fever Small vertebrates Ixodes tick 1–3 days up to 9 days Africa, Asia, Eastern Europe 30% Encephalopathy, early haemorrhage, hepatic failure, acute kidney injury, ARDS Domestic and wild animals Body fluids 3–6 days up to 13 days Rift Valley fever Domestic livestock Contact with animals, mosquito or other insect bites 2–6 days Africa, Arabian peninsula 1% Haemorrhage, blindness, meningoencephalitis (complications only in a minority) Kyasanur fever Monkeys Ticks 3–8 days Karnataka State, India 5–10% Haemorrhage, pulmonary oedema, neurological features, iridokeratitis in survivors Bolivian and Argentinian haemorrhagic fever (Junin and Machupo viruses) Rodents (Calomys spp.) Urine, aerosols Body fluids from case (rare) 5–19 days (3–6 days for parenteral) South America 15–30% Haemorrhage, shock, cerebellar signs (may respond to ribavirin) Haemorrhagic fever with renal syndrome (Hantaan fever) Rodents Aerosols from faeces 5–42 days (typically 14 days) Northern Asia, northern Europe, Balkans 5% Acute kidney injury, cerebrovascular accidents, pulmonary oedema, shock (hepatic failure and haemorrhagic features only in some variants) 1All potentially have circulatory failure. 2Mortality of uncomplicated and haemorrhagic dengue fever, respectively. (ARDS = acute respiratory distress syndrome) Diagnosis The differential diagnosis includes malaria, typhoid, viral hepatitis, leptospirosis, haemorrhagic fevers and aflatoxin poisoning. Diagnosis of yellow fever can be confirmed by detection of virus in the blood in the first 3–4 days of illness (e.g. by culture or reverse transcription polymerase chain reaction (RT-PCR)), the presence of IgM or a fourfold rise in IgG antibody titre. Leucopenia is characteristic. Liver biopsy should be avoided in life due to the risk of fatal bleeding. Postmortem features, such as acute mid-zonal necrosis and Councilman bodies with minimal inflammation in the liver, are suggestive but not specific. Immunohistochemistry for viral antigens improves specificity. Management and prevention Treatment is supportive, with meticulous attention to fluid and electrolyte balance, urine output and blood pressure. Blood transfusions, plasma expanders and peritoneal dialysis may be necessary. Patients should be isolated, as their blood and body products may contain virus particles. A single vaccination with a live attenuated vaccine gives full protection for at least 10 years and many travellers do not require a booster unless specified by individual countries' travel requirements. Potential side-effects include hypersensitivity, encephalitis and systemic features of yellow fever (viscerotropic disease) caused by the attenuated virus. Vaccination is not recommended in people who are significantly immunosuppressed. The risk of vaccine side-effects must be balanced against the risk of infection for less immunocompromised hosts, pregnant women and older patients. An internationally recognised certificate of vaccination is sometimes necessary when crossing borders. Viral haemorrhagic fevers Viral haemorrhagic fevers (VHFs) are zoonoses caused by several different viruses (Box 11.36). They are geographically restricted and previously occurred in rural settings or in health-care facilities. The largest outbreak of VHF to date started in 2014, with Ebola

 treated as being at high risk of VHF; appropriate infection control measures must be implemented and the patient transferred to a centre with biosafety level (BSL) 4 facilities if testing positive. Individuals with a history of travel within 21 days and fever, but without the relevant epidemiological features or signs of VHF, are classified as medium-risk and should have an initial blood sample tested to exclude malaria. If this is negative, relevant specimens

(blood, throat swab, urine and pleural fluid, if available) are collected and sent to an appropriate reference laboratory for nucleic acid detection (PCR), virus isolation and serology. If patients are still felt to be at significant risk of VHF or if infection is confirmed, they should be transferred to a specialised high-security infectious disease unit. All further laboratory tests should be performed at BSL 4. Transport requires an ambulance with BSL 3 facilities. In addition to general supportive measures, ribavirin is given intravenously (100 mg/kg, then 25 mg/kg daily for 3 days and 12.5 mg/kg daily for 4 days) when Lassa fever or South American haemorrhagic fevers are suspected. Prevention Ribavirin has been used as prophylaxis in close contacts in Lassa fever but there are no formal trials of its efficacy. Ebola virus disease (EVD) Ebola virus disease (EVD) is thought to spread to human populations from fruit bats, sometimes indirectly via contact with infected primates or other animals. Person-to-person spread, via contact with blood, secretions or body parts, establishes EVD in populations. Family members, health-care workers and people performing traditional burials are at particular risk. The 2014 outbreak involved the Zaire strain of Ebola virus. Clinical features The incubation period is 2–21 days but typically 8–10 days. Fever and non-specific signs are accompanied by abdominal pain, diarrhoea, vomiting and hiccups. A maculopapular rash occurs after 5–7 days in some. Although bleeding from the gums or venepuncture sites or in the stool occurs, haemorrhage may be less prominent than in other VHFs and is often a terminal event, as observed in the 2014 epidemic. In contrast, fluid losses from diarrhoea are more marked and reach 10 L a day. Complications include meningoencephalitis, uveitis and miscarriages in pregnant women. Investigations Lymphopenia occurs, followed by neutrophilia, atypical lymphocytes, thrombocytopenia and coagulation abnormalities. Elevations of AST/ALT, features of acute kidney injury, electrolyte disturbances and proteinuria are also observed. The virus is detected by a PCR in blood or body fluids, but may need retesting if the duration of symptoms is less than 3 days. Serology provides a retrospective diagnosis. Management Treatment is supportive and aimed at fluid replacement. Bacterial super-infections should be promptly treated. A cocktail of monoclonal antibodies against Ebola virus, ZMapp, has been used in a few cases, but efficacy requires further studies. Mortality is approximately 40%. Survivors recover from the second week of illness but experience late sequelae, including arthritis (76%), uveitis (60%) and deafness (24%), while skin sloughing is common. Relapse with meningitis is reported months after recovery. circulating in Guinea, Liberia and Sierra Leone. The outbreak resulted in over 28 000 cases by 2016. Serological surveys have shown that Lassa fever is widespread in West Africa and may lead to up to 500 000 infections annually. Mortality overall may be low, as 80% of cases are asymptomatic, but in hospitalised cases mortality averages 15%. Ebola outbreaks have occurred at a rate of approximately one per year in Africa, involving up to a few hundred cases prior to the 2014 outbreak. Marburg has been documented less frequently, with outbreaks in the Democratic Republic of Congo and Uganda, but the largest outbreak to date involved 163 cases in Angola in 2005. Mortality rates of Ebola and Marburg are high. VHFs have extended into Europe, with an outbreak of Congo– Crimean haemorrhagic fever (CCHF) in Turkey in 2006, and cases of haemorrhagic fever with renal syndrome in the Balkans and Russia. An outbreak of CCHF in 2011 in Gujarat, India, involved several health-care workers and emphasised the importance of maintaining a high index of suspicion for VHF and implementing appropriate infection control measures at the first opportunity. Kyasanur forest disease is a tick-borne VHF currently confined to a small focus in Karnataka, India; there are about 500 cases annually. Monkeys are the principal hosts but, with forest felling, there are fears that this disease will increase. New outbreaks and new agents are identified sporadically. Details on recent disease outbreaks can be found at the WHO website (see ‘Further information’). Clinical features VHFs present with non-specific fever, malaise, body pains,

sore throat and headache. On examination, conjunctivitis, throat injection, an erythematous or petechial rash, haemorrhage, lymphadenopathy and bradycardia may be noted. The viruses cause endothelial dysfunction with the development of capillary leak. Bleeding is due to endothelial damage and platelet dysfunction. Hypovolaemic shock and ARDS may develop (p. 198). Haemorrhage is a late feature of most VHFs and most patients present with earlier features. In Lassa fever, joint and abdominal pain is prominent. A macular blanching rash may be present but bleeding is unusual, occurring in only 20% of hospitalised patients. Encephalopathy may develop and deafness affects 30% of survivors. In CCHF, bleeding, manifest by haematemesis or bleeding per rectum, may be an early feature, accompanied by derangement of LFTs. The clue to the viral aetiology comes from the travel and exposure history. Travel to an outbreak area, activity in a rural environment and contact with sick individuals or animals within 21 days all increase the risk of VHF. Enquiry should be made about insect bites, hospital visits and attendance at ritual funerals (Ebola virus infection). For Lassa fever, retrosternal pain, pharyngitis and proteinuria have a positive predictive value of 80% in West Africa. Investigations and management Non-specific findings include leucopenia, thrombocytopenia and proteinuria. In Lassa fever, an AST of > 150 U/L is associated with a 50% mortality. It is important to exclude other causes of fever, especially malaria, typhoid and respiratory tract infections. Most patients suspected of having a VHF in the UK turn out to have malaria. A febrile patient from an endemic area within the 21-day incubation period, who has specific epidemiological risk factors (see Fig. 11.6) or signs of organ failure or haemorrhage, should be

Prevention Prevention focuses on avoiding mosquito bites. Since Zika virus may be found in the semen or genital secretions for prolonged periods, infected individuals should practise safe sex for at least 6 months and planned pregnancy should be postponed for at least 6 months. Individuals who have travelled to an endemic area but are asymptomatic should practise safe sex and avoid pregnancy for at least 2 months. As this is an evolving area, updated guidance should be sought. There is currently no vaccine. Viral infections of the skin Herpes simplex virus 1 and 2 Herpes simplex viruses (HSVs) cause recurrent mucocutaneous infection; HSV-1 typically involves the mucocutaneous surfaces of the head and neck (Fig. 11.14), while HSV-2 predominantly involves the genital mucosa (pp. 333 and 336), although there is overlap (see Box 11.29). The seroprevalence of HSV-1 is 30–100%, varying by socioeconomic status, while that of HSV-2 is 20–60%. Infection is acquired by inoculation of viruses shed by an infected individual on to a mucosal surface in a susceptible person. The virus infects sensory and autonomic neurons and establishes latent infection in the nerve ganglia. Primary infection is followed by episodes of reactivation throughout life. Clinical features Primary HSV-1 or 2 infection is more likely to be symptomatic later in life, causing gingivostomatitis, pharyngitis or painful genital tract lesions. The primary attack may be associated with fever and regional lymphadenopathy. Recurrence Recurrent attacks occur throughout life, most often in association with concomitant medical illness, menstruation, mechanical trauma, immunosuppression, psychological stress or, for oral lesions, ultraviolet light exposure. HSV reactivation in the oral mucosa produces the classical ‘cold sore’ or ‘herpes labialis’. Prodromal hyperaesthesia is followed by rapid vesiculation, pustulation and crusting. Recurrent HSV genital disease is a common cause of recurrent painful ulceration (pp. 333 and 336). An inoculation lesion on the finger gives rise to a paronychia, termed a ‘whitlow’, in contacts of patients with herpetic lesions (Fig. 11.14B). Prevention Ebola virus may be detected in the semen

months after recovery. Male survivors are therefore encouraged to practise safe sex for 12 months after symptom onset or until semen tests negative on two occasions, but recommendations are evolving. Public health measures are essential for outbreak control and involve contact surveillance and monitoring through the incubation period, separating healthy from sick individuals, practising safe burial methods and ensuring appropriate infection control measures to protect health-care and laboratory workers, including provision of personal protective equipment such as gloves, gowns and full-face protection (face shield or masks combined with goggles). An Ebola glycoprotein vaccine, rVZV-ZEBOV, was shown to be effective in 2016 after a trial in West Africa. Zika virus Zika virus is a flavivirus spread from primate hosts by Aedes aegypti and Aedes albopictus, which bite during the day. Described in Africa and Asia since 2015, it has been epidemic in the Caribbean and Central and South America, where a mosquito–man–mosquito transmission cycle is established. It also can be transmitted in semen. Clinical features The incubation period is 3–12 days. Infection is asymptomatic or mild, resembling dengue with fever, arthralgia, conjunctivitis and maculopapular rash. Complications include increased reports of Guillain–Barré syndrome. The major concern has been a marked increase in microcephaly in pregnant women infected with Zika virus, as well as increased rates of cerebral calcification, deafness, visual problems such as chorioretinal scarring, joint contractures (arthrogryposis), hydrops fetalis and growth retardation. Zika virus appears to infect neural progenitor cells. Investigations Routine blood tests are usually normal but may show leucopenia, thrombocytopenia or increased transaminases. PCR detects virus in the first week of illness or in urine up to 14 days. Serology provides a retrospective diagnosis but cross-reacts with other flaviviruses. Plaque-reduction neutralisation testing can be used to detect virus-specific neutralising antibodies and distinguish between cross-reacting antibodies in primary flavivirus infections. Fig. 11.14 Cutaneous manifestations of herpes simplex virus 1 (HSV-1). A Acute HSV-1. There were also vesicles in the mouth – herpetic stomatitis. B Herpetic whitlow. C Eczema herpeticum. HSV-1 infection spreads rapidly in eczematous skin. A B C

248 • INFECTIOUS DISEASE appear on buttocks and thighs. Antiviral treatment is not available and management consists of symptom relief with analgesics. Herpangina This infection, caused by Coxsackie viruses, primarily affects children and teenagers in the summer months. It is characterised by a small number of vesicles at the soft/hard palate junction, often associated with high fever, an extremely sore throat and headache. The lesions are short-lived, rupturing after 2–3 days and rarely persisting for more than 1 week. Treatment is with analgesics if required. Culture of the virus from vesicles or DNA detection by PCR differentiates herpangina from HSV. Poxviruses These DNA viruses are rare but potentially important pathogens. Smallpox (variola) Smallpox, which has high mortality, was eradicated worldwide by a global vaccination programme but interest has re-emerged due to its potential as a bioweapon. The virus is spread by the respiratory route or contact with lesions, and is highly infectious. The incubation period is 7–17 days. A prodrome with fever, headache and prostration leads, in 1–2 days, to the rash, which develops through macules and papules to vesicles and pustules, worst on the face and distal extremities. Lesions in one area are all at the same stage of development with no cropping (unlike chickenpox). Vaccination can lead to a modified course of disease with milder rash and lower mortality. If a case of smallpox is suspected, national public health authorities must be contacted. Electron micrography (like Fig. 11.15) and DNA detection tests (PCR) are used to confirm diagnosis. Monkeypox Despite the name, the animal reservoirs for this virus are probably small squirrels and rodents. It causes a rare zoonotic infection in communities in the rainforest belt of Central Africa, producing a vesicular rash that is indistinguishable from smallpox, but differentiated by the

presence of lymphadenopathy. Little person-to-person transmission occurs. Outbreaks outside Complications Disseminated cutaneous lesions can occur in individuals with underlying dermatological diseases, such as eczema (eczema herpeticum) (Fig. 11.14C). Herpes keratitis presents with pain and blurring of vision; characteristic dendritic ulcers are visible on slit-lamp examination and may produce corneal scarring and permanent visual impairment. Primary HSV-2 can cause meningitis or transverse myelitis. HSV is the leading cause of sporadic viral encephalitis (p. 1121); this follows either primary or secondary disease, usually with HSV-1. A haemorrhagic necrotising temporal lobe cerebritis produces temporal lobe epilepsy and altered consciousness/ coma. Without treatment, mortality is 80%. HSV is also implicated in the pathogenesis of Bell's palsy with a lower motor neuron 7th nerve palsy, although antivirals have not been demonstrated to improve outcome. Neonatal HSV disease is usually associated with primary infection of the mother at term (see Box 11.26). In excess of two-thirds of cases develop disseminated disease with cutaneous lesions, hepatitis, pneumonitis and frequently encephalitis. Immunocompromised hosts can develop visceral disease with oesophagitis, hepatitis, pneumonitis, encephalitis or retinitis. Diagnosis Differentiation from other vesicular eruptions is achieved by demonstration of virus in vesicular fluid, usually by direct immunofluorescence or PCR. HSV encephalitis is diagnosed by a positive PCR for HSV in CSF. Serology is of limited value. Management Therapy of localised disease must commence in the first 48 hours of clinical disease (primary or recurrent); thereafter it is unlikely to influence clinical outcome. Oral lesions in an immunocompetent individual may be treated with topical aciclovir. All severe manifestations should be treated, regardless of the time of presentation (see Box 11.30). Suspicion of HSV encephalopathy requires immediate empirical antiviral therapy. Aciclovir resistance is encountered occasionally in immunocompromised hosts, in which case foscarnet is the treatment of choice. Human herpesvirus 8 Human herpesvirus 8 (HHV-8) (see Box 11.29) causes Kaposi's sarcoma in both AIDS-related and endemic non-AIDS-related forms (p. 314). HHV-8 is spread via saliva, and men who have sex with men have an increased incidence of infection. Seroprevalence varies widely, being highest in sub-Saharan Africa. HHV-8 also causes two rare haematological malignancies: primary effusion lymphoma and multicentric Castleman's disease. Current antivirals are not effective. Enterovirus infections Hand, foot and mouth disease This systemic infection is caused by Coxsackie viruses usually, or occasionally by echoviruses. It affects children and occasionally adults, resulting in local or household outbreaks, particularly in the summer months. A relatively mild illness with fever and lymphadenopathy develops after an incubation period of approximately 10 days; 2–3 days later, a painful papular or vesicular rash appears on palmoplantar surfaces of hands and feet, with associated oral lesions on the buccal mucosa and tongue that ulcerate rapidly. A papular erythematous rash may Fig. 11.15 Electron micrograph of molluscum contagiosum, a poxvirus. Courtesy of Prof. Goura Kudesia, Northern General Hospital, Sheffield.

Respiratory viral infections These infections are described on page 581. Adenoviruses, rhinoviruses and enteroviruses (Coxsackie viruses and echoviruses) often produce non-specific upper respiratory tract symptoms but may cause viral pneumonia. Parainfluenza and respiratory syncytial viruses cause upper respiratory tract disease, croup and bronchiolitis in small children and pneumonia in the immunocompromised. Respiratory syncytial virus also causes pneumonia in nursing home residents and may be associated with nosocomial pneumonia. Metapneumovirus and bocavirus cause upper and occasionally lower respiratory tract infection, especially in

immunosuppressed individuals. The severe acute respiratory syndrome (SARS), caused by the SARS coronavirus, emerged as a major respiratory pathogen during an outbreak in 2002–2003, with 8000 cases and 10% mortality (p. 582). Middle East respiratory syndrome coronavirus (MERS-CoV) In 2012, a novel coronavirus, distantly related to the SARS coronavirus, caused several deaths connected with pneumonia in patients originating from the Middle East. The Middle East respiratory syndrome coronavirus (MERS-CoV) appears to be a zoonosis, involving transmission from bats to camels and then to humans. Over 20 countries have reported cases, although most cases have a history of travel to Saudi Arabia or other countries in the Arabian Peninsula. By 2016 there had been over 1700 reported cases. Clinical features The incubation period in person-to-person transmission is 2–14 (average 5) days. Any age may be infected but the severe form of MERS-CoV mainly occurs in patients over 50 with medical comorbidities. Initial symptoms are fever, chills, headache, myalgia, dry cough and dyspnoea. Abdominal pain and diarrhoea may be prominent. The mean period from symptom onset to hospitalisation is 4 days, and 5 days to intensive care unit admission. Illness is complicated by rapid development of respiratory failure and features of ARDS and multi-organ failure. Mortality is 35%. Diagnosis and management Laboratory features include lymphopenia, thrombocytopenia and raised lactate dehydrogenase (LDH). Diagnosis is confirmed by PCR of serum, nasopharyngeal or other respiratory samples. Serology may also be useful. Treatment is supportive. Strict infection control measures should be implemented for anyone with fever, severe respiratory illness and epidemiological risk factors. Patients should be managed in an airborne infection isolation room with contact and airborne infection control measures, including personal protective equipment for health-care workers. Viral infections with neurological involvement See also page 1121. Japanese B encephalitis This flavivirus is an important cause of endemic encephalitis in Japan, China, Russia, South-east Asia, India and Pakistan; outbreaks also occur elsewhere. There are 10 000–20 000 cases reported to the WHO annually. Pigs and aquatic birds are the Africa have been linked to importation of African animals as exotic pets. Diagnosis is by electron micrography or DNA detection (PCR). Cowpox Humans in contact with infected cows develop large vesicles, usually on the hands or arms and associated with fever and regional lymphadenitis. The reservoir is thought to be wild rodents. Vaccinia virus This laboratory strain is the basis of the existing vaccine to prevent smallpox. Widespread vaccination is no longer recommended due to the likelihood of local spread from the vaccination site (potentially life-threatening in those with eczema (eczema vaccinatum) or immune deficiency) and of encephalitis. However, vaccination may still be recommended for key medical staff. Other poxviruses: orf and molluscum contagiosum See page 1239 and Figure 11.15. Gastrointestinal viral infections Norovirus (Norwalk agent) Norovirus is the most common cause of infectious gastroenteritis in the UK and leads to outbreaks in hospital wards, cruise ships and military camps. Food handlers may transmit this virus, which is relatively resistant to decontamination procedures. The incubation period is 24–48 hours. High attack rates and prominent vomiting are characteristic. Diagnosis may be achieved by electron microscopy, antigen or DNA detection (PCR) in stool samples, although the characteristic clinical and epidemiological features mean that microbiological confirmation is not always necessary. The virus is highly infectious and cases should be isolated and environmental surfaces cleaned with detergents and disinfected with bleach. Astrovirus Astroviruses cause diarrhoea in small children and occasionally in immunocompromised adults. Rotavirus Rotaviruses infect enterocytes and are a major cause of diarrhoeal illness in young children worldwide. There are winter epidemics in developed countries, particularly in nurseries. Adults in close contact with cases may develop disease. The incubation period is 48 hours and patients present with watery diarrhoea, vomiting, fever and abdominal pain. Dehydration is prominent. Diagnosis is aided by

commercially available enzyme immunoassay kits, which require fresh or refrigerated stool samples. Immunity develops to natural infection. Monovalent and multivalent vaccines have been licensed in many countries and have now demonstrated efficacy in large trials in Africa and the Americas. Hepatitis viruses (A–E) See Chapter 22. Other viruses Adenoviruses are frequently identified from stool culture and implicated as a cause of diarrhoea in children. They have also been linked to cases of intussusception.

 (HAM) in a subset of those infected (see Box 23.57, p. 964). It is found mainly in Japan, the Caribbean, Central and South America, and the Seychelles. HAM or tropical spastic paraparesis occurs in less than 5% of those with chronic infection, and presents with gait disturbance, spasticity of the lower extremities, urinary incontinence, impotence and sensory disturbance. Myositis and uveitis may also occur with HTLV-1 infection. Serology, sometimes confirmed with PCR, establishes the diagnosis. Treatment is usually supportive. Viral infections with rheumatological involvement Rheumatological syndromes characterise a variety of viral infections ranging from exanthems, such as rubella and parvovirus B19 (p. 237), to blood-borne viruses, such as HBV and HIV-1 and the sequelae of EVD. Chikungunya virus Chikungunya is an alphavirus that causes fever, rash and arthropathy. It is found principally in Africa and Asia, including India. Humans and non-human primates are the main reservoir and the main vector is the Aedes aegypti mosquito. Cases occur in epidemics on a background of sporadic cases. In 2007, an outbreak extended as far north as Italy. The incubation period is 2–12 days. A period of fever may be followed by an afebrile phase and then recrudescence of fever. Children may develop a maculopapular rash. Adults are susceptible to arthritis, which causes early morning pain and swelling, most often in the small joints. Arthritis can persist for months and may become chronic in individuals who are positive for human leucocyte antigen (HLA)-B27. Related alphaviruses causing similar syndromes include Sindbis virus (Scandinavia and Africa), O'nyong-nyong virus (Central Africa), Ross River virus (Australia) and Mayaro virus (Caribbean and South America). Diagnosis is by serology but cross-reactivity between alphaviruses occurs. Treatment is symptomatic. Prion diseases Prions cause transmissible spongiform encephalopathies and are discussed on page 1126. Bacterial infections Bacterial infections of the skin, soft tissues and bones Most infections of the skin, soft tissues and bone are caused by either Staph. aureus or streptococci (mainly Strep. pyogenes) (see pp. 1019 and 1237). Staphylococcal infections Staphylococci are usually found colonising the anterior nares and skin. Some staphylococci produce coagulase, an enzyme that converts fibrinogen to fibrin in rabbit plasma, causing it to clot. Staph. aureus is coagulase-positive, and most other species are coagulase-negative. In modern laboratory practice, however, the identification of Staph. aureus rarely involves the coagulase test. virus reservoirs and transmission is by mosquitoes. Exposure to rice paddies is a recognised risk factor. Clinical features The incubation period is 4–21 days. Most infections are subclinical in childhood and 1% or less of infections lead to encephalitis. Initial systemic illness with fever, malaise and anorexia is followed by headache, photophobia, vomiting and changes in brainstem function. Other neurological features include meningism, seizures, cranial nerve palsies, flaccid or spastic paralysis and extrapyramidal syndromes. Mortality with neurological disease is 25%. Most children die from respiratory failure. Some 50% of survivors have neurological sequelae. Investigations, management and prevention Other infectious causes of encephalitis should be excluded (p. 1121). There is neutrophilia and often hyponatraemia. CSF analysis reveals lymphocytosis and elevated protein. Serological testing of serum and CSF aids diagnosis but may cross-react with dengue and other flaviviruses. Treatment is supportive. Vaccination is recommended for travellers to endemic

areas during the monsoon. Some endemic countries include vaccination in their childhood schedules. West Nile virus This flavivirus is an important cause of neurological disease in an area that extends from Australia, India and Russia through Africa and Southern Europe and across to North America. The disease has an avian reservoir and a mosquito vector. Older people are at increased risk of neurological disease. Clinical features Most infections are asymptomatic. After 2–6 days' incubation, a mild febrile illness and arthralgia may occur. A prolonged incubation may be seen in immunocompromised individuals. Children may develop a maculopapular rash. Neurological disease is seen in 1% and is characterised by encephalitis, meningitis or asymmetric flaccid paralysis with 10% mortality. Diagnosis and management Diagnosis is by serology or detection of viral RNA in blood or CSF. Serological tests may show cross-reactivity with other flaviviruses, including vaccine strains. Treatment is supportive. Enterovirus 71 Enterovirus 71 has caused outbreaks around the globe of enteroviral disease with hand, foot and mouth disease (p. 248) and aseptic meningitis. Some cases have been complicated by encephalitis with flaccid paralysis or by brainstem involvement and death. The virus can be isolated from vesicle fluid, stool or CSF, and viral RNA can be detected in CSF by RT-PCR. Nipah virus encephalitis Nipah virus is a paramyxovirus in the Henipavirus genus, which caused an epidemic of encephalitis amongst Malaysian pig farmers in 1999 and subsequently caused outbreaks in Bangladesh and India. Mortality is around 30%. Diagnosis is by PCR or serology. Human T-cell lymphotropic virus type I Human T-cell lymphotropic virus type I (HTLV-1) is a retrovirus that causes chronic infection with development of adult T-cell leukaemia/lymphoma (ATL) or HTLV-1-associated myelopathy

(Fig. 11.17A). Prevention involves careful attention to hand hygiene, skin preparation and aseptic technique, and the use of topical and systemic antibiotic prophylaxis. Treatment is by drainage of any abscesses plus adequate dosage of antistaphylococcal antibiotics, done early, particularly if prosthetic implants have been inserted. Cannula-related infection Staphylococcal infection associated with cannula sepsis (Fig. 11.17B and p. 196) and thrombophlebitis is an important and common reason for morbidity following hospital admission. The Visual Infusion Phlebitis (VIP) score aids cannula evaluation (Box 11.37). Staphylococci have a predilection for plastic, rapidly Staph. aureus is the main cause of staphylococcal infections. Staph. intermedius is another coagulase-positive staphylococcus, which causes infection following dog bites. Among coagulasenegative organisms, Staph. epidermidis is the predominant commensal organism of the skin, and can cause severe infections in those with central venous catheters or implanted prosthetic materials. Staph. saprophyticus is part of the normal vaginal flora and causes urinary tract infections in sexually active young women. Others implicated in human infections include Staph. lugdunensis, Staph. schleiferi, Staph. haemolyticus and Staph. caprae. Coagulase-negative staphylococci are not usually identified to species level. Staphylococci are particularly dangerous if they gain access to the blood stream, having the potential to disseminate widely (Fig. 11.16). In any patient with staphylococcal bacteraemia, especially injection drug-users, the possibility of endocarditis must be considered (p. 527). Growth of Staph. aureus in blood cultures should not be dismissed as a 'contaminant' unless all possible underlying sources have been excluded and repeated blood culture is negative. Any evidence of spreading cellulitis indicates the urgent need for an antistaphylococcal antibiotic, such as flucloxacillin (unless there is a likely risk of MRSA). This is particularly true for mid-facial cellulitis, which can result in cavernous sinus thrombophlebitis. In addition, Staph. aureus can cause severe systemic disease due to the effects of toxin produced at

superficial sites in the absence of tissue invasion by bacteria. Skin infections Staphylococcal infections cause ecthyma, folliculitis, furuncles, carbuncles, bullous impetigo and the scalded skin syndrome (pp. 1235–1237). They may also be involved in necrotising infections of the skin and subcutaneous tissues (p. 226). Wound infections Many wound infections are caused by staphylococci, which may significantly prolong post-operative hospital stays Fig. 11.16 Infections caused by Staphylococcus aureus. CNS Meningitis Brain abscess (neurosurgical infections in particular) Respiratory Pneumonia Lung abscess Empyema Cardiac Endocarditis Pericarditis Blood stream Blood-stream infection Metastatic abscesses Bone and joint Osteomyelitis Septic arthritis Intestinal Enterocolitis Multisystem Toxic shock syndrome Skin Wound infections Boils, styes, carbuncles, abscesses Fig. 11.17 Manifestations of skin infection with Staphylococcus aureus. A Wound infection. B Cannula-related infection. B A Adapted from Jackson A. Nursing Times 1997; 94:68–71. 11.37 How to assess an intravenous cannula using the Visual Infusion Phlebitis (VIP) score Clinical features Score Assessment and management IV site appears healthy

No signs of phlebitis Observe cannula One of the following is evident: Slight pain near IV site Slight redness near IV site

Possible first signs of phlebitis Observe cannula Two of the following are evident: Pain near IV site Erythema Swelling

Early stage of phlebitis Resite cannula ALL of the following are evident and extensive: Pain along path of cannula Erythema Induration

Medium stage of phlebitis Resite cannula Consider treatment ALL of the following are evident and extensive: Pain along path of cannula Erythema Induration Palpable venous cord

Advanced stage of phlebitis or start of thrombophlebitis Resite cannula Consider treatment ALL of the following are evident: Pain along path of cannula Erythema Induration Palpable venous cord Pyrexia

Advanced stage of thrombophlebitis Initiate treatment Resite cannula

252 • INFECTIOUS DISEASE Streptococcal infections Streptococci are oropharyngeal and gut commensals, which appear as Gram-positive cocci in chains (see Fig. 6.3, p. 102). They are classified by the pattern of haemolysis they produce on blood agar (see Fig. 6.4, p. 102), by their ‘Lancefield groups’ (Box 11.38) and more recently by speciation on matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectometry. Some streptococci (e.g. Strep. milleri group) defy simple classification. Group A streptococci (GAS) are the leading cause of bacterial pharyngitis. Although the presence of fever, tender anterior lymphadenopathy and purulent tonsillar exudate and the absence of cough make streptococcal pharyngitis more likely than viral infection, clinical features alone are unreliable for diagnosing streptococcal pharyngitis. GAS are also the major cause of cellulitis, erysipelas and impetigo (pp. 1237 and 1235). Groups C and G streptococci cause cellulitis, particularly in elderly, diabetic or immunocompromised patients. Group B streptococci (GBS) colonise the gut and vagina. They cause post-partum and neonatal sepsis, as well as other deep infections (infective endocarditis, septic arthritis, osteomyelitis etc.), especially in the elderly. Streptococcal scarlet fever Group A (or occasionally

groups C and G) streptococci causing pharyngitis, tonsillitis or other infection may lead to scarlet fever, if the infecting strain produces a streptococcal pyrogenic exotoxin. Scarlet fever is most common in school-age children, but can also occur in young adults who have contact with young children. A diffuse erythematous rash occurs, which blanches on pressure (Fig. 11.19A), classically with circumoral pallor. The tongue, initially coated, becomes red and swollen ('strawberry tongue', Fig. 11.19B). The disease lasts about 7 days, the rash disappearing in 7–10 days, followed by a fine desquamation. Residual petechial lesions in the antecubital fossa may be seen ('Pastia's sign', Fig. 11.19C). Treatment involves intravenous benzylpenicillin or an oral penicillin plus symptomatic measures. forming a biofilm on cannulae, which remains as a source of bacteraemia. Local poultice application may relieve symptoms but cannula removal and antibiotic treatment with flucloxacillin (or a glycopeptide if MRSA is suspected) are necessary if there is any suggestion of spreading infection. Meticillin-resistant Staph. aureus Resistance to meticillin is due to a penicillin-binding protein mutation in Staph. aureus. Resistance to vancomycin/teicoplanin (glycopeptides) in either glycopeptide intermediate Staph. aureus (GISA) or, rarely, vancomycin-resistant (VRSA) strains threatens the ability to manage serious infections produced by such organisms. Meticillin-resistant Staph. aureus (MRSA) is now a major worldwide health care-acquired pathogen, accounting for up to 40% of staphylococcal bacteraemia in developed countries. Community-acquired MRSA (c-MRSA) currently accounts for 50% of all MRSA infections in the USA. These organisms have also acquired other toxins, such as Panton–Valentine leukocidin (PVL), and cause rapidly fatal infection in young people. Clinicians must be aware of the potential danger of these infections and be prepared to take whatever appropriate infection control measures are locally advised (p. 111). Treatment options for MRSA are shown in Box 6.16 (p. 117). Treatment should always be based on the results of antimicrobial susceptibility testing, since resistance to all these agents occurs. Milder MRSA infections may be treated with clindamycin, tetracyclines or co-trimoxazole. Glycopeptides, linezolid and daptomycin are reserved for treatment of more severe infections. Toxin-producing MRSA infections should be treated with protein-inhibiting antibiotics (clindamycin, linezolid). Staphylococcal toxic shock syndrome Staphylococcal toxic shock syndrome (TSS) is a serious and life-threatening disease associated with infection by Staph. aureus, which produces a specific toxin (toxic shock syndrome toxin 1, TSST1). It was formerly seen in young women in association with the use of highly absorbent intravaginal tampons but can occur with any Staph. aureus infection involving a relevant toxin-producing strain. The toxin acts as a 'superantigen', triggering significant T-cell activation and massive cytokine release. TSS has an abrupt onset with high fever, generalised systemic upset (myalgia, headache, sore throat and vomiting), a widespread erythematous blanching rash resembling scarlet fever, and hypotension. It rapidly progresses over a few hours to multi-organ failure, leading to death in 10–20%. Recovery is accompanied at 7–10 days by desquamation (Fig. 11.18). The diagnosis is clinical and may be confirmed in menstrual cases by finding a retained tampon with staphylococci on Gram stain. Subsequent culture and demonstration of toxin production are confirmatory. Management Treatment is with immediate and aggressive fluid resuscitation and an intravenous antistaphylococcal antimicrobial (flucloxacillin or vancomycin), usually with the addition of a protein synthesis inhibitor (e.g. clindamycin) to inhibit toxin production. Intravenous immunoglobulin is occasionally added in the most severe cases. Women who recover from tampon-associated TSS should avoid tampons for at least 1 year and be advised that the condition can recur. Fig. 11.18 Full-thickness desquamation after staphylococcal toxic shock syndrome.

11.38 Streptococcal and related infections β-haemolytic group A (Strep. pyogenes) • Skin and soft tissue infection (including erysipelas, impetigo, necrotising fasciitis) • Streptococcal toxic shock syndrome • Puerperal sepsis • Scarlet fever • Glomerulonephritis • Rheumatic fever • Bone and joint infection • Tonsillitis β-haemolytic group B (Strep. agalactiae) • Neonatal infections, including meningitis • Female pelvic infections • Cellulitis β-haemolytic group C (various zoonotic streptococci) • Cellulitis • Endocarditis • Pharyngitis • Septic arthritis α-, β- or non-haemolytic group D (Enterococcus faecalis, E. faecium) • Endocarditis • Intra-abdominal infections • Urinary tract infection α- or non-haemolytic group D (Strep. gallolyticus subsp. gallolyticus/S. bovis biotype I) • Bacteraemia/endocarditis associated with large bowel malignancy β-haemolytic group G streptococci • Cellulitis • Endocarditis • Liver abscess • Septic arthritis α-haemolytic optochin-resistant (viridans streptococci – Strep. mitis, Strep. sanguis, Strep. mutans, Strep. salivarius) • Sepsis in immunosuppressed • Endocarditis α-haemolytic optochin-sensitive (Strep. pneumoniae) • Pneumonia • Meningitis • Endocarditis • Otitis media • Sepsis • Spontaneous bacterial peritonitis • Sinusitis Variable haemolysis (Strep. milleri group – Strep. anginosus, Strep. intermedius, Strep. constellatus) • Endocarditis • Intra-abdominal infections • Urinary tract infection Anaerobic streptococci (Peptostreptococcus spp.) • Sepsis in immunosuppressed • Endocarditis N.B. All streptococci can cause sepsis. Fig. 11.19 Clinical features of scarlet fever. A Characteristic rash with blanching on pressure. B ‘Strawberry tongue’. C Pastia’s sign: a petechial rash in the cubital fossa. C B A Streptococcal toxic shock syndrome Group A (or occasionally group C or G) streptococci can produce one of a variety of toxins, such as pyogenic exotoxin A. Like staphylococcal TSST1 (see above), these act as super-antigens. Initially, an influenza-like illness occurs, with signs of localised infection in 50% of cases, most often involving the skin and soft tissues. A faint erythematous rash, mainly on the chest, rapidly progresses to circulatory shock. Without aggressive management, multi-organ failure will develop. Fluid resuscitation must be undertaken, along with parenteral antistreptococcal antibiotic therapy, usually with benzylpenicillin and clindamycin, to inhibit toxin production. Intravenous immunoglobulin is often administered. If necrotising fasciitis is present, it should be treated as described on page 227 with urgent débridement. Treponematoses Syphilis This disease is described on page 337. Endemic treponematoses Yaws Yaws is a granulomatous disease, mainly involving the skin and bones; it is caused by Treponema pertenue, morphologically and serologically indistinguishable from the causative organisms of syphilis and pinta. It is important to establish the geographical origin and sexual history of patients to exclude false-positive syphilis serology due to endemic treponemal infections. Between 1950 and 1960, WHO campaigns treated over 60 million people and eradicated yaws from many areas, but the disease has persisted patchily throughout the tropics; there was a resurgence in the 1980s and 1990s in West and Central Africa and the South Pacific. Organisms are transmitted by bodily contact from a patient with infectious yaws through minor abrasions of the skin of another patient, usually a child. After an incubation period of 3–4 weeks, a proliferative granuloma containing numerous treponemes develops at the site of inoculation. This primary lesion is followed by secondary eruptions. In addition, there may be hypertrophic periosteal lesions of many bones, with underlying cortical rarefaction. Lesions of late yaws are characterised

 after 6 months but granuloma formation and the accompanying fibrosis cause contractures and deformity. Clumps of acid-fast bacilli can be detected in the ulcer floor. A combination of rifampicin and streptomycin can cure the infection. Infected tissue should be removed surgically. Health campaigns in Ghana have successfully focused on early removal of the small, pre-ulcerative nodules. Systemic bacterial infections Brucellosis Brucellosis is an enzootic

infection (i.e. endemic in animals) caused by Gram-negative bacilli. The four species causing human disease and their animal hosts are: Brucella melitensis (goats, sheep and camels in Europe, especially the Mediterranean basin, the Middle East, Africa, India, Central Asia and South America), B. abortus (cattle, mainly in Africa, Asia and South America), B. suis (pigs in South Asia) and B. canis (dogs). B. melitensis causes the most severe disease; B. suis is often associated with abscess formation. Infected animals may excrete Brucella spp. in their milk for prolonged periods and human infection is acquired by ingesting contaminated dairy products (especially unpasteurised milk), uncooked meat or offal. Animal urine, faeces, vaginal discharge and uterine products may transmit infection through abraded skin or via splashes and aerosols to the respiratory tract and conjunctiva. Clinical features Brucella spp. are intracellular organisms that survive for long periods within the reticulo-endothelial system. This explains the disease chronicity and tendency to relapse, even after antimicrobial therapy. Acute illness is characterised by a high swinging temperature, rigors, lethargy, headache, joint and muscle pains, and scrotal pain. Occasionally, there is delirium, abdominal pain and constipation. Physical signs are non-specific, e.g. enlarged lymph nodes. Splenomegaly may cause thrombocytopenia. Localised infection (Fig. 11.20), which occurs in about 30% of patients, is more likely if diagnosis and treatment are delayed. Diagnosis Definitive diagnosis depends on culture of the organism. Blood cultures are positive in 75–80% of B. melitensis and 50% of B. abortus infections. Bone marrow culture is not routine but may increase the diagnostic yield if antibiotics have been used prior to culture. CSF culture in neurobrucellosis is positive in about 30% of cases. The laboratory should be alerted to a suspected diagnosis of brucellosis, as the organism may infect laboratory workers and must be cultured at the appropriate biosafety level. Serology may also aid diagnosis. In endemic areas, a single high antibody titre of more than 1/320 or a fourfold rise in titre is needed to support a diagnosis of acute infection. The test usually takes several weeks to become positive but should eventually detect 95% of acute infections. Management Aminoglycosides show synergistic activity with tetracyclines against brucellae. Treatment regimens for different forms of brucellosis are outlined in Box 11.40. by destructive changes that closely resemble the osteitis and gummas of tertiary syphilis and that heal with scarring and deformity. Investigations and management are outlined in Box 11.39. Improved housing and hygiene, combined with mass chemotherapy programmes, have achieved dramatic success in the control of yaws. Pinta and bejel These two treponemal infections occur in poor rural populations with low standards of domestic hygiene but are found in separate parts of the world. They have features in common, notably that they are transmitted by contact, usually within the family and not sexually, and in the case of bejel, through common eating and drinking utensils. Their diagnosis and management are as for yaws (Box 11.39). • Pinta. Pinta is found only in South and Central America, where its incidence is declining. The infection is confined to the skin. The early lesions are scaly papules or dyschromic patches on the skin. The late lesions are often depigmented and disfiguring. • Bejel. Bejel is the Middle Eastern name for non-venereal syphilis, which has a patchy distribution across subSaharan Africa, the Middle East, Central Asia and Australia. It has been eradicated from Eastern Europe. Transmission is most commonly from the mouth of the mother or child and the primary mucosal lesion is seldom seen. The early and late lesions resemble those of secondary and tertiary syphilis (p. 337) but cardiovascular and neurological disease is rare. Tropical ulcer Tropical ulcer is due to a synergistic bacterial infection caused by a fusobacterium (F. ulcerans, an anaerobe) and Treponema vincentii. It is common in hot, humid regions. The ulcer is most common on the lower legs and develops as a papule that rapidly breaks down to a sharply defined, painful ulcer. The base of the ulcer has a foul slough. Penicillin and metronidazole are useful in the early stages but rest, elevation and dressings are the

mainstays of treatment. Buruli ulcer This ulcer is caused by Mycobacterium ulcerans and occurs widely in tropical rainforests. In 1999, a survey in Ghana found 6500 cases; there are an estimated 10 000 cases in West Africa as a whole. The initial lesion is a small subcutaneous nodule on the arm or leg. This breaks down to form a shallow, necrotic ulcer with deeply undermined edges, which extends rapidly. Healing may occur 11.39 Diagnosis and treatment of yaws, pinta and bejel Diagnosis of early stages • Detection of spirochaetes in exudate of lesions by dark ground microscopy Diagnosis of latent and early stages • Positive serological tests, as for syphilis (see Box 13.8, p. 339) Treatment of all stages • Single intramuscular injection of 1.2 g long-acting penicillin, e.g. benzathine benzylpenicillin

Borrelia infections Borrelia are flagellated spirochaetal bacteria that infect humans after bites from ticks or lice. They cause a variety of human infections worldwide (Box 11.41). Lyme disease Lyme disease (named after the town of Old Lyme in Connecticut, USA) is caused by B. burgdorferi, which occurs in the USA, Europe, Russia, China, Japan and Australia. In Europe, two additional genospecies are also encountered, B. afzelii and B. garinii. The reservoir of infection is ixodid (hard) ticks that feed on a variety of large mammals, particularly deer. Birds may spread ticks over a wide area. The organism is transmitted to humans via the bite of infected ticks; larval, nymphal and adult forms are all capable of spreading infection. Ehrlichiosis is a common co-infection with Lyme disease. Two forms occur: Anaplasma phagocytophilum, human granulocytic anaplasmosis (HGA); and Ehrlichia chaffeensis, human monocytic ehrlichiosis (HME). Clinical features There are three stages of disease. Progression may be arrested at any stage. • Early localised disease. The characteristic feature is a skin reaction around the site of the tick bite, known as erythema migrans (Fig. 11.21). Initially, a red ‘bull’s eye’ macule or papule appears 2–30 days after the bite. It then enlarges peripherally with central clearing and may persist for months. Atypical forms are common. The lesion is not pathognomonic of Lyme disease since similar lesions can occur after tick bites. Acute manifestations, such as fever, headache and regional lymphadenopathy, may develop with or without the rash. Fig. 11.20 Clinical features of brucellosis. Malodorous perspiration Suppurative arthritis Synovitis, bursitis Osteomyelitis Spinal spondylitis or sacroiliitis Paravertebral or psoas abscess Meningitis Intracranial or subarachnoid haemorrhage Stroke Myelopathy Radiculopathy Cranial nerve palsies Uveitis Retinal thrombophlebitis Myocarditis Endocarditis Pneumonitis or abscesses Hilar lymphadenopathy Splenic abscesses or calcification Hepatitis Epididymo-orchitis Pancytopenia 11.40 Treatment of brucellosis Adults with non-localised disease • Doxycycline 100 mg twice daily orally for 6 weeks plus gentamicin 5 mg/kg IV once daily for 7 days or • Doxycycline 100 mg twice daily plus rifampicin 600–900 mg orally once daily for 6 weeks Bone disease • Doxycycline 100 mg twice daily plus rifampicin 600–900 mg once daily orally for 6 weeks plus gentamicin 5 mg/kg IV once daily for 7 days or • Ciprofloxacin 750 mg twice daily orally plus rifampicin 600–900 mg orally once daily for 3 months Neurobrucellosis • Doxycycline 100 mg twice daily plus rifampicin 600–900 mg orally once daily for 6 weeks plus ceftriaxone 2vg IV twice daily until the cerebrospinal fluid is clear (though susceptibility should be confirmed because sensitivity to third-generation cephalosporins varies among strains) Endocarditis • Almost always needs surgical intervention plus • Doxycycline 100 mg twice daily, rifampicin 600–900 mg orally once daily and co-trimoxazole 5 mg/kg of trimethoprim component for 6 months plus gentamicin 5 mg/kg IV once daily for 2–4 weeks Pregnancy • Rifampicin 600–900 mg orally once daily and co-trimoxazole 5 mg/ kg of trimethoprim component for 4 weeks, but caution in last week of

pregnancy due to displacement of bilirubin from albumin by drugs and risk of kernicterus to the fetus

256 • INFECTIOUS DISEASE after initial infection. Carditis, sometimes accompanied by atrioventricular conduction defects, occurs in the USA but is rare in Europe. • Late disease. Late manifestations include arthritis, polyneuritis and encephalopathy. Prolonged arthritis, particularly affecting large joints, and brain parenchymal involvement, causing neuropsychiatric abnormalities, may occur but are rare in the UK. Acrodermatitis chronica atrophicans is an uncommon late complication seen more frequently in Europe than North America. Doughy, patchy discoloration occurs on the peripheries, eventually leading to shiny atrophic skin. The lesions are easily mistaken for those of peripheral vascular disease. In patients coming from an endemic area or having risk factors, who have facial nerve palsy, Lyme disease should be considered. Diagnosis The diagnosis of early Lyme borreliosis is often clinical. Culture from biopsy material is not generally available, has a low yield and may take longer than 6 weeks. Antibody detection is frequently negative early in the course of the disease but sensitivity increases to 90–100% in disseminated or late disease. Immunofluorescence or ELISA can give false-positive reactions in a number of conditions, including other spirochaetal infections, infectious mononucleosis, rheumatoid arthritis and systemic lupus erythematosus (SLE). Immunoblot (Western blot) techniques are more specific and, although technically demanding, should be used to confirm the diagnosis. Microorganism DNA detection by PCR has been applied to blood, urine, CSF and biopsies of skin and synovium. Management Recent evidence suggests that asymptomatic patients with positive antibody tests should not be treated. However, erythema migrans always requires therapy because organisms may persist and cause progressive disease, even if the skin lesions resolve. Standard therapy consists of a 14-day course of doxycycline (200 mg daily) or amoxicillin (500 mg 3 times daily). Some 15% of patients with early disease will develop a mild Jarisch–Herxheimer reaction (JHR) during the first 24 hours of therapy (p. 339). In pregnant women and small children with penicillin allergy, or in those allergic to amoxicillin and doxycycline, 14-day treatment with cefuroxime axetil (500 mg twice daily) or erythromycin (250 mg 4 times daily) may be used. Disseminated disease and arthritis require therapy for a minimum of 28 days. Arthritis may respond poorly and prolonged or repeated courses may be necessary. Neuroborreliosis is treated with parenteral β-lactam antibiotics for 3–4 weeks; thirdgeneration cephalosporins such as ceftriaxone are the preferred therapy. Prevention Protective clothing and insect repellents should be used in tick-infested areas. Since the risk of borrelial transmission is lower in the first few hours of a blood feed, prompt removal of ticks is advisable. Unfortunately, larval and nymphal ticks are tiny and may not be noticed. Where risk of transmission is high, a single 200 mg dose of doxycycline, given within 72 hours of exposure, has been shown to prevent erythema migrans. Fig. 11.21 Rash of erythema migrans in Lyme disease with metastatic secondary lesions. Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield. 11.41 Clinical diseases caused by Borrelia spp. Species Vector Geographical distribution Lyme disease B. burgdorferi sensu stricto Tick: Ixodes scapularis Northern and eastern USA I. pacificus Western USA B. afzelii I. ricinus Europe I. persulcatus Asia B. garinii I. ricinus Europe I. persulcatus Asia Louse-borne relapsing fever B. recurrentis Human louse: Pediculus humanus corporis Worldwide Tick-borne relapsing fever B. hermsii Tick: Ornithodoros hermsii Western North America B. turicatae O. turicatae South-western North America and northern Mexico B. venezuelensis O. rudis Central America and northern South America B. hispanica O. erraticus Iberian peninsula and north-western Africa B. crocidurae O. erraticus North Africa and Mediterranean region B. duttonii O. moubata Central, eastern and southern Africa B. persica O.

tholozani Western China, India, Central Asia, Middle East B. latyschewii O. tartakovskyi Tajikistan, Uzbekistan • Early disseminated disease. Dissemination occurs via the blood stream and lymphatics. There may be a systemic reaction with malaise, arthralgia and, occasionally, metastatic areas of erythema migrans (Fig. 11.21). Neurological involvement may follow weeks or months after infection. Common features include lymphocytic meningitis, cranial nerve palsies (especially unilateral or bilateral facial nerve palsy) and peripheral neuropathy. Radiculopathy, often painful, may present a year or more

Tick-borne relapsing fever Soft ticks (Ornithodoros spp.) transmit B. duttonii (and other Borrelia species) through saliva while feeding on their host. People sleeping in mud houses are at risk, as the tick hides in crevices during the day and feeds on humans during the night. Rodents are the reservoir in all parts of the world except East Africa, where humans are the reservoir. Clinical manifestations are similar to those seen with the louse-borne disease but microorganisms are detected in fewer patients on dark field microscopy. A 7-day course (due to a higher relapse rate than in louse-borne relapsing fever) of treatment with either tetracycline (500 mg 4 times daily) or erythromycin (500 mg 4 times daily) is needed. Leptospirosis Microbiology and epidemiology Leptospirosis is one of the most common zoonotic diseases, favoured by a tropical climate and flooding during the monsoon but occurring worldwide. Leptospires are tightly coiled, thread-like organisms about 5–7 μm in length, which are actively motile; each end is bent into a hook. Leptospira interrogans is pathogenic for humans. The genus can be separated into more than 200 serovars (subtypes) belonging to 23 serogroups. Leptospirosis appears to be ubiquitous in wildlife and in many domestic animals. The organisms persist indefinitely in the convoluted tubules of the kidney and are shed into the urine in massive numbers, but infection is asymptomatic in the host. The most frequent hosts are rodents, especially the common rat (Rattus norvegicus). Particular leptospiral serogroups are associated with characteristic animal hosts; for example, L. ictero-haemorrhagiae is the classical parasite of rats and L. canicola of dogs. There is nevertheless considerable overlap in host–serogroup associations. Leptospires can enter their human hosts through intact skin or mucous membranes but entry is facilitated by cuts and abrasions. Prolonged immersion in contaminated water will also favour invasion, as the spirochaete can survive in water for months. Leptospirosis is common in the tropics and also in freshwater sports enthusiasts. Clinical features After a relatively brief bacteraemia, invading organisms are distributed throughout the body, mainly in kidneys, liver, meninges and brain. The incubation period averages 1–2 weeks. Four main clinical syndromes can be discerned and clinical features can involve multiple different organ systems (Fig. 11.23). Bacteraemic leptospirosis Bacteraemia with any serogroup can produce a non-specific illness with high fever, weakness, muscle pain and tenderness (especially of the calf and back), intense headache and photophobia, and sometimes diarrhoea and vomiting. Conjunctival congestion is the only notable physical sign. The illness comes to an end after about 1 week, or else merges into one of the other forms of infection. Aseptic meningitis Classically associated with L. canicola infection, this illness is very difficult to distinguish from viral meningitis. The conjunctivae may be congested but there are no other differentiating signs. Laboratory clues include a neutrophil leucocytosis, abnormal LFTs, and the occasional presence of albumin and casts in the urine. Louse-borne relapsing fever The human body louse, Pediculus humanus, causes itching. Borreliae (B. recurrentis) are liberated from infected lice when they are crushed during scratching, which also inoculates the borreliae into the skin. The disease occurs worldwide, with

epidemic relapsing fever most often seen in Central/East Africa and South America. The borreliae multiply in the blood, where they are abundant in the febrile phases, and invade most tissues, especially the liver, spleen and meninges. Clinical features Onset is sudden with fever. The temperature rises to 39.5–40.5°C, accompanied by a tachycardia, headache, generalised aching, injected conjunctivae (Fig. 11.22) and herpes labialis. Thrombocytopenia is associated with a petechial rash and epistaxis. As the disease progresses tender hepatosplenomegaly, accompanied by jaundice and elevated transaminases, is common. There may be severe serosal and intestinal haemorrhage, delirium and meningism. The fever ends in crisis between the fourth and tenth days, often associated with profuse sweating, hypotension and circulatory and cardiac failure. There may be no further fever but, in a proportion of patients, after an afebrile period of about 7 days, there are one or more relapses, which are usually milder and less prolonged. In the absence of specific treatment, the mortality rate is up to 40%, especially among the elderly and malnourished. Investigations and management Dark ground microscopy of a wet film or Wright–Giemsa stained thick and thin films demonstrate the organism in blood from a febrile patient. Treatment aims to eradicate the organism and prevent relapses, while minimising the severe JHR that inevitably follows successful chemotherapy. The safest treatment is procaine penicillin 300 mg IM, followed the next day by 0.5 g tetracycline. Tetracycline alone is effective and prevents relapse, but may give rise to a worse reaction. Doxycycline 200 mg once orally in place of tetracycline has the advantage of also being curative for typhus, which often accompanies epidemics of relapsing fever. JHR is best managed in a high-dependency unit with expert nursing and medical care. The patient, clothing and all contacts must be freed from lice, as in epidemic typhus. Fig. 11.22 Louse-borne relapsing fever. Injected conjunctivae.

 elevated protein level and normal glucose content. Acute kidney injury due to interstitial nephritis is common. In the tropics, dengue, malaria, typhoid fever, scrub typhus and hantavirus infection are important differential diagnoses. Definitive diagnosis of leptospirosis depends on isolation of the organism, serological tests or detection of specific DNA. In general, however, it is probably under-diagnosed. • Blood cultures are most likely to be positive if taken before the 10th day of illness. Special media are required and cultures may have to be incubated for several weeks. • Leptospires appear in the urine during the second week of illness, and in untreated patients may be recovered on culture for several months. • Serological tests are diagnostic if seroconversion or a fourfold increase in titre is demonstrated. The microscopic agglutination test (MAT) is the investigation of choice and can become positive by the end of the first week. IgM ELISA and immunofluorescent techniques are easier to perform, however, while rapid immunochromatographic tests are specific but of only moderate sensitivity in the first week of illness. • Detection of leptospiral DNA by PCR is possible in blood in early symptomatic disease, and in urine from the eighth day of illness and for many months thereafter. Management and prevention The general care of the patient is critically important. Blood transfusion for haemorrhage and careful attention to renal function, the usual cause of death, are especially important. Acute kidney injury is potentially reversible with adequate support, such as dialysis. Most infections are self-limiting. Therapy with either oral doxycycline (100 mg twice daily for 1 week) or intravenous penicillin (900 mg 4 times daily for 1 week) is effective but may not prevent the development of renal failure. Parenteral ceftriaxone (1 g daily) is as effective as penicillin. JHR may occur but is usually Icteric leptospirosis (Weil’s disease) Fewer than 10% of symptomatic infections result in severe icteric illness. Weil’s disease is a dramatic life-threatening event, characterised by fever, haemorrhages, jaundice and acute kidney injury. Conjunctival hyperaemia

is a frequent feature. The patient may have a transient macular erythematous rash but the characteristic skin changes are purpura and large areas of bruising. In severe cases there may be epistaxis, haematemesis and melaena, or bleeding into the pleural, pericardial or subarachnoid spaces. Thrombocytopenia, probably related to activation of endothelial cells with platelet adhesion and aggregation, is present in 50% of cases. Jaundice is deep and the liver is enlarged but there is usually little evidence of hepatic failure or encephalopathy. Acute kidney injury, primarily caused by impaired renal perfusion and acute tubular necrosis, manifests as oliguria or anuria, with the presence of albumin, blood and casts in the urine. Weil's disease may also be associated with myocarditis, encephalitis and aseptic meningitis. Uveitis and iritis may appear months after apparent clinical recovery. Pulmonary syndrome This syndrome has long been recognised in the Far East and has been described during an outbreak of leptospirosis in Nicaragua. It is characterised by haemoptysis, patchy lung infiltrates on chest X-ray, and respiratory failure. Total bilateral lung consolidation and ARDS (p. 324) with multi-organ dysfunction may develop, with a high mortality (over 50%). Diagnosis A polymorphonuclear leucocytosis is accompanied in severe infection by thrombocytopenia and elevated blood levels of creatine kinase. In jaundiced patients, there is hepatitis and the prothrombin time may be prolonged. The CSF in leptospiral meningitis shows a variable cellular response, a moderately Fig. 11.23 Clinical syndromes of leptospirosis. (ARDS = acute respiratory distress syndrome) Headache Photophobia Aseptic meningitis Bacteraemic leptospirosis Pulmonary syndrome Weil's disease Epistaxis Haematemesis Conjunctivitis Uveitis Jaundice Pericarditis/ myocarditis/ vasculiitis Myositis Diarrhoea Vomiting Haemoptysis Pulmonary haemorrhage ARDS Hepatomegaly Renal failure Transient macular rash Purpura Bruising

The patient is toxic and may have gastrointestinal symptoms, such as nausea, vomiting, abdominal pain and diarrhoea. DIC may occur, manifested by bleeding from various orifices or puncture sites, along with ecchymoses. Hypotension, shock, renal failure and ARDS may lead to further deterioration. Meningitis, pneumonia and expectoration of blood-stained sputum containing Y. pestis may complicate septicaemic, or occasionally bubonic, plague. Pneumonic plague Following primary infection in the lung, the onset of disease is very sudden, with cough and dyspnoea. The patient soon expectorates copious blood-stained, frothy, highly infective sputum, becomes cyanosed and dies. Chest radiology reveals bilateral infiltrates, which may be nodular and progress to an ARDS-like picture. Investigations The organism may be cultured from blood, sputum and bubo aspirates. For rapid diagnosis, Gram, Giemsa and Wayson's stains (the latter containing methylene blue) are applied to smears from these sites. Y. pestis is seen as bipolar staining coccobacilli, sometimes referred to as having a 'safety pin' appearance. Smears are also subjected to antigen detection by immunofluorescence, using Y. pestis F1 antigen-specific antibodies. The diagnosis may be confirmed by seroconversion or a single high titre (> 128) of anti-F1 antibodies in serum. DNA detection by PCR is under evaluation. Plague is a notifiable disease under international health regulations (p. 114). Management If the diagnosis is suspected on clinical and epidemiological grounds, treatment must be started as soon as, or even before, samples have been collected for laboratory diagnosis. Streptomycin (1 g twice daily) or gentamicin (1 mg/kg 3 times daily) is the drug of choice. Tetracycline (500 mg 4 times daily) and chloramphenicol (12.5 mg/kg 4 times daily) are alternatives. Fluoroquinolones (ciprofloxacin and levofloxacin) may be as effective but there is less clinical experience. Treatment may also be needed for acute circulatory failure, DIC and

hypoxia. Prevention and infection control Rats and fleas should be controlled. In endemic areas, people should avoid handling and skinning wild animals. The patient should be isolated for the first 48 hours or until clinical improvement begins. Attendants must wear gowns, masks and gloves. Exposed symptomatic or asymptomatic people who have been in close contact with a patient with pneumonic plague should receive post-exposure antibiotic prophylaxis (doxycycline 100 mg or ciprofloxacin 500 mg twice daily) for 7 days. A recombinant subunit vaccine (protein antigens F1 + V) is in development. Listeriosis Listeria monocytogenes is an environmental Gram-positive bacillus that can contaminate food. Outbreaks have been associated with raw vegetables, soft cheeses, under-cooked chicken, fish, meat and pâtés. The bacterium demonstrates ‘cold enrichment’, outgrowing other contaminating bacteria during refrigeration. Although food-borne outbreaks of gastroenteritis have been reported in immunocompetent individuals, Listeria causes more significant invasive infection, especially in pregnant women, older adults (over 55 years) and the immunocompromised. mild. Uveitis is treated with a combination of systemic antibiotics and local glucocorticoids. There is no role for the routine use of glucocorticoids in the management of leptospirosis. Trials in military personnel have shown that infection with L. interrogans can be prevented by taking prophylactic doxycycline 200 mg weekly. Plague Plague is caused by Yersinia pestis, a small Gram-negative bacillus that is spread between rodents by their fleas. If domestic rats become infected, infected fleas may bite humans. Hunters and trappers can contract plague from handling rodents. In the late stages of human plague, Y. pestis may be expectorated and spread between humans by droplets, causing ‘pneumonic plague’. Epidemics of plague, such as the ‘Black Death’, have occurred since ancient times. It is often said that the first sign of plague is the appearance of dead rats. Plague foci are widely distributed throughout the world, including the USA; human cases are reported from about 10 countries per year (Fig. 11.24). Y. pestis is a potential bioweapon because of the possibility of person-to-person spread and the high fatality rate associated with pneumonic plague. Clinical features Organisms inoculated through the skin are transported rapidly to the draining lymph nodes, where they elicit a severe inflammatory response that may be haemorrhagic. If the infection is not contained, sepsis ensues and necrotic, purulent or haemorrhagic lesions develop in many organs. Oliguria and shock follow, and disseminated intravascular coagulation may result in widespread haemorrhage. Inhalation of Y. pestis causes alveolitis. The incubation period is 3–6 days but shorter in pneumonic plague. Bubonic plague In this, the most common form of the disease, onset is usually sudden, with a rigor, high fever, dry skin and severe headache. Soon, aching and swelling at the site of the affected lymph nodes begin. The groin is the most common site of this ‘bubo’, made up of the swollen lymph nodes and surrounding tissue. Some infections are relatively mild but, in the majority of patients, toxaemia quickly increases, with a rapid pulse, hypotension and delirium. The spleen is usually palpable. Septicaemic plague Those not exhibiting a bubo usually deteriorate rapidly and have a high mortality. The elderly are more prone to this form of illness. Fig. 11.24 Foci of the transmission of plague. Reproduced by permission of the World Health Organisation. Frequent transmission Infrequent or suspected transmission

 children diarrhoea and vomiting may be prominent early in the illness. The pulse is often slower than would be expected from the height of the temperature, i.e. a relative bradycardia. At the end of the first week, a rash may appear on the upper abdomen and on the back as sparse, slightly raised, rose-red spots, which fade on pressure. It is usually visible only on white skin. Cough and epistaxis occur. Around the 7th–10th day, the spleen becomes palpable. Constipation is followed by diarrhoea and abdominal distension with tenderness. Bronchitis and

delirium may develop. If untreated, by the end of the second week the patient may be profoundly ill. Paratyphoid fever The course tends to be shorter and milder than that of typhoid fever and the onset is often more abrupt with acute enteritis. The rash may be more abundant and the intestinal complications less frequent. Complications These are given in Box 11.43. Haemorrhage from, or a perforation of, the ulcerated Peyer's patches may occur at the end of the second week or during the third week of the illness. A drop in temperature to normal or subnormal levels may be falsely reassuring in patients with intestinal haemorrhage. Additional complications may involve almost any viscus or system because of the bacteraemia present during the first week. Bone and joint infection is common in children with sickle-cell disease. Investigations In the first week, diagnosis may be difficult because, in this invasive stage with bacteraemia, the symptoms are those of a generalised infection without localising features. Typically, there is a leucopenia. Blood culture establishes the diagnosis and multiple cultures increase the yield. Stool cultures are often positive in the second and third weeks. The Widal test detects antibodies to the O and H antigens but is not specific. Management Antibiotic therapy must be guided by in vitro sensitivity testing. Chloramphenicol (500 mg 4 times daily), ampicillin (750 mg 4 times daily) and co-trimoxazole (2 tablets or IV equivalent twice daily) are losing their effect due to resistance in many areas of the world, especially India and South-east Asia. Fluoroquinolones are the drugs of choice (e.g. ciprofloxacin 500 mg twice daily), if nalidixic acid screening predicts susceptibility, but resistance is common, especially in the Indian subcontinent and also in the UK. Extended-spectrum cephalosporins (ceftriaxone and cefotaxime) are useful alternatives but have a slightly increased In pregnancy, in addition to systemic symptoms of fever and myalgia, listeriosis causes chorioamnionitis, fetal deaths, abortions and neonatal infection. In other susceptible individuals, it causes systemic illness due to bacteraemia without focal symptoms. Meningitis, similar to other bacterial meningitis but with normal CSF glucose, is the next most common presentation; CSF usually shows increased neutrophils but occasionally only the mononuclear cells are increased (see Box 25.6, p. 1078). Investigations and management Diagnosis is made by blood and CSF culture. The organism grows readily in culture media. The most effective regimen consists of a combination of intravenous amoxicillin or ampicillin plus an aminoglycoside. A sulfamethoxazole/trimethoprim combination can be used in those with penicillin allergy. Cephalosporins are of no use in this infection, as the organism is inherently resistant, an important consideration when treating meningitis empirically. Proper treatment of foods before eating is the key to preventing listeriosis. Pregnant women are advised to avoid high-risk products, including soft cheeses. Typhoid and paratyphoid (enteric) fevers Typhoid and paratyphoid fevers, which are transmitted by the faecal–oral route, are important causes of fever in the Indian subcontinent, sub-Saharan Africa and Latin America. Elsewhere, they are relatively rare. Enteric fevers are caused by infection with Salmonella Typhi and Salmonella Paratyphi A and B. After a few days of bacteraemia, the bacilli localise, mainly in the lymphoid tissue of the small intestine, resulting in typical lesions in the Peyer's patches and follicles. These swell at first, then ulcerate and usually heal. After clinical recovery, about 5% of patients become chronic carriers (i.e. continue to excrete the bacteria after 1 year); the bacilli may live in the gallbladder for months or years and pass intermittently in the stool and, less commonly, in the urine. Clinical features Typhoid fever Clinical features are outlined in Box 11.42. The incubation period is typically about 10–14 days but can be longer, and the onset may be insidious. The temperature rises in a stepladder fashion for 4 or 5 days with malaise, increasing headache, drowsiness and aching in the limbs. Constipation may be caused by swelling of lymphoid tissue around the ileocaecal junction, although in 11.42 Clinical features of typhoid fever First week • Fever • Headache • Myalgia • Relative bradycardia • Constipation • Diarrhoea

and vomiting in children End of first week • Rose spots on trunk • Splenomegaly • Cough • Abdominal distension • Diarrhoea End of second week • Delirium, complications, then coma and death (if untreated) 11.43 Complications of typhoid fever Bowel • Perforation • Haemorrhage Septic foci • Bone and joint infection • Meningitis • Cholecystitis Toxic phenomena • Myocarditis • Nephritis Chronic carriage • Persistent gallbladder carriage

Clinical features Pneumonia is the most common feature but localised skin nodules and abscesses, or sepsis, especially in diabetics, may occur. Diarrhoea and hepatosplenomegaly may be observed. The chest X-ray can resemble cavitatory tuberculosis. In chronic forms, multiple abscesses occur in subcutaneous tissue, liver, spleen and bone, accompanied by profound weight loss. Investigations and management Culture of blood, sputum or pus on selective media, e.g. Ashdown agar, may yield B. pseudomallei. Latex agglutination has been developed as a rapid diagnostic test in Thailand and PCR-based tests are also available. Indirect haemagglutination testing can be helpful in travellers; however, most people in endemic areas are seropositive. In the acute illness, prompt initiation of empirical therapy is lifesaving. Ceftazidime 100 mg/kg (2 g 3 times daily) or meropenem (0.5–1 g 3 times daily) is given for 2–3 weeks, followed by maintenance therapy of co-trimoxazole (sulfamethoxazole 1600 mg plus trimethoprim 320 mg twice daily) or doxycycline 200 mg daily for 3–6 months. Abscesses should be drained surgically. Actinomycete infections Nocardiosis Nocardiosis is an uncommon infection caused by aerobic Actinomycetes of the genus Nocardia, which are found in the soil. Infection occurs most frequently by direct traumatic inoculation or occasionally via inhalation or ingestion. Nocardiosis can result in localised cutaneous ulcers or nodules, most often in the lower limbs. Chronic destructive infection in tropical countries can result in actinomycetoma, involving soft tissues with occasional penetration to the bone. Actinomycetoma may also be caused by other aerobic Actinomycetes, and a similar clinical syndrome, eumycetoma, is caused by filamentous fungi. Both conditions are discussed on page 301. Systemic Nocardia infection, most commonly in immunocompromised individuals, results in suppurative disease with lung and brain abscesses. On microscopy, Nocardia spp. appear as long, filamentous, branching Gram-positive rods, which are also weakly acidfast. They are easily grown in culture but require prolonged incubation. Treatment of systemic infection is guided by sensitivity testing and typically requires combinations of imipenem with ceftriaxone, amikacin or co-trimoxazole, often for 6–12 months or longer. Meropenem, tigecycline, linezolid and minocycline may also be used with severe disease or with allergy, or when intolerance prevents use of the preferred agents. Abscesses are drained surgically when this is feasible. Localised cutaneous infection is usually treated with a single agent for 1–3 months. Treatment of actinomycetoma is discussed on page 301. Actinomyces spp. Actinomyces are anaerobic Actinomycetes, which are predominantly commensals of the oral cavity. They are capable of causing deep, suppurating infection in the head and neck (cervicofacial actinomycosis) and the lungs (thoracic actinomycosis). They also cause suppurating disease in the pelvis, associated with intrauterine contraceptive devices (IUCDs). Modern diagnostic techniques demonstrate that actinomycosis treatment failure rate. Azithromycin (500 mg once daily) is an alternative when fluoroquinolone resistance is present but has not been validated in severe disease. Treatment should be continued for 14 days. Pyrexia may persist for up to 5 days after the start of specific therapy. Even with effective chemotherapy, there is still a danger of complications, recrudescence of the disease and the development of a carrier state. Chronic carriers were formerly treated for 4 weeks with ciprofloxacin but may require

an alternative agent and duration, as guided by antimicrobial sensitivity testing. Cholecystectomy may be necessary. Prevention Improved sanitation and living conditions reduce the incidence of typhoid. Travellers to countries where enteric infections are endemic should be inoculated with one of the three available typhoid vaccines (two inactivated injectable and one oral live attenuated). Tularaemia Tularaemia is primarily a zoonotic disease of the northern hemisphere. It is caused by a highly infectious Gram-negative bacillus, Francisella tularensis. F. tularensis is passed transovarially (ensuring transmission from parent to progeny) in ticks, which allows persistence in nature without the absolute requirement for an infected animal reservoir. It is a potential weapon for bioterrorism. Wild rabbits, rodents and domestic dogs or cats are potential reservoirs, and ticks, mosquitoes or other biting flies are the vectors. Infection is introduced either through an arthropod or animal bite or via contact with infected animals, soil or water through skin abrasions. The most common 'ulceroglandular' variety of the disease (70–80%) is characterised by skin ulceration with regional lymphadenopathy. There is also a purely 'glandular' form. Alternatively, inhalation of the infected aerosols may result in pulmonary tularaemia, presenting as pneumonia. Rarely, the portal of entry of infection may be the conjunctiva, leading to a nodular, ulcerated conjunctivitis with regional lymphadenopathy (an 'oculoglandular' form). Typhoidal tularaemia is a rare and serious form of tularaemia with vomiting, diarrhoea and hepatosplenomegaly, which may be complicated by pneumonia and meningitis. Investigations and management Demonstration of a single high titre (≥ 1 : 160) or a fourfold rise in 2–3 weeks in the tularaemia tube agglutination test confirms the diagnosis. Bacterial yield from the lesions is extremely poor. DNA detection methods to enable rapid diagnosis are in development. Treatment consists of a 10–21-day course of parenteral aminoglycosides, streptomycin (7.5–10 mg/kg twice daily) or gentamicin (1.7 mg/kg 3 times daily), with doxycycline or ciprofloxacin offered as alternatives. Melioidosis Melioidosis is caused by Burkholderia pseudomallei, a saprophyte found in soil and water (rice paddy fields). Infection is by inoculation or inhalation, leading to bacteraemia, which is followed by the formation of abscesses in the lungs, liver and spleen. Patients with diabetes, renal stones, thalassaemia or severe burns are particularly susceptible. The disease is most common in Southeast Asia and northern Australia, and carries a significant mortality. Disease may present years or decades after the initial exposure.

 Campylobacter jejuni infection This infection is essentially a zoonosis, although contaminated water may be implicated, as the organism can survive for many weeks in fresh water. The most common sources of the infection are chicken, beef and contaminated milk products. Pet puppies have also been sources. Campylobacter infection is now the most common cause of bacterial gastroenteritis in the UK, accounting for some 100 000 cases per annum, most of which are sporadic. The incubation period is 2–5 days. Colicky abdominal pain may be severe and mimic acute appendicitis or other surgical pathology. Nausea, vomiting and significant diarrhoea, frequently containing blood, are common features. The majority of Campylobacter infections affect fit young adults and are self-limiting after 5–7 days. About 10–20% will have prolonged symptomatology, occasionally meriting treatment with a macrolide, most often azithromycin, as many organisms are resistant to ciprofloxacin. Approximately 1% of cases will develop bacteraemia and possible distant foci of infection. Campylobacter spp. have been linked to Guillain–Barré syndrome and post-infectious reactive arthritis (pp. 1140 and 1031). Salmonella spp. infection Salmonella enterica serovars other than Salmonella Typhi and Paratyphi (p. 260), of which there are more than 2000, can cause gastroenteritis. They are widely distributed throughout the animal kingdom. Two serovars are most important worldwide: Salmonella Enteritidis phage type 4 and Salmonella Typhimurium dt.104. The is caused by many different Actinomyces species, the most

common of which is Actinomyces israelii. Treatment of established disease requires prolonged (about 6–12 months) of penicillin or doxycycline. Early disease may respond to shorter antibiotic courses. Gastrointestinal bacterial infections The approach to patients presenting with acute gastroenteritis is described on page 227. Staphylococcal food poisoning Staph. aureus is transmitted via the hands of food handlers to foodstuffs such as dairy products, including cheese, and cooked meats. Inappropriate storage of these foods allows growth of the organism and production of one or more heat-stable enterotoxins that cause the symptoms. Nausea and profuse vomiting develop within 1–6 hours. Diarrhoea may not be marked. The toxins that cause the syndrome act as 'super-antigens' and induce a significant neutrophil leucocytosis that may be clinically misleading. Most cases settle rapidly but severe dehydration can occasionally be life-threatening. Antiemetics and appropriate fluid replacement are the mainstays of treatment. Suspect food should be cultured for staphylococci and demonstration of toxin production. The public health authorities should be notified if food vending is involved. Bacillus cereus food poisoning Ingestion of the pre-formed heat-stable exotoxins of B. cereus causes rapid onset of vomiting and some diarrhoea within hours of food consumption, which resolves within 24 hours. Fried rice and freshly made sauces are frequent sources; the organism grows and produces enterotoxin during storage (Fig. 11.25). If viable bacteria are ingested and toxin formation takes place within the gut lumen, then the incubation period is longer (12–24 hours) and watery diarrhoea and cramps are the predominant symptoms. The disease is self-limiting but can be quite severe. Rapid and judicious fluid replacement and appropriate notification of the public health authorities are all that is required. Clostridium perfringens food poisoning Spores of C. perfringens are widespread in the guts of large animals and in soil. If contaminated meat products are incompletely cooked and stored in anaerobic conditions, C. perfringens spores germinate and viable organisms multiply. Subsequent reheating of the food causes release of enterotoxin. Symptoms (diarrhoea and cramps) occur some 6–12 hours following ingestion. The illness is usually self-limiting. Clostridial enterotoxins are potent and most people who ingest them will be symptomatic. 'Point source' outbreaks, in which a number of cases all become symptomatic following ingestion, classically occur after school or canteen lunches where meat stews are served. Clostridial necrotising enteritis (CNE) or pigbel is an often-fatal type of food poisoning caused by a β-toxin of C. perfringens, type C. The toxin is normally inactivated by certain proteases or by normal cooking. Pigbel is more likely in protein malnutrition or in the presence of trypsin inhibitors, either in foods such as sweet potatoes or during infection with Ascaris sp. roundworms. Fig. 11.25 Bacillus cereus food poisoning. Spores contaminate uncooked cereals, e.g. rice 2° contamination Parboiled (insufficient to kill spores) Storage at warm temperature allows germination Rapid deep-fry kills bacteria not toxins Ingestion of toxin Ingestion of spores or viable bacteria Acute vomiting ± diarrhoea 2 – 4 hours after ingestion Enterocolitis12 – 24 hours after ingestion Bacteria multiply in gut and elute toxin Inadequate reheating Viable bacteria remain

Entero-aggregative E. coli Entero-aggregative E. coli (EAEC) strains adhere to the mucosa but also produce a locally active enterotoxin and demonstrate a particular 'stacked brick' aggregation to tissue culture cells when viewed by microscopy. They have been associated with prolonged diarrhoea in children in South America, South-east Asia and India. Enterohaemorrhagic E. coli A number of distinct 'O' serotypes of E. coli possess both the genes necessary for adherence (see 'EPEC' above) and plasmids encoding two distinct enterotoxins (verotoxins), which are identical to

the toxins produced by Shigella (‘shiga toxins 1 and 2’). E. coli O157:H7 is perhaps the best known of these verotoxin-producing E. coli (VTEC) but others, including types O126 and O11, are also implicated. In 2011, an outbreak of food-borne illness linked to fenugreek seeds occurred in Germany and was due to E. coli O104:H4, an EAEC strain that had acquired genes encoding shiga toxin 2a. Although the incidence of enterohaemorrhagic E. coli (EHEC) is considerably lower than that of Campylobacter and Salmonella infection, it is increasing in the developing world. The reservoir of infection is in the gut of herbivores. The organism has an extremely low infecting dose (10–100 organisms). Runoff water from pasture lands where cattle have grazed, which is used to irrigate vegetable crops, as well as contaminated milk, meat products (especially hamburgers that have been incompletely cooked), lettuce, radish shoots and apple juice have all been implicated as sources (Fig. 11.26). The incubation period is between 1 and 7 days. Initial watery diarrhoea becomes uniformly blood-stained in 70% of cases and latter may be resistant to commonly used antibiotics such as ciprofloxacin. Some strains have a clear relationship to particular animal species, e.g. Salmonella Arizonae and pet reptiles. Transmission is by contaminated water or food, particularly poultry, egg products and minced beef, direct person-to-person spread or the handling of exotic pets such as salamanders, lizards or turtles. The incidence of Salmonella enteritis is falling in the UK due to an aggressive culling policy in broiler chicken stocks, coupled with vaccination. The incubation period of Salmonella gastroenteritis is 12–72 hours and the predominant feature is diarrhoea, sometimes with passage of blood. Vomiting may be present at the outset. Approximately 5% of cases are bacteraemic and invasive nontyphoidal salmonellosis is a leading cause of bacteraemia in sub-Saharan Africa. Reactive (post-infective) arthritis occurs in approximately 2%. Antibiotics are not indicated for uncomplicated Salmonella gastroenteritis but are prescribed for bacteraemia. Salmonellae are notorious for persistent infection and can seed endothelial surfaces such as an atherosclerotic aorta. Mortality, as with other forms of gastroenteritis, is higher in the elderly (see Box 11.12, p. 228). Escherichia coli infection Many serotypes of E. coli constitute part of the human gut microbiome. Clinical disease requires either colonisation with a new or previously unrecognised strain, or the acquisition by current colonising bacteria of a particular pathogenicity factor for mucosal attachment or toxin production. Travel to unfamiliar areas of the world allows contact with different strains of endemic E. coli and the development of travellers’ diarrhoea. Enteropathogenic strains may be found in the gut of healthy individuals and, if these people move to a new environment, close contacts may develop symptoms. At least five different clinico-pathological patterns of diarrhoea are associated with specific strains of E. coli with characteristic virulence factors. Enterotoxigenic E. coli Enterotoxigenic E. coli (ETEC) is the most common cause of travellers’ diarrhoea, although there are other causes (see Box 11.20, p. 232). The organisms produce either a heat-labile or a heat-stable enterotoxin, causing marked secretory diarrhoea and vomiting after 1–2 days’ incubation. The illness is usually mild and self-limiting after 3–4 days. Antibiotics are of questionable value (p. 232). Entero-invasive E. coli Illness caused by entero-invasive E. coli (EIEC) is very similar to Shigella dysentery (p. 265) and is caused by invasion and destruction of colonic mucosal cells. No enterotoxin is produced. Acute watery diarrhoea, abdominal cramps and some scanty blood-staining of the stool are common. The symptoms are rarely severe and are usually self-limiting. Enteropathogenic E. coli Enteropathogenic E. coli (EPEC) organisms are very important in infant diarrhoea. They are able to attach to the gut mucosa, inducing a specific ‘attachment and effacement’ lesion and causing destruction of microvilli and disruption of normal absorptive capacity. The symptoms vary from mild non-bloody diarrhoea to quite severe illness, but without bacteraemia. Fig. 11.26 Verocytotoxigenic Escherichia coli (VTEC) infections. Normal reservoir 2.5%

British cattle excrete VTEC Meat products surface contamination Children camping/ playing on soiled pasture Farm contacts/ visits Water supplies (runoff) contaminated Contaminated milk Poor kitchen hygiene Poor hand hygiene Lack of washing facilities Mincing/ processing Irrigation of vegetables Inadequate pasteurisation Eaten unwashed or uncooked Disease Very low infecting dose < 100 organisms/g food

264 • INFECTIOUS DISEASE fluids and bowel rest. First-line antimicrobial therapy involves metronidazole (500 mg orally 3 times daily for 10 days) or vancomycin (125 mg orally 4 times daily for 7–10 days). Although vancomycin is more effective than metronidazole against hypervirulent C. difficile strains (e.g. ribotype 027), it is more expensive and may drive the emergence of vancomycin resistance in other organisms (e.g. enterococci, Staph. aureus). For these reasons, some authorities reserve its use for relapse (15–30% of patients), failure of initial response or severe infection. Fidaxomicin is associated with a lower relapse rate than vancomycin but is more expensive. Intravenous immunoglobulin and/or glucocorticoids are sometimes given in the most severe or refractory cases, and faecal transplantation from a healthy donor is increasingly used to manage relapses by restoring a more advantageous gut microbiome profile. Surgical intervention needs to be considered early in severe cases. Yersinia enterocolitica infection Yersinia enterocolitica, commonly found in pork, causes mild to moderate gastroenteritis and can produce significant mesenteric adenitis after an incubation period of 3–7 days. It predominantly causes disease in children but adults may also be affected. The illness resolves slowly. Complications include reactive arthritis (p. 1031; 10–13% of cases), which may be persistent, and anterior uveitis. Cholera Cholera, caused by Vibrio cholerae serotype O1, is the archetypal toxin-mediated bacterial cause of acute watery diarrhoea. The enterotoxin activates adenylate cyclase in the intestinal epithelium, inducing net secretion of chloride and water. V. cholerae O1 has two biotypes, classical and El Tor, and each of these has two distinct serotypes, Inaba and Ogawa. Following its origin in the Ganges valley, devastating epidemics have occurred, often in association with large religious festivals, and pandemics have spread worldwide. The seventh pandemic, due to the El Tor biotype, began in 1961 and spread via the Middle East to become endemic in Africa, subsequently spreading throughout South and Central America. Numbers of cases of cholera have been increasing, with outbreaks in Ghana in 2014 and Tanzania in 2015. El Tor is more resistant to commonly used antimicrobials than classical Vibrio, and causes prolonged carriage in 5% of is associated with severe abdominal pain. There is little systemic upset, vomiting or fever. Enterotoxins have both a local effect on the bowel and a distant effect on particular body tissues, such as glomerular apparatus, heart and brain. The potentially life-threatening haemolytic uraemic syndrome (HUS, p. 408) occurs in 10–15% of sufferers from this infection, arising 5–7 days after the onset of symptoms. It is most likely at the extremes of age, is heralded by a high peripheral leucocyte count, and may be induced, particularly in children, by antibiotic therapy. HUS is treated by dialysis if necessary and may be averted by plasma exchange. Antibiotics should be avoided since they can stimulate toxin release. Clostridium difficile infection C. difficile is the most commonly diagnosed cause of antibioticassociated diarrhoea (p. 230), and is an occasional constituent of the gut microbiome. C. difficile can produce two toxins (A and B). C. difficile infection (CDI) usually follows antimicrobial therapy, which alters the composition of the gastrointestinal flora and may result in colonisation with toxigenic C. difficile, if the patient is exposed to C. difficile spores. The combination of toxin production and the ability to produce environmentally stable spores accounts for the clinical features and transmissibility of CDI. A hypervirulent strain of C. difficile, ribotype 027, has emerged, which produces more toxin and more severe disease than

other C. difficile strains. Clinical features Disease manifestations range from diarrhoea to life-threatening pseudomembranous colitis. Around 80% of cases occur in people over 65 years of age, many of whom are frail with comorbid diseases. Symptoms usually begin in the first week of antibiotic therapy but can occur at any time up to 6 weeks after treatment has finished. The onset is often insidious, with lower abdominal pain and diarrhoea that may become profuse and watery. The presentation may resemble acute ulcerative colitis with bloody diarrhoea, fever and even toxic dilatation and perforation. Ileus is also seen in pseudomembranous colitis. Investigations C. difficile can be isolated from stool culture in 30% of patients with antibiotic-associated diarrhoea and over 90% of those with pseudomembranous colitis, but also from 5% of healthy adults and up to 20% of elderly patients in residential care. The diagnosis of CDI therefore rests on detection of toxins A or B in the stool. Current practice in the UK is to screen stool from patients with a compatible clinical syndrome by detection either of glutamate dehydrogenase (GDH), an enzyme produced by C. difficile, or of C. difficile nucleic acid (e.g. by PCR); if screening is positive, a C. difficile toxin ELISA or a tissue culture cytotoxicity assay is performed. The rectal appearances at sigmoidoscopy may be characteristic, with erythema, white plaques or an adherent pseudomembrane (Fig. 11.27), or may resemble ulcerative colitis. In some cases, the rectum is spared and abnormalities are observed in the proximal colon. Patients who are ill require abdominal and erect chest X-rays to exclude perforation or toxic dilatation. CT may be useful when the diagnosis is in doubt. Management The precipitating antibiotic should be stopped and the patient should be isolated. Supportive therapy includes intravenous Fig. 11.27 Clostridium difficile infection. Colonoscopic view showing numerous adherent ‘pseudomembranes’ on the mucosa.

seafood is widespread (e.g. Japan). After an incubation period of approximately 20 hours, explosive diarrhoea, abdominal cramps and vomiting occur. Systemic symptoms of headache and fever are frequent but the illness is self-limiting after 4–7 days. Rarely, a severe septic illness arises; in this case, V. parahaemolyticus can be isolated using specific halophilic culture. Bacillary dysentery (shigellosis) Shigellae are Gram-negative rods, closely related to E. coli, that invade the colonic mucosa. There are four main groups: Sh. dysenteriae, flexneri, boydii and sonnei. In the tropics, bacillary dysentery is usually caused by Sh. flexneri, while in the UK most cases are caused by Sh. sonnei. Shigellae are often resistant to multiple antibiotics, especially in tropical countries. The organism only infects humans and its spread is facilitated by its low infecting dose of around 10 organisms. Spread may occur via contaminated food or flies, but personto-person transmission by unwashed hands after defaecation is the most important factor. Outbreaks occur in psychiatric hospitals, residential schools and other closed institutions, and dysentery is a constant accompaniment of wars and natural catastrophes, which bring crowding and poor sanitation in their wake. Shigella infection may spread rapidly among men who have sex with men. Clinical features Disease severity varies from mild Sh. sonnei infections that may escape detection to more severe Sh. flexneri infections, while those due to Sh. dysenteriae may be fulminating and cause death within 48 hours. In a moderately severe illness, the patient complains of diarrhoea, colicky abdominal pain and tenesmus. Stools are small, and after a few evacuations contain blood and purulent exudate with little faecal material. Fever, dehydration and weakness occur, with tenderness over the colon. Reactive arthritis or iritis may occasionally complicate bacillary dysentery (p. 1031). Management and prevention Oral rehydration therapy or, if diarrhoea is severe, intravenous replacement of water and electrolyte loss is necessary. Antibiotic therapy is

with ciprofloxacin (500 mg twice daily for 3 days) Azithromycin and ceftriaxone are alternatives but resistance occurs to all agents, especially in Asia. The use of antidiarrhoeal medication should be avoided. The prevention of faecal contamination of food and milk and the isolation of cases may be difficult, except in limited outbreaks. Hand-washing is very important. Respiratory bacterial infections Most of these infections are described in Chapter 17. Diphtheria Infection with Corynebacterium diphtheriae occurs most commonly in the upper respiratory tract and is usually spread by droplet infection. Infection may also complicate skin lesions, especially in alcoholics. The organisms remain localised at the site of infection but release of a soluble exotoxin damages the heart muscle and the nervous system. Diphtheria has been eradicated from many parts of the world by mass vaccination using a modified exotoxin but remains infections. An atypical serotype, O139, has been responsible for localised outbreaks in Bangladesh. Infection spreads via the stools or vomit of symptomatic patients or of the much larger number of subclinical cases. Organisms survive for up to 2 weeks in fresh water and 8 weeks in salt water. Transmission is normally through infected drinking water, shellfish and food contaminated by flies, or on the hands of carriers. Clinical features Severe diarrhoea without pain or colic begins suddenly and is followed by vomiting. Following the evacuation of normal gut faecal contents, typical ‘rice water’ material is passed, consisting of clear fluid with flecks of mucus. Classical cholera produces enormous loss of fluid and electrolytes, leading to intense dehydration with muscular cramps. Shock and oliguria develop but mental clarity remains. Death from acute circulatory failure may occur rapidly unless fluid and electrolytes are replaced. Improvement is rapid with proper treatment. The majority of infections, however, cause mild illness with slight diarrhoea. Occasionally, a very intense illness, ‘cholera sicca’, occurs, with loss of fluid into dilated bowel, killing the patient before typical gastrointestinal symptoms appear. The disease is more dangerous in children. Diagnosis and management Clinical diagnosis is easy during an epidemic. Otherwise, the diagnosis should be confirmed bacteriologically. Stool darkfield microscopy shows the typical ‘shooting star’ motility of V. cholerae. Rectal swab or stool cultures allow identification. Cholera is notifiable under international health regulations. Maintenance of circulation by replacement of water and electrolytes is paramount (p. 229). Ringer-Lactate is the best fluid for intravenous replacement. Vomiting usually stops once the patient is rehydrated, and fluid should then be given orally up to 500 mL hourly. Early intervention with oral rehydration solutions that include resistant starch, based on either rice or cereal, shortens the duration of diarrhoea and improves prognosis. Severe dehydration, as indicated by altered consciousness, skin tenting, very dry tongue, decreased pulses, low blood pressure or minimal urine output, mandates intravenous replacement. Total fluid requirements may exceed 50 L over a period of 2–5 days. Accurate records are greatly facilitated by the use of a ‘cholera cot’, which has a reinforced hole under the patient’s buttocks, beneath which a graded bucket is placed. Three days’ treatment with tetracycline 250 mg 4 times daily, a single dose of doxycycline 300 mg or ciprofloxacin 1 g in adults reduces the duration of excretion of V. cholerae and the total volume of fluid needed for replacement. Prevention Strict personal hygiene is vital and drinking water should come from a clean piped supply or be boiled. Flies must be denied access to food. Oral vaccines containing killed V. cholerae with or without the B subunit of cholera toxin are used in specific settings. In epidemics, improvements in sanitation and access to clean water, public education and control of population movement are vital. Mass single-dose vaccination and treatment with tetracycline are valuable. Disinfection of discharges and soiled clothing, and scrupulous hand-washing by medical attendants reduce spread. Vibrio parahaemolyticus infection This marine organism produces a disease similar to enterotoxigenic E. coli (see above). It is very common where ingestion of raw

 should be given half an hour before the full dose in every patient. Adrenaline (epinephrine) solution must be available to deal with any immediate type of reaction (0.5–1.0 mL of 1/1000 solution IM). An antihistamine is also given. In a severely ill patient, the risk of anaphylactic shock is outweighed by the mortal danger of diphtheritic toxaemia. A dose of up to 100 000 IU of antitoxin is injected intravenously if the test dose is tolerated. For disease of moderate severity, 16 000–40 000 IU IM will suffice, and for mild cases 4000–8000 IU. Penicillin (1200 mg 4 times daily IV) or amoxicillin (500 mg 3 times daily) should be administered for 2 weeks to eliminate C. diphtheriae. Patients allergic to penicillin can be given erythromycin. Due to poor immunogenicity of primary infection, all sufferers should be immunised with diphtheria toxoid following recovery. Patients must be managed in strict isolation and attended by staff with a clearly documented immunisation history until three swabs 24 hours apart are culture-negative. Prevention Active immunisation should be given to all children. If diphtheria occurs in a closed community, contacts should be given erythromycin, which is more effective than penicillin in eradicating the organism in carriers. All contacts should also be immunised or given a booster dose of toxoid. Booster doses are required every 10 years to maintain immunity. Pneumococcal infection Strep. pneumoniae (the pneumococcus) is the leading cause of community-acquired pneumonia globally (p. 582) and one of the leading causes of infection-related mortality. Otitis media, meningitis and sinusitis are also frequently caused by Strep. pneumoniae. Occasional patients present with bacteraemia without obvious focus. Asplenic individuals are at risk of fulminant pneumococcal disease with purpuric rash. Increasing rates of penicillin resistance have been reported around the world for Strep. pneumoniae, although they remain low in the UK. Strains with cephalosporin resistance causing meningitis require treatment with a combination of cephalosporins, glycopeptides and rifampicin. Macrolide resistance is also increasing. Newer quinolones are also used (e.g. levofloxacin) but rates of resistance are rising. Vaccination of infants with the protein conjugate pneumococcal vaccine decreases Strep. pneumoniae infection in infants and in their relatives. The polysaccharide pneumococcal vaccine is used in individuals predisposed to Strep. pneumoniae infection and the elderly, but only modestly reduces pneumococcal bacteraemia and does not prevent pneumonia. All asplenic individuals should receive vaccination against Strep. pneumoniae. Anthrax Anthrax is an endemic zoonosis in many countries; it causes human disease following inoculation of the spores of Bacillus anthracis. B. anthracis was the first bacterial pathogen described by Koch and the model pathogen for ‘Koch’s postulates’ (see Box 6.1, p. 100). It is a Gram-positive organism with a central spore. The spores can survive for years in soil. Infection is commonly acquired from contact with animals, particularly herbivores. The ease of production of B. anthracis spores makes this infection a candidate for biological warfare or bioterrorism. B. anthracis produces a number of toxins that mediate the clinical features of disease. important in areas where vaccination has been incomplete, e.g. in Russia and South-east Asia. The disease is notifiable in all countries of Europe and North America, and international guidelines have been issued by the WHO for the management of infection. Clinical features The average incubation period is 2–4 days. The disease begins insidiously with a sore throat (Box 11.44). Despite modest fever, there is usually marked tachycardia. The diagnostic feature is the ‘wash-leather’ elevated, greyish-green membrane on the tonsils. It has a well-defined edge, is firm and adherent, and is surrounded by a zone of inflammation. There may be swelling of the neck (‘bull neck’) and tender enlargement of the lymph nodes. In the mildest infections, especially where there is a high degree of immunity, a membrane may not appear and inflammation is minimal. With anterior nasal infection there is nasal discharge, frequently blood-stained. In laryngeal diphtheria, a husky voice and highpitched cough signal potential respiratory obstruction requiring urgent tracheostomy. If

infection spreads to the uvula, fauces and nasopharynx, the patient is gravely ill. Death from acute circulatory failure may occur within the first 10 days. Late complications arise as a result of toxin action on the heart or nervous system. About 25% of survivors of the early toxaemia may later develop myocarditis with arrhythmias or cardiac failure. These are usually reversible, with no permanent damage other than heart block in survivors. Neurological involvement occurs in 75% of cases. After tonsillar or pharyngeal diphtheria, it usually starts after 10 days with palatal palsy. Paralysis of accommodation often follows, manifest by difficulty in reading small print. Generalised polyneuritis with weakness and paraesthesia may follow in the next 10–14 days. Recovery from such neuritis is always ultimately complete. Management A clinical diagnosis of diphtheria must be notified to the public health authorities and the patient sent urgently to a specialist infectious diseases unit. Empirical treatment should commence after collection of appropriate swabs. Diphtheria antitoxin is produced from hyperimmune horse serum. It neutralises circulating toxin but has no effect on toxin already fixed to tissues, so it must be injected intramuscularly without awaiting the result of a throat swab. However, reactions to this foreign protein include a potentially lethal immediate anaphylactic reaction (p. 75) and a ‘serum sickness’ with fever, urticaria and joint pains, which occurs 7–12 days after injection. A careful history of previous horse serum injections or allergic reactions should be taken and a small test injection of serum 11.44 Clinical features of diphtheria Acute infection • Membranous tonsillitis • or Nasal infection • or Laryngeal infection • or Skin/wound/conjunctival infection (rare) Complications • Laryngeal obstruction or paralysis • Myocarditis • Peripheral neuropathy

Leprosy Leprosy (Hansen’s disease) is a chronic granulomatous disease affecting skin and nerves and caused by Mycobacterium leprae, a slow-growing mycobacterium that cannot be cultured in vitro. The clinical manifestations are determined by the degree of the patient’s cell-mediated immunity (CMI; p. 69) towards M. leprae (Fig. 11.28). High levels of CMI with elimination of leprosy bacilli produces tuberculoid leprosy, whereas absent CMI results in lepromatous leprosy. Complications arise due to nerve damage, immunological reactions and bacillary infiltration. People with leprosy are frequently stigmatised and using the word ‘leper’ is inappropriate. Epidemiology and transmission Some 4 million people have leprosy and around 750 000 new cases are detected annually. About 70% of the world’s leprosy patients live in India, with the disease endemic in Brazil, Indonesia, Mozambique, Madagascar, Tanzania and Nepal. Untreated lepromatous patients discharge bacilli from the nose. Infection occurs through the nose, followed by haematogenous spread to skin and nerve. The incubation period is 2–5 years for tuberculoid cases and 8–12 years for lepromatous cases. Leprosy incidence peaks at 10–14 years, and is more common in males and in household contacts of leprosy cases. Pathogenesis M. leprae has tropism for Schwann cells and skin macrophages. In tuberculoid leprosy, effective CMI controls bacillary multiplication (‘paucibacillary’) and organised epithelioid granulomata form. In lepromatous leprosy, there is abundant bacillary multiplication (‘multibacillary’), e.g. in Schwann cells and perineurium. Between these two extremes is a continuum, varying from patients with Clinical features These depend on the route of entry of the anthrax spores. Cutaneous anthrax This skin lesion is associated with occupational exposure to anthrax spores during processing of hides and bone products. It accounts for the vast majority of clinical cases. Animal infection is a serious problem in Africa, India, Pakistan and the Middle East. Spores are inoculated into exposed skin. A single lesion develops as an irritable papule on an oedematous haemorrhagic base. This progresses to a depressed black

eschar. Despite extensive oedema, pain is infrequent. Gastrointestinal anthrax This is associated with the ingestion of contaminated meat. The caecum becomes infected, which produces nausea, vomiting, anorexia and fever, followed in 2–3 days by severe abdominal pain and bloody diarrhoea. Toxaemia and death can develop rapidly thereafter. Inhalational anthrax This form of the disease is extremely rare but has been associated with bioterrorism. Without rapid and aggressive therapy at the onset of symptoms, the mortality is 50–90%. Fever, dyspnoea, cough, headache and sepsis develop 3–14 days following exposure. Typically, the chest X-ray shows only widening of the mediastinum and pleural effusions, which are haemorrhagic. Meningitis may occur. Management B. anthracis can be cultured from skin swabs from lesions. Skin lesions are readily curable with early antibiotic therapy. Treatment is with ciprofloxacin (500 mg twice daily) until penicillin susceptibility is confirmed; the regimen can then be changed to benzylpenicillin with doses up to 2.4 g IV given 6 times daily or phenoxymethylpenicillin 500–1000 mg 4 times daily administered for 10 days. The addition of an aminoglycoside may improve the outlook in severe disease. In view of concerns about concomitant inhalational exposure, particularly in the era of bioterrorism, a further 2-month course of ciprofloxacin 500 mg twice daily or doxycycline 100 mg twice daily orally is added to eradicate inhaled spores. Inhalational anthrax is treated with ciprofloxacin and clindamycin for at least 14 days, followed by therapy to eradicate spores. Monoclonal antibodies against B. anthracis protective antigen can be added for systemic infection. Prophylaxis with ciprofloxacin (500 mg twice daily for 2 months) is recommended for anyone at high risk of inhalational exposure to anthrax spores and should be combined with three doses of anthrax vaccine adsorbed (AVA). Bacterial infections with neurological involvement Infections affecting the CNS, including bacterial meningitis, botulism and tetanus, are described on page 1117. Mycobacterial infections Tuberculosis Tuberculosis is predominantly, although by no means exclusively, a respiratory disease and is described on page 588. Fig. 11.28 Leprosy: mechanisms of damage and tissue affected. Mechanisms under the broken line are characteristic of disease near the lepromatous end of the spectrum, and those under the solid line are characteristic of the tuberculoid end. They overlap in the centre where, in addition, instability predisposes to type 1 lepra reactions. At the peak in the centre, neither bacillary growth nor cell-mediated immunity has the upper hand. (BL = borderline lepromatous; BT = borderline tuberculoid) Adapted from Bryceson ADM, Pfaltzgraff RE. Leprosy, 3rd edn. Churchill Livingstone, Elsevier Ltd; 1990.

High Zero Cell-mediated immunity Bacillary index Chronic exaggerated cellular hypersensitivity Nerves, skin Acute changes in cellullar hypersensitivity (type 1 lepra reactions) Nerves, skin Complications of nerve damage (anaesthesia, dryness, paralysis, contracture, misuse, tissue destruction) Face, hands, feet Lepromatous Borderline Tuberculoid LL BL BT TT Bacillary invasion Nerves, skin, muscle, bone, mucosae, eye, testis Immune complexes (type 2 lepra reactions) Nerves, skin, eye, testis, kidney

268 • INFECTIOUS DISEASE • Anaesthesia. In skin lesions, the small dermal sensory and autonomic nerve fibres are damaged, causing localised sensory loss and loss of sweating. Anaesthesia can occur in the distribution of a damaged large peripheral nerve. A ‘glove and stocking’ sensory neuropathy is also common in lepromatous leprosy. • Nerve damage. Peripheral nerve trunks are affected at ‘sites of predilection’. These are the ulnar (elbow), median (wrist), radial (humerus), radial cutaneous (wrist), common peroneal (knee), posterior tibial and sural nerves (ankle), facial nerve (zygomatic arch) and great auricular nerve (posterior triangle of the neck). Damage to peripheral nerve trunks produces characteristic signs with regional sensory loss and muscle

dysfunction (Fig. 11.29C). All these nerves should be examined for enlargement and tenderness, and tested for motor and sensory function. The CNS is not affected. • Eye involvement. Blindness is a devastating complication for a patient with anaesthetic hands and feet. Eyelid closure is impaired when the facial nerve is affected. Damage to the trigeminal nerve causes anaesthesia of the cornea and conjunctiva. The cornea is then susceptible to trauma and ulceration. • Other features. Many organs can be affected. Nasal collapse occurs secondary to bacillary destruction of the nasal cartilage and bone. Diffuse infiltration of the testes causes testicular atrophy and the acute orchitis that occurs with type 2 reactions. This results in azoospermia and hypogonadism. Leprosy reactions Leprosy reactions (Box 11.47) are events superimposed on the cardinal features shown in Box 11.45. • Type 1 (reversal) reactions. These occur in 30% of borderline patients (BT, BB or BL – see below) and are delayed hypersensitivity reactions. Skin lesions become moderate CMI (borderline tuberculoid) to patients with little cellular response (borderline lepromatous). Immunological reactions evolve as the immune response develops and the bacillary antigenic stimulus varies, particularly in borderline patients. Delayed hypersensitivity reactions produce type 1 (reversal) reactions, while immune complexes contribute to type 2 (erythema nodosum leprosum) reactions. HIV/leprosy co-infected patients have typical lepromatous and tuberculoid leprosy skin lesions and typical leprosy histology and granuloma formation. Surprisingly, even with low circulating CD4 counts, tuberculoid leprosy may be observed and there is not an obvious shift to lepromatous leprosy. Clinical features Box 11.45 gives the cardinal features of leprosy. Types of leprosy are compared in Box 11.46. • Skin. The most common skin lesions are macules or plaques. Tuberculoid patients have few, hypopigmented lesions (Fig. 11.29A). In lepromatous leprosy, papules, nodules or diffuse infiltration of the skin occur. The earliest lesions are ill defined; gradually, the skin becomes infiltrated and thickened. Facial skin thickening leads to the characteristic leonine facies (Fig. 11.29B). 11.46 Clinical characteristics of the polar forms of leprosy Clinical and tissue-specific features Lepromatous Tuberculoid Skin and nerves Number and distribution Widely disseminated One or a few sites, asymmetrical Skin lesions Definition: Clarity of margin Poor Good Elevation of margin Never Common Colour: Dark skin Slight hypopigmentation Marked hypopigmentation Light skin Slight erythema Coppery or red Surface Smooth, shiny Dry, scaly Central healing None Common Sweat and hair growth Impaired late Impaired early Loss of sensation Late Early and marked Nerve enlargement and damage Late Early and marked Bacilli (bacterial index) Many (5 or 6+) Absent (0) Natural history Progressive Self-healing Other tissues Upper respiratory mucosa, eye, testes, bones, muscle None Reactions Immune complexes (type 2) Cell-mediated (type 1) 11.45 Cardinal features of leprosy • Skin lesions, typically anaesthetic at tuberculoid end of spectrum • Thickened peripheral nerves • Acid-fast bacilli on skin smears or biopsy 11.47 Reactions in leprosy Lepra reaction type 1 (reversal) Lepra reaction type 2 (erythema nodosum leprosum) Mechanism Cell-mediated hypersensitivity Immune complexes Clinical features Painful tender nerves, loss of function Swollen skin lesions New skin lesions Tender papules and nodules; may ulcerate Painful tender nerves, loss of function Iritis, orchitis, myositis, lymphadenitis Fever, oedema Management Prednisolone 40 mg, reducing over 3–6 months1 Moderate: prednisolone 40 mg daily Severe: thalidomide2 or prednisolone 40–80 mg daily, reducing over 1–6 months; local if eye involved3 1Indicated for any new impairment of nerve or eye function. 2Contraindicated in women who may become pregnant. 31% hydrocortisone drops or ointment and 1% atropine drops.

are obtained by scraping dermal material on to a glass slide. The smears are then stained for acid-fast bacilli, the number counted per high-power field and a score derived on a logarithmic scale (0–6): the bacterial index (BI). Smears are useful for confirming the diagnosis and monitoring response to treatment. Neither serology nor PCR is sensitive or specific enough for diagnosis. Management The principles of treatment are outlined in Box 11.48. All leprosy patients require MDT with an approved first-line regimen (Box 11.49). Rifampicin is a potent bactericidal for M. leprae but should always be given in combination with other antileprotics, since a single-step mutation can confer resistance. Dapsone is bacteriostatic. It commonly causes mild haemolysis and rarely anaemia. Clofazimine is a red, fat-soluble crystalline dye, weakly bactericidal for M. leprae. Skin discoloration (red to purple–black) and ichthyosis are troublesome side-effects, particularly on pale skins. New bactericidal drugs against M. leprae have been identified, notably fluoroquinolones (pefloxacin and ofloxacin). Minocycline and clarithromycin may also be used. These agents are now established second-line drugs. Minocycline causes a grey pigmentation of skin lesions. Fig. 11.29 Clinical features of leprosy. A Tuberculoid leprosy. Single lesion with a well-defined active edge and anaesthesia within the lesion. B Lepromatous leprosy. Widespread nodules and infiltration, with loss of the eyebrows. This man also has early collapse of the nose. C Borderline tuberculoid leprosy with severe nerve damage. This boy has several well-defined, hypopigmented, macular, anaesthetic lesions. He has severe nerve damage affecting both ulnar and median nerves bilaterally and has sustained severe burns to his hands. D Reversal (type 1) reactions. Erythematous, oedematous lesions. A B C D erythematous (Fig. 11.29D). Peripheral nerves become tender and painful, with sudden loss of nerve function. These reactions may occur spontaneously, after starting treatment and also after completion of multidrug therapy (MDT). • Type 2 (erythema nodosum leprosum, ENL) reactions. These are partly due to immune complex deposition and occur in BL and LL patients who produce antibodies and have a high antigen load. They manifest with malaise, fever and crops of small pink nodules on the face and limbs. Iritis and episcleritis are common. Other signs are acute neuritis, lymphadenitis, orchitis, bone pain, dactylitis, arthritis and proteinuria. ENL may continue intermittently for several years. Borderline cases In borderline tuberculoid (BT) cases, skin lesions are more numerous than in tuberculoid (TT) cases, and there is more severe nerve damage and a risk of type 1 reactions. In borderline leprosy (BB) cases, skin lesions are numerous and vary in size, shape and distribution; annular lesions are characteristic and nerve damage is variable. In borderline lepromatous (BL) cases, there are widespread small macules in the skin and widespread nerve involvement; both type 1 and type 2 reactions occur. Pure neural leprosy (i.e. without skin lesions) occurs principally in India and accounts for 10% of patients. There is asymmetrical involvement of peripheral nerve trunks and no visible skin lesions. On nerve biopsy, all types of leprosy have been found. Investigations The diagnosis is clinical, made by finding a cardinal sign of leprosy and supported by detecting acid-fast bacilli in slit-skin smears or typical histology in a skin biopsy. Slit-skin smears 11.48 Principles of leprosy treatment • Stop the infection with chemotherapy • Treat reactions • Educate the patient about leprosy • Prevent disability • Support the patient socially and psychologically

 Rickettsial and related intracellular bacterial infections Rickettsial fevers The rickettsial fevers are the most common tick-borne infections. It is important to ask potentially infected patients about contact with ticks, lice or fleas. There are two main groups of rickettsial fevers: spotted fevers and typhus (Box 11.50). Pathogenesis The rickettsiae are intracellular Gram-negative organisms that parasitise the intestinal canal of arthropods. Infection of humans through the skin occurs from the excreta of arthropods, but the saliva of some biting

vectors is infected. The organisms multiply in capillary endothelial cells, producing lesions in the skin, CNS, heart, lungs, liver, kidneys and skeletal muscles. Endothelial proliferation, associated with a perivascular reaction, may cause thrombosis and purpura. In epidemic typhus, the brain is the target organ; in scrub typhus, the cardiovascular system and lungs in particular are attacked. An eschar, a black necrotic crusted sore, is often found in tick- and mite-borne typhus (see Fig. 11.7C, p. 235). This is due to vasculitis following immunological recognition of the inoculated organism. Regional lymph nodes often enlarge. Spotted fever group Rocky Mountain spotted fever Rickettsia rickettsii is transmitted by tick bites. It is widely distributed and increasing in western and south-eastern states of the USA and also in Central and South America. The incubation period is about 7 days. The rash appears on about the third or fourth day of illness, looking at first like measles, but in a few hours a typical maculopapular eruption develops. The rash spreads in 24–48 hours from wrists, forearms and ankles to the back, limbs and chest, and then to the abdomen, where it is least pronounced. Larger cutaneous and subcutaneous haemorrhages may appear in severe cases. The liver and spleen become palpable. At the extremes of life, the mortality is 2–12%. Other spotted fevers R. conorii (boutonneuse fever) and R. africae (African tick bite fever) cause Mediterranean and African tick typhus, which also occurs on the Indian subcontinent. The incubation period is approximately 7 days. Infected ticks may be picked up by walking on grasslands, or dogs may bring ticks into the house. Careful examination might reveal a diagnostic eschar, and the maculopapular rash on the trunk, limbs, palms and soles. There may be delirium and meningeal signs in severe infections but recovery is usual. R. africae can be associated with multiple eschars. Some cases, particularly those with R. africae, present without rash (‘spotless spotted fever’). Other spotted fevers are shown in Box 11.50. Typhus group Scrub typhus fever Scrub typhus is caused by Orientia tsutsugamushi (formerly Rickettsia tsutsugamushi), transmitted by mites. It occurs in the Far East, Myanmar, Pakistan, Bangladesh, India, Indonesia, the South Pacific islands and Queensland, particularly where patches of forest cleared for plantations have attracted rats and mites. In many patients, one eschar or more develops, surrounded by an area of cellulitis (see Fig. 11.7C, p. 235) and Although single-dose treatment is less effective than the conventional 6-month treatment for paucibacillary leprosy, it is an operationally attractive field regimen recommended by the WHO. Lepra reactions are treated as shown in Box 11.47. Chloroquine can also be used. Patient education This is essential and should patients should be informed that, after 3 days of chemotherapy, they are not infectious and can lead a normal social life. It should emphasise that gross deformities are not inevitable. Patients with anaesthetic hands or feet need to avoid and treat burns or other minor injuries. Good footwear is important. Physiotherapy helps maintain range of movement of affected muscles and neighbouring joints. Prognosis Untreated, tuberculoid leprosy has a good prognosis; it may self-heal and peripheral nerve damage is limited. Lepromatous leprosy (LL) is a progressive condition with high morbidity if untreated. After treatment, the majority of patients, especially those who have no nerve damage at the time of diagnosis, do well, with resolution of skin lesions. Borderline patients are at risk of developing type 1 reactions, which may result in devastating nerve damage. Prevention and control The previous strategy of centralised leprosy control campaigns has been superseded by integrated programmes, with primary health-care workers in many countries now responsible for case detection and provision of MDT. It is not yet clear how successful this will be, especially in the time-consuming area of disability prevention. BCG vaccination has been shown to give good but variable protection against leprosy; adding killed M. leprae to BCG does not enhance protection. 11.49 Modified WHO-recommended multidrug therapy (MDT) regimens in leprosy Type of leprosy1 Monthly supervised treatment Daily selfadministered treatment Duration of treatment2

Paucibacillary Rifampicin 600 mg Dapsone 100 mg 6 months Multibacillary Rifampicin 600 mg Clofazimine 50 mg 12 months Clofazimine 300 mg Dapsone 100 mg Paucibacillary single-lesion Ofloxacin 400 mg Rifampicin 600 mg Minocycline 100 mg Single dose 1Classification uses the bacillary index (BI) in slit-skin smears or, if BI is not available, the number of skin lesions: • paucibacillary single-lesion leprosy (1 skin lesion) • paucibacillary (2–5 skin lesions) • multibacillary (> 5 skin lesions). 2Studies from India have shown that multibacillary patients with an initial BI of

> “ 4 need longer treatment, for at least 24 months.

confused. The rash appears on the 4th–6th day. In its early stages, it disappears on pressure but soon becomes petechial with subcutaneous mottling. It appears first on the anterior folds of the axillae, sides of the abdomen or backs of hands, then on the trunk and forearms. The neck and face are seldom affected. During the second week, symptoms increase in severity. Sores develop on the lips. The tongue becomes dry, brown, shrunken and tremulous. The spleen is palpable, the pulse feeble and the patient stuporous and delirious. The temperature falls rapidly at the end of the second week and the patient recovers gradually. In fatal cases, the patient usually dies in the second week from toxaemia, cardiac or renal failure, or pneumonia. Endemic (flea-borne) typhus Flea-borne or ‘endemic’ typhus caused by R. typhi is endemic worldwide. Humans are infected when the faeces or contents of a crushed flea, which has fed on an infected rat, are introduced into the skin. The incubation period is 8–14 days. The symptoms resemble those of a mild louse-borne typhus. The rash may be scanty and transient. Investigation of rickettsial infection Routine blood investigations are not diagnostic. There is usually hepatitis and thrombocytopenia. Diagnosis is made on clinical grounds and response to treatment, and may be confirmed by antibody detection or PCR in specialised laboratories. Differential diagnoses include malaria, which should be excluded, typhoid, meningococcal sepsis and leptospirosis. Management of rickettsial fevers The different rickettsial fevers vary in severity but all respond to tetracycline 500 mg 4 times daily, doxycycline 200 mg daily enlargement of regional lymph nodes. The incubation period is about 9 days. Mild or subclinical cases are common. The onset of symptoms is usually sudden, with headache (often retro-orbital), fever, malaise, weakness and cough. In severe illness, the general symptoms increase, with apathy and prostration. An erythematous maculopapular rash often appears on about the 5th–7th day and spreads to the trunk, face and limbs, including the palms and soles, with generalised painless lymphadenopathy. The rash fades by the 14th day. The temperature rises rapidly and continues as a remittent fever (i.e. the difference between maximum and minimum temperature exceeds 1°C), remaining above normal with sweating until it falls on the 12th–18th day. In severe infection, the patient is prostrate with cough, pneumonia, delirium and deafness. Cardiac failure, renal failure and haemorrhage may develop. Convalescence is often slow and tachycardia may persist for some weeks. Epidemic (louse-borne) typhus Epidemic typhus is caused by R. prowazekii and is transmitted by infected faeces of the human body louse, usually through scratching the skin. Patients suffering from epidemic typhus infect lice, which leave when the patient is febrile. In conditions of overcrowding, the disease spreads rapidly. It is prevalent in parts of Africa, especially Ethiopia and Rwanda, and in the South American Andes and Afghanistan. Large epidemics have occurred in Europe, usually as a sequel to war. The incubation period is

usually 12–14 days. There may be a few days of malaise but the onset is more often sudden, with rigors, fever, frontal headaches, pains in the back and limbs, constipation and bronchitis. The face is flushed and cyanotic, the eyes are congested and the patient becomes 11.50 Features of rickettsial infections Disease Organism Reservoir Vector Geographical area Rash Gangrene Target organs Mortality Spotted fever group Rocky Mountain spotted fever R. rickettsii Rodents, dogs, ticks Ixodes tick North, Central and South America Morbilliform Haemorrhagic Often Bronchi, myocardium, brain, skin 2–12%2 Boutonneuse fever R. conorii Rodents, dogs, ticks Ixodes tick Mediterranean, Africa, South-west Asia, India Maculopapular – Skin, meninges 2.5%3 Siberian tick typhus R. sibirica Rodents, birds, domestic animals, ticks Various ticks Siberia, Mongolia, northern China Maculopapular – Skin, meninges Rare3 Australian tick typhus R. australis Rodents, ticks Ticks Australia Maculopapular – Skin, meninges Rare3 Oriental spotted fever R. japonica Rodents, dogs, ticks Ticks Japan Maculopapular – Skin, meninges Rare3 African tick bite fever1 R. africae Cattle, game, ticks Ixodes tick South Africa Can be spotless – Skin, meninges Rare3 Typhus group Scrub typhus Orientia tsutsugamushi Rodents Trombicula mite South-east Asia Maculopapular Unusual Bronchi, myocardium, brain, skin Rare3 Epidemic typhus R. prowazekii Humans Louse Worldwide Morbilliform Haemorrhagic Often Brain, skin, bronchi, myocardium Up to 40% Endemic typhus R. typhi Rats Flea Worldwide Slight – – Rare3 1Eschar at bite site and local lymphadenopathy. 2Highest in adult males. 3Except in infants, older people and the debilitated.

272 • INFECTIOUS DISEASE • Cat scratch disease. B. henselae causes this common benign lymphadenopathy in children and young adults. A vesicle or papule develops on the head, neck or arms after a cat scratch. The lesion resolves spontaneously but there may be regional lymphadenopathy that persists for up to 4 months before also resolving spontaneously. Rare complications include retinitis and encephalopathy. • Bacillary angiomatosis. This is an HIV-associated disease caused by B. quintana or B. henselae (p. 316). • Oroya fever and verruga peruana (Carrion’s disease). This is endemic in areas of Peru. It is a biphasic disease caused by B. bacilliformis, transmitted by sandflies of the genus Phlebotomus. Fever, haemolytic anaemia and microvascular thrombosis with end-organ ischaemia are features. It is frequently fatal if untreated. Investigations and management Bartonellae can be cultured in specialised laboratories but PCR is often used to diagnose infection. Serum antibody detection is possible but cross-reactions occur with Chlamydia and Coxiella spp. Bartonella spp. are typically treated with macrolides or tetracyclines. Antibiotic use is guided by clinical need. Cat scratch disease usually resolves spontaneously but Bartonella endocarditis requires valve replacement and combination antibiotic therapy with doxycycline and gentamicin. Chlamydial infections These are listed in Box 11.52 and are also described on pages 340 and 582. or chloramphenicol 500 mg 4 times daily for 7 days. Louseborne typhus and scrub typhus can be treated with a single dose of 200 mg doxycycline, repeated for 2–3 days to prevent relapse. Chloramphenicol- and doxycycline-resistant strains of O. tsutsugamushi have been reported from Thailand and patients here may need treatment with rifampicin. Nursing care is important, especially in epidemic typhus. Sedation may be required for delirium and blood transfusion for haemorrhage. Relapsing fever and typhoid are common intercurrent infections in epidemic typhus, and pneumonia in scrub typhus, which require diagnosis and treatment. Convalescence is usually protracted, especially in older people. To prevent rickettsial infection, lice, fleas, ticks and mites need to be controlled with insecticides. Q fever Q fever occurs worldwide and is caused by the rickettsia-like organism Coxiella burnetii, an obligate intracellular organism that survives in the extracellular environment. Cattle, sheep and goats are important reservoirs and the organism is transmitted by inhalation of aerosolised particles. An

important characteristic of C. burnetii is its antigenic variation, called phase variation, due to a change of lipopolysaccharide (LPS). When isolated from animals or humans, C. burnetii expresses phase I antigen and is very infectious (a single bacterium is sufficient to infect a human). In culture, there is an antigenic shift to the phase II form, which is not infectious. Measurement of antigenic shift helps differentiate acute and chronic Q fever. Clinical features The incubation period is 3–4 weeks. The initial symptoms are non-specific with fever, headache and chills; in 20% of cases, a maculopapular rash occurs. Other presentations include pneumonia and hepatitis. Chronic Q fever may present with osteomyelitis, encephalitis and endocarditis. Investigations and management Diagnosis is usually serological and the stage of the infection can be distinguished by isotype tests and phase-specific antigens. Phase I and II IgM titres peak at 4–6 weeks. In chronic infections, IgG titres to phase I and II antigens may be raised. Prompt treatment of acute Q fever with doxycycline reduces fever duration. Treatment of Q fever endocarditis is problematic, requiring prolonged therapy with doxycycline and rifampicin or ciprofloxacin with hydroxychloroquine; even then, organisms are not always eradicated. Valve surgery is often required (p. 526). Bartonellosis This group of diseases is caused by intracellular Gram-negative bacilli closely related to the rickettsiae, which have been discovered to be important causes of ‘culture-negative’ endocarditis. They are found in many domestic pets, such as cats, although for several the host is undefined (Box 11.51). The principal human pathogens are Bartonella quintana, B. henselae and B. bacilliformis. Bartonella infections are associated with the following: • Trench fever. This is a relapsing fever with severe leg pain and is caused by B. quintana. The disease is not fatal but is very debilitating. • Bacteraemia and endocarditis in the homeless. Endocarditis due to B. quintana or B. henselae is associated with severe damage to the heart valves. 11.52 Chlamydial infections Organism Disease caused Chlamydia trachomatis Trachoma Lymphogranuloma venereum (see Box 13.12, p. 341) Cervicitis, urethritis, proctitis (p. 334) Chlamydia psittaci Psittacosis (see Box 17.36, p. 582) Chlamydophila (Chlamydia) pneumoniae Atypical pneumonia (see Box 17.36, p. 582) Acute/chronic sinusitis 11.51 Clinical diseases caused by Bartonella spp. Reservoir Vector Organism Disease Cats Flea B. henselae Cat scratch disease, bacillary angiomatosis, endocarditis Undefined Lice B. quintana Trench fever, bacillary angiomatosis, endocarditis Undefined Sandfly B. bacilliformis Carrion’s disease: Oroya fever and verruga peruana Undefined Flea B. rochalimae Fever, rash, anaemia, splenomegaly

Protozoal infections Protozoa are responsible for many important infectious diseases. They can be categorised according to whether they cause systemic or local infection. Trichomoniasis is described on page 335. Systemic protozoal infections Malaria Malaria in humans is caused by Plasmodium falciparum, P. vivax, P. ovale (subspecies curtisi and wallikeri), P. malariae and the predominantly simian parasite P. knowlesi. It is transmitted by the bite of female anopheline mosquitoes and occurs throughout the tropics and subtropics at altitudes below 1500 metres (Fig. 11.31). The WHO estimates that 214 million cases of clinical malaria occurred in 2015, 88% of these in Africa, especially among children and pregnant women. WHO prevention and treatment campaigns reduced the incidence of malaria between 1950 and 1960, but since 1970 there has been resurgence. Furthermore, P. falciparum has now become resistant to chloroquine and sulfadoxine-pyrimethamine, initially in South-east Asia and now throughout Africa. The WHO’s Millennium Development Goal malaria target aimed to halt the spread of the disease by 2015 and this has been achieved. The ‘Roll Back Malaria’ campaign was designed to halve mortality by 2010

by utilising the ‘best evidence’ vector and disease control methods, such as artemisinin combination therapy (ACT). Travellers are susceptible to malaria (p. 230). Most cases are due to P. falciparum, usually from Africa, and of these 1% die because of late diagnosis. Migrants from endemic countries who spend long periods of time in non-endemic countries are particularly at risk if they visit friends and family in their country of origin. They have lost their partial immunity and frequently do not take malaria prophylaxis. A few people living near airports in Europe have acquired malaria from accidentally imported mosquitoes. Pathogenesis Life cycle of the malarial parasite The female anopheline mosquito becomes infected when it feeds on human blood containing gametocytes, the sexual forms of the malarial parasite (Figs 11.32 and 11.33). Development in the mosquito takes 7–20 days, and results in sporozoites accumulating in the salivary glands and being inoculated into the human blood stream. Sporozoites disappear from human blood within half an hour and enter the liver. After some days, merozoites leave the liver and invade red blood cells, where further asexual cycles of multiplication take place, producing schizonts. Fig. 11.30 Trachoma. Trachoma is characterised by hyperaemia and numerous pale follicles. Courtesy of Institute of Ophthalmology, Moorfields Eye Hospital, London. Trachoma Trachoma is a chronic keratoconjunctivitis caused by Chlamydia trachomatis and is the most common cause of avoidable blindness. The classic trachoma environment is dry and dirty, causing children to have eye and nose discharges. Transmission occurs through flies, on fingers and within families. In endemic areas, the disease is most common in children. Pathology and clinical features The onset is usually insidious. Infection may be asymptomatic, lasts for years, may be latent over long periods and may recrudesce. The conjunctiva of the upper lid is first affected with vascularisation and cellular infiltration. Early symptoms include conjunctival irritation and blepharospasm. The early follicles are characteristic (Fig. 11.30) but clinical differentiation from conjunctivitis due to other causes may be difficult. Scarring causes inversion of the lids (entropion) so that the lashes rub against the cornea (trichiasis). The cornea becomes vascularised and opaque. The problem may not be detected until vision begins to fail. Investigations and management Intracellular inclusions may be demonstrated in conjunctival scrapings by staining with iodine or immunofluorescence. Although chlamydiae may, in theory, be isolated in chick embryo or cell culture or detected by nucleic acid amplification tests, these methods are rarely available in the areas where trachoma is encountered, and in any case their sensitivity and specificity are poorly established. Diagnosis of trachoma is therefore based on clinical and epidemiological features. A single dose of azithromycin (20 mg/kg) has been shown to be superior to 6 weeks of tetracycline eye ointment twice daily for individuals in mass treatment programmes. Deformity and scarring of the lids, and corneal opacities, ulceration and scarring require surgical treatment after control of local infection. Prevention Personal and family hygiene should be improved. Proper care of the eyes of newborn and young children is essential. Family contacts should be examined. The WHO is promoting the SAFE strategy for trachoma control (surgery, antibiotics, facial cleanliness and environmental improvement). Fig. 11.31 Distribution of malaria. (For up-to-date information see the Malaria Atlas Project (MAP): map.ox.ac.uk.)

 from multiplication of parasites in red cells that have not been eliminated by treatment and immune processes (Box 11.53). Pathology Red cells infected with malaria are prone to haemolysis. This is most severe with P. falciparum, which invades red cells of all ages but especially young cells; P. vivax and P. ovale invade reticulocytes, and P. malariae normoblasts, so that infections Fig. 11.32 Scanning electron micrograph of Plasmodium falciparum oöcysts lining an anopheline mosquito’s stomach. Fig. 11.33 Malarial parasites: life cycle.

Hypnozoites(*) are present only in Plasmodium vivax and P. ovale infections. (RBC = red blood cell) IN FEMALE ANOPHELINE MOSQUITO IN HUMANS Primary exo-erythrocytic cycle (liver) Sexual differentiation (RBCs) Bite Bite Female gametocyte being fertilised by male gamete Maturation of female gamete Exflagellating male gametocyte Zygote Stomach wall Young oöcyst Segmenting oöcyst Ruptured oöcyst Sporozoites invading salivary glands Hypnozoite∗ Trophozoite Schizont Immature gametocytes Male and female gametocytes Merozoites Ring form Merozoites Oökinete Sexual cycle Erythrocytic (asexual) cycle (RBCs) 11.53 Relationships between life cycle of parasite and clinical features of malaria Cycle/ feature Plasmodium vivax, P. ovale P. malariae P. falciparum Pre-patent period (minimum incubation) 8–25 days 15–30 days 8–25 days Exoerythrocytic cycle Persistent as hypnozoites Pre-erythrocytic only Pre-erythrocytic only Asexual cycle 48 hrs synchronous 72 hrs synchronous < 48 hrs asynchronous Fever periodicity Alternate days Every third day None Delayed onset Common Rare Rare Relapses Common up to 2 years Recrudescence many years later Recrudescence up to 1 year Rupture of the schizont releases more merozoites into the blood and causes fever, the periodicity of which depends on the species of parasite. P. vivax and P. ovale may persist in liver cells as dormant forms, hypnozoites, capable of developing into merozoites months or years later. Thus the first attack of clinical malaria may occur long after the patient has left the endemic area, and the disease may relapse after treatment with drugs that only kill the erythrocytic stage of the parasite. P. falciparum, P. knowlesi and P. malariae have no persistent exo-erythrocytic phase but recrudescence of fever may result

P. falciparum infection This is the most dangerous of the malarias. The onset is often insidious, with malaise, headache and vomiting. Cough and mild diarrhoea are also common. The fever has no particular pattern. Jaundice is common due to haemolysis and hepatic dysfunction. The liver and spleen enlarge and may become tender. Anaemia develops rapidly, as does thrombocytopenia. A patient with falciparum malaria, apparently not seriously ill, may rapidly develop dangerous complications (Fig. 11.34 and Box 11.54). Cerebral malaria is manifested by delirium, seizures or coma, usually without localising signs. Children die rapidly without any specific symptoms other than fever. Immunity is impaired in pregnancy and the parasite can preferentially bind to the placental protein chondroitin sulphate A. Abortion and intrauterine growth retardation from parasitisation of the maternal side of the placenta are frequent. Previous splenectomy increases the risk of severe malaria. P. vivax and P. ovale infection In many cases, the illness starts with several days of continued fever before the development of classical bouts of fever on alternate days. Fever starts with a rigor. The patient feels cold and the temperature rises to about 40°C. After half an hour to remain lighter. Anaemia may be profound and is worsened by dyserythropoiesis, splenomegaly and depletion of folate stores. In P. falciparum malaria, red cells containing trophozoites adhere to vascular endothelium in post-capillary venules in brain, kidney, liver, lungs and gut by the formation of ‘knob’ proteins. They also form ‘rosettes’ and rouleaux with uninfected red cells. Vessel congestion results in organ damage, which is exacerbated by rupture of schizonts, liberating toxic and antigenic substances (Fig. 11.33). P. falciparum has influenced human evolution, with the appearance of protective mutations such as sickle-cell (HbS; p. 951), thalassaemia (p. 953), glucose-6-phosphate dehydrogenase (G6PD) deficiency (p. 948) and HLA-B53. P. falciparum does not grow well in red cells that contain haemoglobin F, C or especially S. Haemoglobin S heterozygotes (AS) are protected against the lethal complications of malaria. P. vivax cannot enter red cells that lack the Duffy blood group; therefore many West Africans and

African Americans are protected. Clinical features The clinical features of malaria are non-specific and the diagnosis must be suspected in anyone returning from an endemic area who has features of infection. Fig. 11.34 Features of Plasmodium falciparum infection. (RBC = red blood cell) Insets (malaria retinopathy) Courtesy of Dr Nicholas Beare, Royal Liverpool University Hospital; (blood films of P. vivax and P. falciparum) Courtesy of Dr Kamolrat Silamut, Mahidol Oxford Research Unit, Bangkok, Thailand. Neurological Coma Hypoglycaemia Seizures Cranial nerve palsies Opisthotonus Respiratory Pulmonary oedema Secondary bacterial pneumonia Abdomen Jaundice Tender liver edge with hepatitis Pain in left upper quadrant with splenomegaly Fever Cardiovascular Shock Cardiac failure (‘algid malaria’) Dysrhythmias with quinine Renal Acute kidney injury Severe haemolysis resulting in haemoglobinuria (‘blackwater fever’) Optic fundi Blood Parasitaemia Anaemia Thrombocytopenia Coagulopathy Disconjugate gaze due to cranial nerve palsy Malaria retinopathy with Roth’s spots Ring form Ring form in RBCs Trophozoite Schizont P. vivax in RBCs Blood film showing parasitaemia P. falciparum

276 • INFECTIOUS DISEASE to quantify the parasite load (by counting the percentage of infected erythrocytes). P. falciparum parasites may be very scanty, especially in patients who have been partially treated. With P. falciparum, only ring forms are normally seen in the early stages (Fig. 11.34); with the other species, all stages of the erythrocytic cycle may be found. Gametocytes appear after about 2 weeks, persist after treatment and are harmless, except that they are the source by which more mosquitoes become infected. Immunochromatographic rapid diagnostic tests (RDTs) for malaria antigens, such as OptiMAL (which detects the Plasmodium LDH of P. falciparum and vivax) and Parasight-F (which detects the P. falciparum histidine-rich protein 2), are extremely sensitive and specific for falciparum malaria but less so for other species. They should be used in parallel with blood film examination but are especially useful where the microscopist is less experienced in examining blood films (e.g. in the UK). They are less sensitive for low-level parasitaemia and positivity may persist for a month or more in some individuals. The QBC Malaria Test is a fluorescence microscopy-based malaria diagnostic test that is also widely used. DNA detection (PCR) is used mainly in research and is useful for determining whether a patient has a recrudescence of the same malaria parasite or a reinfection with a new parasite. an hour, the hot or flush phase begins. It lasts several hours and gives way to profuse perspiration and a gradual fall in temperature. The cycle is repeated 48 hours later. Gradually, the spleen and liver enlarge and may become tender. Anaemia develops slowly. Relapses are frequent in the first 2 years after leaving the malarious area and infection may be acquired from blood transfusion. P. malariae and P. knowlesi infection This is usually associated with mild symptoms and bouts of fever every third day. Parasitaemia may persist for many years, with the occasional recrudescence of fever or without producing any symptoms. Chronic P. malariae infection causes glomerulonephritis and long-term nephrotic syndrome in children. P. knowlesi is usually mild but can deteriorate rapidly. Investigations Giemsa-stained thick and thin blood films should be examined whenever malaria is suspected. In the thick film, erythrocytes are lysed, releasing all blood stages of the parasite. This, as well as the fact that more blood is used in thick films, facilitates the diagnosis of low-level parasitaemia. A thin film is essential to confirm the diagnosis, species and, in P. falciparum infections, Coma (cerebral malaria) • Maintain airway • Nurse on side • Exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis) • Avoid harmful ancillary treatments such as glucocorticoids, heparin and adrenaline (epinephrine) • Intubate if necessary Hyperpyrexia • Tepid sponging, fanning, cooling blanket • Antipyretic drug (paracetamol) Convulsions • Maintain airway • Treat promptly with diazepam or paraldehyde injection Hypoglycaemia • Measure blood

glucose • Give 50% dextrose injection followed by 10% dextrose infusion (glucagon may be ineffective) Severe anaemia (packed cell volume < 15%) • Transfuse fresh whole blood or packed cells if pathogen screening of donor blood is available Acute pulmonary oedema • Nurse at 45°, give oxygen, venesect 250 mL of blood, give diuretic, stop intravenous fluids • Intubate and add PEEP/CPAP (p. 202) in life-threatening hypoxaemia • Haemofilter Acute kidney injury • Exclude pre-renal causes • Fluid resuscitation if appropriate • Peritoneal dialysis (haemofiltration or haemodialysis if available) Spontaneous bleeding and coagulopathy • Transfuse screened fresh whole blood (cryoprecipitate/fresh frozen plasma and platelets if available) • Vitamin K injection Metabolic acidosis • Exclude or treat hypoglycaemia, hypovolaemia and Gram-negative sepsis • Fluid resuscitation • Give oxygen Shock (‘algid malaria’) • Suspect Gram-negative sepsis • Take blood cultures • Give parenteral antimicrobials • Correct haemodynamic disturbances Aspiration pneumonia • Give parenteral antimicrobial drugs • Change position • Physiotherapy • Give oxygen Hyperparasitaemia • Consider exchange transfusion (e.g. > 10% of circulating erythrocytes parasitised in non-immune patient with severe disease) Specific therapy • Intravenous artesunate • Mefloquine should be avoided due to increased risk of post-malaria neurological syndrome From WHO. Severe falciparum malaria. In: Severe and complicated malaria, 3rd edn. Trans Roy Soc Trop Med Hyg 2000; 94 (suppl. 1):S1–41. (CPAP = continuous positive airway pressure; PEEP = positive end-expiratory pressure) 11.54 Severe manifestations/complications of falciparum malaria and their immediate management

Complicated P. falciparum malaria Severe malaria should be considered in any non-immune patient with a parasite count greater than 2% or with complications, and is a medical emergency (see Box 11.54). Management includes early and appropriate antimalarial chemotherapy, active treatment of complications, correction of fluid, electrolyte and acid–base balance, and avoidance of harmful ancillary treatments. The treatment of choice is intravenous artesunate. Late haemolysis is a treatment side-effect in some patients. Rectal administration of artesunate is also being developed to allow administration in remote rural areas. Quinine salt is the alternative. Exchange transfusion has not been tested in randomised controlled trials but may be beneficial for non-immune patients with persisting high parasitaemias (> 10% circulating erythrocytes). Non-falciparum malaria P. vivax, P. ovale, P. knowlesi and P. malariae infections should be treated with oral chloroquine but some chloroquine resistance has been reported from Indonesia. ‘Radical cure’ is achieved in patients with P. vivax or P. ovale malaria using a course of primaquine, which destroys the hypnozoite phase in the liver. Haemolysis may develop in those who are G6PD-deficient. Cyanosis due to the formation of methaemoglobin in the red cells is more common but not dangerous (see Fig. 7.1, p. 135). All are sensitive to ACTs. Prevention Clinical attacks of malaria may be preventable with chemoprophylaxis using chloroquine, atovaquone plus proguanil (Malarone), doxycycline or mefloquine. Box 11.56 gives the recommended doses for protection of the non-immune. The risk of malaria in the area to be visited and the degree of chloroquine resistance guide the recommendations for prophylaxis. Updated recommendations are summarised at fitfortravel.nhs.uk. Fansidar should not be used for chemoprophylaxis, as deaths have occurred from agranulocytosis or Stevens–Johnson syndrome (pp. 1224 and 1254). Mefloquine is useful in areas of multiple drug resistance, such as East and Central Africa and Papua New Guinea. Experience shows it to be safe for at least 2 years but there are several contraindications to its use (Box 11.56). Expert advice is required for individuals unable to tolerate the first-line agents listed

or in whom they are contraindicated. Mefloquine should be started 2–3 weeks before travel to give time for assessment of side-effects. Chloroquine should not be taken continuously as a prophylactic for more than 5 years without regular ophthalmic examination, as it may cause irreversible retinopathy. Pregnant and lactating women may take proguanil or chloroquine safely. Prevention also involves advice about the use of highpercentage diethyltoluamide (DEET), covering up extremities when out after dark, and sleeping under permethrin-impregnated mosquito nets. Malaria control in endemic areas There are major initiatives to reduce and eliminate malaria in endemic areas. Successful programmes combine vector control, including indoor residual spraying, use of long-lasting insecticide-treated bed nets (ITNs) and intermittent preventative therapy (IPT; repeated dose of prophylactic drugs in high-risk groups, such as children and pregnant women, which reduces malaria and anaemia). Research to produce a fully protective malaria vaccine is ongoing. Management Mild P. falciparum malaria Since P. falciparum is now resistant to chloroquine and sulfadoxine-pyrimethamine (Fansidar) almost worldwide, an artemisinin-based treatment is recommended (Box 11.55) and WHO policy in Africa recommends always using ACT, e.g. co-artemether or artesunate–amodiaquine. Unfortunately, artemisinin resistance has now been reported in South-east Asia. 11.55 Malaria treatment Mild malaria Preferred therapy • Co-artemether (CoArtem or Riamet); contains artemether and lumefantrine (4 tablets orally at 0, 8, 24, 36, 48 and 60 hrs) Alternative therapy • Quinine (600 mg of quinine salt 3 times daily orally for 5–7 days), together with or followed by doxycycline (200 mg once daily orally for 7 days) Use clindamycin not doxycycline if the patient is a pregnant woman or young child or • Atovaquone–proguanil (Malarone, 4 tablets orally once daily for 3 days) Pregnancy • Co-artemether but avoid in early pregnancy. • If not using co-artemether, use quinine plus clindamycin (450 mg 3 times daily orally for 7 days) Other regimens • Artesunate (200 mg orally daily for 3 days) and mefloquine (1 g orally on day 2 and 500 mg orally on day 3) Severe malaria Preferred therapy • Artesunate 2.4 mg/kg IV at 0, 12 and 24 hrs and then once daily for 7 days. Once the patient is able to recommence oral intake, switch to 2 mg/kg orally once daily, to complete a total cumulative dose of 17–18 mg/kg Alternative therapy • Quinine, loading dose 20 mg/kg IV over 4 hrs, up to a maximum of 1.4 g, then maintenance doses of 10 mg/kg quinine salt given as 4-hr infusions 3 times daily for the first 48 hrs then twice a day, up to a maximum of 700 mg per dose or until the patient can take drugs orally. Combine with doxycycline (or clindamycin if there are contraindications to doxycycline) • Note the loading dose should not be given if quinine, quinidine or mefloquine has been administered in the previous 24 hrs • Patients should be monitored by ECG while receiving quinine, with special attention to QRS duration and QT interval Non-falciparum malaria Preferred therapy • Chloroquine: 600 mg chloroquine base orally, followed by 300 mg base in 6 hrs, then 150 mg base twice daily for 2 more days plus primaquine (30 mg orally daily (for P. vivax) or 15 mg orally daily (for P. ovale) for 14 days) after confirming G6PD-negative Patients with mild to moderate G6PD deficiency and P. vivax or P. ovale • Chloroquine plus primaquine 0.75 mg/kg weekly orally for 8 weeks Chloroquine-resistant P. vivax • Co-artemether as for P. falciparum (G6PD = glucose-6-phosphate dehydrogenase)

 the patient is usually severely ill and may have developed pleural effusions and signs of myocarditis or hepatitis. There may be a petechial rash. The patient may die before there are signs of involvement of the CNS. If the illness is less acute, drowsiness, tremors and coma develop. Babesiosis Babesiosis is a tick-borne intra-erythrocytic protozoon parasite. There are more than 100 species of Babesia, all of which have an animal reservoir, typically either rodents or cattle, and are transmitted to humans via the tick vector Ixodes scapularis. Most

American cases of babesiosis are due to B. microti and most European cases to B. divergens. Patients present with fever and malaise 1–4 weeks after a tick bite. Illness may be complicated by haemolytic anaemia. Severe illness is seen in splenectomised patients. The diagnosis is made by blood-film examination. Treatment is with quinine and clindamycin. African trypanosomiasis (sleeping sickness) African sleeping sickness is caused by trypanosomes (Fig. 11.35) conveyed to humans by the bites of infected tsetse flies, and is unique to sub-Saharan Africa (Fig. 11.36). The incidence of sleeping sickness across Africa has declined by over 60% since 1990 due to better control measures. Trypanosoma brucei gambiense trypanosomiasis has a wide distribution in West and Central Africa and accounts for 90% of human African trypanosomiasis (HAT). T. brucei rhodesiense trypanosomiasis is found in parts of East and Central Africa. In West Africa, transmission is mainly at the riverside, where the fly rests in the shade of trees; no animal reservoir has been identified for T. gambiense. T. rhodesiense has a large reservoir in numerous wild animals and transmission takes place in the shade of woods bordering grasslands. Rural populations employed in agriculture, fishing and animal husbandry are susceptible. Local people and tourists visiting forests infested with tsetse flies and animal reservoirs may become infected. Clinical features A bite by a tsetse fly is painful and commonly becomes inflamed; if trypanosomes are introduced, the site may again become painful and swollen about 10 days later (‘trypanosomal chancre’), associated with regional lymphadenopathy. Within 2–3 weeks of infection, the trypanosomes invade the blood stream. The disease is characterised by an early haematolymphatic (stage 1) and a late encephalitic phase (stage 2), in which the parasite crosses the blood–brain barrier and chronic encephalopathy develops. Rhodesiense infections In these infections, the disease is more acute and severe than in gambiense infections, so that, within days or a few weeks, Fig. 11.35 Trypanosomiasis. Scanning electron micrograph showing trypanosomes swimming among erythrocytes. Fig. 11.36 Distribution of human African trypanosomiasis. Data are from 2009. From Simarro PP, Diarra A, Ruiz Postigo JA, et al. The human African trypanosomiasis control and surveillance programme of the World Health Organization 2000–2009: the way forward. PLoS Negl Trop Dis 2011; 5(2):e1007. Non-endemic None 1–100 101–500 501–1000

> “ 1000 No. of cases Antimalarial tablets Adult prophylactic dose Regimen Chloroquine resistance high Mefloquine2 250 mg weekly Started 2–3 weeks before travel and continued until 4 weeks after or Doxycycline3,4 100 mg daily Started 1 week before and continued until 4 weeks after travel or Malarone4 1 tablet daily From 1–2 days before travel until 1 week after return Chloroquine resistance absent Chloroquine5 and proguanil 300 mg base weekly 100–200 mg daily Started 1 week before and continued until 4 weeks after travel } 1Choice of regimen is determined by area to be visited, length of stay, level of malaria transmission, level of drug resistance, presence of underlying disease in the traveller and concomitant medication taken. 2Contraindicated in the first trimester of pregnancy, lactation, cardiac conduction disorders, epilepsy, psychiatric disorders; may cause neuropsychiatric disorders. 3Causes photosensitisation and sunburn if high-protection sunblock is not used. 4Avoid in pregnancy. 5British preparations of chloroquine usually contain 150 mg base, French preparations 100 mg base and American preparations 300 mg base. 11.56 Chemoprophylaxis of malaria1

American trypanosomiasis (Chagas' disease) Chagas' disease occurs widely in South and Central America. The cause is Trypanosoma cruzi, transmitted to humans from the faeces of a reduviid (triatomine) bug, in which the trypanosomes develop before infecting humans. These bugs live in wild forests in crevices, burrows and palm trees. The Triatoma infestans bug has become domesticated in the Southern Cone countries (Argentina, Brazil, Chile, Paraguay and Uruguay). It lives in the mud and wattle walls and thatched roofs of simple rural houses and emerges at night to feed and defaecate on the sleeping occupants. Infected faeces are rubbed in through the conjunctiva, mucosa of mouth or nose, or abrasions of the skin. Over 100 species of mammal – domestic, peridomestic and wild – may serve as reservoirs of infection. In some areas, blood transfusion accounts for about 5% of cases. Congenital transmission occasionally occurs. Pathology The trypanosomes migrate via the blood stream, develop into amastigote forms in the tissues and multiply intracellularly by binary fission. In the acute phase (primarily cell-mediated), inflammation of parasitised, as well as non-parasitised, cardiac muscles and capillaries occurs, resulting in acute myocarditis. In the chronic phase, focal myocardial atrophy, signs of chronic passive congestion and thromboembolic phenomena, cardiomegaly and apical cardiac aneurysm are salient findings. In the digestive form of disease, focal myositis and discontinuous lesions of the intramural myenteric plexus are seen, predominantly in the oesophagus and colon. Clinical features Acute phase Clinical manifestations of the acute phase are seen in only 1–2% of individuals infected before the age of 15 years. Young children (1–5 years) are most commonly affected. The entrance of T. cruzi through an abrasion produces a dusky-red, firm swelling and enlargement of regional lymph nodes. A conjunctival lesion, although less common, is characteristic; the unilateral firm, reddish swelling of the lids may close the eye and constitutes 'Romaña's sign'. In a few patients, an acute generalised infection soon appears, with a transient morbilliform or urticarial rash, fever, lymphadenopathy and enlargement of the spleen and liver. In a small minority of patients, acute myocarditis and heart failure or neurological features, including personality changes and signs of meningoencephalitis, may be seen. The acute infection may be fatal to infants. Chronic phase About 50–70% of infected patients become seropositive and develop an indeterminate form when no parasitaemia is detectable. They have a normal lifespan with no symptoms but are a natural reservoir for the disease and maintain the life cycle of parasites. After a latent period of several years, 10–30% of chronic cases develop low-grade myocarditis and damage to conducting fibres, which causes cardiomyopathy characterised by cardiac dilatation, arrhythmias, partial or complete heart block and sudden death. In nearly 10% of patients, damage to Auerbach's plexus results in dilatation of various parts of the alimentary canal, especially the colon and oesophagus, so-called 'mega' disease. Dilatation of the bile ducts and bronchi are also recognised sequelae. Autoimmune processes may be responsible for much of the damage. There are geographical variations of the basic pattern Gambiense infections The distinction between early and late stages may not be apparent in gambiense infections. The disease usually runs a slow course over months or years, with irregular bouts of fever and enlargement of lymph nodes. These are characteristically firm, discrete, rubbery and painless, and are particularly prominent in the posterior triangle of the neck ('Winterbottom's sign'). The spleen and liver may become palpable. After some months without treatment, the CNS is invaded. Patients develop headache, altered behaviour, blunting of higher mental functions, insomnia by night and sleepiness by day, delirium and eventually tremors, pareses, wasting, coma and death. Investigations Trypanosomiasis should be considered in any febrile patient from an endemic area. In rhodesiense infections, thick and thin malaria blood films

will reveal trypanosomes. The trypanosomes may be seen in the blood or from puncture of the primary lesion in the earliest stages of gambiense infections, but it is usually easier to demonstrate them by aspiration of a lymph node. Concentration methods include buffy coat microscopy and miniature anion exchange chromatography. Due to the cyclical nature of parasitaemia, the diagnosis is often made by demonstration of antibodies using a simple, rapid screening card agglutination trypanosomiasis test (CATT) for gambiense HAT, followed by parasitological confirmation. No reliable serological test is available for rhodesiense HAT. PCR diagnosis is available, although technical requirements limit its availability in endemic regions. If the CNS is affected, the cell count (> 20 × 109 leucocytes/L) and protein content of the CSF are increased and the glucose is diminished. A very high level of serum IgM or the presence of IgM in the CSF is suggestive of trypanosomiasis. Recognition of CNS involvement is critical, as failure to treat it might be fatal. Management Therapeutic options for African trypanosomiasis are limited and most antitrypanosomal drugs are toxic and expensive. The prognosis is good if treatment is begun early, before the brain has been invaded. At this stage, intravenous suramin, after a test dose of 100–200 mg, should be given for rhodesiense infections, followed by five injections of 20 mg/kg every 7 days. For gambiense infections, deep intramuscular or intravenous pentamidine 4 mg/kg for 7 days is given. For the treatment of stage 2 (nervous system) infection caused by gambiense HAT, patients were previously treated with melarsoprol (an arsenical). Treatment-related mortality with melarsoprol is 4–12% due to reactive encephalopathy. Now eflornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase (100 and 150 mg/kg IV 4 times daily for 14 days for adults and children, respectively), is a safer and cost-effective option. Combinations of eflornithine (400 mg daily for 7 days) with oral nifurtimox (15 mg/kg daily for 15 days) have been shown to decrease relapses, deaths and drug toxicity. Stage 2 rhodesiense infection is treated with melarsoprol 2.2 mg/kg IV for 10 days. Prevention In endemic gambiense areas, various measures are taken against tsetse flies, and field teams help detect and treat early HAT. In rhodesiense endemic areas, control is difficult.

280 • INFECTIOUS DISEASE Clinical features In most immunocompetent individuals, including children and pregnant women, the infection goes unnoticed. In approximately 10% of patients, it causes a self-limiting illness, most common in adults aged 25–35 years. The presenting feature is usually localised or generalised painless lymphadenopathy. The cervical nodes are primarily involved but mediastinal, mesenteric or retroperitoneal groups may be affected. The spleen is seldom palpable. Most patients have no systemic symptoms but some complain of malaise, fever, fatigue, muscle pain, sore throat and headache. Complete resolution usually occurs within a few months, although symptoms and lymphadenopathy tend to fluctuate unpredictably and some patients do not recover completely for a year or more. Encephalitis, myocarditis, polymyositis, pneumonitis or hepatitis occasionally occur in immunocompetent patients but are more frequent in immunocompromised hosts. Retinochoroiditis (Fig. 11.38) is usually the result of congenital infection but has also been reported in acquired disease. Congenital toxoplasmosis Acute toxoplasmosis, mostly subclinical, affects 0.3–1% of pregnant women, with an approximately 60% transmission rate to the fetus, which rises with increasing gestation. Seropositive females infected 6 months before conception have no risk of fetal transmission. Congenital disease affects approximately 40% of infected fetuses, and is more likely and more severe with infection early in gestation (see Box 11.26, p. 235). Many fetal infections are subclinical at birth but long-term sequelae include retinochoroiditis, microcephaly and hydrocephalus. of disease. Reactivation of Chagas’ disease can occur in patients with HIV if the CD4 count falls lower than 200 cells/mm3; this

can cause space-occupying lesions with a presentation similar to Toxoplasma gondii, encephalitis, encephalitis, meningoencephalitis or myocarditis. Investigations T. cruzi is easily detectable in a blood film in the acute illness. In chronic disease, it may be recovered in up to 50% of cases by xenodiagnosis, in which infection-free, laboratory-bred reduviid bugs feed on the patient; subsequently, the hindgut or faeces of the bug are examined for parasites. Parasite DNA detection by PCR in the patient's blood is a highly sensitive method for documentation of infection and, in addition, can be employed in faeces of bugs used in xenodiagnosis tests to improve sensitivity. Antibody detection is also highly sensitive. Management and prevention Parasiticidal agents are used to treat the acute phase, congenital disease and early chronic phase (within 10 years of infection). Nifurtimox is given orally. The dose, which has to be carefully supervised to minimise toxicity while preserving parasiticidal activity, is 10 mg/kg daily orally, divided into three equal doses for 90 days. The paediatric dose is 15 mg/kg daily. Cure rates of 80% in acute disease are obtained. Benznidazole is an alternative, given at a dose of 5 mg/kg daily orally, in two divided doses for 60 days; children receive 10 mg/kg daily. Both nifurtimox and benznidazole are toxic, with adverse reaction rates of 30–55%. Parasiticidal treatment of the chronic phase is usually performed but, in the cardiac or digestive 'mega' diseases, does not reverse tissue damage. Surgery may be needed. Preventative measures include improvement of housing and destruction of reduviid bugs by spraying of houses with insecticides. Blood and organ donors should be screened. Toxoplasmosis Toxoplasma gondii is an intracellular parasite. The sexual phase of the parasite's life cycle (Fig. 11.37) occurs in the small intestinal epithelium of the domestic cat. Oöcysts are shed in cat faeces and are spread to intermediate hosts (pigs, sheep and also humans) through widespread contamination of soil. Oöcysts may survive in moist conditions for weeks or months. Once they are ingested, the parasite transforms into rapidly dividing tachyzoites through cycles of asexual multiplication. Microscopic tissue cysts develop containing bradyzoites, which persist for the lifetime of the host. Cats become infected or reinfected by ingesting tissue cysts in prey such as rodents and birds. Human infection occurs via oöcyst-contaminated soil, salads and vegetables, or by ingestion of raw or under-cooked meats containing tissue cysts. Sheep, pigs and rabbits are the most common meat sources. Outbreaks of toxoplasmosis have been linked to the consumption of unfiltered water. In developed countries, toxoplasmosis is the most common protozoal infection; around 22% of adults in the UK are seropositive. Most primary infections are subclinical; however, toxoplasmosis is thought to account for about 15% of heterophile antibody-negative infectious mononucleosis (p. 241). In India or Brazil, approximately 40–60% of pregnant females are seropositive for T. gondii. In HIV-1 infection (p. 320), toxoplasmosis is an important opportunistic infection with considerable morbidity and mortality. Generalised toxoplasmosis has been described after accidental laboratory infection with highly virulent strains. Fig. 11.37 Life cycle of Toxoplasma gondii. Cat Rodents Birds Oöcysts in faeces Contaminated food, water or soil Tissue cysts Oöcysts Oöcysts Tissue cysts Humans Vertical transmission Congenital infection Transfusion Transplantation Food animals

plastidae). There are 21 leishmanial species that cause diverse clinical syndromes, which can be placed into three broad groups: • visceral leishmaniasis (VL, kala-azar) • cutaneous leishmaniasis (CL) • mucosal leishmaniasis (ML). Epidemiology and transmission Although most clinical syndromes are caused by zoonotic transmission of parasites from animals (chiefly canine and rodent reservoirs) to humans through phlebotomine sandfly vectors (Fig. 11.39A), humans are the

only known reservoir (anthroponotic person-to-person transmission) in major VL foci in the Indian subcontinent and in injection drug-users (Fig. 11.39B and C). Leishmaniasis occurs in approximately 100 countries around the world, with an estimated annual incidence of 0.9–1.3 million new cases (25% VL). The life cycle of Leishmania is shown in Figure 11.40. Flagellar promastigotes (10–20 µm) are introduced by the feeding female sandfly. The promastigotes are taken up by neutrophils, which undergo apoptosis and are then engulfed by macrophages, in which the parasites transform into amastigotes (2–4 µm; Leishman–Donovan body). These multiply, causing macrophage Investigations In contrast to immunocompromised patients, in whom the diagnosis often requires direct detection of parasites, serology is often used in immunocompetent individuals. The Sabin–Feldman dye test (indirect fluorescent antibody test), which detects IgG antibody, is most commonly used. Recent infection induces a fourfold or greater increase in titre when paired sera are tested in parallel. Peak titres of 1/1000 or more are reached within 1–2 months of the onset of infection, and serology then becomes an unreliable indicator of recent infection. The detection of significant levels of Toxoplasma-specific IgM antibody may be useful in confirming acute infection. A false-positive result or persistence of IgM antibodies for years after infection makes interpretation difficult; however, negative IgM antibodies virtually rule out acute infection. During pregnancy, it is critical to differentiate recent from past infection; the presence of high-avidity IgG antibodies excludes infection acquired in the preceding 3–4 months. If necessary, the presence of Toxoplasma organisms in a lymph node biopsy or other tissue can be detected histochemically with T. gondii antiserum, or by the use of PCR to detect Toxoplasmaspecific DNA. Management In immunocompetent subjects, uncomplicated toxoplasmosis is self-limiting and responds poorly to antimicrobial therapy. Treatment with sulfadiazine, pyrimethamine and folinic acid is usually reserved for severe or progressive disease, and for infection in immunocompromised patients. In pregnant women with established recent infection, spiramycin (3 g daily in divided doses) is given until term. Once fetal infection is established, treatment with sulfadiazine and pyrimethamine plus calcium folinate is recommended (spiramycin does not cross the placental barrier). The cost/benefit of routine Toxoplasma screening and treatment in pregnancy is being debated in many countries. There is insufficient evidence to determine the effects on mother or baby of current antiparasitic treatment for women who seroconvert in pregnancy. Leishmaniasis Leishmaniasis is caused by unicellular, flagellate, intracellular protozoa belonging to the genus Leishmania (order KinetoFig. 11.38 Retinochoroiditis due to toxoplasmosis. Fig. 11.39 Transmission of leishmaniasis. A Zoonotic transmission. B Anthroponotic transmission. C Anthroponotic transmission in the injection drug-user. (CL = cutaneous leishmaniasis; VL = visceral leishmaniasis) Zoonotic VL, CL L. infantum L. major L. mexicana complex L. (V.) brasiliensis complex Anthroponotic VL, CL L. donovani L. tropica Anthroponotic in injection drug-users HIV-VL co-infection L. infantum A B C

 may become afebrile for intervening periods ranging from weeks to months. This is followed by a relapse of fever, often of lesser intensity. Splenomegaly develops quickly in the first few weeks and becomes massive as the disease progresses. Moderate hepatomegaly occurs later. Lymphadenopathy is common in Africa, the Mediterranean and South America but is rare in the Indian subcontinent. Blackish discoloration of the skin, from which the disease derived its name, kala-azar (the Hindi word for ‘black fever’), is a feature of advanced illness but is now rarely seen. Pancytopenia is common. Moderate to severe anaemia develops rapidly and can cause cardiac failure. Thrombocytopenia, often compounded by hepatic dysfunction, may result in bleeding from the retina, gastrointestinal tract and nose. In advanced

illness, hypoalbuminaemia may manifest as pedal oedema, ascites and anasarca (gross generalised oedema and swelling). As disease progresses, there is profound immunosuppression and secondary infections are very common. These include tuberculosis, pneumonia, gastroenteritis, severe amoebic or bacillary dysentery, boils, cellulitis, chickenpox, shingles and scabies. Without adequate treatment, most patients with clinical VL die. Investigations Pancytopenia is the dominant feature, with granulocytopenia and monocytosis. Polyclonal hypergammaglobulinaemia, chiefly IgG followed by IgM, and hypoalbuminaemia are seen later. Demonstration of amastigotes (Leishman–Donovan bodies) in splenic smears is the most efficient means of diagnosis, with 98% sensitivity (Fig. 11.42); however, it carries a risk of serious haemorrhage in inexperienced hands. Safer methods, such as bone marrow or lymph node smears, are not as sensitive but lysis and infection of other cells. Sandflies pick up amastigotes when feeding on infected patients or animal reservoirs. In the sandfly, the parasite transforms into a flagellar promastigote, which multiplies by binary fission in the gut of the vector and migrates to the proboscis to infect a new host. Sandflies live in hot and humid climates in the cracks and crevices of mud or straw houses and lay eggs in organic matter. People living in such conditions are more prone to leishmaniasis. Female sandflies bite during the night and preferentially feed on animals; humans are incidental hosts. Visceral leishmaniasis (kala-azar) VL is caused by the protozoon Leishmania donovani complex (comprising L. donovani, L. infantum and L. chagasi). India, Sudan, Bangladesh and Brazil account for 90% of cases of VL. Other affected regions include the Mediterranean, East Africa, China, Arabia, Israel and other South American countries (Fig. 11.41). In addition to sandfly transmission, VL has also been reported to follow blood transfusion, and disease can present unexpectedly in immunosuppressed patients – for example, after renal transplantation and in HIV infection. The majority of people infected remain asymptomatic. In visceral disease, the spleen, liver, bone marrow and lymph nodes are primarily involved. Clinical features In the Indian subcontinent, adults and children are equally affected; elsewhere, VL is mainly a disease of small children and infants, except in adults with HIV co-infection. The incubation period ranges from weeks to months (occasionally, several years). The first sign of infection is high fever, usually accompanied by rigor and chills. Fever intensity decreases over time and patients Fig. 11.40 Life cycle of Leishmania. From Knight R. Parasitic disease in man. Churchill Livingstone, Elsevier Ltd; 1982. Sandfly (Phlebotomus in eastern hemisphere, Lutzomyia and Psychodopygus in western hemisphere) Stomach Pharynx Bite Proboscis Macrophage Promastigote Amastigote Amastigote Dermis only L. tropica L. mexicana etc. Dermis and mucosae (sometimes) L. brasiliensis Viscera and dermis (sometimes) L. donovani Fig. 11.41 World distribution of visceral leishmaniasis. L. chagasi L. infantum L. donovani Fig. 11.42 Splenic smear showing numerous intracellular, and a few extracellular, amastigotes. Courtesy of Dr S. Sundar and Dr H.W. Murray.

of 10 mg/kg of AmBisome cured 96% of Indian patients. The manufacturer of AmBisome has donated a large quantity of the drug for use in the Kala-azar Elimination Programme in India, Nepal and Bangladesh, leading to its adoption as the first-line drug in treatment. Other drugs The oral drug miltefosine, an alkyl phospholipid, has been approved in several countries for the treatment of VL. A daily dose of 50 mg (patient’s body weight < 25 kg) to 100 mg (≥ 25 kg), or 2.5 mg/kg for children, for 28 days cures over 90% of patients. Side-effects include mild to moderate vomiting and diarrhoea, and rarely skin allergy or renal or liver toxicity. Since it is a teratogenic drug, it cannot be used in pregnancy; female patients are advised not to become pregnant for the duration

of treatment and 3 months thereafter because of its half-life of nearly 1 week. Paromomycin is an aminoglycoside that has undergone trials in India and Africa, and is highly effective if given intramuscularly at 11 mg/kg of paromomycin base, daily for 3 weeks. No significant auditory or renal toxicity is seen. The drug is approved in India for VL treatment. Pentamidine isethionate was used to treat Sb-refractory patients with VL. However, declining efficacy and serious side-effects, such as type 1 diabetes mellitus, hypoglycaemia and hypotension, have led to it being abandoned. Multidrug therapy of VL is likely to be used increasingly to prevent emergence of drug resistance, and in India short-course combinations (a single dose of AmBisome 5 mg/kg with either 7 days of miltefosine or 10 days of paromomycin, or 10 days each of miltefosine and paromomycin) were as effective as standard therapy. In India, in treatment centres where the cold chain (a temperature-controlled supply chain) is not maintained, 10 days of paromomycin combined with miltefosine is an alternative treatment regimen. Response to treatment A good response results in fever resolution, improved well-being, reduction in splenomegaly, weight gain and recovery of blood counts. Patients should be followed regularly for 6–12 months, as some may experience relapse irrespective of the treatment regimen. HIV–visceral leishmaniasis co-infection HIV-induced immunosuppression (Ch. 12) increases the risk of contracting VL 100–1000 times. Most cases of HIV–VL co-infection have been reported from Spain, France, Italy and Portugal. Antiretroviral therapy (ART) has led to a remarkable decline in the incidence of VL co-infection in Europe. However, numbers are increasing in Africa (mainly Ethiopia), Brazil and the Indian subcontinent. Although the clinical triad of fever, splenomegaly and hepatomegaly is found in the majority of co-infected patients, those with low CD4 count may have atypical clinical presentations. VL may present with gastrointestinal involvement (stomach, duodenum or colon), ascites, pleural or pericardial effusion, or involvement of lungs, tonsil, oral mucosa or skin. Diagnostic principles remain the same as those in non-HIV patients. Parasites are numerous and easily demonstrable, even in buffy coat preparations. Sometimes amastigotes are found in unusual sites, such as bronchoalveolar lavage fluid, pleural fluid or biopsies of the gastrointestinal tract. Serological tests have low sensitivity. DNA detection by PCR of the blood or its buffy coat is at least 95% sensitive and accurately tracks recovery and relapse. are frequently employed. Parasites may be demonstrated in buffy coat smears, especially in immunosuppressed patients. Sensitivity is improved by culturing the aspirate material or by using PCR for DNA detection and species identification, but these tests can only be performed in specialised laboratories. Serodiagnosis, by ELISA or immunofluorescence antibody test, is employed in developed countries. In endemic regions, a highly sensitive direct agglutination test using stained promastigotes and an equally efficient rapid immunochromatographic k39 strip test have become popular. These tests remain positive for several months after cure has been achieved, so do not predict response to treatment or relapse. The vast majority of people exposed to the parasite do not develop clinical illness but may have positive serological tests thereafter. Formal gel (aldehyde) or other similar tests based on the detection of raised globulin have limited value and should not be employed for the diagnosis of VL. Differential diagnosis This includes malaria, typhoid, tuberculosis, schistosomiasis and many other infectious and neoplastic conditions, some of which may coexist with VL. Fever, splenomegaly, pancytopenia and non-response to antimalarial therapy may provide clues before specific laboratory diagnosis is made. Management Pentavalent antimonials Antimony (Sb) compounds were the first drugs to be used for the treatment of leishmaniasis and remain the mainstay of treatment in most parts of the world. The exception is the Indian subcontinent, especially Bihar state, where almost two-thirds of cases are refractory to Sb treatment. Traditionally, pentavalent antimony is available as sodium stibogluconate (100 mg/mL) in English-

speaking countries and meglumine antimoniate (85 mg/mL) in French-speaking ones. The daily dose is 20 mg/ kg body weight, intravenously or intramuscularly, for 28–30 days. Side-effects are common and include arthralgia, myalgia, raised hepatic transaminases, pancreatitis (especially in patients co-infected with HIV) and ECG changes (T-wave inversion and reduced amplitude). Severe cardiotoxicity, manifest by concave ST segment elevation, prolongation of QTc greater than 0.5 msec and ventricular dysrhythmias, is not uncommon. The incidence of cardiotoxicity and death is particularly high with improperly manufactured Sb. Amphotericin B Amphotericin B deoxycholate, given once daily or on alternate days at a dose of 0.75–1.00 mg/kg for 15–20 doses, is used as the first-line drug in many regions where there is a significant level of Sb unresponsiveness. It has a cure rate of nearly 100%. Infusion-related side-effects, such as high fever with rigor, thrombophlebitis, diarrhoea and vomiting, are extremely common. Serious side-effects, including renal or hepatic toxicity, hypokalaemia and thrombocytopenia, are observed frequently. Lipid formulations of amphotericin B (p. 126) are less toxic. AmBisome is first-line therapy in Europe for VL. Dosing recommendations vary according to geographical region. In the Indian subcontinent, a total dose of 10 or 15 mg/kg, administered in a single dose or as multiple doses over several days, respectively, is considered adequate, whereas in Africa 14–18 mg/kg, and in South America and Europe 21–24 mg/kg, in divided doses, typically spread over 10 days, is recommended for immunocompetent patients. High daily doses of the lipid formulations are well tolerated, and in one study a single dose

 Treatment of PKDL is difficult. In India, Sb for 120 days, several courses of amphotericin B infusions, or miltefosine for 12 weeks is required. In Sudan, Sb for 2 months is considered adequate. In the absence of a physical handicap, most patients are reluctant to complete the treatment. PKDL patients are a human reservoir, and focal outbreaks have been linked to patients with PKDL in areas previously free of VL. Prevention and control Sandfly control through insecticide spray is very important. Mosquito nets or curtains treated with insecticides will keep out the tiny sandflies. In endemic areas with zoonotic transmission, infected or stray dogs should be destroyed. In areas with anthroponotic transmission, early diagnosis and treatment of human infections, to reduce the reservoir and control epidemics of VL, is extremely important. Serology is useful in diagnosis of suspected cases in the field. No vaccine is currently available. Cutaneous and mucosal leishmaniasis Cutaneous leishmaniasis CL (oriental sore) occurs in both the Old World (Asia, Africa and Europe) and the New World (the Americas). Transmission is described on page 281. In the Old World, CL is mild. It is found around the Mediterranean basin, throughout the Middle East and Central Asia as far as Pakistan, and in sub-Saharan West Africa and Sudan (Fig. 11.44). The causative organisms for Old World zoonotic CL are L. major, L. tropica and L. aethiopica (Box 11.57). Anthroponotic CL is caused by L. tropica, and is confined to urban or suburban areas of the Old World. Afghanistan is currently the biggest focus but infection is endemic in Pakistan, the western deserts of India, Iran, Iraq, Syria and other areas of the Middle East. In recent years, there has been an increase in the incidence of zoonotic CL in both the Old and the New Worlds due to urbanisation and deforestation, which led to peridomestic transmission (in and around human dwellings). Treatment of VL with HIV co-infection is essentially the same as in immunocompetent patients but there are some differences in outcome. Conventional amphotericin B (0.7 mg/kg/day for 28 days) may be more effective in achieving initial cure than Sb (20 mg/kg/day for 28 days). Using high-dose liposomal amphotericin B (4 mg/kg on days 1–5, 10, 17, 24, 31 and 38), a high cure rate is possible. However, co-infected patients have a tendency to relapse within 1 year and maintenance chemotherapy with monthly liposomal amphotericin B is

useful. Post-kala-azar dermal leishmaniasis After treatment and apparent recovery from VL in India and Sudan, some patients develop dermatological manifestations due to local parasitic infection. Clinical features In India, dermatological changes occur in a small minority of patients 6 months to at least 3 years after the initial infection. They are seen as macules, papules, nodules (most frequently) and plaques, which have a predilection for the face, especially the area around the chin. The face often appears erythematous (Fig. 11.43A). Hypopigmented macules can occur over all parts of the body and are highly variable in extent. There are no systemic symptoms and little spontaneous healing occurs. In Sudan, approximately 50% of patients with VL develop post-kala-azar dermal leishmaniasis (PKDL), experiencing skin manifestations concurrently with VL or within the following 6 months. In addition to the dermatological features, a measles-like micropapular rash (Fig. 11.43B) may be seen all over the body. In Sudan, children are more frequently affected than in India. Spontaneous healing occurs in about three-quarters of cases within 1 year. Investigations and management The diagnosis is clinical, supported by demonstration of scanty parasites in lesions by slit-skin smear and culture. Immunofluorescence and immunohistochemistry may demonstrate the parasite in skin tissues. In the majority of patients, serological tests (direct agglutination test or k39 strip tests) are positive. Fig. 11.43 Post-kala-azar dermal leishmaniasis. A In India, with macules, papules, nodules and plaques. B In Sudan, with micronodular rash. A, From Sundar S, Kumar K, Chakravarty J, et al. Cure of antimony-unresponsive Indian post-kala-azar dermal leishmaniasis with oral miltefosine. Trans R Soc Trop Med Hyg 2006; 100(7):698–700. B, Courtesy of Dr E.E. Zijlstra. A B

the vector bite. The small, red papules may be single or multiple and increase gradually in size, reaching 2–10 cm in diameter. A crust forms, overlying an ulcer with a granular base and with raised borders (Fig. 11.45). These ulcers develop a few weeks or months after the bite. There can be satellite lesions, especially in L. major and occasionally in L. tropica infections. Regional lymphadenopathy, pain, pruritus and secondary bacterial infections may occur. Lesions of L. mexicana and L. peruviana closely resemble those seen in the Old World, but lesions on the pinna of the ear are common and are chronic and destructive. L. mexicana is responsible for chiclero ulcers, the self-healing sores of Mexico. If immunity is effective, there is usually spontaneous healing in L. tropica, L. major and L. mexicana lesions. In some patients with anergy to Leishmania, the skin lesions of L. aethiopica, L. mexicana and L. amazonensis infections progress to the development of diffuse CL; this is characterised by spread of the infection from the initial ulcer, usually on the face, to involve the whole body in the form of non-ulcerative nodules. Occasionally, in L. tropica infections, sores that have apparently healed relapse persistently (recidivans or lupoid leishmaniasis). Mucosal leishmaniasis The Viannia subgenus extends widely from the Amazon basin as far as Paraguay and Costa Rica, and is responsible for deep sores and ML. In L. (V.) brasiliensis complex infections, cutaneous lesions may be followed by mucosal spread of the disease simultaneously or even years later. Young men with chronic lesions are particularly at risk, and 2–40% of infected persons develop ‘espundia’, metastatic lesions in the mucosa of the nose or mouth. This is characterised by thickening and erythema of the nasal mucosa, typically starting at the junction of the nose and upper lip. Later, ulceration develops. The lips, soft palate, fauces and larynx may also be invaded and destroyed, leading to considerable suffering and deformity. There is no spontaneous healing, and death may result from severe respiratory tract infections due to massive destruction of the pharynx. Investigations in CL and ML CL is often diagnosed on the basis

of the lesions' clinical characteristics. Parasitological confirmation is important, however, because clinical manifestations may be mimicked by other infections. Amastigotes can be demonstrated on a slit-skin smear with Giemsa staining; alternatively, they can be cultured from the sores early during the infection. Parasites seem to be particularly New World CL is a more significant disease, which may disfigure the nose, ears and mouth, and is caused by the L. mexicana complex (comprising L. mexicana, L. amazonensis and L. venezuelensis) and by the Viannia subgenus L. (V.) brasiliensis complex (comprising L. (V.) guyanensis, L. (V.) panamensis, L. (V.) brasiliensis and L. (V.) peruviana). CL is commonly imported and should be considered in the differential diagnosis of an ulcerating skin lesion, especially in travellers who have visited endemic areas of the Old World or forests in Central and South America. Pathogenesis Inoculated parasites are taken up by dermal macrophages, in which they multiply and form a focus for lymphocytes, epithelioid cells and plasma cells. Self-healing may occur with necrosis of infected macrophages, or the lesion may become chronic with ulceration of the overlying epidermis, depending on the aetiological pathogen. Clinical features The incubation period is typically 2–3 months (range 2 weeks to 5 years). In all types of CL a papule develops at the site of Fig. 11.44 World distribution of cutaneous leishmaniasis. L. mexicana L. brasiliensis L. infantum L. tropica L. major L. aethiopica 11.57 Types of Old World cutaneous leishmaniasis Leishmania spp. Host Clinical features L. tropica Dogs Slow evolution, less severe L. major Gerbils, desert rodents Rapid necrosis, wet sores L. aethiopica Hyraxes Solitary facial lesions with satellites Fig. 11.45 Cutaneous leishmaniasis. A Papule. B Ulcer. B, Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield. A B

286 • INFECTIOUS DISEASE effective in New World CL caused by L. guyanensis. In ML, 8 injections of pentamidine (4 mg/kg on alternate days) cure the majority of patients. Ketoconazole (600 mg daily for 4 weeks) has shown some potential against L. mexicana infection. In Saudi Arabia, fluconazole (200 mg daily for 6 weeks) reduced healing times and cured 79% of patients with CL caused by L. major. In India, itraconazole (200 mg daily for 6 weeks) produced good results in CL. Prevention of CL and ML Personal protection against sandfly bites is important. No effective vaccine is yet available. Gastrointestinal protozoal infections Amoebiasis Amoebiasis is caused by Entamoeba histolytica, which is spread between humans by its cysts. It is one of the leading parasitic causes of morbidity and mortality in the tropics and is occasionally acquired in non-tropical countries. Two nonpathogenic Entamoeba species (E. dispar and E. moshkovskii) are morphologically identical to E. histolytica, and are distinguishable only by molecular techniques, isoenzyme studies or monoclonal antibody typing. However, only E. histolytica causes amoebic dysentery or liver abscess. The life cycle of the amoeba is shown in Figure 11.46A. Pathology Cysts of E. histolytica are ingested in water or uncooked foods contaminated by human faeces. Infection may also be acquired through anal/oral sexual practices. In the colon, trophozoite forms emerge from the cysts. The parasite invades the mucous membrane of the large bowel, producing lesions that are maximal difficult to isolate from sores caused by L. brasiliensis, responsible for the vast majority of cases in Brazil. Touch preparations from biopsies and histopathology usually have a low sensitivity. Culture of fine needle aspiration material has been reported to be the most sensitive method. ML is more difficult to diagnose parasitologically. The leishmanin skin test measures delayed-type hypersensitivity to killed Leishmania organisms. A positive test is defined as induration of more than 5 mm, 48 hours after intradermal injection. The test is positive, except in diffuse CL and during active VL. PCR is used increasingly for diagnosis and speciation, which is useful in selecting therapy. Management of CL and ML Small lesions may self-heal or are treated by freezing with liquid nitrogen or curettage. There is no ideal antimicrobial therapy. Treatment should

be individualised on the basis of the causative organism, severity of the lesions, availability of drugs, tolerance of the patient for toxicity, and local resistance patterns. In CL, topical application of paromomycin 15% plus methylbenzethonium chloride 12% is beneficial. Intralesional antimony (Sb 0.2–0.8 mL/lesion) up to 2 g seems to be rapidly effective in suitable cases; it is well tolerated and economic, and is safe in patients with cardiac, liver or renal diseases. In ML, and in CL when the lesions are multiple or in a disfiguring site, it is better to treat with parenteral Sb in a dose of 20 mg/ kg/day (usually given for 20 days for CL and 28 days for ML), or with conventional or liposomal amphotericin B (see treatment of VL above). Sb is also indicated to prevent the development of mucosal disease, if there is any chance that a lesion acquired in South America is due to an L. brasiliensis strain. Refractory CL or ML should be treated with an amphotericin B preparation. Other regimens may be effective. Two to four doses of pentamidine (2–4 mg/kg), administered on alternate days, are Fig. 11.46 Amoebiasis. A The life cycle of Entamoeba histolytica. B The chocolate-brown appearance of aspirated material from an amoebic liver abscess. A, From Knight R. Parasitic disease in man. Churchill Livingstone, Elsevier Ltd; 1982. B, Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield. B Trophozoite in faeces (do not encyst) Cyst maturation in distal colon and faeces Ingested mature cyst Encystment in colon Excystment in small bowel Lumen Colonic mucosa Ulcer Amoeboma Amoebic abscess Ingested erythrocytes Tissue trophozoite A trophozoite

Management Intestinal and early hepatic amoebiasis responds quickly to oral metronidazole (800 mg 3 times daily for 5–10 days) or other long-acting nitroimidazoles like tinidazole or ornidazole (both in doses of 2 g daily for 3 days). Nitazoxanide (500 mg twice daily for 3 days) is an alternative drug. Either diloxanide furoate or paromomycin, in doses of 500 mg orally 3 times daily for 10 days after treatment, should be given to eliminate luminal cysts. If a liver abscess is large or threatens to burst, or if the response to chemotherapy is not prompt, aspiration is required and is repeated if necessary. Rupture of an abscess into the pleural cavity, pericardial sac or peritoneal cavity necessitates immediate aspiration or surgical drainage. Small serous effusions resolve without drainage. Prevention Personal precautions against contracting amoebiasis include not eating fresh, uncooked vegetables or drinking unclean water. Giardiasis Infection with Giardia lamblia is found worldwide and is common in the tropics. It particularly affects children, tourists and immunosuppressed individuals, and is the parasite most commonly imported into the UK. In cystic form, it remains viable in water for up to 3 months and infection usually occurs by ingesting contaminated water. Its flagellar trophozoite form attaches to the duodenal and jejunal mucosa, causing inflammation. Clinical features and investigations After an incubation period of 1–3 weeks, there is diarrhoea, abdominal pain, weakness, anorexia, nausea and vomiting. On examination, there may be abdominal distension and tenderness. Chronic diarrhoea and malabsorption may occur, with bulky stools that float. Stools obtained at 2–3-day intervals should be examined for cysts. Duodenal or jejunal aspiration by endoscopy gives a higher diagnostic yield. The ‘string test’ may be used, in which one end of a piece of string is passed into the duodenum by swallowing and retrieved after an overnight fast; expressed fluid is then examined for the presence of G. lamblia trophozoites. A number of stool antigen detection tests are available. Jejunal biopsy specimens may show G. lamblia on the epithelial surface. Management Treatment is with a single dose of tinidazole 2 g, metronidazole 400 mg 3 times daily for 10 days, or nitazoxanide 500 mg orally twice daily for 3 days. Cryptosporidiosis Cryptosporidium spp. are coccidian protozoal parasites of

humans and domestic animals. Infection is acquired by the faecal–oral route through contaminated water supplies. The incubation period is approximately 7–10 days and is followed by watery diarrhoea and abdominal cramps. The illness is usually self-limiting but in immunocompromised patients, especially those with HIV, the illness can be devastating, with persistent severe diarrhoea and substantial weight loss (p. 317). Cyclosporiasis Cyclospora cayetanensis is a globally distributed coccidian protozoal parasite of humans. Infection is acquired by ingestion in the caecum but extend to the anal canal. These are flaskshaped ulcers, varying greatly in size and surrounded by healthy mucosa. A localised granuloma (amoeboma), presenting as a palpable mass in the rectum or a filling defect in the colon on radiography, is a rare complication that should be differentiated from carcinoma. Amoebic ulcers may cause severe haemorrhage but rarely perforate the bowel wall. Amoebic trophozoites can emerge from the vegetative cyst from the bowel and be carried to the liver in a portal venule. They can multiply rapidly and destroy the liver parenchyma, causing an abscess (see also p. 879). The liquid contents at first have a characteristic pinkish colour, which may later change to chocolate-brown (said to resemble anchovy sauce). Cutaneous amoebiasis, though rare, causes progressive genital, perianal or peri-abdominal surgical wound ulceration. Clinical features Intestinal amoebiasis – amoebic dysentery Most amoebic infections are asymptomatic. The incubation period of amoebiasis ranges from 2 weeks to many years, followed by a chronic course with abdominal pains and two or more unformed stools a day. Offensive diarrhoea, alternating with constipation, and blood or mucus in the stool are common. There may be abdominal pain, especially in the right lower quadrant (which may mimic acute appendicitis). A dysenteric presentation with passage of blood, simulating bacillary dysentery or ulcerative colitis, occurs particularly in older people, in the puerperium and with super-added pyogenic infection of the ulcers. Amoebic liver abscess The abscess is usually found in the right hepatic lobe. There may not be associated diarrhoea. Early symptoms may be only local discomfort and malaise; later, a swinging temperature and sweating may develop, usually without marked systemic symptoms or signs. An enlarged, tender liver, cough and pain in the right shoulder are characteristic but symptoms may remain vague and signs minimal. A large abscess may penetrate the diaphragm, rupturing into the lung, and may be coughed up through a hepatobronchial fistula. Rupture into the pleural or peritoneal cavity, or rupture of a left lobe abscess in the pericardial sac, is less common but more serious. Investigations The stool and any exudate should undergo prompt microscopic examination for motile trophozoites containing red blood cells. Movements cease rapidly as the stool preparation cools. Several stools may need to be examined in chronic amoebiasis before cysts are found. Sigmoidoscopy may reveal typical flask-shaped ulcers, which should be scraped and examined immediately for E. histolytica. In endemic areas, one-third of the population are symptomless passers of amoebic cysts. An amoebic abscess of the liver is suspected on clinical grounds; there is often a neutrophil leucocytosis and a raised right hemidiaphragm on chest X-ray. Confirmation is by ultrasonic scanning. Aspirated pus from an amoebic abscess has the characteristic chocolate-brown appearance but only rarely contains free amoebae (Fig. 11.46B). Serum antibodies are detectable by immunofluorescence in over 95% of patients with hepatic amoebiasis and intestinal amoeboma, but in only about 60% of dysenteric amoebiasis. DNA detection by PCR has been shown to be useful in diagnosis of E. histolytica infections but is not generally available.

 adult hookworm is 1 cm long and lives in the duodenum and upper jejunum. Eggs are passed in the faeces. In warm, moist, shady soil, the larvae develop into rhabditiform and then the infective filariform stages; they then penetrate human skin and are

carried to the lungs. After entering the alveoli, they ascend the bronchi, are swallowed and mature in the small intestine, reaching maturity 4–7 weeks after infection. The worms attach to the mucosa of the small intestine by their buccal capsule (Fig. 11.48) and withdraw blood. The mean daily blood loss from one A. duodenale is 0.15 mL and that from N. americanus 0.03 mL. Hookworm infection is a leading cause of anaemia in the tropics and subtropics. A. duodenale is endemic in the Far East and Mediterranean coastal regions, and is also present in Africa, while N. americanus is endemic in West, East and Central Africa, and Central and South America, as well as in the Far East. of contaminated water and recent food-borne outbreaks have been associated with raspberries and coriander (cilantro). The incubation period of approximately 2–11 days is followed by diarrhoea with abdominal cramps, which may remit and relapse. Although usually self-limiting, the illness may last as long as 6 weeks, with significant weight loss and malabsorption, and is more severe in immunocompromised individuals. Diagnosis is by detection of oöcysts on faecal microscopy or PCR of stool. Treatment may be necessary in a few cases, using co-trimoxazole 960 mg twice daily for 7 days. Infections caused by helminths Helminths (from the Greek helmins, meaning worm) include three groups of parasitic worm (Box 11.58), large multicellular organisms with complex tissues and organs. Intestinal human nematodes Adult nematodes living in the human gut can cause disease. There are two types: • the hookworms, which have a soil stage in which they develop into larvae that then penetrate the host • a group of nematodes that survive in the soil merely as eggs, which have to be ingested for their life cycle to continue. The geographical distribution of hookworms is limited by the larval requirement for warmth and humidity. Soil-transmitted nematode infections can be prevented by avoidance of faecal soil contamination (adequate sewerage disposal) or skin contact (wearing shoes), and by strict personal hygiene. Ancylostomiasis (hookworm) Ancylostomiasis is caused by Ancylostoma duodenale or Necator americanus. The complex life cycle is shown in Figure 11.47. The 11.58 Classes of helminth that parasitise humans Nematodes or roundworms • Intestinal human nematodes: Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis, Ascaris lumbricoides, Enterobius vermicularis, Trichuris trichiura • Tissue-dwelling human nematodes: Wuchereria bancrofti, Brugia malayi, Loa loa, Onchocerca volvulus, Dracunculus medinensis, Mansonella perstans, Dirofilaria immitis • Zoonotic nematodes: Trichinella spiralis Trematodes or flukes • Blood flukes: Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi, S. intercalatum • Lung flukes: Paragonimus spp. • Hepatobiliary flukes: Clonorchis sinensis, Fasciola hepatica, Opisthorchis felineus • Intestinal flukes: Fasciolopsis buski Cestodes or tapeworms • Intestinal tapeworms: Taenia saginata, T. solium, Diphyllobothrium latum, Hymenolepis nana • Tissue-dwelling cysts or worms: Taenia solium, Echinococcus granulosus Fig. 11.47 Ancylostomiasis. Life cycle of Ancylostoma. Warm, moist shady soil Pharynx Bronchi Lungs Eosinophilia Duodenum Adult worm Blood loss Faecal eggs Blood stream Larvae Ova Fig. 11.48 Ancylostoma duodenale. Electron micrograph showing the ventral teeth. From Gibbons LM. SEM guide to the morphology of nematode parasites of vertebrates. Farnham Royal, Slough: Commonwealth Agricultural Bureau International; 1986.

manifestations, either urticaria or larva currens (a highly characteristic pruritic, elevated, erythematous lesion, rapidly advancing along the course of larval migration), are characteristic and occur in 66% of patients. Systemic strongyloidiasis (the Strongyloides hyperinfection syndrome), with dissemination of larvae throughout the body, occurs with immune suppression (HIV or HTLV-1 infection, immunosuppressant treatment). Patients present with severe, generalised abdominal

pain, abdominal distension and shock. Massive larval invasion of the lungs causes cough, wheeze and dyspnoea; cerebral involvement has manifestations ranging from subtle neurological signs to coma. Gram-negative sepsis frequently complicates the picture. Investigations There is eosinophilia. Serology (ELISA) is helpful but definitive diagnosis depends on finding the larvae. The faeces should be examined microscopically for motile larvae; excretion is intermittent and so repeated examinations are necessary. Larvae may be found in jejunal aspirates or detected using the string test (p. 287). Larvae may also be cultured from faeces. Management A course of two doses of ivermectin (200 µg/kg), administered on successive days, is effective. Alternatively, albendazole is given orally (15 mg/kg twice daily for 3 days). A second course may be required. For the Strongyloides hyperinfection syndrome, ivermectin is given at 200 µg/kg for 5–7 days. Ascaris lumbricoides (roundworm) This pale yellow nematode is 20–35 cm long. Humans are infected by eating food contaminated with mature ova. Ascaris larvae hatch in the duodenum, migrate through the lungs, ascend the bronchial tree, are swallowed and mature in the small intestine. This tissue migration can provoke both local and general hypersensitivity reactions, with pneumonitis, eosinophilic granulomas, wheezing and urticaria. Clinical features Intestinal ascariasis causes symptoms ranging from vague abdominal pain to malnutrition. The large size of the adult worm and its tendency to aggregate and migrate cause obstructive complications. Tropical and subtropical areas are endemic for ascariasis, and here it causes up to 35% of all intestinal obstructions, most commonly in the terminal ileum. Obstruction can be complicated further by intussusception, volvulus, haemorrhagic infarction and perforation. Other complications include blockage of the bile or pancreatic duct and obstruction of the appendix by adult worms. Ascariasis in non-endemic areas has been associated with pig husbandry and may be caused by Ascaris suum, which is indistinguishable from (and possibly the same species as) Ascaris lumbricoides. Investigations The diagnosis is made microscopically by finding ova in the faeces. Adult worms are frequently expelled rectally or orally. Occasionally, the worms are demonstrated radiographically by a barium examination. There is eosinophilia. Management A single dose of albendazole (400 mg), pyrantel pamoate (11 mg/kg; maximum 1 g), or ivermectin (150–200 µg/kg), or alternatively mebendazole (100 mg twice daily for 3 days) Clinical features An allergic dermatitis, usually on the feet (ground itch), may be experienced at the time of infection. The passage of the larvae through the lungs in a heavy infection causes a paroxysmal cough with blood-stained sputum, associated with patchy pulmonary consolidation and eosinophilia. When the worms reach the small intestine, vomiting and epigastric pain resembling peptic ulcer disease may occur. Sometimes, frequent loose stools are passed. The degree of iron and protein deficiency depends not only on the worm burden but also on patient nutrition and iron stores. Anaemia with high-output cardiac failure may result. The mental and physical development of children may be delayed in severe infection. Investigations There is eosinophilia. The characteristic ovum can be recognised in the stool. If hookworms are present in numbers sufficient to cause anaemia, faecal occult blood testing will be positive. Management A single dose of albendazole (400 mg) is the treatment of choice. Alternatively, mebendazole 100 mg twice daily for 3 days may be used. Anaemia and heart failure associated with hookworm infection respond well to oral iron, even when severe; blood transfusion is rarely required. Strongyloidiasis (threadworm) Strongyloides stercoralis is a small nematode (2 mm × 0.4 mm) that parasitises the mucosa of the upper part of the small intestine, often in large numbers, causing persistent eosinophilia. The eggs hatch in the bowel but only larvae are passed in the faeces. In moist soil, they moult and become the infective filariform larvae. After penetrating human skin, they undergo a development cycle similar to that of hookworms, except that the female worms burrow into the intestinal mucosa and submucosa. Some larvae in the intestine may

develop into filariform larvae, which may then penetrate the mucosa or the perianal skin and lead to autoinfection and persistent infection. Patients with Strongyloides infection persisting for more than 35 years have been described. Strongyloidiasis occurs in the tropics and subtropics, and is especially prevalent in the Far East. Clinical features These are shown in Box 11.59. The classic triad of symptoms consists of abdominal pain, diarrhoea and urticaria. Cutaneous 11.59 Clinical features of strongyloidiasis Penetration of skin by infective larvae • Itchy rash Presence of worms in gut • Abdominal pain, diarrhoea, steatorrhoea, weight loss Allergic phenomena • Urticarial plaques and papules, wheezing, arthralgia Autoinfection • Transient itchy, linear, urticarial weals across abdomen and buttocks (larva currens) Systemic (super-)infection • Diarrhoea, pneumonia, meningoencephalitis, death

290 • INFECTIOUS DISEASE Trichuris trichiura (whipworm) Whipworm infections are common worldwide with poor hygiene. Infection follows ingestion of earth or food contaminated with ova, which have become infective after lying for 3 weeks or more in moist soil. The adult worm is 3–5 cm long and has a coiled anterior end resembling a whip. Whipworms inhabit the caecum, lower ileum, appendix, colon and anal canal. There are usually no symptoms, but intense infections in children may cause persistent diarrhoea or rectal prolapse, and growth retardation. The diagnosis is readily made by identifying ova in faeces. Treatment is with mebendazole in doses of 100 mg twice daily or albendazole 400 mg daily for 3 days for patients with light infections, and for 5–7 days for those with heavy infections. Tissue-dwelling human nematodes Filarial worms are tissue-dwelling nematodes. The larval stages are inoculated by biting mosquitoes or flies, each specific to a particular filarial species. The larvae develop into adult worms (2–50 cm long), which, after mating, produce millions of microfilariae (170–320 μm long) that migrate in blood or skin. The life cycle is completed when the vector takes up microfilariae by biting humans. In the insect, ingested microfilariae develop into infective larvae for inoculation in humans, normally the only host. Disease is due to the host’s immune response to the worms (both adult and microfilariae), particularly dying worms, and its pattern and severity vary with the site and stage of each species (Box 11.60). The worms are long-lived: microfilariae survive 2–3 years and adult worms 10–15 years. The infections are chronic and worst in individuals constantly reinfected. Lymphatic filariasis The filarial worms Wuchereria bancrofti and Brugia malayi infect approximately 120 million people globally and cause clinical outcomes ranging from subclinical infection to hydrocele and elephantiasis. W. bancrofti is usually transmitted by night-biting culicine or anopheline mosquitoes (Fig. 11.50). The adult worms, 4–10 cm in length, live in the lymphatics, and the females produce microfilariae that circulate in large numbers in the peripheral blood, usually at night. The infection is widespread in tropical Africa, on the North African coast, in coastal areas of Asia, Indonesia and northern Australia, the South Pacific islands, the West Indies and also in North and South America. treats intestinal ascariasis. Patients should be warned that they might expel numerous whole, large worms. Obstruction due to ascariasis should be treated with nasogastric suction, piperazine and intravenous fluids. Complete intestinal obstruction and its complications require urgent surgical intervention. Prevention Community chemotherapy programmes reduce Ascaris infection. The whole community can be treated every 3 months for several years. Alternatively, schoolchildren are targeted; treating them lowers the prevalence of ascariasis in the community. Enterobius vermicularis (threadworm) This helminth is common worldwide and affects mainly children. After the ova are swallowed, development takes place in the small intestine but the adult worms are found chiefly in the colon. Clinical features The female lays ova around the anus, causing intense itching, especially at night. The ova are often carried to the mouth on the fingers and so reinfection

or human-to-human infection occurs (Fig. 11.49). In females, the genitalia may be involved. The adult worms may be seen moving on the buttocks or in the stool. Investigations Ova are detected in stool samples or by applying the adhesive surface of cellophane tape to the perianal skin in the morning. This is then examined on a glass slide under the microscope. A perianal swab, moistened with saline, also allows diagnosis. Management A single dose of mebendazole (100 mg), albendazole (400 mg), pyrantel pamoate (11 mg/kg) or piperazine (4 g) treats infection and is repeated after 2 weeks to control auto-reinfection. If infection recurs in a family, each member should be treated. All nightclothes and bed linen are laundered during treatment. Fingernails must be kept short and hands washed carefully before meals. Subsequent therapy is reserved for family members with recurrent infection. Fig. 11.49 Threadworm. Life cycle of Enterobius vermicularis. Adult worm in colon Itch Ova 11.60 Pathogenicity of filarial infections depending on site and stage of worms Worm species Adult worm Microfilariae Wuchereria bancrofti and Brugia malayi Lymphatic vessels+++ Blood− Pulmonary capillaries++ Loa loa Subcutaneous+ Blood+ Onchocerca volvulus Subcutaneous+ Skin+++ Eye+++ Mansonella perstans Retroperitoneal− Blood− Mansonella streptocerca Skin+ Skin++ (+++ severe; ++ moderate; + mild; − rarely pathogenic)

of the lymphatic system. Silicates absorbed from volcanic soil can also cause non-filarial elephantiasis. Tropical pulmonary eosinophilia is a complication, seen mainly in India, due to microfilariae trapped in the pulmonary capillaries that are destroyed by allergic inflammation. Patients present with paroxysmal cough, wheeze and fever. If untreated, this may progress to debilitating chronic interstitial lung disease. Investigations In the earliest stages of lymphangitis, the diagnosis is made on clinical grounds, supported by eosinophilia and sometimes by positive filarial serology. Filarial infections cause the highest eosinophil counts of all helminthic infections. Microfilariae can be found in the peripheral blood at night, and either are seen moving in a wet blood film or are detected by microfiltration of a sample of lysed blood. They are usually present in hydrocele fluid, which may occasionally yield an adult filaria. By the time elephantiasis develops, microfilariae become difficult to find. Calcified filariae may sometimes be demonstrable by radiography. Movement of adult worms can be seen on scrotal ultrasound. PCR-based tests for detection of W. bancrofti and B. malayi DNA from blood have been developed. Indirect fluorescence and ELISA detect antibodies in over 95% of active cases and 70% of established elephantiasis. The test becomes negative 1–2 years after cure. Serological tests cannot distinguish the different filarial infections. Highly sensitive and specific, commercially available, immunochromatographic card tests detect circulating W. bancrofti antigen using fingerprick blood samples taken at any time of the day. In tropical pulmonary eosinophilia, serology is strongly positive and IgE levels are massively elevated but circulating microfilariae are not found. The chest X-ray shows miliary changes or mottled opacities. Pulmonary function tests show a restrictive picture. Management Treatment is aimed at halting and reversing disease progression. Diethylcarbamazine (DEC, 2 mg/kg orally 3 times daily for 12 days, or 6 mg/kg as a single dose) kills microfilariae and adult worms. Most adverse effects seen with DEC treatment are due to the host response to dying microfilariae, which is directly proportional to the microfilarial load. The main symptoms are fever, headache, nausea, vomiting, arthralgia and prostration. These usually occur within 24–36 hours of the first dose of DEC. Antihistamines or glucocorticoids treat these allergic phenomena. Combining albendazole (400 mg) with ivermectin (200 µg/kg) in a single dose, with or without DEC (300 mg),

is also highly effective in clearing the parasites. Treatment of Wolbachia with doxycycline (200 mg/day) for 4–8 weeks provides additional benefit by eliminating the bacteria; this leads to interruption of parasite embryogenesis. For tropical pulmonary eosinophilia, DEC for 14 days is the treatment of choice. Chronic lymphatic pathology Experience in India and Brazil shows that active management of chronic lymphatic pathology can alleviate symptoms. Patients should be taught meticulous skin care of their lymphoedematous limbs to prevent secondary bacterial and fungal infections. Tight bandaging, massage and bed rest with elevation of the affected limb help to control the lymphoedema. Prompt diagnosis and antibiotic therapy of bacterial cellulitis prevent further lymphatic damage and worsening of existing elephantiasis. Plastic surgery may be indicated in established elephantiasis. Relief can be obtained by removal of excess tissue but recurrences are probable B. malayi usually causes less severe disease than W. bancrofti and is transmitted by Mansonia or Anopheles mosquitoes in Indonesia, Borneo, Malaysia, Vietnam, South China, South India and Sri Lanka. Pathology Several factors contribute to the pathogenesis of lymphatic filariasis. Toxins released by adult worms cause lymphangiectasia; this dilatation of the lymphatic vessels leads to lymphatic dysfunction and the chronic clinical manifestations of lymphatic filariasis, lymphoedema and hydrocele. Death of the adult worm results in acute filarial lymphangitis. The filariae are symbiotically infected with rickettsia-like bacteria (Wolbachia spp.), and lipopolysaccharide released from Wolbachia triggers inflammation. Lymphatic obstruction persists after death of the adult worm. Secondary bacterial infections cause tissue destruction. The host response to microfilariae is central to the pathogenesis of tropical pulmonary eosinophilia. Clinical features Acute filarial lymphangitis presents with fever, pain, tenderness and erythema along the course of inflamed lymphatic vessels. Inflammation of the spermatic cord, epididymis and testis is common. Episodes last a few days but may recur several times a year. Temporary oedema becomes more persistent and regional lymph nodes enlarge. Progressive enlargement, coarsening, corrugation, fissuring and bacterial infection of the skin and subcutaneous tissue develop gradually, causing irreversible ‘elephantiasis’. The scrotum may reach an enormous size. Chyluria and chylous effusions are milky and opalescent; on standing, fat globules rise to the top. Acute lymphatic manifestations of filariasis must be differentiated from thrombophlebitis and infection. Oedema and lymphatic obstructive changes must be distinguished from congestive cardiac failure, malignancy, trauma and idiopathic abnormalities Fig. 11.50 Wuchereria bancrofti and Brugia malayi. Life cycle of organisms and pathogenesis of lymphatic filariasis. Microfilariae in blood and trapped in pulmonary capillaries Infective larva Mosquito Microfilariae Adult worm in lymphatics Epididymo-orchitis and hydrocele Lymphangitis and lymphoedema

 feeding, they pick up the microfilariae, which mature into the infective larva and are transmitted to a new host in subsequent bites. Humans are the only known hosts (Fig. 11.51). Onchocerciasis is endemic in sub-Saharan Africa, Yemen and a few foci in Central and South America. It is estimated that 26 million people are infected, of whom 500 000 are visually impaired and 270 000 blind. Due to onchocerciasis, huge tracts of fertile land lie virtually untilled and individuals and communities are impoverished. Pathology After inoculation of larvae by a bite, the worms mature in 2–4 months and live for up to 17 years in subcutaneous and connective tissues. At sites of trauma, over bony prominences and around joints, fibrosis may form nodules around adult worms, which otherwise cause no direct damage. Innumerable microfilariae, discharged by the female O. volvulus, move actively in these nodules and in the adjacent tissues. The microfilariae are widely distributed in the skin and may invade the eye. Live microfilariae elicit little tissue reaction but dead ones may cause severe allergic inflammation, leading to hyaline

necrosis and loss of collagen and elastin. Death of microfilariae in the eye causes inflammation and may lead to blindness. Clinical features The infection may remain symptomless for months or years. The first symptom is usually itching, localised to one quadrant of the body and later becoming generalised and involving the eyes. Transient oedema of part or all of a limb is an early sign, followed by papular urticaria spreading gradually from the site of infection. This is difficult to see on dark skins, in which the most common signs are papules excoriated by scratching, spotty hyperpigmentation from resolving inflammation, and chronic changes of a rough, thickened or inelastic, wrinkled skin. Both infected and uninfected superficial lymph nodes enlarge and may hang down in folds of loose skin in the groin. Hydrocele, femoral hernias and scrotal elephantiasis can occur. Firm subcutaneous nodules of more than 1 cm in diameter (onchocercomas) occur in chronic infection. unless new lymphatic drainage is established. Hydroceles and chyluria can be repaired surgically. Prevention Treatment of the whole population in endemic areas with annual single-dose DEC (6 mg/kg), either alone or in combination with albendazole or ivermectin, can reduce filarial transmission. Mass treatment should be combined with mosquito control programmes. Loiasis Loiasis is caused by infection with the filaria Loa loa. The disease is endemic in forested and swampy parts of Western and Central Africa. The adult worms, 3–7 cm × 4 mm, chiefly parasitise the subcutaneous tissue of humans, releasing larval microfilariae into the peripheral blood in the daytime. The vector is Chrysops, a forest-dwelling, day-biting fly. The host response to Loa loa is usually absent or mild, so that the infection may be harmless. From time to time a shortlived, inflammatory, oedematous swelling (a Calabar swelling) is produced around an adult worm. Heavy infections, especially when treated, may cause encephalitis. Clinical features The infection is often symptomless. The incubation period is commonly over a year but may be just 3 months. The first sign is usually a Calabar swelling: an irritating, tense, localised swelling that may be painful, especially if it is near a joint. The swelling is generally on a limb; it measures a few centimetres in diameter but may be diffuse and extensive. It usually disappears after a few days but may persist for 2–3 weeks. Several swellings may appear at irregular intervals, often in adjacent sites. Sometimes, there is urticaria and pruritus elsewhere. Occasionally, a worm may be seen wriggling under the skin, especially that of an eyelid, and may cross the eye under the conjunctiva, taking many minutes to do so. Investigations Diagnosis is by demonstrating microfilariae in blood taken during the day, but they may not always be found in patients with Calabar swellings. Antifilarial antibodies are positive in 95% of patients and there is massive eosinophilia. Occasionally, a calcified worm may be seen on X-ray. Management DEC (see above) is curative, in a dose of 9–12 mg/kg daily, continued for 21 days. Treatment may precipitate a severe reaction in patients with a heavy microfilaraemia, characterised by fever, joint and muscle pain, and encephalitis; microfilaraemic patients should be given glucocorticoid cover. Prevention Building houses away from trees and having dwellings wirescreened reduce infections. Protective clothing and insect repellents are also useful. DEC in a dose of 5 mg/kg daily for 3 days each month is partially protective. Onchocerciasis (river blindness) Onchocerciasis results from infection by the filarial Onchocerca volvulus. The infection is conveyed by flies of the genus Simulium, which breed in rapidly flowing, well-aerated water. Adult flies inflict painful bites during the day, both inside and outside houses. While Fig. 11.51 Onchocerca volvulus. Life cycle of organism and pathogenesis of onchocerciasis. Adult worm in subcutaneous nodule Microfilariae in dermis: dermatitis Microfilariae in eyes: 'river blindness' Infective larva Simulium fly Microfilariae

be broken. Antibiotics for secondary infection and prophylaxis of tetanus are also required. A global eradication campaign aims to provide clean drinking water and eradicate water fleas from drinking water by simple filtration of water through a plastic mesh filter and chemical treatment of water supplies. Other filariases Mansonella perstans This filarial worm is transmitted by the midges Culicoides austeni and C. grahami. It is common throughout equatorial Africa, as far south as Zambia, and also in Trinidad and parts of northern and eastern South America. M. perstans has never been proven to cause disease but it may be responsible for a persistent eosinophilia and occasional allergic manifestations. M. perstans is resistant to ivermectin and DEC, and the infection may persist for many years. Dirofilaria immitis This dog heartworm infects humans, causing skin and lung lesions. It is not uncommon in the USA, Japan and Australia. Zoonotic nematodes Trichinosis (trichinellosis) Trichinella spiralis is a nematode that parasitises rats and pigs, and is transmitted to humans by ingestion of partially cooked infected pork, particularly sausage or ham, or occasionally by bear meat. Symptoms result from invasion of intestinal submucosa by ingested larvae, which develop into adult worms, and the secondary invasion of striated muscle by fresh larvae produced by these adult worms. Outbreaks have occurred in countries where pork is eaten. Clinical features The clinical features of trichinosis are determined by the larval numbers. A light infection with a few worms may be asymptomatic; a heavy infection causes nausea and diarrhoea 24–48 hours after the infected meal. A few days later, the symptoms associated with larval invasion predominate: there is fever and oedema of the face, eyelids and conjunctivae; invasion of the diaphragm may cause pain, cough and dyspnoea; and involvement of the muscles of the limbs, chest and mouth causes stiffness, pain and tenderness in affected muscles. Larval migration may cause acute myocarditis and encephalitis. Eosinophilia is observed after the second week. An intense infection may prove fatal but those who survive recover completely. Investigations Frequently, people who have eaten infected pork from a common source develop symptoms at about the same time. Biopsy from the deltoid or gastrocnemius muscle after the third week of symptoms may reveal encysted larvae. Serological tests are also helpful. Management Treatment is with albendazole (400 mg twice daily for 8–14 days) or mebendazole (200–400 mg three times daily for 3 days, followed by 400–500 mg three times daily for 10 days). Treatment commenced early in infection kills newly formed adult worms in the submucosa and reduces the number of larvae reaching the Eye disease is most common in highly endemic areas and is associated with chronic heavy infections and nodules on the head. Early manifestations include itching, lacrimation and conjunctival injection. These cause conjunctivitis; sclerosing keratitis with pannus formation; uveitis, which may lead to glaucoma and cataract; and, less commonly, choroiditis and optic neuritis. Classically, ‘snowflake’ deposits are seen in the edges of the cornea. Investigations The finding of nodules or characteristic lesions of the skin or eyes in a patient from an endemic area, associated with eosinophilia, is suggestive. Skin snips or shavings, taken with a corneoscleral punch or scalpel blade from calf, buttock and shoulder, are placed in saline under a cover slip on a microscope slide and examined after 4 hours. Microfilariae are seen wriggling free in all but the lightest infections. Slit-lamp examination may reveal microfilariae moving in the anterior chamber of the eye or trapped in the cornea. A nodule may be removed and incised, showing the coiled, thread-like adult worm. Filarial antibodies are positive in up to 95% of patients. Rapid strip tests to detect antibody or antigen are under clinical evaluation. When there is a strong suspicion of onchocerciasis but tests are negative, a provocative Mazzotti test, in which administration of 0.5–1.0 mg/kg of DEC exacerbates pruritus or dermatitis, strongly suggests onchocerciasis. Management Ivermectin is recommended, in a single dose of 100–200 μg/kg, repeated several times at 3-monthly intervals to prevent relapses. It kills microfilariae and has minimal toxicity. In

the rare event of a severe reaction causing oedema or postural hypotension, prednisolone 20–30 mg may be given daily for 2 or 3 days. Ivermectin has little macrofilaricidal effect so that, 1 year after ivermectin treatment, skin microfilarial densities regain at least 20% of pre-treatment levels; repeated treatments are required for the lifespan of the adult worm. Eradication of Wolbachia with doxycycline (100 mg daily for 6 weeks) prevents worm reproduction. Prevention Mass treatment with ivermectin reduces community morbidity and slows the progression of eye disease but it does not clear worm infection. Simulium can be destroyed in its larval stage by the application of insecticide to streams. Long trousers, skirts and sleeves discourage the fly from biting. Dracunculiasis (Guinea worm) Infestation with the Guinea worm Dracunculus medinensis manifests when the female worm, over a metre long, emerges from the skin. Humans are infected by ingesting a small crustacean, Cyclops, which inhabits wells and ponds, and contains the infective larval stage of the worm. The worm was widely distributed across Africa and the Middle East but successful global eradication programmes have limited the infection to a few countries in sub-Saharan Africa. However, recent findings of dog dracunculiasis in Chad and Ethiopia pose a new threat to eradication efforts. Management and prevention Traditionally, the protruding worm is extracted by winding it out gently over several days on a matchstick. The worm must never

294 • INFECTIOUS DISEASE Gnathostomiasis Gnathostomiasis is a nematode infection that occurs predominantly in South-east Asia and is due to Gnathostoma spinigerum. It also occurs in other parts of Asia, Central and South America, and Africa. Humans are infected by the larvae from intermediate hosts (raw or under-cooked freshwater fish, shrimps and frogs) and are not definitive hosts, so the life cycle is incomplete. Pruritic, painful, migratory nodules appear 3–4 weeks after ingestion due to larval migration. Complications include cough, visual disturbance, eosinophilic meningitis or encephalitis. Serology confirms diagnosis and the preferred treatment is albendazole (400 mg twice daily) for 21 days, but its role in visual or neurological disease is uncertain as it may increase larval migration. Trematodes (flukes) These leaf-shaped worms are parasitic to humans and animals. Their complex life cycles may involve one or more intermediate hosts, often freshwater molluscs. Schistosomiasis Schistosomiasis is a major cause of morbidity in the tropics. The species commonly causing disease in humans are: Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi and S. intercalatum. S. haematobium is sometimes called bilharzia or bilharziasis. Schistosome eggs have been found in Egyptian mummies. The life cycle is shown in Figure 11.53A. The ovum is passed in the urine or faeces of infected individuals and gains access to fresh water, where the ciliated miracidium inside it is liberated; it enters its intermediate host, a species of freshwater snail, and multiplies. Large numbers of fork-tailed cercariae are then liberated into the water, where they may survive for 2–3 days. Cercariae can penetrate the skin or the mucous membrane of the mouth of humans. They transform into schistosomulae and moult as they pass through the lungs; then they are carried by the blood stream to the liver, and so to the portal vein, where they mature. The male worm is up to 20 mm in length and the more slender cylindrical female, usually enfolded longitudinally by the male, is longer (Fig. 11.53B). Within 4–6 weeks of infection, they migrate to the venules draining the pelvic viscera, where the females deposit ova. Pathology Disease is usually due to passage of eggs through mucosa and to the granulomatous reaction to eggs deposited in tissues. The eggs of S. haematobium pass mainly through the bladder wall but may also involve the rectum, seminal vesicles, vagina, cervix and uterine tubes. S. mansoni and S. japonicum eggs pass mainly through the wall of the lower bowel or are carried to the liver. The most serious, although rare, site of ectopic egg deposition is the CNS. Granulomas are composed of macrophages, eosinophils, and epithelioid and giant cells

around an ovum. Later, there is fibrosis and eggs calcify, which is often visible radiologically. Eggs of S. haematobium may leave the vesical plexus and be carried directly to the lung. Those of S. mansoni and S. japonicum may also reach the lungs after the development of portal hypertension and consequent portasystemic collateral circulation. Egg deposition in the pulmonary vasculature, and the resultant host response, can lead to pulmonary hypertension. muscles. Glucocorticoids are necessary to control the serious effects of acute inflammation. Anisakiasis (herring worm) This infection is caused by the larvae of a fish nematode (Anisakis simplex or Pseudoterranova decipiens) and is associated with consumption of under-cooked fish or squid. The parasite cannot complete its life cycle in humans but larval ingestion is associated with pharyngeal tingling, abdominal pain, diarrhoea and vomiting. Diagnosis is made by identification of the larva by patients or endoscopists, and albendazole (400 mg twice a day for 5 days) can be used in treatment if larvae are not removed. Cutaneous larva migrans Cutaneous larva migrans (CLM) is the most common linear lesion seen in travellers (Fig. 11.52). Intensely pruritic, linear, serpiginous lesions result from the larval migration of the dog hookworm (Ancylostoma caninum). The track moves across the skin at a rate of 2–3 cm/day. This contrasts with the fast-moving transient rash of Strongyloides (p. 289). Although the larvae of dog hookworms frequently infect humans, they do not usually develop into the adult form. The most common site for CLM is the foot but elbows, breasts and buttocks may be affected. Most patients with CLM have recently visited a beach where the affected part was exposed. The diagnosis is clinical. Treatment may be local with 12-hourly application of 15% thiabendazole cream, or systemic with a single dose of albendazole (400 mg) or ivermectin (150–200 µg/kg). Angiostrongylus cantonensis The rat lungworm infects humans in Asia and the Pacific basin, via infected snails or contaminated water. It causes eosinophilic meningitis. The role of combination therapy with glucocorticoids and albendazole remains controversial. Fig. 11.52 Cutaneous larva migrans. Courtesy of Dr Ravi Gowda, Royal Hallamshire Hospital, Sheffield.

association of S. haematobium infection with squamous cell carcinoma of the bladder. Disease of the seminal vesicles may lead to haematospermia. Females may develop schistosomal papillomas of the vulva, and schistosomal lesions of the cervix may be mistaken for cancer. Intestinal symptoms may follow Clinical features Recent travellers, especially those overlanding through Africa, may present with allergic manifestations and eosinophilia; residents of schistosomiasis-endemic areas are more likely to present with chronic urinary tract pathology or portal hypertension. During the early stages of infection, there may be itching lasting 1–2 days at the site of cercarial penetration (‘swimmer’s itch’). After a symptom-free period of 3–5 weeks, acute schistosomiasis (Katayama syndrome) may present with allergic manifestations, such as urticaria, fever, muscle aches, abdominal pain, headaches, cough and sweating. On examination, hepatomegaly, splenomegaly, lymphadenopathy and pneumonia may be present. These allergic phenomena may be severe in infections with S. mansoni and S. japonicum, but are rare with S. haematobium. The features subside after 1–2 weeks. Chronic schistosomiasis is due to egg deposition and occurs months to years after infection. The symptoms and signs depend on the intensity of infection and the species of infecting schistosome (Box 11.61). Schistosoma haematobium Humans are the only natural hosts of S. haematobium, which is highly endemic in Egypt and East Africa, and occurs throughout Africa and the Middle East (Fig. 11.54). Infection can be acquired after a brief exposure, such as swimming in freshwater lakes in Africa. Painless terminal haematuria is usually the first and most common symptom. Frequency of micturition

follows, due to bladder neck obstruction. Later, frequent urinary tract infections, bladder or ureteric stones, hydronephrosis, and ultimately renal failure with a contracted calcified bladder may occur. Pain is often felt in the iliac fossa or in the loin, and radiates to the groin. In several endemic areas, there is a strong epidemiological Fig. 11.53 Schistosoma. A Life cycle. B Scanning electron micrograph of adult schistosome worms, showing the larger male worm embracing the thinner female.

Lungs Portal vein Blood stream Adult worm in vesical and rectal veins River Nile etc. Miracidium Snail Cercariae Ovum A B 11.61 Pathogenesis of schistosomiasis Time Schistosoma haematobium S. mansoni and S. japonicum Cercarial penetration Days Papular dermatitis at site of penetration As for S. haematobium Larval migration and maturation Weeks Pneumonitis, myositis, hepatitis, fever, ‘serum sickness’, eosinophilia, seroconversion As for S. haematobium Early egg deposition Months Cystitis, haematuria Colitis, granulomatous hepatitis, acute portal hypertension Ectopic granulomatous lesions: skin, CNS etc. Immune complex glomerulonephritis As for S. haematobium Late egg deposition Years Fibrosis and calcification of ureters, bladder: bacterial infection, calculi, hydronephrosis, carcinoma Colonic polyposis and strictures, periportal fibrosis, portal hypertension Pulmonary granulomas and pulmonary hypertension As for S. haematobium

296 • INFECTIOUS DISEASE fibrosis with splenic enlargement is usual. Deposition of eggs or worms in the CNS, especially in the brain or spinal cord, causes symptoms in about 5% of infections, notably epilepsy, blindness, hemiplegia or paraplegia. Investigations There is marked eosinophilia. Serological tests (ELISA) are useful as screening tests but remain positive after treatment. In S. haematobium infection, dipstick urine testing shows blood and albumin. The eggs can be found by microscopic examination of the centrifuged deposit of terminal stream urine (Fig. 11.55). Ultrasound assesses the urinary tract; bladder wall thickening, hydronephrosis and bladder calcification can be detected. Cystoscopy reveals ‘sandy’ patches, bleeding mucosa and later distortion. In a heavy infection with S. mansoni or S. japonicum, the characteristic egg with its lateral spine can usually be found in the stool. When the infection is light or of long duration, a rectal biopsy can be examined. Sigmoidoscopy may show inflammation or bleeding. Biopsies should be examined for ova. Management The object of therapy is to kill the adult schistosomes and stop egg-laying. Praziquantel (20 mg/kg orally twice daily for 1 day) is the drug of choice for all forms of schistosomiasis except S. japonicum and S. mekongi, for which 60 mg/kg (20 mg for 3 doses) is recommended. The drug produces parasitological cure in 80% of treated individuals and over 90% reduction in egg counts in the remainder. Side-effects are uncommon but include nausea and abdominal pain. Praziquantel therapy in early infection reverses hepatomegaly, bladder wall thickening and granulomas. Surgery may be required to deal with residual lesions such as ureteric stricture, small fibrotic urinary bladders, or granulomatous masses in the brain or spinal cord. Removal of rectal papillomas by diathermy or by other means may provide symptomatic relief. Prevention No single means of controlling schistosomiasis has been established to date. The life cycle is terminated if fresh water containing the snail host is not contaminated by ova-containing urine or faeces. The provision of latrines and of a safe water supply, however, remains a major problem in rural areas throughout the Fig. 11.54 Geographical distribution of schistosomiasis. From Cook GC, ed. Manson’s tropical diseases, 20th edn. Saunders, Elsevier Inc.; 1995. } S. mansoni S. haematobium S. japonicum S. mekongi S. intercalatum Fig. 11.55 Ova of Schistosoma haematobium in urine. Note the terminal spike. involvement of the bowel wall. Ectopic worms cause skin or spinal cord lesions. The severity of S. haematobium infection varies greatly and many

with a light infection are asymptomatic. However, as adult worms can live for 20 years or more and lesions may progress, these patients should always be treated. Schistosoma mansoni S. mansoni is endemic throughout Africa, the Middle East, Venezuela, Brazil and the Caribbean (Fig. 11.54). Characteristic symptoms begin 2 months or more after infection. They may be slight – no more than malaise – or consist of abdominal pain and frequent stools that contain blood-stained mucus. With severe advanced disease, increased discomfort from rectal polyps may be experienced. The early hepatomegaly is reversible but portal hypertension may cause massive splenomegaly, fatal haematemesis from oesophageal varices, or progressive ascites (p. 868). Liver function is initially preserved because the pathology is fibrotic rather than cirrhotic. S. mansoni and other schistosome infections predispose to the carriage of Salmonella, in part because Salmonella may attach to the schistosomes and in part because shared antigens on schistosomes may induce immunological tolerance to Salmonella. Schistosoma japonicum, S. mekongi and S. intercalatum In addition to humans, the adult worm of S. japonicum infects the dog, rat, field mouse, water buffalo, ox, cat, pig, horse and sheep. Although other Schistosoma spp. can infect species other than humans, the non-human reservoir seems to be particularly important only in transmission for S. japonicum. S. japonicum is prevalent in the Yellow River and Yangtze–Jiang basins in China, where the infection is a major public health problem. It also has a focal distribution in the Philippines, Indonesia and Thailand (Fig. 11.54). The related S. mekongi occurs in Laos, Thailand and Myanmar, and S. intercalatum in West and Central Africa. The pathology of S. japonicum is similar to that of S. mansoni, but as this worm produces more eggs, the lesions tend to be more extensive and widespread. The clinical features resemble those of severe infection with S. mansoni, with added neurological features. The small and large bowel may be affected, and hepatic

is ingested, and cysticercosis (systemic infection from larval migration) if ova are ingested. Echinococcus granulosus (dog tapeworm) does not cause human intestinal infection, but causes hydatid disease (which is analogous to cysticercosis) following ingestion of ova and subsequent larval migration. tropics. Furthermore, S. japonicum has so many hosts besides humans that latrines would have little impact. Population mass treatment annually helps prevent S. haematobium and S. mansoni infection but so far has had little success with S. japonicum. Targeting the intermediate host, the snail, is problematic and has not, on its own, proved successful. For personal protection, contact with infected water must be avoided. Liver flukes Liver flukes infect at least 20 million people and remain an important public health problem in endemic areas. They are associated with abdominal pain, hepatomegaly and relapsing cholangitis. Clonorchis sinensis and Opisthorchis felineus are major aetiological agents of bile duct cancer. The three major liver flukes have similar life cycles and pathologies, as outlined in Box 11.62. Other flukes of medical importance include lung and intestinal flukes (see Box 11.58). Cestodes (tapeworms) Cestodes are ribbon-shaped worms that inhabit the intestinal tract. They have no alimentary system and absorb nutrients through the tegumental surface. The anterior end, or scolex, has suckers for attaching to the host. From the scolex, a series of progressively developing segments arise, the proglottides, which may continue to show active movements when shed. Cross-fertilisation takes place between segments. Ova, present in large numbers in mature proglottides, remain viable for weeks, and during this period they may be consumed by the intermediate host. Larvae liberated from the ingested ova pass into the tissues of the intermediate host, forming larval cysticerci. Tapeworms cause two distinct patterns of disease: either intestinal

infection or systemic cysticercosis (Fig. 11.56). Taenia saginata (beef tapeworm), Taenia asiatica and Diphyllobothrium latum (fish tapeworm) cause only intestinal infection in humans, following ingestion of intermediate hosts. Taenia solium causes intestinal infection if a cysticerci-containing intermediate host 11.62 Diseases caused by flukes in the bile duct Clonorchiasis Opisthorchiasis Fascioliasis Parasite Clonorchis sinensis Opisthorchis felineus Fasciola hepatica Other mammalian hosts Dogs, cats, pigs Dogs, cats, foxes, pigs Sheep, cattle Mode of spread Ova in faeces, water As for C. sinensis Ova in faeces on to wet pasture 1st intermediate host Snails Snails Snails 2nd intermediate host Freshwater fish Freshwater fish Encysts on vegetation Geographical distribution Far East, especially South China Far East, especially North-east Thailand Cosmopolitan, including UK Pathology Escherichia coli cholangitis, abscesses, biliary carcinoma As for C. sinensis Toxaemia, cholangitis, eosinophilia Symptoms Often symptom-free, recurrent jaundice As for C. sinensis Unexplained fever, tender liver, may be ectopic, e.g. subcutaneous fluke Diagnosis Ova in stool or duodenal aspirate As for C. sinensis As for C. sinensis, also serology Prevention Cook fish Cook fish Avoid contaminated watercress Treatment Praziquantel 25 mg/kg 3 times daily for 2 days As for C. sinensis but for 1 day only Triclabendazole 10 mg/kg single dose; repeat treatment may be required* *In the UK, available from the Hospital for Tropical Diseases, London. Fig. 11.56 Cysticercosis. Life cycle of Taenia solium. Adult worms in gut Pig Eggs passed in human faeces Human pork tapeworm infection results from eating undercooked pork containing cysticerci Eggs ingested by pig become cysticerci in muscles If cysticerci are swallowed they develop to adult tapeworms in the human intestine Ingestion of meat Faecal–oral route Human cysticercosis results from ingestion of the tapeworm eggs as a result of faecal contamination of food If eggs are swallowed by humans they develop to cysticerci in various sites, e.g. brain, muscle Cysticerci

 Heavy brain infections, especially in children, may cause features of encephalitis. More commonly, however, cerebral signs do not occur until the larvae die, 5–20 years later. Epilepsy, including new-onset focal seizures, personality changes, staggering gait and signs of hydrocephalus are the most common features. Investigations Calcified cysts in muscles can be recognised radiologically. In the brain, however, less calcification takes place and larvae are only occasionally visible by plain X-ray; CT or magnetic resonance imaging (MRI) will usually show them. Epileptic fits starting in adult life suggest the possibility of cysticercosis if the patient has lived in or travelled to an endemic area. The subcutaneous tissue should be palpated and any nodule excised for histology. Radiological examination of the skeletal muscles may be helpful. Antibody detection is available for serodiagnosis. Management and prevention Albendazole (15 mg/kg daily for a minimum of 8 days) has now become the drug of choice for parenchymal neurocysticercosis. Praziquantel (50 mg/kg in 3 divided doses daily for 10 days) is another option. Prednisolone (10 mg 3 times daily) is also given for 14 days, starting 1 day before the albendazole or praziquantel. In addition, antiepileptic drugs should be given until the reaction in the brain has subsided. Operative intervention is indicated for hydrocephalus. Studies from India and Peru suggest that most small, solitary cerebral cysts will resolve without treatment. Echinococcus granulosus (Taenia echinococcus) and hydatid disease Dogs are the definitive hosts of the tiny tapeworm E. granulosus. The larval stage, a hydatid cyst, normally occurs in sheep, cattle, Intestinal tapeworm Humans acquire tapeworm by eating under-cooked beef infected with the larval stage of T. saginata, under-cooked pork containing the larval stage of T. solium or T. asiatica, or under-cooked freshwater fish containing larvae of D. latum. Usually, only one adult tapeworm is present in the gut but up to 10 have been reported. The ova of all the three Taenia are indistinguishable microscopically. However, examination of scolex and proglottides can differentiate them: T. solium

has a rostellum and two rows of hooklets on the scolex, and discharges multiple proglottides (3–5) attached together with lower degrees of uterine branching (approximately 10); T. saginata has only four suckers in its scolex, and discharges single proglottids with greater uterine branching (up to 30); T. asiatica has a rostellum without hooks on its scolex and is difficult to differentiate from T. saginata, except that there are fewer uterine branches (16–21). Taenia solium T. solium, the pork tapeworm, is common in central Europe, South Africa, South America and parts of Asia. It is not as large as T. saginata. The adult worm is found only in humans following the ingestion of pork containing cysticerci. Intestinal infection is treated with praziquantel (5–10 mg/kg) or niclosamide (2 g), both as a single dose, or alternatively with nitazoxanide (500 mg twice daily for 3 days). These are followed by a mild laxative (after 1–2 hours) to prevent retrograde intestinal autoinfection. Cooking pork well prevents intestinal infection. Great care must be taken while attending a patient harbouring an adult worm to avoid ingestion of ova or segments. Taenia saginata Infection with T. saginata occurs in all parts of the world. The adult worm may be several metres long and produces little or no intestinal upset in human beings, but identification of segments in the faeces or on underclothing may distress the patient. Ova may be found in the stool. Praziquantel is the drug of choice; niclosamide or nitazoxanide is an alternative. Prevention depends on efficient meat inspection and the thorough cooking of beef. Taenia asiatica T. asiatica is a newly recognised species of Taenia, restricted to Asia. It is acquired by eating uncooked meat or viscera of pigs. Clinical features and treatment are similar to those of T. saginata. Cysticercosis Human cysticercosis is acquired by ingesting T. solium tapeworm ova, from either contaminated fingers or food (Fig. 11.56). The larvae are liberated from eggs in the stomach, penetrate the intestinal mucosa and are carried to many parts of the body, where they develop and form cysticerci, 0.5–1 cm cysts that contain the head of a young worm. They do not grow further or migrate. Common locations are the subcutaneous tissue, skeletal muscles and brain (Fig. 11.57). Clinical features Superficial cysts can be palpated under the skin or mucosa as pea-like ovoid bodies, but cause few or no symptoms and will eventually die and become calcified. Fig. 11.57 Neurocysticercosis. T2-weighted axial image of the brain showing multiple lesions of neurocysticercosis (large arrows show the largest lesions).

Management and prevention Hydatid cysts should be excised wherever possible. Great care is taken to avoid spillage and cavities are sterilised with 0.5% silver nitrate or 2.7% sodium chloride. Albendazole (400 mg twice daily for 3 months) should also be used and is often combined with PAIR (percutaneous puncture, aspiration, injection of scolicidal agent and re-aspiration). Praziquantel (20 mg/kg twice daily for 14 days) also kills protoscolices perioperatively. Prevention is difficult when there is a close association with dogs. Personal hygiene, satisfactory disposal of carcasses, meat inspection and deworming of dogs reduces the prevalence of disease. Other tapeworms Other cestodes' adult or larval stages may infect humans. Sparganosis is a condition in which an immature worm develops in humans, usually subcutaneously, as a result of eating or applying to the skin the secondary or tertiary intermediate host, such as frogs or snakes. Ectoparasites Ectoparasites only interact with the outermost surfaces of the host; see also page 1241. Jiggers (tungiasis) This is widespread in tropical America and Africa, and is caused by the sand flea Tunga penetrans. The pregnant flea burrows into the skin around toes and produces large numbers of eggs. Fig. 11.58 Hydatid disease. A Life cycle of Echinococcus granulosus. B Daughter cysts removed at surgery. C Within the daughter cysts are the protoscolices. Human Hydatid cysts

in liver, lung etc. Sheep etc. Hydatid cysts in liver, lung etc. Ova Faeces Dog etc. Worms in gut A B C camels and other animals that are infected from contaminated pastures or water. By handling a dog or drinking contaminated water, humans may ingest eggs (Fig. 11.58). The embryo is liberated from the ovum in the small intestine and invades the blood stream, spreading to the liver. The resultant cyst grows very slowly, sometimes intermittently. It is composed of an enveloping fibrous pericyst, laminated hyaline membrane (ectocyst) and inner germinal layers (endocyst) that give rise to daughter cysts, or a germinating cystic brood capsule in which larvae (protoscolices) develop. Over time, some cysts calcify and become non-viable. The disease is common in the Middle East, North and East Africa, Australia and Argentina. Foci of infection persist in the UK in rural Wales and Scotland. E. multilocularis, which has a cycle between foxes and voles, causes a similar but more severe infection, ‘alveolar hydatid disease’, which invades the liver like cancer. Clinical features A hydatid cyst is typically acquired in childhood and, after growing for years, may cause pressure symptoms. These vary, depending on the site involved. In nearly 75% of patients with hydatid disease, the right lobe of the liver is invaded and contains a single cyst. In others, a cyst may be found in lung, bone, brain or elsewhere. Investigations The diagnosis depends on the clinical, radiological and ultrasound findings in a patient that has close contact with dogs in an endemic area. Complement fixation and ELISA are positive in 70–90% of patients.

300 • INFECTIOUS DISEASE Candidiasis (thrush) Superficial candidiasis is caused by Candida spp., mainly C. albicans. Manifestations include oropharyngeal (pp. 790 and 1240) and vaginal candidiasis (‘thrush’), intertrigo and chronic paronychia. Superficial candidiasis often follows antibiotic therapy. Intertrigo is characterised by inflammation in skin folds with surrounding ‘satellite lesions’. Chronic paronychia is associated with frequent wetting of the hands. Superficial candidiasis is treated mainly with topical azoles (p. 126), oral azoles being reserved for refractory or recurrent disease. Severe oropharyngeal and oesophageal candidiasis is a consequence of CD4+ T-lymphocyte depletion/ dysfunction, as in HIV infection (p. 316). Recurrent vaginal or penile candidiasis may be a manifestation of diabetes mellitus. Rarely, mutations in the autoimmune regulator gene (AIRE) or signal transducer and activator of transcription 1 (STAT1) cause a syndrome of chronic mucocutaneous candidiasis (p. 689). This is characterised by Candida infections of skin, mucosa and nails, with hyperkeratotic nails and erythematous periungual skin. Patients have cell-mediated immune defects against Candida and may have polyendocrinopathy and autoimmune features. Subcutaneous mycoses Chromoblastomycosis Chromoblastomycosis is a predominantly tropical or subtropical disease caused by environmental dematiaceous (dark-pigmented) fungi, most commonly Fonsecaea pedrosoi. Other causes include F. compacta, Cladophialophora carrionii and Phialophora verrucosa. The disease is a cutaneous/subcutaneous mycosis acquired by traumatic inoculation. Commonly affected areas The burrows are intensely irritating and the whole inflammatory nodule should be removed with a sterile needle. Secondary infection of lesions is common. Myiasis Myiasis is due to skin infestation with larvae of the South American botfly, Dermatobia hominis, or the African tumbu fly, Cordylobia anthropophaga. The larvae develop in a subcutaneous space with a central sinus. This orifice is the air source for the larvae, and periodically the larval respiratory spiracles protrude through the sinus. Patients with myiasis feel movement within the larval burrow and can experience intermittent sharp, lancinating pains. Myiasis is diagnosed clinically and should be suspected with any furuncular lesion accompanied by pain and a crawling sensation in the skin. The larva may be suffocated by blocking the respiratory orifice with petroleum jelly and gently removing it with tweezers. Secondary infection of myiasis is rare and rapid healing follows removal of intact larvae. Fungal infections

Fungal infections, or mycoses, are classified as superficial, subcutaneous or systemic (deep), depending on the degree of tissue invasion. They are caused by filamentous fungi (moulds), by yeasts or by fungi that vary between these two forms, depending on environmental conditions (dimorphic fungi; Fig. 11.59). Superficial mycoses Superficial cutaneous fungal infections caused by dermatophyte fungi are described in Chapter 29. Fig. 11.59 Classification of medically important fungi. Fungal classification is based on simple morphological characteristics. Pneumocystis jirovecii is morphologically distinct from other fungi and does not fit into this classification. *Although Candida albicans exists in a number of forms, including filamentous (hyphae and pseudohyphae), it is generally encountered in its yeast form so is classified in this category. Insets (dimorphic fungi) Courtesy of Beatriz Gomez and Angela Restrepo, CIB, Medellín, Colombia. Filamentous fungi (moulds) Characterised by the production of elongated, cylindrical, often septate cells (hyphae) and conidia (spores) Examples: • Aspergillus spp. (A. fumigatus shown here) • Fusarium spp. • Dermatophyte fungi (Tricophyton spp., Microsporum spp. etc.) • Mucorales Dimorphic fungi Yeasts Exist in filamentous (top) or yeast (bottom) form, depending on environmental conditions Examples: • Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides brasiliensis (shown here), Blastomyces dermatidis • Sporothrix schenkii • Talaromyces marneffei • Malassezia spp. Characterised by the production of oval or round cells, which reproduce by binary fission (budding) Examples: • Candida spp.* • Cryptococcus spp. (C. neoformans shown here)

disease. Success has also been reported wth co-trimoxazole plus amikacin, with rifampicin added in difficult cases and to prevent recurrence. Phaeohyphomycosis Phaeohyphomycoses are a heterogeneous group of fungal diseases caused by a large number (more than 70) of dematiaceous fungi. In phaeohyphomycosis, the tissue form of the fungus is predominantly mycelial (filamentous), as opposed to eumycetoma (grain) or chromoblastomycosis (sclerotic body). Disease may be superficial, subcutaneous or deep. The most serious manifestation is cerebral phaeohyphomycosis, which presents with a ring-enhancing, space-occupying cerebral lesion. Optimal therapy for this condition has not been established but usually consists of neurosurgical intervention and antifungal (usually triazole) therapy. Causative agents are Cladophialophora bantiana, Fonsecaea spp. and Rhinocladiella mackenziei, which occurs mainly in the Middle East and is usually fatal. Sporotrichosis Sporotrichosis is caused by Sporothrix schenckii, a dimorphic fungal saprophyte of plants in tropical and subtropical regions. Disease is caused by dermal inoculation of the fungus, usually from a thorn (occasionally from a cat scratch). In fixed cutaneous sporotrichosis, a subcutaneous nodule develops at the site of infection and subsequently ulcerates, with a purulent discharge. The disease may then spread along the cutaneous lymphatic channels, resulting in multiple cutaneous nodules that ulcerate and discharge (lymphocutaneous sporotrichosis). Rarer forms include cutaneous disease presenting with arthritis. Later, draining sinuses may form. Pulmonary sporotrichosis occurs as a result of inhalation of the conidia (spores) and causes chronic cavitary fibronodular disease with haemoptysis and constitutional symptoms. Disseminated disease may occur, especially in patients with HIV. Investigations Typical yeast forms detected on histology confirm diagnosis but are rarely seen; the fungus can also be cultured from biopsy specimen. A latex agglutination test detects S. schenckii antibodies in serum. Management Cutaneous and lymphocutaneous disease is treated with itraconazole (200–400 mg daily, prescribed as the oral solution, which has better bioavailability than the capsule formulation) for 3–6 months. Alternative agents include a saturated solution of potassium iodide (SSKI, given

orally), initiated with 5 drops and increased to 40–50 drops 3 times daily, or terbinafine (500 mg twice daily). Localised hyperthermia may be used in pregnancy (to avoid azole use). Osteoarticular disease requires a longer course of therapy (at least 12 months). Severe or lifethreatening disease is treated with amphotericin B (lipid formulation preferred). Systemic mycoses Aspergillosis Aspergillosis is an opportunistic systemic mycosis, which affects the respiratory tract predominantly. It is described on page 596. include the foot, ankle and lower leg. Lesions may start several months after the initial injury, and medical attention is often sought several years later. The initial lesion is a papule. Further papules develop and coalesce to form irregular plaques. Nodular lesions may produce a characteristic ‘cauliflower’ appearance. Diagnosis is by histopathological examination of infected material, which shows dematiaceous, rounded, thick-walled ‘sclerotic bodies’ with septa at right angles to each other. The aetiological agent is confirmed by culture. Therapeutic approaches include antifungal agents, cryosurgery and surgical excision, alone or in combination, but the optimal therapy is unknown. Itraconazole and terbinafine are the most effective antifungal agents. However, posaconazole has also been used with a good outcome. Mycetoma (eumycetoma and actinomycetoma) Mycetoma is a chronic suppurative infection of the deep soft tissues and bones, most commonly of the limbs but also of the abdominal or chest wall or head. It is caused by either filamentous fungi, Eumyces (eumycetoma – 40%) or aerobic Actinomycetes (actinomycetoma – 60%). Many fungi cause eumycetomas, the most common being Madurella mycetomatis, M. grisea, Leptosphaeria senegalensis and Scedosporium apiospermum; causes of actinomycetoma include Nocardia, Streptomyces and Actinomadura spp. Both groups produce characteristically coloured ‘grains’ (microcolonies), the colour depending on the organism (black grains – eumycetoma, red and yellow grains – actinomycetoma, white grains – either). The disease occurs mostly in the tropics and subtropics. Clinical features The disease is acquired by inoculation (e.g. from a thorn) and most commonly affects the foot (Madura foot). Mycetoma begins as a painless swelling at the implantation site, which becomes chronic and progressive, grows and spreads steadily within the soft tissues, eventually extending into bone. Nodules develop under the epidermis and these rupture, revealing sinuses through which grains may be discharged. Sinuses heal with scarring, while fresh sinuses appear elsewhere. Deeper tissue invasion and bone involvement are less rapid and extensive in eumycetoma than actinomycetoma. There is little pain and usually no fever or lymphadenopathy, but there is progressive disability. Investigations Diagnosis of mycetoma involves identification of grains in pus, and/ or histopathological examination of tissue. Culture is necessary for species identification and susceptibility testing. Serological tests are not available. Management Eumycetoma is usually treated with a combination of surgery and antifungal therapy. Antifungal susceptibility testing, if available, is recommended, although clinical outcome does not necessarily correspond to in vitro test results. Itraconazole and ketoconazole (both 200–400 mg/day) are used most commonly. Success has also been reported with terbinafine monotherapy, and refractory cases have responded to voriconazole or posaconazole. Amphotericin B is not usually effective. Therapy is continued for 6–12 months or longer. In extreme cases, amputation may be required. Actinomycetoma is treated with prolonged antibiotic combinations, most commonly streptomycin and dapsone. Dapsone is replaced by co-trimoxazole in intolerance or refractory

302 • INFECTIOUS DISEASE Cryptococcosis Cryptococcosis is a systemic mycosis caused by two environmental yeast species, Cr. neoformans and Cr. gattii. Cr. neoformans is distributed worldwide and is primarily an opportunistic pathogen, most commonly associated with HIV infection (p. 321). Cr. gattii is a primary pathogen with a widespread distribution that includes

Australasia, Africa, Canada (Vancouver Island) and the north-western USA. Cryptococcosis is acquired by inhalation of yeasts. These may disseminate to any organ, most commonly the CNS and skin. The manifestations of Cr. neoformans are most severe in immunocompromised individuals. Conversely, Cr. gattii causes severe disease in immunocompetent hosts. Disseminated cryptococcosis (sepsis with cryptococci present in the blood stream or at multiple sites) is largely restricted to immunocompromised patients. CNS manifestations of cryptococcosis include meningitis (p. 321) and cryptococcoma (Fig. 11.60), the latter more likely with Cr. gattii infection. Manifestations of pulmonary cryptococcosis range from severe pneumonia (in more immunocompromised patients) to asymptomatic disease with single or multiple pulmonary nodules, sometimes exhibiting cavitation (in patients with lesser immunosuppression). Cryptococcal nodules may mimic other causes of lung pathology, such as tuberculosis or malignancy, and diagnosis requires histopathology and/or culture. Treatment of severe cryptococcosis is the same as for cryptococcal meningitis, initially with liposomal amphotericin B (p. 321). Mild pulmonary disease is usually treated with fluconazole, although for asymptomatic nodules resection of the lesions is likely to be sufficient. Fusariosis Fusarium spp. cause disseminated disease in patients with prolonged neutropenia. The disease presents with Candidiasis Systemic candidiasis is an opportunistic mycosis caused by Candida spp. The most common cause is C. albicans. Other agents include C. dubliniensis, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis. Candida species identification often predicts susceptibility to fluconazole: C. krusei is universally resistant, many C. glabrata isolates have reduced susceptibility or are resistant, and other species are mostly susceptible. Candidiasis is usually an endogenous disease that originates from oropharyngeal, genitourinary or skin colonisation, although nosocomial spread occurs. C. auris is an emerging species, which has a particular propensity for nosocomial transmission. Syndromes of systemic candidiasis Acute disseminated candidiasis This usually presents as candidaemia (isolation of Candida spp. from the blood). The main predisposing factor is the presence of a central venous catheter. Other major factors include recent abdominal surgery, total parenteral nutrition (TPN), recent antimicrobial therapy and localised Candida colonisation. Up to 40% of cases will have ophthalmic involvement, with characteristic retinal ‘cotton wool’ exudates. As this is a sightthreatening condition, candidaemic patients should have a full ophthalmoscopy review. Skin lesions (non-tender pink/ red nodules) may be seen. Although predominantly a disease of intensive care and surgical patients, acute disseminated candidiasis and/or Candida endophthalmitis is seen occasionally in injection drug-users, due to candidal contamination of citric acid or lemon juice used to dissolve heroin. Chronic disseminated candidiasis (hepatosplenic candidiasis) Persistent fever in a neutropenic patient, despite antibacterial therapy and neutrophil recovery, associated with the development of abdominal pain, raised alkaline phosphatase and multiple lesions in abdominal organs (e.g. liver, spleen and/or kidneys) on radiological imaging, suggests a diagnosis of hepatosplenic candidiasis. This represents a form of immune reconstitution syndrome (p. 104) in patients recovering from neutropenia and usually lasts for several months, despite appropriate therapy. Other manifestations Renal tract candidiasis, osteomyelitis, septic arthritis, peritonitis, meningitis and endocarditis are all well recognised and are usually sequelae of acute disseminated disease. Diagnosis and treatment of these conditions require specialist mycological advice. Management Blood cultures positive for Candida spp. must never be ignored. Acute disseminated candidiasis is treated with antifungal therapy, removal of any in-dwelling central venous catheter (whether known to be the source of infection or not) and removal of any documented source. Candidaemia should be treated initially with an echinocandin (p. 126), with subsequent adjustment (usually to

intravenous or oral fluconazole) guided by clinical response, species identification and susceptibility testing. Treatment should continue for a minimum of 14 days. Alternative therapies include voriconazole and amphotericin B formulations. Chronic disseminated candidiasis requires prolonged treatment over several months with fluconazole or other agents, depending on species and clinical response. The duration of the condition may be reduced by adjuvant therapy with systemic glucocorticoids. Fig. 11.60 Cryptococcal disease. A 23-year-old HIV-positive male developed headache and left-sided weakness. A MRI scan of the brain showed a space-occupying lesion (arrow) with surrounding oedema. B Histopathological examination of the lesion stained with Grocott's silver stain showed encapsulated yeasts. Cryptococcus neoformans was cultured. A B

Talaromyces (formerly Penicillium) marneffei infection T. marneffei is a thermally dimorphic pathogen (filamentous in environmental conditions and yeast at body temperature), which causes disease in South-east Asia, mainly in association with HIV infection (although immunocompetent patients may also be infected). Acquisition is usually by inhalation of environmental spores, with primary lung infection followed by haematogenous dissemination. A generalised papular rash, which progresses to widespread necrosis and ulceration, is a characteristic feature. Skin lesions may resemble molluscum contagiosum. Diagnosis is by histopathology and/or culture of respiratory secretions, blood or any infected clinical material (e.g. skin lesions, bone marrow, biopsies). Treatment involves an amphotericin B formulation followed by itraconazole (in severe infection), or itraconazole alone. Histoplasmosis Histoplasmosis is a primary systemic mycosis caused by the dimorphic fungus Histoplasma capsulatum. H. capsulatum var. capsulatum is endemic to east-central USA (especially the Mississippi and Ohio river valleys), parts of Canada, Latin America, the Caribbean, East and South-east Asia, and Africa. It occurs sporadically in Australia and India, and is very rare in Europe. H. capsulatum var. duboisii is found in West Africa and Madagascar. The primary reservoir of H. capsulatum is soil enriched by bird and bat droppings, in which the fungus remains viable for many years. Infection is by inhalation of infected dust. Natural infections are found in bats, which represent a secondary reservoir of infection. Histoplasmosis is a specific hazard for explorers of caves and people who clear out bird (including chicken) roosts. Pathology The organism is inhaled in the form of conidia or hyphal fragments and transforms to the yeast phase during infection. Conidia or yeasts are phagocytosed by alveolar macrophages and neutrophils, and this may be followed by haematogenous dissemination to any organ. Subsequent development of a T-lymphocyte response brings the infection under control, resulting in a latent state in most exposed individuals. Clinical features Disease severity depends on the quantity of spores inhaled and the immune status of the host. In most cases, infection is asymptomatic. Pulmonary symptoms are the most common presentation, with fever, non-productive cough and an influenzalike illness. Erythema nodosum, myalgia and joint pain frequently occur, and chest radiography may reveal a pneumonitis with hilar or mediastinal lymphadenopathy. Patients with pre-existing lung disease, such as chronic obstructive pulmonary disease (COPD) or emphysema, may develop chronic pulmonary histoplasmosis (CPH). The predominant features of this condition, which may easily be mistaken for tuberculosis, are fever, cough, dyspnoea, weight loss and night sweats. Radiological findings include fibrosis, nodules, cavitation and hilar/mediastinal lymphadenopathy. Disease caused by H. capsulatum var. duboisii presents more commonly with papulonodular and ulcerating lesions of the skin and underlying subcutaneous tissue and bone (sometimes referred to as 'African histoplasmosis'). Multiple lesions of the ribs are common and the

bones of the limbs may be affected. Lung involvement is relatively rare. Radiological examination may show rounded foci of bone destruction, sometimes associated Fig. 11.61 Fusarium infection. A patient presented with fever and skin nodules after developing neutropenia secondary to haematopoietic stem cell transplantation and chemotherapy for relapsed leukaemia. Fusarium solani was cultured from skin lesions and blood cultures. A Tender, erythematous papules/nodules on upper arm. B Gram stain of Fusarium in blood culture medium. A B antibiotic-resistant fever and evidence of dissemination (e.g. skin nodules, endophthalmitis, septic arthritis, pulmonary disease; Fig. 11.61). In contrast to Aspergillus spp., Fusarium spp. is often recovered from blood cultures. Treatment is challenging because of resistance to antifungal agents; voriconazole, posaconazole or lipid-formulated amphotericin B is most often prescribed. Mucormycosis Mucormycosis is a severe but uncommon opportunistic systemic mycosis caused by a number of 'mucoraceous' moulds, most commonly Lichtheimia (formerly Absidia) spp., Rhizomucor spp., Mucor spp. and Rhizopus spp. Disease patterns include rhinocerebral/craniofacial, pulmonary, cutaneous and systemic disease. All are characterised by the rapid development of severe tissue necrosis, which is almost always fatal if left untreated. The most common predisposing factors are profound immunosuppression from neutropenia and/or haematopoietic stem cell transplantation, uncontrolled diabetes mellitus, iron chelation therapy with desferrioxamine and severe burns. Definitive diagnosis is by culture but histopathological confirmation is required, as the fungi may be environmental contaminants. Treatment requires a combination of antifungal therapy and surgical débridement, with correction of predisposing factor(s) if possible. High-dose lipid-formulated amphotericin B is most commonly used. Posaconazole is active against many mucoraceous moulds in vitro and may be used as a second-line agent or as oral 'step-down' therapy.

 Coccidioides meningitis (which may be associated with CSF eosinophils) is the most severe disease manifestation; it is fatal if untreated and requires life-long suppressive therapy with antifungal azoles. Investigations and management Diagnosis is by direct histopathological detection in specimens, culture of infected tissue or fluids, or antibody detection. IgM may be detected after 1–3 weeks of disease by precipitin tests. IgG appears later and is detected with the complement fixation test. Change in IgG titre may be used to monitor clinical progress. Treatment depends on specific disease manifestations and ranges from regular clinical reassessment without antifungal therapy (in mild pulmonary, asymptomatic cavitary or single nodular disease) to high-dose treatment with an antifungal azole, which may be continued indefinitely (e.g. in meningitis). Amphotericin B is used in diffuse pneumonia, disseminated disease and, intrathecally, in meningitis. Posaconazole has been used successfully in refractory disease. Paracoccidioidomycosis This is a primary systemic mycosis caused by inhalation of the dimorphic fungus Paracoccidioides brasiliensis, which is restricted to South America. The disease affects the lungs, mucous membranes (painful destructive ulceration in 50% of cases), skin, lymph nodes and adrenal glands (hypoadrenalism). Diagnosis is by microscopy and culture of lesions, and antibody detection. Oral itraconazole solution (200 mg/day) has demonstrated 98% efficacy and is currently the treatment of choice (mean duration 6 months). Ketoconazole, fluconazole, voriconazole and 2–3-year courses of sulphonamides are alternatives. Amphotericin B is used in severe or refractory disease, followed by an azole or sulphonamide. Blastomycosis Blastomyces dermatitidis is a dimorphic fungus endemic to restricted parts of North America, mainly around the Mississippi and Ohio rivers. Very occasionally, it is reported from Africa. The disease usually presents as a chronic pneumonia similar to pulmonary tuberculosis. Bones, skin and the genitourinary tract may also be affected. Diagnosis is by culture of the organism or identification of the characteristic yeast form in a clinical specimen. Antibody detection is rarely helpful. Treatment is with amphotericin B (severe

disease) or itraconazole. Further information Websites britishinfection.org British Infection Association; source of general information on communicable diseases. cdc.gov Centers for Disease Control, USA; source of general information about infectious diseases. fitfortravel.nhs.uk Scottish site with valuable information for travellers. https://www.gov.uk/government/organisations/public-health-england Public Health England; information on infectious diseases in the UK. idsociety.org Infectious Diseases Society of America; source of general information relating to infectious diseases and of authoritative practice guidelines. who.int. especially www.who.int/csr/don World Health Organisation; invaluable links on travel medicine with updates on outbreaks of infections, changing resistance patterns and vaccination requirements. with abscess formation. Other disease patterns include a visceral form with liver and splenic invasion, and disseminated disease. Acute disseminated histoplasmosis is seen with immunocompromise, including HIV infection. Features include fever, pancytopenia, hepatosplenomegaly, lymphadenopathy and often a papular skin eruption. Chronic disseminated disease presents with fever, anorexia and weight loss. Cutaneous and mucosal lesions, lymphadenopathy, hepatosplenomegaly and meningitis may develop. Emergomyces africanus (formerly Emmonsia sp.) is a dimorphic fungus recently described in South Africa, which causes a disseminated histoplasmosis-like illness, mainly associated with HIV infection. Histopathologically, yeast forms appear similar to histoplasmosis and can be distinguished only by PCR. Investigations Histoplasmosis should be suspected in endemic areas with every undiagnosed infection in which there are pulmonary signs, enlarged lymph nodes, hepatosplenomegaly or characteristic cutaneous/bony lesions. Radiological examination in long-standing cases may show calcified lesions in the lungs, spleen or other organs. In the more acute phases of the disease, single or multiple soft pulmonary shadows with enlarged tracheobronchial nodes are seen on chest X-ray. Laboratory diagnosis is by direct detection (histopathology or antigen detection), culture and serology; although antigen detection is the most effective method, it is not widely available. Serology utilises complement fixation testing or immunodiffusion; interpretation is complex and requires a specialist. Histoplasma antigen may be detectable in blood or urine. Culture is definitive but slow (up to 12 weeks). Histopathology may show characteristic intracellular yeasts. Diagnosis of subcutaneous or bony infection is mainly by histopathological examination and/or culture. Management Mild pulmonary disease does not require treatment. However, if prolonged, it may be treated with itraconazole. More severe pulmonary disease is treated with an amphotericin B formulation for 2 weeks, followed by itraconazole for 12 weeks, with methylprednisolone added for the first 2 weeks of therapy if there is hypoxia or ARDS. CPH is treated with itraconazole oral solution for 12–24 months, and disseminated histoplasmosis with an amphotericin B formulation followed by itraconazole. Lipid formulations of amphotericin B are preferred but their use is subject to availability. In subcutaneous and bone infection, patterns of remission and relapse are more common than cure. A solitary bony lesion may require local surgical treatment only. Coccidioidomycosis This is a primary systemic mycosis caused by the dimorphic fungi Coccidioides immitis and C. posadasii, found in the south-western USA and Central and South America. The disease is acquired by inhalation of conidia (arthrospores). In 60% of cases it is asymptomatic but in the remainder it affects the lungs, lymph nodes and skin. Rarely (in approximately 0.5%), it may spread haematogenously to bones, adrenal glands, meninges and other organs, particularly in those with immunocompromise. Pulmonary coccidioidomycosis has two forms: primary and progressive. If symptomatic, primary coccidioidomycosis presents with cough, fever, chest pain, dyspnoea and (commonly) arthritis and a rash (erythema multiforme). Progressive disease presents with systemic upset (e.g. fever, weight loss, anorexia) and features of lobar pneumonia, and may resemble tuberculosis.

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