Immunology and infectious diseases

The brunt of infectious disease falls on children because of their immature immune systems. The greatest worldwide killers of the under-5s are pneumonia, acute diarrhoea (generally of infectious cause), measles, malaria and tuberculosis. Poliomyelitis, which tends to maim rather than kill, is at the point of probable global eradication as a result of vigorously conducted vaccine initiatives. In developed countries, better nutrition, immunization and availability of treatment has reduced mortality. Nevertheless toddlers will suffer an infectious disease (most commonly upper respiratory) every 6 weeks, and the majority of acute hospital admissions are either directly or indirectly infection-associated (for example by precipitation of asthma symptoms or febrile convulsions).

Advances in the treatment of malignant diseases and immunopathological disorders in children, as well as the HIV epidemic, have led to an increase in the number of children with secondary immunodeficiency. Taken together with children with primary (genetic) disorders of the immune system, paediatricians are having to deal increasingly with complex infections in immunocompromised children.

Immunology

A knowledge of immunology is important to the understanding of many disease processes including the extremely common allergic disorders. Deficiency of the immune response, either primary or secondary, leads to problems with infection which may be complex and atypical in presentation. Newborn babies and young children have a physiological immune deficiency, partly compensated by passive transfer of immunoglobulin across the placenta and through breast milk.

Some forms of primary immunodeficiency, such as IgA deficiency, are relatively common while other more major deficiencies are rare. It is important to recognize the latter, as treatments such as immunoglobulin replacement or bone marrow transplantation may be lifesaving.

The discipline of immunology also encompasses autoimmune and allergy. Autoimmune disorders are discussed in the organ specialty chapters and in the Rheumatology chapter (p. •••). Allergic diseases are also covered in the organ specialty chapters, mainly
Important immunodeficiency disorders are listed below.

**Asplenia**

Absence of the spleen is associated with:
- Midline liver
- Right-sided stomach
- Dextrocardia
- Complex cyanotic congenital heart disease
- Increased risk of sepsis
- Howell—Jolly and Heinz bodies in pitted erythrocytes.

Both lungs have three lobes. When multiple spleens are present (polysplenia) both lungs have two lobes. The manifestations of asplenia occur except for sepsis and red cell changes.

**Antibody deficiency disorders**

The most common infections associated with these disorders are caused by pyogenic bacteria, particularly the polysaccharide-encapsulated organisms such as pneumococcus. In severe antibody deficiency states there are problems handling the enteroviruses, which include ECHO, coxsackie and polio viruses. Opportunistic infections are rare and their presence usually indicates a cell-mediated deficiency component to the disorder.

**Agammaglobulinaemia (Bruton disease)**

This panhypogammaglobulinaemia affects all immunoglobulin classes. Inheritance is X-linked, with an incidence of 1 in 100,000. The disorder is caused by a defect in an intracellular enzyme, Bruton tyrosine kinase (Btk), necessary for the development of B lymphocytes, which are therefore usually absent or very low in the blood.

Repeated bacterial infections start from around 4 months of age, as maternal antibodies are waning. Treatment comprises:
- Lifelong immunoglobulin replacement therapy
- Frequent use of antibiotics for respiratory infections

**Selective IgA deficiency**

Selective IgA deficiency has two forms:
- Complete IgA deficiency, with absence of IgA in blood and secretions
- Partial IgA deficiency, with detectable but low levels of IgA.

The complete form, usually permanent, has an incidence of 1 in 500. The partial form occurs in early childhood and often resolves (transient). The disorder may be linked with disturbed IgG subclass levels.

It is associated with recurrent respiratory tract (including ear) and gastrointestinal infections, and increased incidence of coeliac disease and autoimmune disorders. The susceptibility to infections improves with age, even if the deficiency persists. Treatment comprises:
- Prophylactic antibiotics, especially during winter months
- Monitoring and treating associated complications.

Immunoglobulin replacement therapy is not indicated. Some patients occasionally develop antibodies to IgA in blood products, which potentially may cause severe reactions.

**Common variable immunodeficiency (CVID)**

This variable hypogammaglobulinaemia affects IgA and IgG, with or without IgM. Some patients have a degree of T-cell deficiency. The condition may be present from birth or develop later (late-onset hypogammaglobulinaemia).

It is familial, with complex genetics linked to selective IgA deficiency and autoimmune disease. The incidence is 1:20,000, and both sexes are affected. B lymphocytes are usually present in the blood.

CVID may present with:
- Repeated respiratory tract infections
- Gastrointestinal problems (infective or inflammatory)
- Autoimmune phenomena
- Opportunistic infections (if there is a significant T-cell deficiency component).

Treatment comprises:
- Lifelong immunoglobulin replacement therapy
- Frequent use of antibiotics for respiratory infections
- Monitoring and treating associated complications.

**Immunoglobulin G subclass deficiencies**

These are a relatively common finding in children with recurrent infections. The deficiencies are usually caused by an immunoregulatory problem, and rarely, due to deletions in the relevant Ig heavy chain genes.
IgG2 deficiency, which may be partial or complete, is the most common. It is often transient in early childhood, and may be associated with IgA deficiency. It can be associated with recurrent respiratory infections, although not always.

IgG1 and IgG3 deficiencies are also associated with infections, but are less well characterized. IgG4 deficiency is of doubtful clinical significance.

Management may be expectant or involve prophylactic antibiotics. Immunoglobulin replacement is rarely required, and is restricted to children with persistent chest problems and/or a failure of antibody response to vaccines.

**Antibody deficiency with normal immunoglobulins**

This condition is poorly understood; it may occur as part of a combined immunodeficiency or as an isolated problem. It is diagnosed by finding absence of specific antibody responses to vaccine antigens following booster doses. Immunoglobulin replacement therapy may be required, depending on clinical status.

Defective antipolysaccharide responsiveness is a form of this problem in which response to protein or conjugate protein—polysaccharide antigens is normal, but there is failure of response to pure polysaccharide (such as pneumococcal) vaccine. This problem cannot be diagnosed in the first 2 years of life when polysaccharide responses are inherently poor. Prophylactic antibiotic therapy or immunoglobulin replacement may be required, depending on clinical status.

**Transient hypogammaglobulinaemia of infancy**

In this poorly defined condition there are low levels of one or more immunoglobulin classes. It is often an incidental finding or associated with relatively minor infections, and usually resolves by 36 months of age.

Differential diagnoses include Bruton disease (see p. 262) and CVID. B cells are present in blood, and specific antibody responses to vaccines are present.

Management is expectant. Antibiotic prophylaxis is sometimes used.

**Combined immunodeficiency disorders**

Nearly all defects of T cells (cell-mediated immune defects) result in at least a degree of failure of antibody production. They are therefore called combined (T-cell and antibody) defects. Affected children suffer a wide range of infections including bacterial, fungal, viral and protozoal types. Many of these are called opportunistic infections, meaning that the organism does not normally cause the problem in immunocompetent children but is acting opportunistically. Examples include the fungus *Pneumocystis carinii* and cytomegalovirus. Although the latter may be responsible for mild illness in normal children, it can cause severe life-threatening illness in immunodeficient children.

**Severe combined immunodeficiency (SCID)**

This is a group of disorders, with an overall incidence of around 1 in 50,000, which result in profound deficiency of cell-mediated and humoral immunity. Several different molecular defects have been identified as causes. Inheritance is autosomal recessive in some cases or X-linked in others.

The disorder presents in infancy with:

- Pneumonitis
- Diarrhoea
- Failure to thrive
- Candidiasis.

Lymphopenia is present in most cases, compared with age-related levels; this provides a clue for early diagnosis. The T cells are invariably absent (or very low). B cells and NK cells are present or absent depending on the molecular type of SCID.

Supportive treatment includes prophylactic cotrimoxazole and immunoglobulin. Blood products should be CMV-negative and irradiated to prevent transfusion-acquired graft versus host disease. Bone marrow transplantation is curative if performed early before excessive morbidity develops, and somatic gene therapy is being explored.

Antenatal diagnosis is available; in the first trimester if the molecular defect is known, otherwise in the second trimester, by fetal blood analysis of T cell numbers.

**Combined immunodeficiency**

This is similar to SCID but slightly less severe with some T cells present. Some have the same molecular defect as SCID but with incomplete expression; others have different or as yet unidentified defects. It presents with similar problems to SCID, particularly diarrhoea, often due to a noninfective, presumed autoimmune enteropathy.

Management is on the same lines as for SCID. Antenatal diagnosis is only available where the molecular defect in the family is known.
Immunity and infectious diseases

Hyper-IgM syndrome

This condition, usually inherited in an X-linked fashion but occasionally in an autosomal recessive fashion, results in failure to produce IgG and IgA. The IgM level is high or normal. In the X-linked variety the defect is due to a failure to express the molecule CD40 ligand on activated T cells.

This molecule is important in enabling B cells to switch immunoglobulin isotype production. The molecule is also important in signalling to macrophages to facilitate killing of intracellular organisms. Affected individuals suffer recurrent bacterial infections, but are also susceptible to *Pneumocystis carinii*, mycobacterial and cryptosporidial infections.

Management involves immunoglobulin replacement and *Pneumocystis carinii* prophylaxis. Bone marrow transplantation is under evaluation.

In the long term liver problems (sclerosing cholangitis) may occur, often due to chronic infection with *Cryptosporidium parvenu*.

X-linked lymphoproliferative disease

Affected boys remain well with normal immune function until they encounter the Epstein–Barr virus. They then develop serious life-threatening illness. Severe chronic infectious mononucleosis with secondary immune depression leads to susceptibility to a wide range of other pathogens, including:

- Hypogammaglobulinaemia
- Lymphoproliferative disease
- Aplastic anemia.

Mortality is very high, being greater than 80%. Management involves:

- Supportive care
- Immunoglobulin replacement
- Bone marrow transplantation.

Recent identification of the gene will allow the diagnosis to be made (and possibly corrected by bone marrow transplantation) in at-risk boys before the disease develops.

Disorders associated with syndromes

Di George anomalad

In 90% of cases this is associated with a microdeletion on chromosome 22q which can be detected using a fluorescent in situ hybridization (FISH) technique. It forms part of a wider developmental problem causing velofacial cardiac (Shprintzen) syndrome involving structures derived from the 3rd and 4th pharyngeal arches.

Affected children have an unusual face with:

- Fish-mouth deformity
- Hypertelorism
- Antemongoloid (downward sloping) slanting eyes
- Low set ears
- Bifid uvula.

The condition is also associated with congenital heart disease (usually aortic arch anomalies), hypoparathyroidism and thymic hypoplasia.

Early assessment of immune function is required. Significant immunodeficiency occurs in the minority of cases and comprises:

- Low T-cell numbers and defective T-cell responses
- Defective antibody responses (usually with normal immunoglobulin levels).

There is a tendency for the immune deficiency to improve with time. In those with severe immunodeficiency, avoidance of live vaccines, *Pneumocystis carinii* pneumonia prophylaxis, immunoglobulin therapy and sometimes bone marrow transplantation are required.

Ataxia telangiectasia (see also Neurology, Ch. 18)

This is caused by a defect in a cell cycle control protein ATM. Immunodeficiency of variable severity is found in 80% of cases. In order of frequency: IgA deficiency, defective polysaccharide responses, low IgG, T-cell lymphopenia and defective T-cell responses may occur.

There may be recurrent respiratory infections leading to bronchiectasis, and there is a high incidence of malignancy, mainly of the lymphoid system.

Treatment comprises prophylactic antibiotics and, in some cases, immunoglobulin.

Hyper immunoglobulin E syndrome (Job syndrome)

In this condition, there is extreme elevation of serum IgE, associated with deep-seated bacterial and fungal infections. Inheritance is autosomal dominant with incomplete penetrance.

The syndrome is associated with dermatitis (not true eczema), abnormal (coarse) facies, delayed dentition and osteopenia with increased risk of fractures. Staphylococcal lung infections typically lead to pneumatoceles which often require surgical removal to prevent secondary fungal infection. There is defective
neutrophil chemotaxis and sometimes poor polysaccharide antibody response.

Treatment is with:

- Prophylactic antistaphylococcal antibiotics
- Immunoglobulin replacement if there is a demonstrated deficiency of antibody response.

(Job was a red-headed, fair-skinned Biblical character who was afflicted with a plague of boils, and the condition was first described in fair red-headed children.)

**Wiskott–Aldrich syndrome**

This X-linked recessive condition is caused by a mutation in the gene encoding a protein (Wiskott–Aldrich syndrome protein, WASP) involved in cytoskeletal functioning of haemopoietic cells. Features include:

- Eczema
- Thrombocytopenia with abnormally small platelets
- Recurrent bacterial infections
- Risk of opportunistic infections
- Low serum IgM and high IgE and IgA
- Progressive lymphopenia
- Risk of developing autoimmune and vasculitic disorders
- High incidence of lymphoid malignancy.

Treatment includes immunoglobulin replacement, prophylaxis against *Pneumocystis carinii*, splenectomy (to control bleeding), and bone marrow transplantation if a suitable donor can be found.

**Chronic mucocutaneous candidiasis**

This probably represents a heterogenous group of genetic disorders with susceptibility to candida infection. Inheritance is variable but often autosomal dominant.

Patients suffer recurrent or persistent candidal infections of skin, nails and mucous membranes. They can also suffer an excess of other (mainly bacterial) infections. In some pedigrees the disorder is associated with autoimmune endocrinopathy, as the APECED syndrome (autoimmune poly-endocrinopathy, candidiasis and ectodermal dystrophy), inherited as a single gene defect. Hypoparathyroidism, hypothyroidism, diabetes mellitus, pernicious anaemia, Addison disease and gonadal failure may all occur in this condition. (Cancer of the mouth and oesophagus may occur in adults.)

Treatment is with systemic imidazole class antifungals (such as itraconazole) but resistance may be a problem.

**Neutrophil disorders**

Lack of neutrophils (neutropenia) is covered in the Haematology chapter (p. •••). Neutrophil function disorders result in problems handling bacterial (especially staphylococcal) and fungal infections.

**Chronic granulomatous disease**

This may be X-linked (in two-thirds) or autosomal recessive (in one-third). It represents a group of defects of neutrophil NADPH oxidase, which prevents generation of hydrogen peroxide and hydroxyl radicals in the neutrophil phagolysosome, resulting in a failure of microbial killing.

Clinical features include:

- Recurrent bacterial and fungal infections affecting skin, lymph nodes, bone, lung and gastrointestinal tract
- Hepatosplenomegaly
- Recurrent noninfective granuloma formation particularly in the gastrointestinal and urinary tracts.

Stimulated neutrophils fail to reduce the dye nitroblue tetrazolium; this is used as a diagnostic test.

Continuous prophylaxis is required with:

- Cotrimoxazole, as an antibacterial agent which penetrates well into neutrophils
- Itraconazole; a broad-spectrum antifungal agent.

Steroid therapy may be required to combat the noninfective granulomatous problems. Bone marrow transplantation is being evaluated, and the possibility of somatic gene therapy is being explored.

Antenatal diagnosis is possible using umbilical cord blood obtained by fetoscopy.

**Leukocyte adhesion deficiency**

In this disorder there is a defect of a leukocyte surface molecule used in helping cells adhere to other cells by receptor—ligand interaction. Such interaction is essential to permit neutrophils to egress from the circulation. Inheritance is autosomal recessive.

Affected children show:

- Delayed separation of the umbilical cord (which depends on migration of neutrophils)
- Recurrent bacterial infections with poor pus formation
- Severe periodontitis
- Necrotizing skin lesions
- Poor wound healing
High circulating neutrophil count (cells can t get out).

Partial forms are described, with less severe problems. The full blown form is usually fatal in early life.
Bone marrow transplantation is indicated.

Complement disorders
Primary deficiencies of complement factors are rare, but secondary consumption of C3 and C4 may occur in certain autoimmune diseases and in nephritis. Deficiency of any one factor breaks the complement cascade, but the alternative complement pathway can bypass C1, C4 and C2 to activate C3 which is the main factor involved in opsonization of bacteria. Deficiency of one of the terminal components (C6-9), relatively common in some Middle Eastern and Japanese populations, affects complement-mediated bacterial lysis.

C1, C4 and C2 predispose to autoimmune diseases such as systemic lupus erythematosus (SCE), rather than to infections.

C3 deficiency (nearly always secondary to consumption) leads to a high susceptibility to pyogenic infections, whereas C5 deficiency is associated with a mild excess of infections.

C6—9 deficiencies lead to specific problems only with neisserial species (meningococcus and gonococcus).

Management involves monitoring for autoimmune disease, use of prophylactic antibiotics and immunization against meningococcus.

Hereditary angioedema
This is a deficiency of C1 esterase inhibitor, a protein which inhibits early complement activation. Inheritance is autosomal dominant.

Patients develop inappropriate complement activation leading to localized areas of increased vascular permeability and angioedema. This occurs spontaneously or is induced by physical trauma, including surgery and dental treatment. Attacks affecting the airway are life-threatening. Gastrointestinal involvement may produce a picture mimicking appendicitis or other acute abdomen.

Attacks are self-limiting, but if they are life-threatening they can be limited by infusing the purified inhibitor. Infusions of C1 inhibitor concentrate can be used prophylactically prior to surgery or dental work. Frequency of attacks is reduced by prophylaxis with tranexamic acid or retarded anabolic steroids such as danazol. Use of the latter is best avoided before puberty.

Secondary immunodeficiencies
Many disease states as well as treatments may cause immune suppression. Table 15.1 gives some of the more common examples and their consequences. The list is not exhaustive and many other disease processes, including malignancy, diabetes and uraemia, all cause ill-defined depression of immunity. Recognition of some of the susceptibilities allows appropriate prophylactic measures to be taken such as penicillin prophylaxis and pneumococcal immunization in hyposplenic patients. The list of prophylactic drugs that some children have to take can get very long, for example after bone marrow transplantation. It should be borne in mind that no prophylaxis is 100% effective.

Bacterial infections
Congenital bacterial infections are covered in Chapter 1.

Group A beta-haemolytic streptococcal pharyngitis
Pharyngitis presents with fever, sore throat and enlarged cervical (tonsillar) glands. There is usually but not always a purulent pharyngeal exudate though similar appearances may be seen with viral pharyngitis. A positive throat swab in the presence of symptoms confirms the diagnosis. Treatment is with penicillin for a full 10 days or a macrolide antibiotic if the child is penicillin-allergic.

Complications include peritonsillar abscess (quinsy), suppurative cervical lymphadenopathy, scarlet fever or, rarely, streptococcal toxic shock syndrome. Post-streptococcal glomerulonephritis (see p. 269) can occur after infection with particular nephritogenic strains. Raised levels of antistreptococcal antibodies (anti-streptolysin O or anti DNA-ase) may help confirm this diagnosis. Rheumatic fever (see p. 269) following streptococcal infection is nowadays a rare event which is preventable by antibiotic treatment of the initial infection.

Scarlet fever (scarlatina)
This group A streptococcal infection has an incubation period of 2—5 days.

Clinical manifestations include pharyngitis and a strawberry tongue see Fig 15.3, page 269. There is a generalized erythematous rash (day 2), and desquamation with healing (Fig. 15.1). The syndrome can be prevented with early penicillin treatment.
Bacterial infections

Rare complications include rheumatic fever, acute glomerulonephritis and other poststreptococcal syndromes. Streptococcal toxic shock may also occur.

**Group B β-haemolytic Streptococcus**

*S. agalactiae* causes serious invasive infection (pneumonia, sepsicaemia and meningitis) in newborn infants (see Ch. 2, p. ***).

**α-haemolytic streptococcal infection: endocarditis**

See Chapter 7, Cardiology, page ***.

**Streptococcus pneumoniae (pneumococcus) infection**

See Pneumonia (p. ***), Otitis media (p. ***), and Meningitis (p. ***).

### Table 15.1 Secondary immunodeficiency states

<table>
<thead>
<tr>
<th>Cause</th>
<th>System affected</th>
<th>Clinical problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection, e.g. measles, varicella, overwhelming sepsis</td>
<td>Immune responses, neutrophil function</td>
<td>Secondary infections, mainly bacterial or fungal</td>
</tr>
<tr>
<td>Chronic infection, e.g. viral, malaria, TB See also HIV, p. ****</td>
<td>Immune responses</td>
<td>Secondary infections, all types</td>
</tr>
<tr>
<td>Major trauma, burns, surgery and anaesthesia</td>
<td>Immune responses and neutrophil function</td>
<td>Bacterial and fungal infections</td>
</tr>
<tr>
<td><em>Drugs</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids*</td>
<td>Immune responses and inflammation</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>Chemotherapy, acute</td>
<td>Myelosuppression</td>
<td>Fungal, especially candida</td>
</tr>
<tr>
<td>Chemotherapy, longer term</td>
<td>Immune responses</td>
<td>Viral — varicella</td>
</tr>
<tr>
<td>Immunosuppressives, e.g. cyclosporin A</td>
<td>Specifically depressed immune responses</td>
<td>Bacterial/fungal sepsis</td>
</tr>
<tr>
<td>Bone marrow transplant with chem- and/or radiotherapy</td>
<td>Early myelosuppression and prolonged depression of immune responses</td>
<td>Opportunistic infections, e.g. <em>Pneumocystis carinii</em> pneumonia</td>
</tr>
<tr>
<td>Splenectomy/hyposplenism</td>
<td>Handling of capsulated bacteria</td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Protein-losing states (nephrotic syndrome, gastrointestinal disease)</td>
<td>Loss of IgG antibody</td>
<td>Bacterial infections especially pneumococcal</td>
</tr>
</tbody>
</table>

* The immunosuppressive dose of steroids in children is not well established. A dose of 2 mg/kg for >1 week or 1 mg/kg for 2 weeks is often taken as being significant.

### Impetigo and furunculosis

See Chapter 9, Dermatology, page ***.

### Deep-seated staphylococcal infections

See relevant organ specialty section.

### Toxic epidermal necrolysis (scalded skin syndrome)

This is caused by toxin (epidermolsyn)-producing *Staphylococcus aureus*. It is commonest in neonates.

Clinical manifestations include extensive superficial fragile blistering, which desquamates to leave raw areas. The skin can come off on the examiner’s hands (Nikolski sign). Toxic shock may be associated. In older children the disease is often localized. It may complicate chickenpox.

Complications include hypovolaemia, because of oozing from raw skin areas, and shock.
Toxic shock syndrome

This is caused by toxin-producing *Staphylococcus aureus*, or occasionally by group A Streptococcus.

It presents with fever, vomiting with or without diarrhoea, impaired consciousness and a generalized erythematous rash. Nonpurulent conjunctivitis may or may not be found. There is a focus of staphylococcal infection, which is often minor, and shock.

Complications of shock may occur.

Meningococcal infections

See Meningitis (p. ...) and Septicaemia (p. ...)

**Haemophilus infections**

*Haemophilus influenzae* may be capsulated in serotypes a–g. Type b causes the vast majority of invasive disease: bacteraemia, meningitis and epiglottitis. The introduction of conjugate vaccine against the type b capsulated organism (Hib vaccine) has virtually eliminated invasive disease due to this serotype, and the few cases now seen are due to other serotypes or to nonencapsulated strains. Nonencapsulated (or nontypable) strains are important causes of bronchitis, pneumonia and otitis media. The vaccination programme has not reduced the incidence of these problems.

Treatment of serious *H. influenzae* infections is with a third-generation cephalosporin such as cefotaxime. Amoxycillin can be used in the first instance for less serious infections, such as otitis media, but there is an antibiotic resistance rate of around 15%.

**Enteric fever (typhoid fever)**

**Epidemiology**

Common in developing countries. Occurs only in humans.

This is infection with *Salmonella typhi*, *S. paratyphi* A, *S. schottmuelleri* (previously *S. paratyphi* B) and *S. hirschfield* (previously *S. paratyphi* C). After ingestion of contaminated water or food, the salmonellae reach the bloodstream via Peyer patches of the small intestine. They collect in reticuloendothelial cells and re-seed the bloodstream.

Symptoms commence on average 14 days after exposure and can vary from an apparently mild febrile illness to severe septicemia. Typically there is constipation in the early phases, though young children tend to suffer diarrhoea. A dry cough is a common symptom. A sparse maculopapular rash may occur over the chest and abdomen (rose spots) (Fig. 15.2). There is lymphocytosis and a relative bradycardia in the face of fever. The illness can be complicated by intestinal haemorrhage and perforation. The organisms can be isolated from blood cultures and later in the illness from urine and stool.

Treatment with chloramphenicol or cotrimoxazole is required. Two vaccines are available, an injectable killed preparation based on the carbohydrate Vi antigen of *S. typhi* and a live oral vaccine based on an attenuated strain of *S. typhi* called Ty21a.
Diphtheria

Diphtheria is prevented by immunization with a toxoid derived from the toxin of *Corynebacterium diphtheriae*.

The organism infects the upper respiratory tract and, after an incubation period of 4–6 days, the released toxin damages first the local tissues, and then the heart, kidneys and nervous system by inhibiting protein synthesis. A firmly adherent greyish-white pseudomembrane of fibrin, erythrocytes, epithelial and inflammatory cells is seen on the nasal septum or pharynx (Fig. 15.3). Nasal diphtheria may be less easy to diagnose and produces a serosanguinous discharge. Oedema of the neck results in the so-called bull neck appearance. Heart failure, coma and death may occur after 1 week due to systemic effects of the toxin. Extension of the local infection to the larynx causes severe obstruction. Diagnosis is confirmed by culturing the organism from nasal or throat swabs and demonstrating toxin production.

Antitoxin (antiserum raised in horses) must be administered immediately after first excluding sensitivity to horse serum (administration of a small dose intradermally). Anaphylactic reactions are treated with adrenaline. Sensitivity is an indication for desensitization with progressively increasing doses. Penicillin or erythromycin are also given. Contacts should be immunized if they have not received a booster for 5 years. Unimmunized close contacts should receive antibiotics, although the efficacy of chemoprophylaxis has not been established.

**Tetanus**

**Epidemiology**

Rare in countries with a high immunization rate.

Tetanus is caused by the toxin of *Clostridium tetani*. Spores of the organism are widespread in the environment.
environment, including the intestinal tract of humans and other animals. Newborn babies can be infected in developing countries if there is a practice of placing cow dung on the umbilical cord stump. In many areas health education programmes and maternal immunization are reducing this problem.

More usually a wound is contaminated by spores. The spores germinate and the bacteria release tetanus toxin which binds to motor nerves. The toxin then migrates up the nerves to the central nervous system. Prolonged and painful muscle spasms develop, usually within 2 weeks of injury. Spasm of the facial muscles produces a fixed sardonic grin (risus sardonicus). Consciousness is not affected.

The disease can be prevented by immunization with tetanus toxoid. Maternal immunization prevents neonatal tetanus. Wounds should be carefully debrided and human tetanus immune globulin given to nonimmune individuals sustaining deep or dirty wounds.

Tetanus immune globulin is also given in established tetanus together with wound debridement. Intravenous penicillin G is administered. The affected patient is nursed in a darkened room. Muscle spasms are treated with diazepam. Paralysis with pancuronium and artificial ventilation may be required. The illness may continue for up to 6 weeks. Immunization is required after recovery because the tiny amount of toxin required to produce the disease is not necessarily immunogenic.

In primary pulmonary infection, bacilli infect the periphery of the lungs and draining lymph nodes at the hilum. The infection is asymptomatic initially but cough (if there is bronchial involvement), fever, and erythema nodosum may develop later. The enlarged lymph nodes may compress the bronchi and other mediastinal structures such as the oesophagus. The Mantoux test is positive. Most infections resolve with or without treatment. Chest X-ray examination may be normal or may show lymphadenopathy which may be accompanied by a focus of infection in the middle or lower lobe which calcifies during healing. Mycobacteria are usually cultivated from the sputum. In children too young to expectorate, samples are obtained from fibreoptic bronchoscopy or from early morning stomach washings via nasogastric tube.

Rarely the primary pulmonary infection may spread to involve a whole lobe of the lung, causing cough, fever and anorexia. The primary infection may reactivate in adult life in the apices of the lungs. The infection causes fever and night sweats. Cough with haemoptysis begins when the infected lung cavitates.

Primary infections can disseminate throughout the body. This form is called miliary tuberculosis because of the resemblance of the tuberculous granulomata to millet seeds. The symptoms of fever, anorexia and cough, TB meningitis, may be present (see Meningitis, p. 416). M. tuberculosis can cause cervical lymphadenopathy which is managed with antituberculous chemotherapy. If biopsy is required this should ideally be a full excision in case the cause turns out to be a nontuberculous mycobacterium (see below).

Commonly used antituberculous drugs are rifampicin, which is hepatotoxic and colours urine, sweat, tears (and contact lenses) orange. Ethambutol can rarely cause visual disturbance including colour blindness. Pyrazinamide can cause hepatotoxicity. Isoniazid, which can cause hepatotoxicity and peripheral neuropathy, is given as prophylaxis for 9 months to children who are Mantoux positive but well, to prevent reactivation and potential development of miliary TB. Established tuberculosis is treated with isoniazid, rifampicin and pyrazinamide for 6 months.

Prevention involves contact tracing, chemoprophylaxis and BCG vaccination.

**Tuberculosis**

**Epidemiology**

The global burden of infection with this disease is enormous. It has been estimated that 35% of the world population is infected. Most of the burden is in developing countries, where low standards of living and in some cases HIV infection are contributory factors. In the UK the incidence of tuberculosis fell dramatically through the 20th century in the 1990s there was a rise in the number of cases reported.

Most tuberculous infections are caused by *Mycobacterium tuberculosis*. Prior to the introduction of tuberculin testing of cattle *M. bovis* was another cause but this is now very rare. The main route of infection is by inhalation of infected droplets produced by coughing and sneezing. Two months after infection the patient will respond to the intradermal injection of *Mycobacterium tuberculosis* antigens (purified protein derivative; PPD) by development of induration after 2–3 days at the site of injection. The induration is produced by activated lymphocytes accumulating at the site of antigen injection (Mantoux test, Fig. 5.21, p. 152).

**Nontuberculous mycobacterial infection**

**Epidemiology**

Unlike *M. tuberculosis* and *M. bovis* these organisms are widely distributed in soil and water. Person-to-person spread does not occur.
The organisms mainly responsible are *M. avium*, *M. intracellulare*, *M. scrofulaceum*, *M. kansasii*, *M. fortuitum*, *M. marinum* and *M. chelonae*. In young children they cause cervical lymphadenitis or occasionally pulmonary infection. The last three organisms listed can cause localized cutaneous granulomas. Disseminated disease only occurs in the profoundly immunocompromised. The natural history of these infections is to resolve spontaneously but this may take many months or even years.

The differential diagnosis of cervical lymphadenitis due to one of these organisms includes tuberculosis, cat scratch disease and lymphoma. Biopsy of the lesions is therefore often undertaken. This should ideally be a complete excision biopsy otherwise chronically discharging sinus may result. If complete excision can be achieved this is usually curative.

The organisms are mostly inherently resistant to standard antituberculous drugs, but some other antibiotics such as ciprofloxacin, clarithromycin and cotrimoxazole may be of some benefit in difficult cases.

Children affected by these infections are not seriously ill but a lot of anxiety can be generated because of the chronicity of the symptoms and the disfigurement which can occur with discharging sinuses.

---

**Fungal infections**

### Candida infections

These are most commonly caused by *Candida albicans* but others, for example *C. tropicalis*, also occur.

Oral and napkin candidiasis are common in newborn infants (see Ch. 2). Candidal infections are less common in other age groups, but risk factors include general debility, treatment with antibiotics, steroids or other immunosuppressives. They usually respond to topical therapy such as nystatin or miconazole.

In immunosuppressed children there may be recurrent superficial infection, resistant to treatment or involving unusual sites such as the oesophagus. Deep (invasive) infection, for example pneumonia or septicaemia, occurs in the immunosuppressed, particularly in those with prolonged periods of neutropenia.

Invasive disease is treated with amphotericin B which can be administered in a liposomal form to reduce its toxicity. Azole drugs such as fluconazole are also used, but resistance may be a problem.

---

### Aspergillus infections

*Aspergillus fumigatus*, *A. flavus* and other species are ubiquitous in the environment. Transmission is by inhalation of spores.

Allergic bronchopulmonary aspergillosis occurs in atopic patients, especially those with asthma, causing wheezing with flitting perihilar opacities seen on chest radiography. In immunocompetent individuals, sinus and external ear infections can occur. Aspergilloma is a fungal ball which develops in pre-existing lung cavities/cysts.

Serious invasive aspergillosis, causing pneumonia, a fungaemia and widespread fungal abscess formation, occurs in immunocompromised patients particularly those undergoing prolonged myelosuppressive treatment and those with neutrophil function disorders. Mortality is high.

Treatment is with amphotericin B. Newer imidazole drugs, such as itraconazole, may be useful prophylactically in high risk patients.

### Dermatophytoses

These superficial fungal infections are caused by trichophyton and microsporidium species, and are commonly known as ringworm, affecting the scalp (tinea capitis), body (tinea corporis), feet (tinea pedis or athlete’s foot) and nails (tinea unguium). Transmission is by direct or indirect contact with affected humans, animals or fomites.

Tinea pedis can be treated with topical antifungal agents such as clotrimazole or miconazole. Other forms of the infection require systemic treatment with griseofulvin (taken for a prolonged period in the case of nail infections), which can be combined with topical preparations.

### Other fungal infections

For cryptococcosis, see below; for *Pneumocystis carinii* pneumonia, see Chapter 23, Respiratory, page ...
Immunology and infectious diseases

**Measles (rubeola)** (Fig. 15.4)

The incubation period is 8–14 days.

Measles presents with coryza, cough, fever and Koplik spots which resemble grains of sugar on the buccal membranes (days 1–2). The rash, which appears on days 3–4, is florid and maculopapular. It starts at the hairline and spreads down. It is nonpruritic and leaves brown staining.

Complications of measles include secondary bacterial infection, which may cause conjunctivitis, otitis media or pneumonia. Post infectious encephalitis occurs in 1–2 per 1000. Subacute sclerosing panencephalitis, a chronic, degenerative brain disease due to measles, is late and very rare.

**Mumps**

The incubation period is 12–25 days.

The illness may be subclinical. Clinical presentation includes fever, parotitis (Fig. 15.5) or other salivary gland inflammation, and aseptic meningitis.

It may be complicated by epididymo-orchitis, postinfectious encephalitis, pancreatitis, deafness or facial nerve paralysis.

**Rubella**

The incubation period is 14–21 days.

Rubella presents as a mild, often asymptomatic, illness. There is lymphadenopathy, especially postauricular, and low grade fever. The rash, which usually appears on day 1 of the illness, is transient and less florid than that of measles (Fig. 15.6).

Complications include polyarthritis, especially of the hands; this is more common in adults. Other complications are postinfectious encephalitis and congenital rubella syndrome.

**Erythema infectiosum (fifth disease, slapped cheek disease)**

This is a parvovirus infection with an incubation period of 4–14 days.

Clinical manifestations include a rubella-like rash with or without a slapped cheek appearance, which can persist or recur for several weeks. There is fever, coryza and pharyngitis with cervical lymphadenopathy.

Polyarthritis may occur as a complication, usually in adults. The virus transiently switches off red cell production. This may cause an aplastic crisis in disorders with increased red blood cell turnover, such as sickle cell anaemia, G6PD deficiency or spherocytosis.

---

Fig 15.4

Measles.

Fig 15.5

Parotid gland enlargement caused by mumps.

Fig 15.6

Rubella. (Courtesy of Milupa.)
Hydrops fetalis may occur as a result of in utero infection.

**Roseola infantum (erythema subitum)**

This is caused by human herpes virus 6 or 7. The incubation period is 7–15 days.

The illness presents with high fever and irritability which lasts 3 days.

As the fever resolves, a faint macular rash is seen on the trunk (Fig. 15.7). Febrile convulsions are a common complication.

**Varicella (chickenpox)**

The incubation period is 10–21 days.

Chickenpox presents with coryza, fever, and a rash developing after 24–48 hours (Fig. 15.8) which evolves through papular, vesicular, and pustular phases. Once the lesions are dry the patient is noninfectious. Permanent scarring may occur, particularly after secondary bacterial infection.

It may be complicated by encephalitis which is often cerebellar. Other complications are secondary bacterial infection or VZV pneumonia, the latter occurring especially in adults and smokers. Shingles may be a late complication, occasionally occurring in childhood.

**Herpes simplex infections**

**Gingivostomatitis**

The first contact with *Herpes simplex* virus can induce multiple small ulcers in the mouth. These are intensely painful, often preventing eating and sometimes drinking.

Acyclovir is probably of no benefit. Antifungal (nystatin) and antibiotic (fluocoxacillin) treatment may be needed for secondary infection. Some children require hospital admission for nasogastric or intravenous fluid therapy.

The lesions heal in 7—10 days, but recurrence is likely as a localized lesion on the lip (herpes labialis or cold sore) which will respond to topical aciclovir if given early.

**Neonatal herpes infections**

Most of these are caused by type II (genital) *Herpes simplex*, acquired from the maternal genital tract at delivery. Primary infection in the mother carries the highest risk.
Other *Herpes simplex* infections

Herpetic whitlows are localized lesions on the fingers whose main significance is that they are highly infectious. Ocular herpes infections involve the conjunctiva and cornea. Dendritic ulcers affecting the latter can cause permanent scarring; specialist treatment is required. Eczema herpeticum is a serious extensive cutaneous herpetic eruption in a child with atopic eczema, and requires hospitalization and intravenous aciclovir therapy. Herpes encephalitis in children is rare but devastating. It should be considered as a possible diagnosis in any child with unexplained encephalitic symptoms.

Other viral infections

**Enterovirus infections**

These may be caused by coxsackie A, B or ECHO viruses. The incubation period is 2–6 days. Clinical features include those of a nonspecific febrile illness, with pharyngitis, myalgia and headache. A nonspecific rash and mild gastro-intestinal symptoms may or may not be present. With specific agents there may be:

- Herpangina (coxsackie A)
- Pharyngeal ulceration
- Hand, foot and mouth disease (coxsackie A16)
- Anterior mouth ulcers
- Pleurodynia (Bornholm disease; coxsackie B group).

Complications include the following:

- Conjunctivitis
- Myositis
- Pneumonia
- Myocarditis
- Encephalitis
- Aseptic meningitis
- Postviral fatigue syndrome
- Fulminant septic shock-like illness in neonates, with or without hepatic necrosis.

**Infectious mononucleosis**

The incubation period is 14–21 days. The illness presents with fever, pharyngitis (Fig. 15.3) (cervical adenopathy), a maculopapular rash (in 15%) and anicteric hepatitis with splenomegaly. A florid rash follows ampicillin or amoxycillin treatment almost invariably. Complications include:

- Upper airway obstruction
- Myocarditis (pericarditis)
- Ruptured spleen
- Chronic infectious mononucleosis
- Encephalitis (mainly in the immunocompromised)
- Postviral fatigue.

**Cytomegalovirus infections**

This is caused by a herpes virus which becomes latent after primary infection, and is the commonest cause of congenital infection (see Ch. 1, p. •••). Postnatal primary infection usually results in an asymptomatic or mild illness. Cytomegalovirus can cause an infectious mononucleosis type illness. Serious life-threatening illness occurs in the immunocompromised as a result of the realighting of latent infection. After bone marrow transplantation severe pneumonitis and viremia may occur. HIV-infected children suffer focal infections including retinitis, encephalitis, colitis.

**Adenovirus infections**

Adenovirus is a DNA virus with nearly 50 different types, most of which cause respiratory disease. Upper respiratory illness usually manifests as pharyngitis or laryngitis (croup) with cervical lymphadenopathy. Conjunctivitis may occur (keratoconjunctival fever). In very young children (<2 years), lower respiratory illness may occur including bronchiolitis or pneumonia. The latter may result in severe lung damage. Types 40 and 41 are associated with gastrointestinal infection (see p. •••).

Adenoviruses are a particular problem in severely immunocompromised patients.

**Respiratory viral infections**

See Respirology, Chapter 23, page •••.

**Gastrointestinal viral infections**

See Gastroenterology, Chapter 11, page •••.

**Hepatitis viruses**

See Hepatology, Chapter 14, page •••.

**HIV/AIDS** (Fig. 15.9)

**INTRODUCTION**

HIV infection is caused by one of the two known human immunodeficiency viruses, HIV1 and HIV2. Affected
Viral infections

Individuals may be symptomatic or asymptomatic. In the immune system the virus infects the helper (CD4-positive) cells which gradually decline in number, leading to a weakening of the immune system and secondary susceptibility to infections including those caused by opportunist agents. The virus may also directly infect other organs leading to encephalopathy, cardiac disease, renal disease, etc. Acquired immunodeficiency syndrome (AIDS) is the end stage of symptomatic HIV infection when the patient develops certain AIDS indicator diseases (see below).

**Epidemiology and Incidence**

The World Health Organization has estimated that by the year 2000, 10 million children will have been infected with the virus. The great majority of these children are from the African and Asian continents.

Infection occurs in children mainly by vertical transmission from an infected mother, in utero, during delivery or postnatally through breast milk. The rate of transmission from an infected mother in the absence of breastfeeding varies from 15—25% in developed countries to 39% in Africa. Transmission can also occur through use of infected blood products, from intravenous drug abuse (in adolescence) and by sexual transmission, which in children usually means sexual abuse. Fortunately this mode of transmission is uncommon. Horizontal transmission by other means is extremely rare, and when reported has involved potential mixing of blood or other body fluids.

Blood product transfusion has produced a sizeable cohort of infected children in the UK (mainly boys with haemophilia) and a larger and even more tragic problem in Romanian orphans who were given repeated blood transfusions. Now that the problem has been identified, the numbers of children in Europe who have acquired infection by this route will slowly dwindle. However, this mode of transmission remains a major concern in developing countries.

The main concern for paediatricians is the epidemic of HIV infection in the heterosexual population and the resultant increase in children who have been vertically infected. In Africa the number of children infected by this route is vast. In certain East African countries the seroprevalence of HIV in the general population is approximately one in five. There is also a large and rapidly increasing problem of heterosexual HIV transmission in the Indian subcontinent. In the United Kingdom and Europe the numbers are still relatively small and largely restricted to high risk groups. Unlinked anonymous testing of neonatal dried blood spots (see Neonatal screening Ch. 2) facilitates good epidemiological monitoring in the UK.

In recent years it has become evident that certain interventions such as the avoidance of breastfeeding and the use of antiretroviral therapy in pregnancy and labour can greatly reduce the risk of vertical transmission from HIV-positive mothers. The implementation of these measures has significantly reduced the number of new paediatric cases in the USA and continental European countries. This is only just being achieved in the UK, because until recently there were very low levels of uptake of antenatal testing and therefore identification of women at risk. Recent evidence suggests that even a single dose of a relatively cheap antiviral agent given in labour can halve the risk of transmission and this offers hope for controlling the problem in developing countries.

**Aetiology and Pathogenesis**

When infection occurs, DNA proviral copies of the viral genome are made and integrated into the host cell DNA. Latent infection is therefore set up and, as for other viruses that exhibit latency, there is no known way of eliminating this proviral DNA from the body. The virus has a predilection for three major cell types; the CD4-positive helper T lymphocyte, the macrophage, and the cells of the central nervous system. In young children many of the manifestations of HIV infection can be attributed to infection in these cell types and involve development of immunodeficiency and neurological disorders.

**Clinical Presentation**

In older children who acquire the virus from blood transfusions or sexually, the disease behaves much as it does in adults. The reader is referred to textbooks of
adult medicine for details. There are certain differences however from adults, in that opportunistic infection with realighted infections such as toxoplasma is less common in children, simply because those in this age group are less likely to have previously encountered these agents and to have established latent infection. Possibly for the same reason, Kaposi sarcoma is relatively unusual in children.

The spectrum of the disease in infants who have acquired the virus from their mothers is often quite different from that in older individuals. Clinical presentation may occur in the following ways:

- The mother is identified as having HIV infection and the child is then screened (see below for problems in confirming infection in infants)
- The infant presents within the first 6 months of life with an AIDS-defining illness (see Information box 15.1), most commonly *Pneumocystis carinii* pneumonia
- An infant or young child develops symptoms suggestive of HIV infection which include:
  - Recurrent respiratory infections
  - Tachypnoea with chest radiological appearances of lymphoid interstitial pneumonitis
  - Diarrhoea
  - Candidiasis, persistent or recurrent
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Parotid enlargement
  - Neurological symptoms: motor disorder, e.g. spastic diplegia, developmental regression

Not all of these are AIDS-defining; see Information box 15.1.

### Diagnosis

In the older child the diagnosis when suspected is easily confirmed with an HIV antibody test. Pre-test counselling and post-test support from a counsellor specifically trained in dealing with children and adolescents is mandatory.

In infants and young children making the diagnosis of HIV infection is not straightforward because the HIV antibody test will detect passively acquired maternal antibody which may persist until up to 18 months of age. While viral culture and antigen detection tests have been used to circumvent this problem, these are expensive and time-consuming. The method of choice for diagnosis in early life is the polymerase chain reaction (PCR) test to detect proviral DNA. This is highly specific and sensitive after 2 weeks of age and should be blood tested on two separate occasions to confirm a positive result.

### Management

Follow up is best conducted in a family clinic because the mother, father and siblings are often affected.

In older children the management of HIV and AIDS is similar to that in adults with the disease. Prophylaxis against *P. carinii* and bacterial infections is along standard lines, being related to the circulating CD4 cell count. Early identification and treatment of opportunistic infections are required and antiretroviral treatment is useful in slowing down the progress of the disease (see below). The paediatrician’s role will include tackling specific problems which may occur in relation to schooling and in helping the child and family cope with this life-threatening and stigmatizing disease. Counselling and support should be provided by persons experienced with dealing with children and adolescents suffering chronic and fatal disorders.
In infants born to known HIV-positive mothers, initial management will be aimed at trying to establish whether or not the infant is infected. In developed countries, breastfeeding is discouraged to decrease the risk of HIV transmission. In developing countries the benefits of breastfeeding outweigh the risks of viral transmission, although very prolonged breastfeeding may unnecessarily increase the risks; this is an issue currently under study.

Monitoring of growth development and susceptibility to infection will form part of clinical assessment.

Infection prophylaxis involves immunizations, which should all be given except for BCG. The last is omitted (because of the risk of disseminated BCGosis) in this country, though it is given in developing countries where the risks of tuberculosis outweigh the risks of vaccine-related problems. The killed injectable polio vaccine is preferred to the standard live oral vaccine because of the risk of vaccine-associated poliomyelitis in the recipient or in family contacts who may also be immunodeficient. All other vaccines including the live MMR vaccine are safe and are indicated.

Drug prophylaxis includes the use of cotrimoxazole against P. carinii pneumonia, and this also provides some protection against bacterial infections. The use of intravenous immunoglobulin has also been suggested in those with recurrent bacterial infections which happen despite antibiotic prophylaxis, but is not employed generally. Other types of secondary antimicrobial prophylaxis, for example antifungal agents, antivirals against cytomegalovirus and antimycobacterial drugs, also need to be employed in some cases.

There have been considerable advances in the use of antiretroviral drugs in the last 5 years. A number of different agents, including nucleoside and non-nucleoside reverse transcriptase inhibitors and viral protease inhibitors, are used in combinations of three or four drugs, known as highly active antiretroviral therapy (HAART). Such treatments have been shown to arrest the progress of the disease and sometimes can reverse the immune incompetence that has developed. There has been a significant fall in hospitalization rates for complications of HIV in both adults and children since the introduction of this treatment. There is concern that the development of viral resistance will reverse this trend and this is being monitored. It has not yet been fully established in which children and at what stage of the illness this treatment should be started, but it depends on clinical parameters, HIV viral load and CD4 count. There is no doubt that treatment should be commenced when AIDS-defining illnesses develop. Marked improvement, at least on a temporary basis, can be seen in neurological manifestations when drug regimens which include zidovudine are used.

The overall outcomes for children who prove to be infected from their mothers are shown in Information box 15.2.

**Protozoal diseases**

**Gastrointestinal protozoa**

See Gastroenterology, Chapter 11 (Amoebiasis, Giardiasis and Cryptosporidiosis).

**Malaria**

**Epidemiology**

Globally this is one of the most important causes of death and disability particularly in Africa.

Because of increased world travel, it is a possible cause of fever in any country.

In the UK there are 200—300 imported cases each year in children.

A small number of individuals die in the UK each year, nearly all due to falciparum malaria and usually associated with delayed diagnosis and treatment.

Malaria is an infection due to *Plasmodium falciparum* (most severe), *P. ovale*, *P. vivax* and *P. ovale*, acquired from the bite of the female anopheline mosquito. The disease...
Immunology and infectious diseases

occurs in the tropics but is commonly imported into temperate climates. The diagnosis should be considered in children returned from the tropics who develop fever.

The parasites develop in red cells causing haemolysis. Symptoms include malaise, very high fever, headache, myalgia, abdominal pain, diarrhoea, vomiting and jaundice. P. falciparum produces convulsions and coma (cerebral malaria) and haemoglobinuria (blackwater fever).

The diagnosis is made by detecting the parasites in thick and thin blood films. Repeated examinations may be required and the most useful samples are taken just as the fever is rising. The differential diagnosis will include other diseases acquired in the tropics, including typhoid fever, and it should be remembered that in returning travellers it is not unusual for more than one disease to be present.

The infection is prevented by avoidance of mosquito bites (using insect repellents and mosquito nets impregnated with insecticide) and chemoprophylaxis. The choice of chemoprophylactic agents is determined by local parasite sensitivity but examples include a combination of proguanil and chloroquine or mefloquine.

Malaria caused by P. falciparum is treated with quinine because of the possibility of chloroquine resistance. A 5-day course of this treatment is followed up with a single dose ofFansidar (pyrimethamine and sulfadoxine) unless the child is glucose-6-phosphate dehydrogenase (G6PD)-deficient. In the UK all cases of malaria are tested for G6PD deficiency since its presence will influence subsequent treatment (see p. 336). The deficiency is particularly common in certain populations in West Africa, probably because it confers a degree of protection against severe malaria.

In other (more benign) forms of malaria oral chloroquine is used. Since these forms have an exoerythrocytic phase, patients who will not be returning to endemic areas should also be treated with primaquine unless they are G6PD-deficient.

Severe falciparum malaria (high parasite load with or without coma) should be treated with intravenous quinine in a specialist centre, with close monitoring for both the effects of the disease and the side-effects of the treatment. Research is in progress to develop a vaccine.

Helminthic infections

Epidemiology

Virtually all higher life forms and the surface of the earth are colonized by helminths.

Nematodes (roundworms)

Illnesses caused

Ancylostomiasis, ascariasis, strongyloidiasis, enterobiasis and trichuriasis.

Intestinal nematodes are diagnosed by finding the ova of the causative parasite in the stool. Tissue nematodes cause visceral larva migrans, and filariasis.

Ancylostomiasis is caused by hookworm (Ancylostoma duodenale, Ancylostoma ceylanicum or Necator americanus) in the tropics. Hookworm larvae living in damp, warm soil can infect the human host by direct penetration through the skin. Children living in farming communities in tropical countries are particularly at risk. The larvae travel in the circulation to the lungs where they enter and travel up the bronchial tree to the larynx, then pharynx, where they are swallowed and pass to the small intestine. After a month the mature worms develop. They are about 1 cm long and attach to the mucosa of the small intestine by specialized mouth parts through which they suck blood. Worm eggs are passed in the faeces and hatch to produce larvae capable of infecting the next host. The main manifestations of infection are anaemia due to iron loss and protein-losing enteropathy. The diagnosis is made by finding ova in fresh faecal smears. Mebendazole eradicates the parasite.

Ascariasis is acquired by ingesting eggs of the roundworm Ascaris lumbricoides, which hatch in the small intestine. The larvae gain access to the circulation by penetrating the intestinal wall. They enter in the lungs, penetrate the alveoli, then ascend the bronchial tree and are swallowed. The adult worm (15—35 cm) develops in the small intestine, the female shedding eggs in the stool of the host. The transit of larvae through the lungs may produce the Löffler syndrome of pulmonary infiltration and eosinophilia (see p. 336). Watery diarrhoea is induced with heavy infestations causing intestinal obstruction. Mebendazole is an effective treatment.

Strongyloidiasis is acquired in the same way as ancylostomiasis. Ova from mature Strongyloides stercoralis can hatch in the intestinal lumen, allowing the larvae to penetrate the colonic or perianal skin and establish an overwhelming infection. Disseminated strongyloidiasis is more likely in immunodeficient states, as occur in severe malnutrition or AIDS. The symptoms are those of malabsorption, with disseminated strongyloidiasis sometimes producing shock. The treatment is thiabendazole.

Enterobiasis is caused worldwide by Enterobius vermicularis (pinworm or threadworm) which is acquired by ingesting eggs from clothing or bedding. The eggs hatch in the stomach and the larvae travel to the caecum.
Specific infections in children

Specific infections in children

Specific infections in children

Specific infections in children

to mature. Mature female worms (1 cm long) deposit eggs on perianal skin. Scratching the irritated skin results in dissemination of the infection under fingernails. The pinworm eggs are more easily seen if a piece of clear adhesive tape is pressed against the perianal skin first thing in the morning, rather than in faeces. Mebendazole is given to all infected, symptomatic members of the family. Repeated treatment may be required.

Trichuriasis, caused by *Trichuris trichiura* (whipworm) is acquired in the same way as enterobiasis. As the worm attaches to the colon and sucks blood, heavy infections are associated with iron deficiency and bloody diarrhoea (dysentery). Once again mebendazole reduces the worm burden.

Visceral larva migrans (toxocariasis) is caused by the dog and cat parasites *Toxocara canis*, *T. catti* and *T. leonina*. Ingestion of eggs from animal faeces by children results in dissemination from the gastrointestinal tract to lung, liver, eye, brain, kidney and heart. Migration of the parasites produces fever, myalgia, cough and wheeze and convulsions. Eye involvement produces decreased visual acuity. Granulomata, which have been mistaken for retinoblastoma, can be seen on the retina. The blood shows a marked eosinophilia, and measurement of antibodies against the eggs of toxocara confirms the diagnosis. The treatment is diethylcarbamazine.

Infection of lymphatic vessels with minute worms called filariae results in filariasis, lymphoedema (hydrocele and elephantiasis) 10—20 years after infection, caused by lymphatic obliteration by scarring. People may be infected by mosquitoes bearing larval forms of the worm. The diagnosis is made by demonstrating larval forms (microfilariae) in blood samples. Treatment with diethylcarbamazine or ivermectin must be given early in the disease when there is lymphangitis; there is no therapy for elephantiasis. Other forms of filariasis infect the eye (onchocerciasis, river blindness). The vector is the blackfly (*simulium*). Microfilariae can be seen by slit lamp in the anterior chamber of the eye. Tabanid flies transmit a form of filariasis called loa loa, which can cause seizures if localized in the brain. Treatment is nicosamide, or praziquantel for cysticercosis.

The larvae of *T. saginata* and *T. solium* are found in undercooked meat. The tapeworms mature in the intestine to lengths of up to 10 metres. Infection is usually asymptomatic. Infection with *T. solium* may cause dissemination of larvae in the tissues (cysticercosis) which can cause seizures if localized in the brain. Treatment is nicosamide, or praziquantel for cysticercosis.

The larvae of *Echinococcus granulosus* are acquired by contact with faeces of dogs that have become infected by ingestion of the viscera of parasitized sheep and cattle. The eggs hatch in the duodenum, penetrate the intestinal wall and travel to the liver, where the hydatid cyst forms. The cyst may grow to 20 cm in diameter. Cysts are also found in the lungs, bone and brain. Surgical removal is hazardous, since spillage of the cyst contents can result not only in disease dissemination but also in an overwhelming anaphylactoid reaction. The need for surgery may be avoided with the use of albendazole.

The larvae of trematodes are released into water from parasitized snails. They penetrate human skin and migrate to the lungs, then to the liver. After maturing (4–2 mm in length) they migrate again to the blood vessels of the bladder (*Schistosoma haematobium*) or gut to lay eggs. Granulomata form around eggs that are not released externally.

Acute schistosomiasis occurs shortly after infection, with fever, lymphadenopathy, hepatosplenomegaly and eosinophilia. Chronic schistosomiasis due to *Schistosoma haematobium* causes frequency, dysuria and haematuria leading to chronic kidney failure and bladder cancer. The other species of schistosomes produce bloody diarrhoea and portal hypertension.

Schistosomiasis is diagnosed by finding the eggs in the urine (best in the terminal part of the urinary stream) or stool. There are also serological tests.

The treatment is praziquantel.

Cestodes (tapeworms)

Aetiology

Taeniasis is caused by ingesting the larvae of *Taenia saginata* (beef tapeworm) or *Taenia solium* (pig tapeworm).

Echinococcosis (hydatid disease) is caused by *Echinococcus granulosus*.

Trematodes (flukes) – schistosomiasis

Aetiology

Schistosomiasis is caused by blood flukes *Schistosoma haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*, and *S. mekongi* which infect children.

Otitis media

See Chapter 4, The child from 1 to 5 years, page •••.
Septicaemia

Epidemiology
The commonest cause of septicaemia is meningococcus. This causes septicaemia and/or meningitis. About two-thirds of meningococcal disease involves both processes with the remainder divided between a pure meningitis and a pure septicaemia without meningitis. The prognosis is worst for the last variety. Overall 4000 cases of meningococcal disease are reported per annum in the UK, of which 10% are total. Prior to the introduction of the conjugated meningococcal C vaccine, around 60% of these are caused by Group B organisms, one-third by Group C organisms and a small number by other groups. In developing countries, including the meningitis belt in sub-Saharan Africa, Group A disease predominates.

Bacteraemia is defined as the presence of bacteria in the blood as identified on blood culture. This may be a primary process following invasion of organisms, for example from the nasopharynx, or it may be secondary and associated with a focal infection such as pneumonia or osteomyelitis. In septicaemia, bacteria are not only present in the blood but are actively multiplying. This leads to a profound illness with circulatory disturbance leading to shock in its most severe form. Damage to the endothelial lining of blood vessels, metabolic disturbance and coagulopathy all contribute to the development of multiorgan dysfunction and damage, thus compounding the problem. Asia bacteraemia, septicaemia may be primary or secondary to bloodstream invasion from a site of focal infection.

Causative organisms in newborn infants include group B Streptococcus, *Escherichia coli*, and rarely *Listeria monocytogenes* (see Ch. 2).

In post-neonatal childhood the commonest and most devastating cause of septicaemia is *Neisseria meningitidis* (meningococcus). Other causes include *E. coli*, salmonella species including *S. typhi*, other Gram-negative bacilli, *S. aureus* and *S. pneumoniae*. *H. influenzae* type b is now a very rare cause.

The clinical presentation of sepsis in children will include fever and a number of nonspecific signs of being unwell which are described in Chapters 2—5. Meningococcal septicaemia usually but not invariably causes a haemorrhagic petechial or purpuric rash. In about one-third of cases this characteristic rash is preceded by a nonspecific maculopapular rash which can be mistaken for a nonspecific viral exanthem or the early stages of chickenpox. Petechial spots may coexist with this rash and should be looked for very carefully. Unlike most other childhood rashes the spots do not blanch on pressure and this is the basis of the tumbler test in which a glass tumbler is pressed to the skin over the spots and blanching or nonblanching observed. Purpuric spots are larger areas of haemorrhage in the skin secondary to the blood vessel damage which occurs in meningococcal sepsis.

Treatment of septicaemia is a medical emergency. From the first appearance of the rash to the stage of irreversible shock may take a matter of a few hours. Doctors seeing children with rashes suspected of being due to meningococcal infection must administer intravenous or intramuscular penicillin without delay and before transfer to hospital. Once in hospital treatment in an intensive care setting is usually required and involves treatment of shock and multiorgan dysfunction.

Prevention of meningococcal disease is a major research goal. A polysaccharide vaccine against group A and C organisms has been available for some time but is poorly effective in very young children (<2 years). It is recommended for travellers to developing countries with a high incidence of group A disease. Recently a conjugate group C vaccine has been licensed in the UK; this is immunogenic in young infants and should greatly reduce the proportion of disease due to this serogroup. Unfortunately a group B vaccine is not yet available. This is because the group B polysaccharide cross-reacts with a human antigen and is therefore nonimmunogenic. Attempts at vaccine development are therefore aimed at using a meningococcal protein antigen rather than the polysaccharide.

Meningitis

INTRODUCTION
Two main forms of meningitis are viral (or aseptic) meningitis, and bacterial. A subtype of bacterial meningitis, often considered as a separate entity because it behaves differently, is tuberculous meningitis. In immunocompromised individuals, such as those with HIV and AIDS, fungal meningitis may also occur.

In viral meningitis there is usually an accompanying encephalitis to produce the clinical picture of meningoencephalitis. Sometimes there is a pure aseptic meningitis and in other cases a pure encephalitis without any meningeal inflammation. The range of possible viruses causing aseptic meningitis and meningoencephalitis is large. Some causes, particularly the insect-borne viruses (arboviruses), are only found in certain parts of the world. The main viral causes of aseptic meningitis in the UK are: enteroviruses (ECHO and coxsackie viruses) and mumps. A variety of other common viral illnesses may occasionally may be complicated by meningoencephalitis including infection with influenza, parainfluenza, RSV, measles,
rubella and Epstein—Barr virus. Lymphocytic choriomeningitis virus is a rare but much vaunted cause of aseptic meningitis contracted from rodents.

The normal course of events is that there is a systemic illness with the virus then homing in on the central nervous system.

PATHOGENESIS AND AETIOLOGY OF BACTERIAL MENINGITIS

In bacterial meningitis the organisms gain access to the central nervous system via the bloodstream. A very small proportion of cases is associated with direct invasion of the central nervous system, either through defects in the dura, often in the region of the cribriform plate or from pericranial sepsis such as middle ear, sinus or dental sepsis. In those spread by the haematogenous route the three commonest organisms are *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). The proliferation of the bacteria in meninges produces a purulent response that gives rise to the symptoms and signs of the illness. Occasionally the cerebral tissue itself may become involved causing cerebritis. In neonates, the range of organisms causing meningitis is much greater and includes those derived from the maternal genital tract at birth such as group B Streptococcus and *Escherichia coli*. *Listeria monocytogenes* is also an important cause of meningitis in this age group. In the immunocompromised child, and in those with ventriculoperitoneal shunts in situ, the range of potential causative organisms is also much greater.

Tuberculous meningitis, caused by *Mycobacterium tuberculosis*, usually occurring following haematogenous spread from a primary focus elsewhere; most commonly the lungs. Multiple tubercles are produced throughout the meninges. There may also be larger foci of infection in the brain tissue itself, called tuberculomas.

INCIDENCE

There are approximately 4000 cases of bacterial meningitis reported annually in the UK. The greatest incidence occurs in infants and young children. *H. influenzae* and *N. meningitidis* (meningococcus) were previously the two commonest varieties with *Streptococcus pneumoniae* (pneumococcus) in third place. We have now seen a marked fall in the incidence of *H. influenzae* meningitis, due to the introduction of a vaccine. There is a seasonal variation with an excess of cases occurring during the winter months.

CLINICAL PRESENTATION

Inflammation of the meninges produces characteristic clinical findings. There will be fever, headache, bulging fontanelle (if patent), photophobia, pallor, vomiting, and signs of cerebral irritation such as high-pitched cry in young infants. The inflammation of the meninges produces reflex spasm of the neck muscles (neck stiffness) and pain on stretching the meninges, for instance in straight leg raising. These latter specific signs may be absent in children under 2 years of age. At that age the child often presents with a nonspecific febrile illness without specific signs. Most children will show an impaired conscious level that may range from mild drowsiness to coma. Seizures may be a presenting feature and occasionally focal neurological deficits. In meningococcal meningitis, the accompanying septicaemic component may produce a vasculitis leading to shock. In this condition there is usually but not inevitably a typical rash (Fig. 15.11) that is purpuric/petechial in appearance (this is caused by small haemorrhages due to leaky capillaries). The rash does not blanch on pressure in contrast to most other rashes that children get. In viral meningitis the signs and symptoms may be accompanied by evidence of a systemic viral infection and if these are specific as in mumps this may make the diagnosis easy.

In tuberculous meningitis the onset of symptoms is more insidious than with the other forms, with the features of drowsiness, headache, neck stiffness and vomiting often developing over several days to weeks. Mood changes, anorexia and vomiting progress to neck stiffness and cranial nerve palsies followed by coma. Focal neurological deficits such as squint or ophthalmoplegia are more likely to be present in this form of the disease. Disease elsewhere in the body may not be evident.

DIAGNOSIS

In some cases the diagnosis may be made on clinical grounds, e.g. a meningitic illness associated with the
typical features of mumps or, more seriously, meningitis associated with the typical meningococcal rash. In most other cases the establishment of the diagnosis depends on the cerebrospinal fluid (CSF) appearances at lumbar puncture (Fig. 15.12). Performing the lumbar puncture carries some risks since there is usually raised intracranial pressure. As a rule if the symptoms are prolonged, the child is drowsy or if there have been focal seizures or a focal neurological deficit it is advisable to obtain a CT scan of the head before proceeding to lumbar puncture. However, even with a normal CT scan, if there are clinical signs of raised intracranial pressure a lumbar puncture may be contraindicated. Table 15.2 presents the typical findings in the main forms of meningitis.

In most cases the main forms of meningitis can be readily determined from the CSF findings but particular difficulties may occur in children who have received antibiotics and who therefore have a partially treated meningitis. Rapid bacterial antigen detection may be helpful in these cases. Polymerase chain reaction (PCR) techniques for detection of specific bacterial nucleic acid sequences allows precise diagnosis.

Poliomyelitis is dealt with on page ... generation cephalosporin such as ceftriaxone. In children under 3 months of age, ampicillin is added to cover the possibility of listeria meningitis.

Rifampicin is given to eliminate nasal carriage of N. meningitidis and H. influenzae. A 2- or 4-day course, respectively, is also given to household contacts (but only if there are members of the household who are less than school age in the case of H. influenzae meningitis).

In tuberculous meningitis, bacteriological culture may take several weeks. Once clinical diagnosis is made the patient should be started on antituberculous chemotherapy. Mortality may be as high as 50% if treatment is delayed, with permanent handicap in most of the survivors.

In viral meningitis there is usually a benign self-limiting course which does not require specific therapy. Antibiotics or antituberculous drugs are sometimes given if there is uncertainty about the possibility of bacterial or tuberculous meningitis. In suspected Herpes simplex encephalitis, aciclovir treatment is given.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Cell count</th>
<th>Protein</th>
<th>Glucose</th>
<th>Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>↑ Mainly neutrophils</td>
<td>Mildly ↑</td>
<td>↓</td>
<td>Positive Gram stain and culture</td>
</tr>
<tr>
<td>Partially treated bacterial</td>
<td>↑ (Mixed mononuclear/neutrophil)</td>
<td>Normal or slightly ↑</td>
<td>Normal or ↓</td>
<td>Gram stain and culture often negative</td>
</tr>
<tr>
<td>Viral</td>
<td>↑ (Or occasionally normal, predominantly mononuclear)</td>
<td>Normal or ↑</td>
<td>Normal</td>
<td>Negative bacterial culture</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>↑ (Mononuclear cells)</td>
<td>↑ May be very high</td>
<td>↓</td>
<td>Positive Ziehl–Neelsen stain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Culture takes 6 weeks</td>
</tr>
</tbody>
</table>

* Polymerase chain reaction for detection of specific nucleic acid fragments of the bacteria or viruses
In addition to antibiotic treatment, it has recently been shown that with H. influenzae meningitis the use of corticosteroids reduces the likelihood of hearing loss and other damage after the infection. There is evidence that it may also help in cases of tuberculous meningitis. The antibiotic regimes used are now so powerful that the use of these immunosuppressive agents does not compromise the treatment.

In addition to the specific antimicrobial therapy, supportive care for the child is very important. In particular the management of the child’s fluid balance may make all the difference to the outcome. Meningitis tends to cause inappropriate ADH secretion with water retention and a risk of developing cerebral oedema. On the other hand the severely ill child who has been vomiting and who may have septicaemic shock may need large volumes of fluid therapy. A great deal of experience is needed in judging how much and which fluid to give, and the child’s fluid status and electrolytes should be carefully monitored throughout treatment. Analgesics are often underemployed in meningitis particularly if the child is too young to specifically complain of headache. Regular paracetamol should be given until improvement occurs.

Meningitis may be complicated by brain abscess which can also follow sinusitis, otitis, facial cellulitis and penetrating head injuries. Children with cyanotic congenital heart disease are predisposed to this. Infections may result from mixed aerobic and anaerobic bacteria. Early symptoms of headache, lethargy and fever proceed to hemiparesis with papilloedema. CSF examination shows a few leukocytes and increased protein. After demonstration of an abscess on CT, drainage and/or prolonged antibiotic therapy are required. Mortality is high, especially if the abscess ruptures, and permanent neurological deficits are common.

PREVENTION
Prevention of some types of meningitis is possible. Hib vaccination has virtually eliminated this type of meningitis over the last few years. Vaccines are also present against types A and C meningococcus, including the recently introduced type C conjugate vaccine, which is already having an impact in the UK. Unfortunately type B, the predominant cause of disease in the UK, cannot be vaccinated against at the present time. When families travel to certain parts of the world, particularly East Africa and the Middle East, they should receive immunization. In tuberculous meningitis, contact tracing and BCG immunization where appropriate should help reduce the risk. Mumps immunization has virtually eliminated what was the commonest cause of viral meningitis.

Bone and joint infections

Epidemiology
Up to 80% of osteomyelitis and septic arthritis in children is caused by S. aureus. Other causes include streptococcal species, Gram-negative bacilli including salmonella species and Haemophilus influenzae type b. Tuberculosis should always be borne in mind as a possible cause of these infections. In sickle cell diseases and in immunocompromised individuals, osteomyelitis is more common and more likely to be caused by an unusual organism such as salmonella.

The organism usually finds its way to the skeleton via the bloodstream following a usually subclinical bacteraemia (haematogenous spread). The metaphyseal region of a long bone is most commonly affected in osteomyelitis or a single large joint in septic arthritis. In a small number of cases infection is caused by a penetrating injury or direct spread from an infected adjacent focus.

In acute infection the child will be febrile and ill. There will be failure to move the affected part of the body or failure to weight bear on an affected limb. The joint or bone will be swollen and tender. In chronic infections, such as those due to tuberculosis, the acute inflammatory signs are less and fever may not be present. Radiographic changes of osteomyelitis (areas of rarefaction and periosteal reaction) take at least 10 days though soft tissue swelling may be evident earlier. Isotope bone scan is much more sensitive from early in the illness except in very young infants (less than 3 months of age). Magnetic resonance imaging (MRI) may be useful, particularly in chronic or complicated cases. In septic arthritis joint aspiration is both diagnostically and therapeutically useful. The causative organism may be grown directly from aspirates or from blood cultures where it is found in approximately 60% of osteomyelitis and 40% of septic arthritis cases.

Treatment is with intravenous antibiotics in high dose to achieve good bone penetration. If the organism is not isolated then a broad-spectrum combination such as fluclaxacillin and cefotaxime (or ampicillin) is used in previously healthy children. Wider Gram-negative antibiotic cover is needed in children with underlying disorders. After initial clinical response antibiotics are switched to the oral route and then must be continued for 4 weeks in septic arthritis and 6 weeks in osteomyelitis. Failure to respond suggests a resistant organism or abscess formation, and surgical exploration may be required. Serial measurement of inflammatory markers such as C-reactive protein or
sedimentation rate may be useful for monitoring treatment progress.

**Less common but important infections**

The following infectious diseases are important on a global basis but are uncommon in the UK.

**Brucellosis**

Infected dairy products are the usual source of this disease (zoonoses, diseases of animals which can be transmitted to man). Organisms involved may be:

- \( \textit{Brucella abortus} \) (cows)
- \( \textit{B. melitensis} \) (goats)
- \( \textit{B. suis} \) (pigs)
- \( \textit{B. canis} \) (dogs)
- \( \textit{B. ovis} \) (sheep)
- \( \textit{B. neotomae} \) (desert rats).

The disease presents as an influenza-like illness. Diagnosis is by means of:

- Agglutinating and complement-fixing antibodies
- ELISA assay
- Blood assay and bone marrow cultures, the latter being most likely to be positive.

Treatment is with tetracycline or cotrimoxazole with or without streptomycin for 4 weeks.

**Cat-scratch disease**

The organism causing this disease, acquired as the name suggests, is \( \textit{Rochalimaea henselae} \). A papule appears 10 days after the scratch or bite and there is massive enlargement of regional lymph nodes. The disease resolves spontaneously after 2 months.

Diagnosis is by means of:

- Agglutinating and complement-fixing antibodies
- ELISA assay
- Blood assay and bone marrow cultures, the latter being most likely to be positive.

Treatment is with tetracycline or cotrimoxazole with or without streptomycin for 4 weeks.

**Cryptococcosis**

This is caused by \( \textit{Cryptococcus neoformans} \). The yeast spores are inhaled, usually by an immunocompromised host. From the lungs they spread to the meninges, and the commonest form of presentation in children is as a subacute meningitis. Diagnosis is by microscopy of CSF.

Treatment is with antifungals including amphotericin B and flucytosine. Long-term prophylaxis with fluconazole may be required in immunocompromised children to prevent relapse.

**Dengue fever**

Dengue fever is a viral infection, the source being mosquitoes in tropical countries.

The disease presents with fever, headache and transient macular rash. There is myalgia and a second, morbilliform rash after the fever resolves. A second attack may be more severe with a haemorrhagic illness and shock. Diagnosis is by means of serological testing. Mosquito control helps prevention.

**Histoplasmosis**

This is a mycosis (fungal infection), caused by \( \textit{Histoplasma capsulatum} \), when fungal spores shed by birds and bats are inhaled. It presents as an influenza-like illness, becoming disseminated in immuno-compromised patients.

Diagnosis is by means of culture of blood, bone marrow, urine, CSF and sputum, if the disease is disseminated. Treatment is with amphotericin B.

**Leishmaniasis (kala-azar)**

This protozoal infection is caused by \( \textit{Leishmania donovani} \), and the source is the sandfly, found in all continents except Australia.

Incubation may be up to 10 years. Nonspecific symptoms include fever, and malaise. These are accompanied by abdominal pain from a hugely enlarged spleen. The cutaneous form produces ulcerating erythematous macules. The illness may progress to involve the respiratory tract (mucocutaneous leishmaniasis).

Diagnosis is by means of serology, examination of biopsies of the lesion and specialized culture techniques.

Pentavalent antimony compounds, such as sodium stibogluconate and meglumine antimonate are standard treatments, but liposomal amphotericin is also effective and less toxic. Amphotericin is given for cutaneous leishmaniasis. Splenectomy may be required.

Prevention is by sandfly control.

**Leptospirosis (Weil disease)**

This illness is caused by \( \textit{Leptospira interrogans} \), the source being contamination of water and soil near rivers by rat urine.

The clinical features are:

- \( \textit{B. canis} \) (dogs)
- \( \textit{B. ovis} \) (sheep)
- \( \textit{B. neotomae} \) (desert rats).

Less common but important infections

The following infectious diseases are important on a global basis but are uncommon in the UK.

**Brucellosis**

Infected dairy products are the usual source of this disease (zoonoses, diseases of animals which can be transmitted to man). Organisms involved may be:

- \( \textit{Brucella abortus} \) (cows)
- \( \textit{B. melitensis} \) (goats)
- \( \textit{B. suis} \) (pigs)
- \( \textit{B. canis} \) (dogs)
- \( \textit{B. ovis} \) (sheep)
- \( \textit{B. neotomae} \) (desert rats).

The disease presents as an influenza-like illness. Diagnosis is by means of:

- Agglutinating and complement-fixing antibodies
- ELISA assay
- Blood assay and bone marrow cultures, the latter being most likely to be positive.

Treatment is with tetracycline or cotrimoxazole with or without streptomycin for 4 weeks.

**Cat-scratch disease**

The organism causing this disease, acquired as the name suggests, is \( \textit{Rochalimaea henselae} \). A papule appears 10 days after the scratch or bite and there is massive enlargement of regional lymph nodes. The disease resolves spontaneously after 2 months.

Diagnosis is by means of:

- Agglutinating and complement-fixing antibodies
- ELISA assay
- Blood assay and bone marrow cultures, the latter being most likely to be positive.

Treatment is with tetracycline or cotrimoxazole with or without streptomycin for 4 weeks.

**Cryptococcosis**

This is caused by \( \textit{Cryptococcus neoformans} \). The yeast spores are inhaled, usually by an immunocompromised host. From the lungs they spread to the meninges, and the commonest form of presentation in children is as a subacute meningitis. Diagnosis is by microscopy of CSF.

Treatment is with antifungals including amphotericin B and flucytosine. Long-term prophylaxis with fluconazole may be required in immunocompromised children to prevent relapse.

**Dengue fever**

Dengue fever is a viral infection, the source being mosquitoes in tropical countries.

The disease presents with fever, headache and transient macular rash. There is myalgia and a second, morbilliform rash after the fever resolves. A second attack may be more severe with a haemorrhagic illness and shock. Diagnosis is by means of serological testing. Mosquito control helps prevention.

**Histoplasmosis**

This is a mycosis (fungal infection), caused by \( \textit{Histoplasma capsulatum} \), when fungal spores shed by birds and bats are inhaled. It presents as an influenza-like illness, becoming disseminated in immuno-compromised patients.

Diagnosis is by means of culture of blood, bone marrow, urine, CSF and sputum, if the disease is disseminated. Treatment is with amphotericin B.

**Leishmaniasis (kala-azar)**

This protozoal infection is caused by \( \textit{Leishmania donovani} \), and the source is the sandfly, found in all continents except Australia.

Incubation may be up to 10 years. Nonspecific symptoms include fever, and malaise. These are accompanied by abdominal pain from a hugely enlarged spleen. The cutaneous form produces ulcerating erythematous macules. The illness may progress to involve the respiratory tract (mucocutaneous leishmaniasis).

Diagnosis is by means of serology, examination of biopsies of the lesion and specialized culture techniques.

Pentavalent antimony compounds, such as sodium stibogluconate and meglumine antimonate are standard treatments, but liposomal amphotericin is also effective and less toxic. Amphotericin is given for cutaneous leishmaniasis. Splenectomy may be required.

Prevention is by sandfly control.

**Leptospirosis (Weil disease)**

This illness is caused by \( \textit{Leptospira interrogans} \), the source being contamination of water and soil near rivers by rat urine.

The clinical features are:

- \( \textit{B. canis} \) (dogs)
- \( \textit{B. ovis} \) (sheep)
- \( \textit{B. neotomae} \) (desert rats).
Less common but important infections

- 1 month of aseptic meningitis
- 1 month of hepatic and renal dysfunction.

Diagnosis is made by prolonged culture for leptospires from blood, CSF or urine, and the slide agglutination test for serological diagnosis.

Treatment is with penicillin (tetracycline in children over 12-years-old), but there is doubt about its effectiveness. There is no proven method of prevention except avoidance of exposure.

**Lyme disease**

This illness, named after a town in Connecticut, is caused by *Borrelia burgdorferi*, the source being the bite of a tick of genus *Ixodes*, which is parasitic on deer.

Clinical features include:

- An expanding annular rash (erythema migrans) beginning at the site of the tick bite
- Lymphadenopathy
- Fever
- After 1 month, may become latent for several months
- Then neurological symptoms (meningitis, facial nerve palsy, peripheral neuropathy) can occur
- Cardiac involvement, with heart block and myocarditis occurs in this secondary phase
- Arthritis is a late occurrence.

Diagnosis is from the clinical history.

Amoxicillin, or tetracycline in older children, is effective. Those with meningitis are given ceftriaxone.

Prevention is by means of insect repellent, protective clothing and frequent inspection of limbs for ticks when walking near deer.

**Toxoplasmosis** (Fig. 15.13)

This is caused by *Toxoplasma gondii*, an obligate intracellular protozoan. Toxoplasma oocysts are found in the faeces of cats infected by ingesting infected meat.

The disease presents as a glandular fever-like illness with lymphadenopathy. Congenital infection causes infection of the retina (chorioretinitis), calcification of the brain and hydrocephalus.

Diagnosis is by culture of the organism or PCR, or by serological diagnosis using the Sabin—Feldman dye test.

Infants with congenital toxoplasmosis are treated for 1 year with pyrimethamine and sulphadiazine. Pregnant women should be advised to avoid raw and rare meat, and cat faeces.

**Kawasaki disease** (Fig. 15.14)

The causative agent of this illness is not known.

This illness presents with fever (>5 days), irritability
and lymphadenopathy, before the macular rash appears. There is oedema, redness of hands and feet (Fig. 15.15) and nonpurulent conjunctivitis. There is late desquamation, especially fingers and toes.

Acute complications include:

- Myocarditis
- Myositis
- Arthritis
- Renal failure
- Aseptic meningitis.

Late complications include coronary artery aneurysms and myocardial infarctions, which may be prevented by the use of intravenous immunoglobulin during the acute illness.