:Typhoid and paratyphoid (enteric) fevers

- Typhoid and paratyphoid fevers, which are transmitted by the faecal–oral route, are important causes of fever in India, sub-Saharan Africa and Latin America. Elsewhere they are relatively rare.
- Enteric fevers are caused by infection with *Salmonella typhi* and *S. paratyphi* A and B.

- After a few days of bacteraemia, the bacilli localise, mainly in the lymphoid tissue of the small intestine, resulting in typical lesions in the Peyer's patches and follicles.
- These swell at first, then ulcerate and usually heal.
- After clinical recovery, about 5% of patients become chronic carriers; the bacilli may live in the gallbladder for months or years and pass intermittently in the stool and less commonly in the urine.

:Clinical features

Typhoid fever:

- The incubation period is about 10–14 days and the onset may be insidious.
- The temperature rises in a stepladder fashion for 4 or 5 days with malaise, increasing headache, drowsiness and aching in the limbs.

13.44 Clinical features of typhoid fever

1st week

- Fever
- Headache
- Myalgia
- Relative bradycardia
- Constipation
- Diarrhoea and vomiting in children

End of 1st week

- Rose spots on trunk
- Splenomegaly
- Cough
- Abdominal distension
- Diarrhoea

End of 2nd week

- Delirium, complications, then coma and death (if untreated)

- Constipation may be present, although in children diarrhoea and vomiting may be prominent early in the illness.
- The pulse is often slower than would be expected from the height of the temperature, i.e. a relative bradycardia.

- At the end of the first week, a rash may appear on the upper abdomen and on the back as sparse, slightly raised, rose-red spots, which fade on pressure. It is usually visible only on white skin.
- Cough and epistaxis occur.

- Around the 7th–10th day the spleen becomes palpable.
- Constipation is then succeeded by diarrhoea and abdominal distension with tenderness.
- Bronchitis and delirium may develop.
- If untreated, by the end of the 2nd week the patient may be profoundly ill.

:Paratyphoid fever

- The course tends to be shorter and milder than that of typhoid fever and the onset is often more abrupt with acute enteritis.
- The rash may be more abundant and the intestinal complications less frequent.

:Complications

- Haemorrhage from, or a perforation of, the ulcerated Peyer's patches may occur at the end of the 2nd week or during the 3rd week of the illness.

13.45 Complications of typhoid fever

Bowel	
• Perforation	• Haemorrhage
Septicaemic foci	
• Bone and joint infection • Meningitis	• Cholecystitis
Toxic phenomena	
• Myocarditis	• Nephritis
Chronic carriage	
• Persistent gallbladder carriage	

- A drop in temperature to normal or subnormal levels may be falsely reassuring in patients with intestinal haemorrhage.
- Additional complications may involve almost any viscus or system because of the septicaemia present during the 1st week.
- Bone and joint infection is common in children with sickle-cell disease.

:Investigations

- In the first week the diagnosis may be difficult because in this invasive stage with bacteraemia the symptoms are those of a generalised infection without localising features.
- A white blood count may be helpful, as there is typically a leucopenia.
- Blood culture is the most important diagnostic method.
- The faeces will contain the organism more frequently during the 2nd and 3rd weeks.

:Management

- Antibiotic therapy must be guided by in vitro sensitivity testing.
- Chloramphenicol (500 mg 6-hourly), ampicillin (750 mg 6-hourly) and co-trimoxazole (2 tablets or i.v. equivalent 12-hourly) are losing their effect due to resistance in many areas of the world, especially India and South-east Asia.

- The fluoroquinolones are the drugs of choice (e.g. ciprofloxacin 500 mg 12-hourly) if the organism is susceptible, but resistance is common, especially in the Indian subcontinent; 40% of cases in the UK are now resistant.

- Extended-spectrum cephalosporins (ceftriaxone and cefotaxime) are useful alternatives but have a slightly increased treatment failure rate.
- Azithromycin (500 mg once daily) is an alternative where fluoroquinolone resistance is present but has not been validated in severe disease.
- Treatment should be continued for 14 days.

- Pyrexia may persist for up to 5 days after the start of specific therapy.
- Even with effective chemotherapy there is still a danger of complications, recrudescence of the disease and the development of a carrier state.
- Chronic carriers are treated for 4 weeks with ciprofloxacin; cholecystectomy may be necessary.

:Prevention

- Improved sanitation and living conditions reduce the incidence of typhoid.
- Travellers to countries where enteric infections are endemic should be inoculated with one of the three available typhoid vaccines (two inactivated injectable and one oral live attenuated).

:Tularaemia

- Tularaemia is primarily a zoonotic disease of the northern hemisphere.
- It is caused by a highly infectious Gram-negative bacillus, *Francisella tularensis*.
- *F. tularensis* is passed transovarially (ensuring transmission from parent to progeny) in ticks, which allows persistence in nature without the absolute requirement for an infected animal reservoir.

- It is a potential weapon for bioterrorism.
- Wild rabbits, rodents, and domestic dogs or cats are some of the many potential reservoirs, and ticks, mosquitoes or other biting flies are the vectors.

- Infection is introduced either through an arthropod or animal bite or via contact with infected animals, soil or water through skin abrasions.
- This results in the most common ‘ulceroglandular’ variety of the disease (70–80%), characterised by skin ulceration with regional lymphadenopathy. There is also a purely ‘glandular’ form.

- Alternatively, inhalation of the infected aerosols may result in pulmonary tularaemia, presenting as pneumonia.
- Rarely, the portal of entry of infection may be the conjunctiva, leading to a nodular, ulcerated conjunctivitis with regional lymphadenopathy (an ‘oculoglandular’ form).

:Investigations and management

- Demonstration of a single high titre (≥ 1:160) or a fourfold rise in 2–3 weeks in the tularaemia tube agglutination test confirms the diagnosis.
- Bacterial yield from the lesions is extremely poor.
- DNA detection methods to enable rapid diagnosis are in development.

- Treatment consists of a 7–10-day course of parenteral aminoglycosides, streptomycin (7.5–10 mg/kg 12-hourly) or gentamicin (1.7 mg/kg 8-hourly).
- *F. tularensis* is not susceptible to most other antibiotics.

:Melioidosis

- Melioidosis is caused by *Burkholderia pseudomallei,* a saprophyte found in soil and water (rice paddy fields).
- Infection is by inoculation or inhalation leading to bacteraemia, which is followed by the formation of abscesses in the lungs, liver and spleen.

- Patients with diabetes, renal stones, thalassaemia or severe burns are particularly susceptible.
- The disease is most common in South India, East Asia and northern Australia, and carries a significant mortality.
- Disease may present many years or decades after the initial exposure.

:Clinical features

- There is high fever, prostration and sometimes diarrhoea, with signs of pneumonia and enlargement of the liver and spleen.
- The chest X-ray resembles that of acute caseous tuberculosis.
- In more chronic forms multiple abscesses occur in subcutaneous tissue and bone, and profound wasting is a major problem.

:Investigations and management

- Culture of blood, sputum or pus may yield *B. pseudomallei.*
- Indirect haemagglutination testing can be helpful in travellers; however, most people in endemic areas are seropositive.

- In the acute illness prompt treatment, without waiting for confirmation by culture, may be life-saving.
- Ceftazidime 100 mg/kg (2 g 8-hourly), imipenem 50 mg/kg (1 g 6-hourly) or meropenem (0.5–1 g 8-hourly) is given for 2–3 weeks.
- This is followed by maintenance therapy of doxycycline 200 mg daily, plus co-trimoxazole (sulfamethoxazole 1600 mg plus trimethoprim 320 mg 12-hourly) for a minimum of 12 weeks. Abscesses should be drained surgically.

:Actinomycete infections

a. Nocardiosis:

- Nocardiosis is an uncommon Gram-positive bacterial infection caused by aerobic actinomycetes of the genus *Nocardia*.

- They can cause localised or systemic suppurative disease in immunocompromised humans and animals, especially lung and brain abscesses.
- On microscopy, nocardia appear as long filamentous branching Gram-positive rods which are also weakly acid-fast.
- They are easily grown in culture but require prolonged incubation.

- Co-trimoxazole is the treatment of choice but third-generation cephalosporins and carbapenems have also been used successfully.
- For severe infections an aminoglycoside such as amikacin is usually added.
- Surgical drainage of large abscesses may be necessary.
- Oral treatment is usually continued for a year if there is CNS involvement.

:b. *Actinomyces israelii*

- *Actinomyces israelii* can cause deep infection in the head and neck, and also suppurating disease in the pelvis associated with intrauterine contraceptive devices (IUCDs).
- Treatment is usually with penicillin or doxycycline.

:Gastrointestinal bacterial infections

Staphylococcal food poisoning:

- *Staph. aureus* transmission takes place via the hands of food handlers to foodstuffs such as dairy products, including cheese, and cooked meats.

- Inappropriate storage of these foods allows growth of the organism and production of one or more heat-stable enterotoxins which cause the symptoms.

- Nausea and profuse vomiting develop within 1–6 hours.
- Diarrhoea may not be marked.
- The toxins which cause the syndrome act as ‘super-antigens’, inducing a significant neutrophil leucocytosis which may be clinically misleading.

- Super-antigens are secreted proteins (exotoxins) that exhibit highly potent lymphocyte-transforming (mitogenic) activity directed towards T lymphocytes.
- Most cases settle rapidly but severe dehydration can occasionally be life-threatening.

- Antiemetics and appropriate fluid replacement are the mainstays of treatment.
- Suspect food should be cultured for staphylococci and demonstration of toxin production.
- The public health authorities should be notified if food vending is involved.

:*Bacillus cereus food poisoning*

- Ingestion of the pre-formed heat-stable exotoxins of *B. cereus* causes rapid onset of vomiting and some diarrhoea within hours of food consumption, which resolves within 24 hours.

- Fried rice and freshly made vanilla sauces are frequent sources; the organism grows and produces enterotoxin during storage.

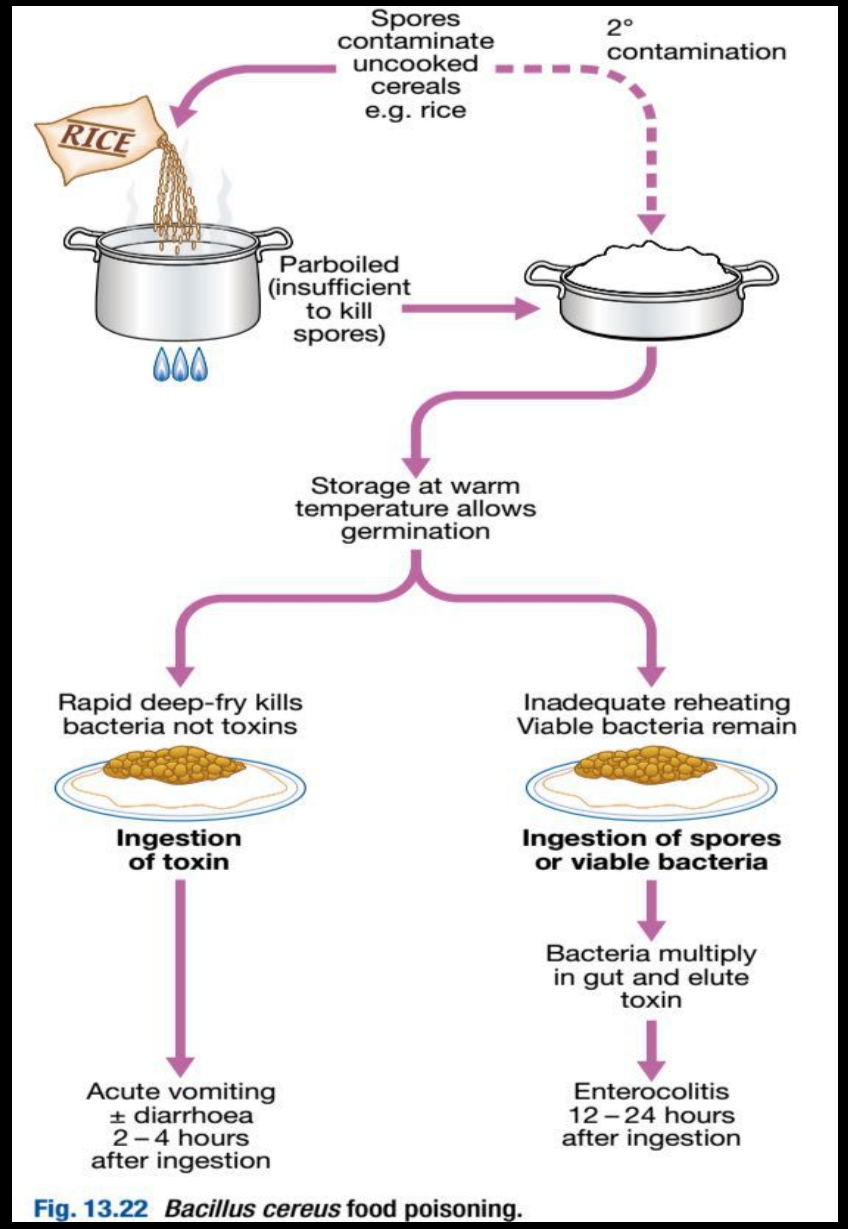

Fig. 13.22 *Bacillus cereus* food poisoning.

- If viable bacteria are ingested and toxin formation takes place within the gut lumen, then the incubation period is longer (12–24 hours) and watery diarrhoea and cramps are the predominant symptoms.
- The disease is self-limiting but can be quite severe.

- Rapid and judicious fluid replacement and appropriate notification of the public health authorities are all that is required.

:*Clostridium perfringens* food poisoning

- Spores of *C. perfringens* are widespread in the guts of large animals and in soil.
- If contaminated meat products are incompletely cooked and stored in anaerobic conditions, *C. perfringens* spores germinate and viable organisms multiply to give large numbers.

- Subsequent reheating of the food causes heat-shock sporulation of the organisms, during which they release an enterotoxin.
- Symptoms (diarrhoea and cramps) occur some 6–12 hours following ingestion.
- The illness is usually self-limiting.

- Clostridial enterotoxins are potent and most people who ingest them will be symptomatic.
- ‘Point source’ outbreaks, in which a number of cases all become symptomatic following ingestion, classically occur after school or canteen lunches where meat stews are served.

- Clostridial necrotising enteritis (CNE) or pigbel is an often fatal type of food poisoning caused by a β-toxin of *C. perfringens,* type C. It occurs in association with protein malnutrition or food containing trypsinases such as sweet potatoes.
- The toxin is normally inactivated by proteolytic enzymes and by normal cooking, but when these protections are impeded, the disease emerges.

:Campylobacter jejuni infection

- This infection is essentially a zoonosis, although contaminated water may be implicated, as the organism can survive for many weeks in fresh water.
- The most common sources of the infection are chicken, beef and contaminated milk products.

- There has been an association with pet puppies.
- *Campylobacter* infection is now the most common cause of bacterial gastroenteritis in the UK, accounting for some 100 000 cases per annum, most of which are sporadic.

- The incubation period is 2–5 days.
- Colicky abdominal pain, which may be quite severe and mimic surgical pathology, occurs with nausea, vomiting and significant diarrhoea, frequently containing blood.
- The majority of *Campylobacter* infections affect fit young adults and are self-limiting after 5–7 days.

- About 10–20% will have prolonged symptomatology, occasionally meriting treatment with antibiotics such as ciprofloxacin.
- Approximately 1% of cases will develop bacteraemia and possible distant foci of infection.
- *Campylobacter* species have been linked to Guillain–Barré syndrome and post-infectious reactive arthritis

:*Salmonella* spp. Infection

- *Salmonella* serotypes other than *S. typhi* and *S. paratyphi*, of which there are more than 2000, are subdivided into five distinct subgroups which produce gastroenteritis.
- They are widely distributed throughout the animal kingdom. T
- wo serotypes are most important world-wide: *S. enteritidis* phage type 4 and *S. typhimurium* dt.104.

- The latter may be resistant to commonly used antibiotics such as ciprofloxacin.
- Some strains have a clear relationship to particular animal species, e.g. *S. arizonae* and pet reptiles.
- Transmission is by contaminated water or food, particularly poultry, egg products and related fast foods, direct person-to-person spread or the handling of exotic pets such as salamanders, lizards or turtles.

- The incidence of *Salmonella* enteritis is falling in the UK due to an aggressive culling policy in broiler chicken stocks, coupled with vaccination.

- The incubation period of *Salmonella* gastroenteritis is 12–72 hours and the predominant feature is diarrhoea.
- Vomiting may be present at the outset and blood is quite frequently noted in the stool.
- Approximately 5% of cases are bacteraemic.
- Reactive (post-infective) arthritis occurs in approximately 2%.

- Antibiotics are not indicated for uncomplicated *Salmonella* gastroenteritis

EBM 13.46 Antibiotics in *Salmonella* gastroenteritis

'In otherwise healthy adults or children with non-severe *Salmonella* diarrhoea, antibiotics have no clinical benefit over placebo, increase side-effects and prolong *Salmonella* detection.'

- However, evidence of bacteraemia is a clear indication for antibiotic therapy, as salmonellae are notorious for persistent infection and often colonise endothelial surfaces such as an atherosclerotic aorta or a major blood vessel.
- Mortality, as with other forms of gastroenteritis, is higher in the elderly.

:*Escherichia coli infection*

- Many serotypes of *E. coli* are present in the human gut at any given time.
- Production of disease depends on either colonisation with a new or previously unrecognised strain, or the acquisition by current colonising bacteria of a particular pathogenicity factor for mucosal attachment or toxin production.

- Travel to unfamiliar areas of the world allows contact with different strains of endemic *E. coli* and the development of travellers' diarrhoea.
- Enteropathogenic strains may be found in the gut of healthy individuals and, if these people move to a new environment, close contacts may develop symptoms.
- At least five different clinico-pathological patterns of diarrhoea are associated with specific strains of *E. coli* with characteristic virulence factors.

:a. *Enterotoxigenic E. coli (ETEC)*

- These cause the majority of cases of travellers' diarrhoea in developing countries, although there are other causes.
- The organisms produce either a heat-labile or a heat-stable enterotoxin, causing marked secretory diarrhoea and vomiting after 1–2 days' incubation.
- The illness is usually mild and self-limiting after 3–4 days.
- Antibiotics, such as ciprofloxacin, have been used to limit the duration of symptoms but are of questionable value.

:b. Entero-invasive E. coli (EIEC)

- This illness is very similar to *Shigella* dysentery and is caused by invasion and destruction of colonic mucosal cells.
- No enterotoxin is produced.
- Acute watery diarrhoea, abdominal cramps and some scanty blood-staining of the stool are common.
- The symptoms are rarely severe and are usually self-limiting.

:c. Enteropathogenic E. coli (EPEC)

- These organisms are very important in infant diarrhoea.
- They are able to attach to the gut mucosa, inducing a specific ‘attachment and effacement’ lesion, and causing destruction of microvilli and disruption of normal absorptive capacity.
- The symptoms vary from mild non-bloody diarrhoea to quite severe illness, but without bacteraemia.

:d.Entero-aggregative E. coli (EAEC)

- These strains adhere to the mucosa but also produce a locally active enterotoxin and demonstrate a particular ‘stacked brick’ aggregation to tissue culture cells when viewed by microscopy.
- They have been associated with prolonged diarrhoea in children in South America, South-east Asia and India.

:e. *Enterohaemorrhagic E. coli (EHEC)*

- A number of distinct ‘O’ serotypes of *E. coli* possess both the genes necessary for adherence and plasmids encoding for two distinct enterotoxins (verotoxins) which are identical to the toxins produced by *Shigella* (‘shiga-toxins 1 and 2’).
- *E. coli* O157:H7 is perhaps the best known of these verotoxin-producing *E. coli* (VTEC), but others, including types O126 and O11, are also implicated.

- Although the incidence is considerably lower than *Campylobacter* and *Salmonella* infection, it is increasing in the developing world.

- The reservoir of infection is in the gut of herbivores.
- The organism has an extremely low infecting dose (10–100 organisms).
- Runoff water from pasture lands where cattle have grazed which is used to irrigate vegetable crops, as well as contaminated milk, meat products (especially hamburgers which have been incompletely cooked), lettuce, radish shoots and apple juice, have all been implicated as sources.

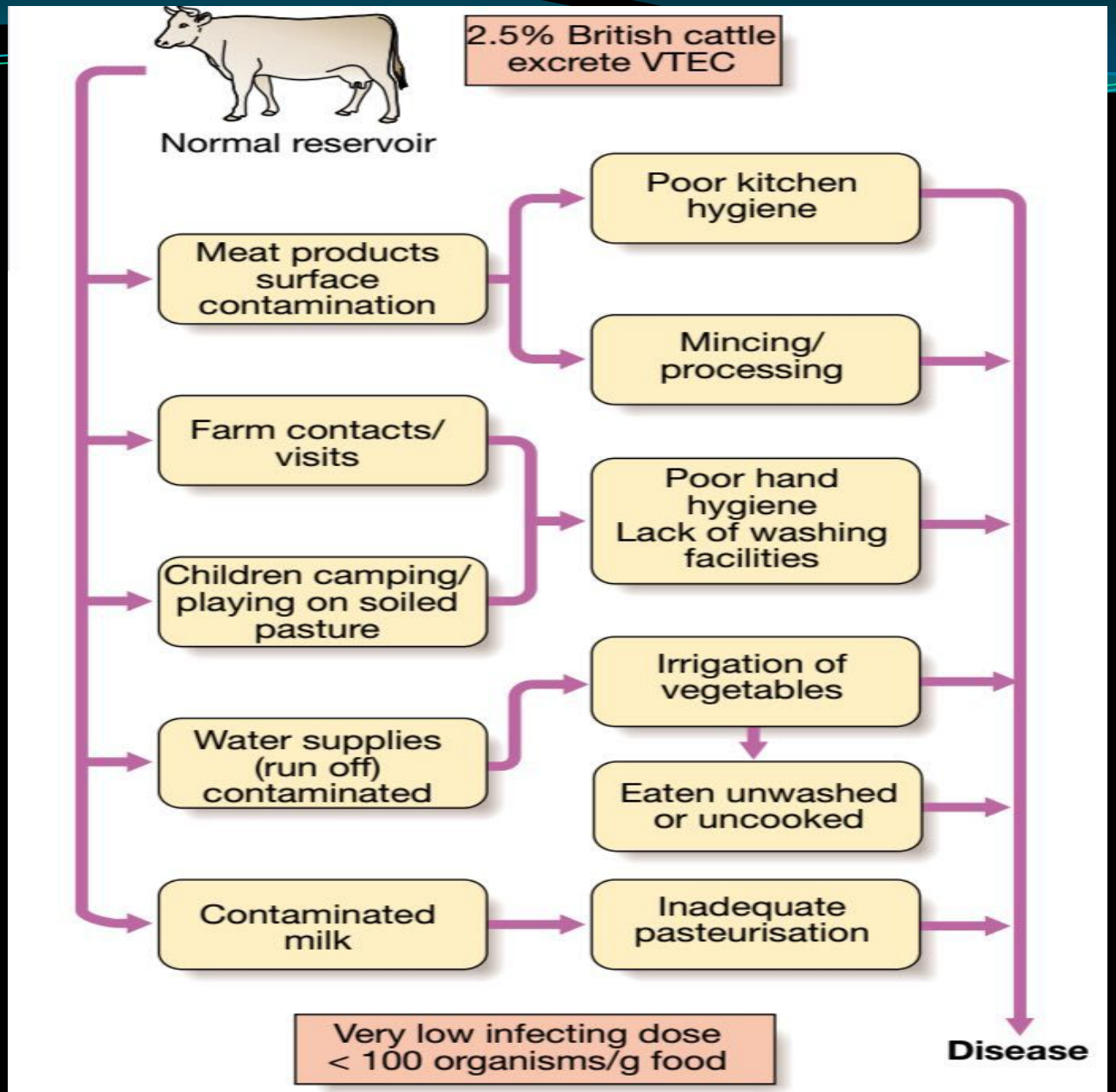

Fig. 13.23 Verocytotoxigenic *E. coli* (VTEC) infections.

- The incubation period is between 1 and 7 days.
- Initial watery diarrhoea becomes frankly and uniformly bloodstained in 70% of cases and is associated with severe and often constant abdominal pain.
- There is little systemic upset, vomiting or fever.

- Enterotoxins have both a local effect on the bowel and a distant effect on particular body tissues such as glomerular apparatus, heart and brain.

- The potentially life-threatening haemolytic uraemic syndrome (HUS) occurs in 10–15% of sufferers from this infection, arising 5-7 days after the onset of symptoms.
- It is most likely at the extremes of age, is heralded by a high peripheral leucocyte count and may be induced, particularly in children, by antibiotic therapy.
- HUS is treated by dialysis if necessary and may be averted by plasma exchange.
- Antibiotics should be avoided since they can stimulate toxin release.

:*Clostridium difficile infection*

- *C. difficile* is the most commonly diagnosed cause of antibiotic-associated diarrhoea, and is an occasional constituent of the normal intestinal flora.
- *C. difficile* is capable of producing two toxins (A and B).
- *C. difficile* infection (CDI) usually follows antimicrobial therapy. It has been assumed that disease results from abolition of colonisation resistance following broad-spectrum antibiotic therapy.

- However, antibiotic exposure itself can also stimulate toxin production.
- The combination of toxin production and the ability to produce environmentally stable spores accounts for the clinical features and transmissibility of CDI.
- A hypervirulent strain of *C. difficile*, ribotype 027, has emerged, which produces more toxin than other *C. difficile* strains and thus more severe disease.

:Clinical features

- Disease manifestations range from diarrhoea to life-threatening pseudomembranous colitis.
- Around 80% of cases occur in people over 65 years of age, many of whom are frail with comorbid diseases.
- Symptoms usually begin in the first week of antibiotic therapy but can occur at any time up to 6 weeks after treatment has finished.

- The onset is often insidious, with lower abdominal pain and diarrhoea which may become profuse and watery.
- The presentation may resemble acute ulcerative colitis with bloody diarrhoea, fever and even toxic dilatation and perforation.
- Ileus is also seen in pseudomembranous colitis.

:*Investigations*

- *C. difficile* can be isolated from stool culture in 30% of patients with antibiotic-associated diarrhoea and over 90% of those with pseudomembranous colitis, but also from 5% of healthy adults and up to 20% of elderly patients in residential care.
- The diagnosis of CDI therefore rests on detection of toxins A or B in the stool using ELISA or tissue culture cytotoxicity assays.

- The rectal appearances at sigmoidoscopy may be characteristic, with erythema, white plaques or an adherent pseudomembrane.

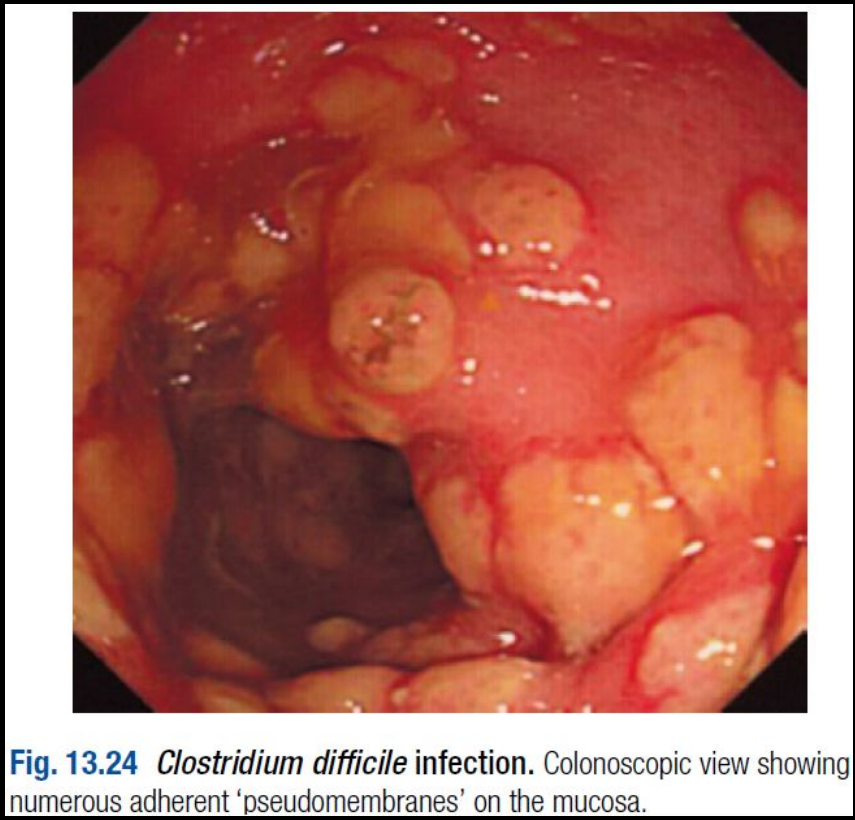

Fig. 13.24 ***Clostridium difficile*** **infection.** Colonoscopic view showing numerous adherent 'pseudomembranes' on the mucosa.

- Appearances may also resemble those of ulcerative colitis.
- In some cases, the rectum is spared and abnormalities are observed in the proximal colon.
- Patients who are ill may require abdominal and erect chest X-rays to exclude perforation or toxic dilatation, respectively.
- CT may be useful when the diagnosis is in doubt.

:Management

- The precipitating antibiotic should be stopped and the patient should be isolated.
- Supportive therapy with intravenous fluids and resting of the bowel is often needed.
- CDI is treated with antibiotics. Traditionally, metronidazole (500 mg orally 8-hourly for 10 days) was used as first-line therapy, with a switch to vancomycin (125 mg orally 6-hourly for 7–10 days) if there was a relapse (15–30% of patients), failure of initial response or evidence of more fulminant infection.

- However, some authorities now recommend vancomycin as initial therapy, in view of reports of metronidazole resistance and better efficacy of vancomycin against hypervirulent *C. difficile* strains.
- Fusidic acid, nitazoxanide and rifaximin have been used successfully in some studies, while intravenous immunoglobulin is sometimes given in the most severe cases.

:*Yersinia enterocolitica infection*

- This organism, commonly found in pork, causes mild to moderate gastroenteritis and can produce significant mesenteric adenitis after an incubation period of 3–7 days.
- It predominantly causes disease in children but adults may also be affected.
- The illness resolves slowly, with 10–30% of cases complicated by persistent arthritis or Reiter’s syndrome.

:Cholera

- Cholera, caused by *Vibrio cholerae* serotype 01, is the archetypal toxin-mediated bacterial cause of acute watery diarrhoea.
- The enterotoxin activates adenylate cyclase in the intestinal epithelium, inducing net secretion of chloride and water.
- Following its origin in the Ganges valley, devastating epidemics have occurred, often in association with large religious festivals, and pandemics have spread world-wide.

- The seventh pandemic, due to the El Tor biotype, began in 1961 and spread via the Middle East to become endemic in Africa. In 1990 it reached Peru and spread throughout South and Central America. Since 2005 numbers of cases of cholera have been increasing.

- There are recurrent outbreaks and epidemics in Africa, often related to flooding.
- El Tor is more resistant to commonly used antimicrobials than classical *Vibrio,* and causes prolonged carriage in 5% of infections.
- A new classical toxigenic strain, serotype 0139, established itself in Bangladesh in 1992 and started a new pandemic.

- Infection spreads via the stools or vomit of symptomatic patients or of the much larger number of subclinical cases.
- Organisms survive for up to 2 weeks in fresh water and 8 weeks in salt water.
- Transmission is normally through infected drinking water, shellfish and food contaminated by flies, or on the hands of carriers.

:Clinical features

- Severe diarrhoea without pain or colic begins suddenly and is followed by vomiting.
- Following the evacuation of normal gut faecal contents, typical ‘rice-water’ material is passed, consisting of clear fluid with flecks of mucus.
- Classical cholera produces enormous loss of fluid and electrolytes, leading to intense dehydration with muscular cramps.

- Shock and oliguria develop but mental clarity remains.
- Death from acute circulatory failure may occur rapidly unless fluid and electrolytes are replaced.
- Improvement is rapid with proper treatment.

- The majority of infections, however, cause mild illness with slight diarrhoea.
- Occasionally, a very intense illness, ‘cholera sicca’, occurs, with loss of fluid into dilated bowel, killing the patient before typical gastrointestinal symptoms appear.
- The disease is more dangerous in children.

:*Diagnosis and management*

- Clinical diagnosis is easy during an epidemic.
- Otherwise the diagnosis should be confirmed bacteriologically.
- Stool dark-field microscopy shows the typical ‘shooting star’ motility of *V. cholerae.*
- Rectal swab or stool cultures allow identification.
- Cholera is notifiable under international health regulations.

- Maintenance of circulation by replacement of water and electrolytes is paramount.
- Ringer-Lactate is the best fluid for intravenous replacement.
- Vomiting usually stops once the patient is rehydrated, and fluid should then be given orally up to 500 mL hourly.

- Early intervention with oral rehydration solutions that include resistant starch shortens the duration of diarrhoea and improves prognosis.
- Total fluid requirements may exceed 50 L over a period of 2–5 days. Accurate records are greatly facilitated by the use of a ‘cholera cot’, which has a reinforced hole under the patient’s buttocks beneath which a graded bucket is placed.

- Three days’ treatment with tetracycline 250 mg 6-hourly, a single dose of doxycycline 300 mg or ciprofloxacin 1 g in adults reduces the duration of excretion of *V. cholerae* and the total volume of fluid needed for replacement.

:*Prevention*

- Strict personal hygiene is vital and drinking water should come from a clean piped supply or be boiled.
- Flies must be denied access to food.
- Parenteral vaccination with a killed suspension of *V. cholerae* provides some protection. Oral vaccines containing killed *V. cholerae* and the B subunit of cholera toxin are available but are of limited efficacy.

- In epidemics, public education and control of water sources and population movement are vital. Mass single-dose vaccination and treatment with tetracycline are valuable. Disinfection of discharges and soiled clothing, and scrupulous hand-washing by medical attendants reduce the danger of spread.

:Vibrio parahaemolyticus infection

- This marine organism produces a disease similar to enterotoxigenic *E. coli* .
- It is acquired from raw seafood and is very common where ingestion of such food is widespread (e.g. Japan).
- After an incubation period of approximately 20 hours, explosive diarrhoea, abdominal cramps and vomiting occur.

- Systemic symptoms of headache and fever are frequent but the illness is self-limiting after 4–7 days.
- Rarely, a severe septicaemic illness arises; in this case *V. parahaemolyticus* can be isolated using specific halophilic culture.

:Bacillary dysentery (shigellosis)

- Shigellae are Gram-negative rods, closely related to *E. coli*, that invade the colonic mucosa.
- There are four main groups: *Sh. dysenteriae, flexneri, boydii* and *sonnei.*
- In the tropics bacillary dysentery is usually caused by *Sh. flexneri,* whilst in the UK most cases are caused by *Sh. sonnei.*

- Shigellae are often resistant to multiple antibiotics, especially in tropical countries.
- The organism only infects humans and its spread is facilitated by its low infecting dose of around 10 organisms.
- Spread may occur via contaminated food or flies, but transmission by unwashed hands after defecation is by far the most important factor.

- Outbreaks occur in mental hospitals, residential schools and other closed institutions, and dysentery is a constant accompaniment of wars and natural catastrophes, which bring crowding and poor sanitation in their wake.
- *Shigella* infection may spread rapidly amongst men who have sex with men.

:*Clinical features*

- Disease severity varies from mild *Sh. sonnei* infections that may escape detection to more severe *Sh. Flexneri* infections, while those due to *Sh. dysenteriae* may be fulminating and cause death within 48 hours.

- In a moderately severe illness, the patient complains of diarrhoea, colicky abdominal pain and tenesmus.
- Stools are small, and after a few evacuations contain blood and purulent exudate with little faecal material.
- Fever, dehydration and weakness occur, with tenderness over the colon.
- Arthritis or iritis may occasionally complicate bacillary dysentery (Reiter's syndrome), associated with HLA-B27.

:Management and prevention

- Oral rehydration therapy or, if diarrhoea is severe, intravenous replacement of water and electrolyte loss is necessary.
- Antibiotic therapy with ciprofloxacin (500 mg 12-hourly for 3 days) is effective in known shigellosis and appropriate in epidemics.
- The use of antidiarrhoeal medication should be avoided.

- The prevention of faecal contamination of food and milk and the isolation of cases may be difficult, except in limited outbreaks. Hand-washing is very important.

:Respiratory bacterial infections

Diphtheria:

- Infection with *Corynebacterium diphtheriae* occurs most commonly in the upper respiratory tract and is usually spread by droplet infection from cases or carriers.

- Infection may also complicate skin lesions, especially in those who misuse alcohol.
- The organisms remain localised at the site of infection but serious consequences result from the absorption of a soluble exotoxin which damages the heart muscle and the nervous system.

- Diphtheria has been eradicated from many parts of the world by mass vaccination using a modified exotoxin but remains important in areas where vaccination has been incomplete, e.g. in Russia and South-east Asia.
- The disease is notifiable in all countries of Europe and North America and international guidelines have been issued by the WHO for the management of infection.

:Clinical features

13.47 Clinical features of diphtheria

Acute infection

- Membranous tonsillitis
- *or* Nasal infection
- *or* Laryngeal infection
- *or* Skin/wound/conjunctival infection (rare)

Complications

- Laryngeal obstruction or paralysis
- Myocarditis
- Peripheral neuropathy

- The average incubation period is 2–4 days.
- The disease begins insidiously with a sore throat.
- Despite modest fever there is usually marked tachycardia.
- The diagnostic feature is the ‘wash-leather’ elevated greyish-green membrane on the tonsils. It has a well-defined edge, is firm and adherent, and is surrounded by a zone of inflammation.
- There may be swelling of the neck (‘bull-neck’) and tender enlargement of the lymph nodes.

- In the mildest infections, especially in the presence of a high degree of immunity, a membrane may never appear and the throat is merely slightly inflamed.

- With anterior nasal infection there is nasal discharge, frequently blood-stained.
- In laryngeal diphtheria a husky voice and high-pitched cough signal potential respiratory obstruction requiring urgent tracheostomy.
- If infection spreads to the uvula, fauces and nasopharynx, the patient is gravely ill.

- Death from acute circulatory failure may occur within the first 10 days.
- Late complications occur as a result of toxin action on the heart or nervous system.
- About 25% of survivors of the early toxaemia may later develop myocarditis with arrhythmias or cardiac failure. These are usually reversible with no permanent damage other than heart block in survivors.

- Neurological involvement occurs in 75% of cases.
- After tonsillar or pharyngeal diphtheria it usually starts after 10 days with palatal palsy. Paralysis of accommodation often follows, manifest by difficulty in reading small print.
- Generalised polyneuritis with weakness and paraesthesia may follow in the next 10–14 days. Recovery from such neuritis is always ultimately complete.

:Management

- A clinical diagnosis of diphtheria must be notified to the public health authorities and the patient sent urgently to a specialist infectious diseases unit.
- Treatment should begin once appropriate swabs have been taken before waiting for microbiological confirmation.

- Diphtheria antitoxin is produced from hyperimmune horse serum. It neutralises circulating toxin, but has no effect on toxin already fixed to tissues, so it must be injected intramuscularly without awaiting the result of a throat swab. However, reactions to this foreign protein include a potentially lethal immediate anaphylactic reaction and a ‘serum sickness’ with fever, urticaria and joint pains, which occurs 7–12 days after injection.

- A careful history of previous horse serum injections or allergic reactions should be taken and a small test injection of serum should be given half an hour before the full dose in every patient. Adrenaline (epinephrine) solution must be available to deal with any immediate type of reaction (0.5–1.0 mL of 1/1000 solution i.m.). An antihistamine is also given.

- In a severely ill patient the risk of anaphylactic shock is outweighed by the mortal danger of diphtheritic toxaemia, and up to 100000 U of antitoxin are injected intravenously if the test dose has not given rise to symptoms. For disease of moderate severity, 16000–40000 U i.m. will suffice, and for mild cases 4000–8000 U.

- Penicillin (1200 mg 6-hourly i.v.) or amoxicillin (500 mg 8-hourly) should be administered for 2 weeks to eliminate *C. diphtheriae*.
- Patients allergic to penicillin can be given erythromycin.
- Due to poor immunogenicity of primary infection all sufferers should be immunised with diphtheria toxoid following recovery.

- Patients must be managed in strict isolation attended by staff with a clearly documented immunisation history until three swabs 24 hours apart are culture-negative.

:Prevention

- Active immunisation should be given to all children.
- If diphtheria occurs in a closed community, contacts should be given erythromycin, which is more effective than penicillin in eradicating the organism in carriers. All contacts should also be immunised or given a booster dose of toxoid. Booster doses are required every 10 years to maintain immunity.

:Pneumococcal infection

- *Strep. pneumoniae* (the pneumococcus) is the leading cause of community-acquired pneumonia globally and one of the leading causes of infection-related mortality.
- Otitis media, meningitis and sinusitis are also frequently due to *Strep. pneumoniae*.
- Occasional patients present with bacteraemia without obvious focus.
- Asplenic individuals are at risk of fulminant pneumococcal disease with purpuric rash.

- Increasing rates of penicillin resistance have been reported for *Strep. pneumoniae,* and strains with high-level resistance require treatment with glycopeptides rather than with penicillins or cephalosporins. Newer quinolones are also used but rates of resistance are rising.

- Vaccination of infants with the protein conjugate pneumococcal vaccine decreases *Strep. pneumoniae* infection in infants and in their relatives. The polysaccharide pneumococcal vaccine is used in individuals predisposed to *Strep. pneumoniae* infection and the elderly, but only modestly reduces pneumococcal bacteraemia and does not prevent pneumonia.
- All asplenic individuals should receive vaccination against *Strep. pneumoniae.*

:Anthrax

- Anthrax is an endemic zoonosis in many countries; it causes human disease following inoculation of the spores of *Bacillus anthracis*.
- *B. anthracis* was the first recognised bacterial pathogen described by Koch and became the model pathogen for ‘Koch’s postulates’. It is a Gram-positive organism with a central spore.

- The spores can survive for years in soil.
- Infection is commonly acquired from contact with animals, particularly herbivores.
- The ease of production of *B. anthracis* spores makes this infection a candidate for biological warfare or bioterrorism.
- *B. anthracis* produces a number of toxins which mediate the clinical features of disease.

:Clinical features

These depend on the route of entry of the anthrax spores.

Cutaneous anthrax:

- This skin lesion is associated with occupational exposure to anthrax spores during processing of hides and bone products, or with bioterrorism.

- It accounts for the vast majority of clinical cases. Animal infection is a serious problem in Africa, India, Pakistan and the Middle East.
- Spores are inoculated into exposed skin. A single lesion develops as an irritable papule on an oedematous haemorrhagic base. This progresses to a depressed black eschar. Despite extensive oedema, pain is infrequent.

:Gastrointestinal anthrax

- This is associated with the ingestion of meat products that have been contaminated or incompletely cooked.
- The caecum is the seat of the infection, which produces nausea, vomiting, anorexia and fever, followed in 2–3 days by severe abdominal pain and bloody diarrhoea.
- Toxaemia and death can develop rapidly thereafter.

:Inhalational anthrax

- This form of the disease is extremely rare, unless associated with bioterrorism.
- Without rapid and aggressive therapy at the onset of symptoms, the mortality is 50–90%.
- Fever, dyspnoea, cough, headache and symptoms of septicaemia develop 3–14 days following exposure.
- Typically, the chest X-ray shows only widening of the mediastinum and pleural effusions which are haemorrhagic.
- Meningitis may occur.

:*Management*

- *B. anthracis* can be cultured from skin swabs from lesions.
- Skin lesions are readily curable with early antibiotic therapy.
- Treatment is with ciprofloxacin (500 mg 12-hourly) until penicillin susceptibility is confirmed; the regimen can then be changed to benzylpenicillin with doses up to 2.4 g i.v. given 4-hourly or phenoxy-methylpenicillin 500–1000 mg 6-hourly administered for 10 days.

- The addition of an aminoglycoside may improve the outlook in severe disease.
- In view of concerns about concomitant inhalational exposure, particularly in the era of bioterrorism, a further 2-month course of ciprofloxacin 500 mg 12-hourly or doxycycline 100 mg 12-hourly orally is added.

- Prophylaxis with ciprofloxacin (500 mg 12-hourly) is recommended for anyone at high risk of exposure to anthrax spores.

Bacterial infections with neurological involvement:

- Infections affecting the CNS include bacterial meningitis, botulism and tetanus.

:Mycobacterial infections

- Tuberculosis is predominantly, although by no means exclusively, a respiratory disease.

:Leprosy

- Leprosy (Hansen's disease) is a chronic granulomatous disease affecting skin and nerves, caused by *Mycobacterium leprae*, a slow-growing mycobacterium which cannot be cultured in vitro.

- The clinical manifestations are determined by the degree of the patient's cell-mediated immunity (CMI) towards *M. leprae*.

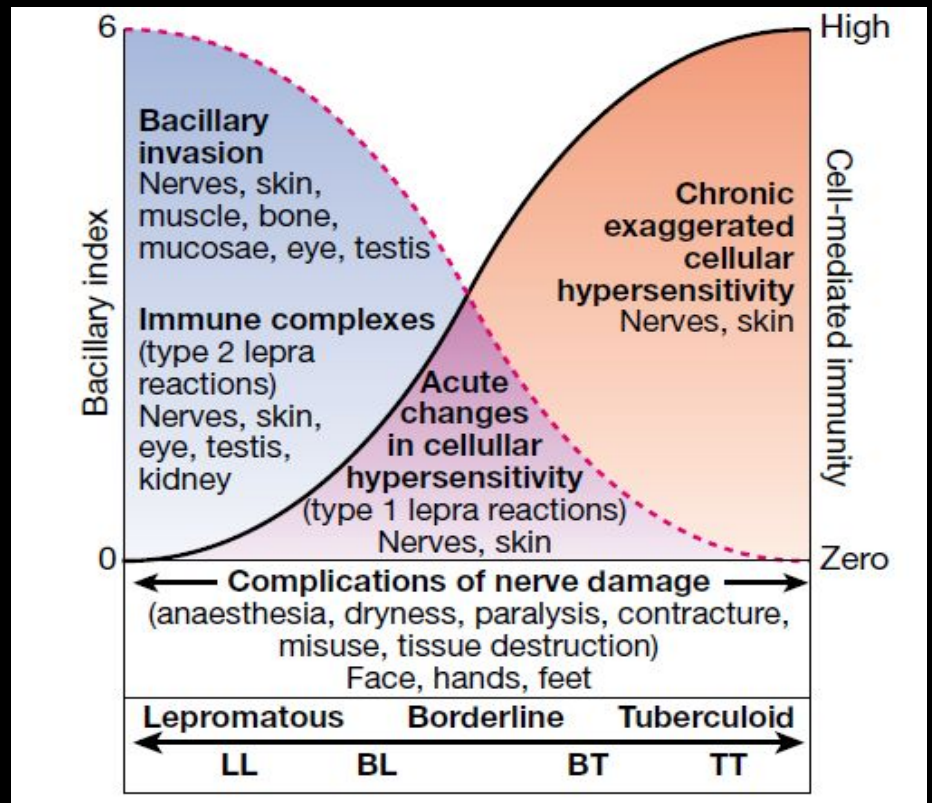

Fig. 13.25 Leprosy: mechanisms of damage and tissue affected. Mechanisms under the broken line are characteristic of disease near the lepromatous end of the spectrum, and those under the solid line are characteristic of the tuberculoid end. They overlap in the centre where, in addition, instability predisposes to type 1 lepra reactions. At the peak in the centre neither bacillary growth nor cell-mediated immunity has the upper hand. (BL = borderline lepromatous; BT = borderline tuberculoid)

- High levels of CMI with elimination of leprosy bacilli produce tuberculoid leprosy, whereas absent CMI results in lepromatous leprosy.
- The complications of leprosy are due to nerve damage, immunological reactions and bacillary infiltration.
- Leprosy patients are frequently stigmatised and using the word ‘leper’ is inappropriate.

:Epidemiology and transmission

- Some 4 million people have leprosy and around 750000 new cases are detected annually.
- About 70% of the world's leprosy patients live in India, with the disease endemic in Brazil, Indonesia, Mozambique, Madagascar, Tanzania and Nepal.

- Untreated lepromatous patients discharge bacilli from the nose.
- Infection occurs through the nose, followed by haematogenous spread to skin and nerve.
- The incubation period is 2–5 years for tuberculoid cases and 8–12 years for lepromatous cases.
- Leprosy incidence peaks at 10–14 years, and is more common in males and in those with close household exposure to leprosy cases.

:*Pathogenesis*

- *M. leprae* has a predilection for infecting Schwann cells and skin macrophages.
- In tuberculoid leprosy, effective CMI controls bacillary multiplication (‘paucibacillary’) but organised epithelioid granulomas are formed.
- In lepromatous leprosy, there is abundant bacillary multiplication (‘multibacillary’), e.g. in Schwann cells and perineurium.

- Between these two extremes is a continuum, varying from patients with moderate CMI (borderline tuberculoid) to patients with little cellular response (borderline lepromatous).

- In addition, immunological reactions to the infection occur as the immune response develops and the antigenic stimulus from the bacilli varies, particularly in borderline patients.
- Delayed hypersensitivity reactions produce type 1 (reversal) reactions, while immune complexes contribute to type 2 (erythema nodosum leprosum) reactions.

- HIV/leprosy co-infected patients have typical lepromatous and tuberculoid leprosy skin lesions and typical leprosy histology and granuloma formation. Surprisingly, even with low circulating CD4 counts, tuberculoid leprosy may be observed and there is not an obvious shift to lepromatous leprosy.

:Clinical features

13.48 Cardinal features of leprosy

- Skin lesions, typically anaesthetic at tuberculoid end of spectrum
- Thickened peripheral nerves
- Acid-fast bacilli on skin smears or biopsy

13.49 Clinical characteristics of the polar forms of leprosy

Clinical and tissue-specific features	Lepromatous	Tuberculoid
Skin and nerves		
Number and distribution	Widely disseminated	One or a few sites, asymmetrical
Skin lesions		
Definition		
Clarity of margin	Poor	Good
Elevation of margin	Never	Common
Colour		
Dark skin	Slight hypopigmentation	Marked hypopigmentation
Light skin	Slight erythema	Coppery or red
Surface	Smooth, shiny	Dry, scaly
Central healing	None	Common
Sweat and hair growth	Impaired late	Impaired early
Loss of sensation	Late	Early and marked
Nerve enlargement and damage	Late	Early and marked
Bacilli (bacterial index)	Many (5 or 6+)	Absent (0)
Natural history	Progressive	Self-healing
Other tissues	Upper respiratory mucosa, eye, testes, bones, muscle	None
Reactions	Immune complexes (type 2)	Cell-mediated (type 1)

- **Skin:**The most common skin lesions are macules or plaques. Tuberculoid patients have few, hypopigmented lesions. In lepromatous leprosy, papules, nodules or diffuse infiltration of the skin occur. The earliest lesions are ill defined; gradually, the skin becomes infiltrated and thickened. Facial skin thickening leads to the characteristic leonine facies.

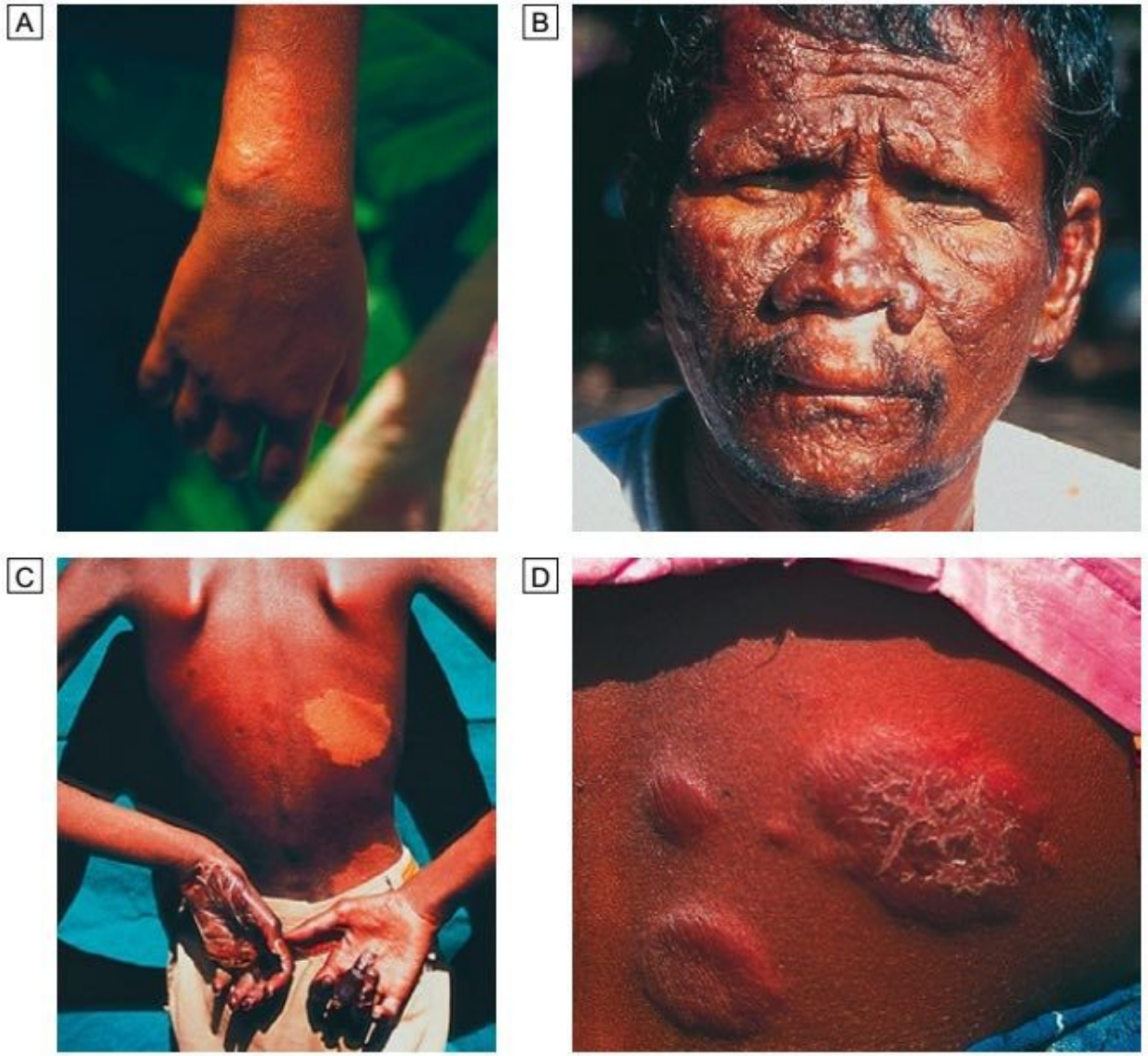

Fig. 13.26 Clinical features of leprosy. A Tuberculoid leprosy. Single lesion with a well-defined active edge and anaesthesia within the lesion. B Lepromatous leprosy. Widespread nodules and infiltration, with loss of the eyebrows. This man also has early collapse of the nose. C Borderline tuberculoid leprosy with severe nerve damage. This boy has several well-defined, hypopigmented, macular, anaesthetic lesions. He has severe nerve damage affecting both ulnar and median nerves bilaterally and has sustained severe burns to his hands. D Reversal (type 1) reactions. Erythematous, oedematous lesions.

- **Anaesthesia:** In skin lesions the small dermal sensory and autonomic nerve fibres are damaged, causing local sensory loss and loss of sweating within that area. Anaesthesia may also occur in the distribution of a damaged large peripheral nerve. A ‘glove and stocking’ sensory neuropathy is also common in lepromatous leprosy.

- **Nerve damage:** Peripheral nerve trunks are affected at ‘sites of predilection’. These are the ulnar (elbow), median (wrist), radial (humerus), radial cutaneous (wrist), common peroneal (knee), posterior tibial and sural nerves (ankle), facial nerve (zygomatic arch) and great auricular nerve (posterior triangle of the neck).

Damage to peripheral nerve trunks produces characteristic signs with regional sensory loss and muscle dysfunction. All these nerves should be examined for enlargement and tenderness and tested for motor and sensory function. The CNS is not affected.

- **Eye involvement:** Blindness is a devastating complication for a patient with anaesthetic hands and feet. Eyelid closure is impaired when the facial nerve is affected. Damage to the trigeminal nerve causes anaesthesia of the cornea and conjunctiva. The cornea is then susceptible to trauma and ulceration.

- Other features: Many organs can be affected. Nasal collapse occurs secondary to bacillary destruction of the bony nasal spine. Diffuse infiltration of the testes causes testicular atrophy and the acute orchitis that occurs with type 2 reactions. This results in azoospermia and hypogonadism.

:Leprosy reactions

- Leprosy reactions are events superimposed on the cardinal features.

13.50 Reactions in leprosy

	Lepra reaction type 1 (reversal)	Lepra reaction type 2 (erythema nodosum leprosum, ENL)
Mechanism	Cell-mediated hypersensitivity	Immune complexes
Clinical features	Painful tender nerves, loss of function Swollen skin lesions New skin lesions	Tender papules and nodules; may ulcerate Painful tender nerves, loss of function Iritis, orchitis, myositis, lymphadenitis Fever, oedema
Management	Prednisolone 40 mg, reducing over 3–6 months[1]	Moderate: prednisolone 40 mg daily Severe: thalidomide[2] or prednisolone 40–80 mg daily, reducing over 1–6 months; local if eye involved[3]

[1]Indicated for any new impairment of nerve or eye function.
[2]Contraindicated in fertile women.
[3]1% hydrocortisone drops or ointment and 1% atropine drops.

- **Type 1 (reversal) reactions:** These occur in 30% of borderline patients (BT, BB or BL) and are delayed hypersensitivity reactions. Skin lesions become erythematous. Peripheral nerves become tender and painful, with sudden loss of nerve function. These reactions may occur spontaneously, after starting treatment and also after completion of multidrug therapy.

- **Type 2 (erythema nodosum leprosum—ENL) reactions:** These are partly due to immune complex deposition and occur in BL and LL patients who produce antibodies and have a high antigen load. They manifest with malaise, fever and crops of small pink nodules on the face and limbs. Iritis and episcleritis are common. Other signs are acute neuritis, lymphadenitis, orchitis, bone pain, dactylitis, arthritis and proteinuria. ENL may continue intermittently for several years.

:Borderline cases

- In borderline tuberculoid (BT) cases, skin lesions are more numerous than in tuberculoid (TT) cases, and there is more severe nerve damage and a risk of type 1 reactions.
- In borderline leprosy (BB) cases, skin lesions are numerous and vary in size, shape and distribution; annular lesions are characteristic and nerve damage is variable.

- In borderline lepromatous (BL) cases, there are widespread small macules in the skin and widespread nerve involvement; both type 1 and type 2 reactions occur.

- Pure neural leprosy (i.e. without skin lesions) occurs principally in India and accounts for 10% of patients. There is asymmetrical involvement of peripheral nerve trunks and no visible skin lesions. On nerve biopsy all types of leprosy have been found.

:Investigations

- The diagnosis is clinical, made by finding a cardinal sign of leprosy and supported by finding acid-fast bacilli in slit-skin smears or typical histology in a skin biopsy. Slit-skin smears are obtained by scraping dermal material on to a glass slide.

- The smears are then stained for acid-fast bacilli, the number counted per high-power field and a score derived on a logarithmic scale (0–6): the bacterial index (BI).
- Smears are useful for confirming the diagnosis and monitoring response to treatment.
- Neither serology nor PCR testing for *M. leprae* DNA is sensitive or specific enough for diagnosis.

:Management

- All leprosy patients should be given multidrug treatment (MDT) with an approved first-line regimen.

13.52 Modified WHO-recommended multidrug therapy (MDT) regimens in leprosy

Type of leprosy[1]	Monthly supervised treatment	Daily self-administered treatment	Duration of treatment[2]
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6 mths
Multibacillary	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	12 mths
Paucibacillary single-lesion	Ofloxacin 400 mg Rifampicin 600 mg Minocycline 100 mg		Single dose

[1]Classification uses the bacillary index (BI) in slit-skin smears or, if BI is not available, the number of skin lesions:
- paucibacillary single-lesion leprosy (one skin lesion)
- paucibacillary (2–5 skin lesions)
- multibacillary (> 5 skin lesions).

[2]Studies from India have shown that multibacillary patients with an initial BI > 4 need longer treatment, for at least 24 months.

13.51 Principles of leprosy treatment

- Stop the infection with chemotherapy
- Treat reactions
- Educate the patient about leprosy
- Prevent disability
- Support the patient socially and psychologically

- Rifampicin is a potent bactericidal for *M. leprae* but should always be given in combination with other antileprotics since a single-step mutation can confer resistance.

- Dapsone is bacteriostatic. It commonly causes mild haemolysis but rarely anaemia.
- Clofazimine is a red, fat-soluble crystalline dye, weakly bactericidal for *M. leprae*. Skin discoloration (red to purple-black) and ichthyosis are troublesome side-effects, particularly on pale skins.

- New drugs that are bactericidal for *M. leprae* have been identified, notably the fluoroquinolones pefloxacin and ofloxacin, minocycline and clarithromycin. These agents are now established second-line drugs. Minocycline causes a grey pigmentation of skin lesions.

- Although single-dose treatment is less effective than the conventional 6-month treatment for paucibacillary leprosy, it is an operationally attractive field regimen and has been recommended for use by the WHO.
- Chloroquine can also be used.

:Patient education

- Educating leprosy patients about their disease is vital.
- Patients should be reassured that after 3 days of chemotherapy they are not infectious and can lead a normal social life.
- It should be emphasised that gross deformities are not inevitable.

- Patients with anaesthetic hands or feet need to take special care to avoid and treat burns and other minor injuries.
- Good footwear is important.
- Physiotherapy may be required to maintain range of movement of affected muscles and neighbouring joints.

:Prognosis

- Untreated, tuberculoid leprosy has a good prognosis; it may self-heal and peripheral nerve damage is limited.
- Lepromatous leprosy (LL) is a progressive condition with high morbidity if untreated.
- After treatment, the majority of patients, especially those who have no nerve damage at the time of diagnosis, do well, with resolution of skin lesions.
- Borderline patients are at risk of developing type 1 reactions which may result in devastating nerve damage.

:*Prevention and control*

- The previous strategy of centralised leprosy control campaigns has now been superseded by integrated programmes, with primary health-care workers in many countries now responsible for case detection and provision of MDT. It is not yet clear how successful this will be, especially in the time-consuming area of disability prevention.

- BCG vaccination has been shown to give good but variable protection against leprosy; adding killed *M. leprae* to BCG does not enhance protection.

Rickettsial and related intracellular :bacterial infections

Rickettsial fevers:

- The rickettsial fevers are the most common tick-borne infections.
- Patients present acutely with headache, rash and sometimes neurological disturbance.

- It is important to ask about exposures that would put patients at risk of bites or contact with ticks, lice or fleas.
- There are two main groups of rickettsial fevers: spotted fevers and typhus.

13.53 Features of rickettsial infections

Disease	Organism	Reservoir	Vector	Geographical area	Rash	Gangrene	Target organs	Mortality
Spotted fever group								
Rocky Mountain spotted fever	*R. rickettsii*	Rodents, dogs, ticks	*Ixodes* tick	North, Central and South America	Morbilliform Haemorrhagic	Often	Bronchi, myocardium, brain, skin	2–12%[2]
Boutonneuse fever	*R. conorii*	Rodents, dogs, ticks	*Ixodes* tick	Mediterranean, Africa, South-west Asia, India	Maculopapular	–	Skin, meninges	2.5%[3]
Siberian tick typhus	*R. siberica*	Rodents, birds, domestic animals, ticks	Various ticks	Siberia, Mongolia, northern China	Maculopapular	–	Skin, meninges	Rare[3]
Australian tick typhus	*R. australis*	Rodents, ticks	Ticks	Australia	Maculopapular	–	Skin, meninges	Rare[3]
Oriental spotted fever	*R. japonica*	Rodents, dogs, ticks	Ticks	Japan	Maculopapular	–	Skin, meninges	Rare[3]
African tick bite fever[1]	*R. africae*	Cattle, game, ticks	*Ixodes* tick	South Africa	Can be spotless	–	Skin, meninges	Rare[3]
Typhus group								
Scrub typhus	*Orientia tsutsugamushi*	Rodents	*Trombicula* mite	SE Asia	Maculopapular	Unusual	Bronchi, myocardium, brain, skin	Rare[3]
Epidemic typhus	*R. prowazekii*	Humans	Louse	World-wide	Morbilliform Haemorrhagic	Often	Brain, skin, bronchi, myocardium	Up to 40%
Endemic typhus	*R. typhi*	Rats	Flea	World-wide	Slight	–	–	Rare[3]

[1]Eschar at bite site and local lymphadenopathy
[2]Highest in adult males.
[3]Except in infants, older people and the debilitated.

:Pathogenesis

- The rickettsiae are intracellular Gram-negative organisms which parasitise the intestinal canal of arthropods.
- Infection is usually conveyed to humans through the skin from the excreta of arthropods, but the saliva of some biting vectors is infected.
- The organisms multiply in capillary endothelial cells, producing lesions in the skin, CNS, heart, lungs, liver, kidneys and skeletal muscles.

- Endothelial proliferation, associated with a perivascular reaction, may cause thrombosis and purpura.
- In epidemic typhus the brain is the target organ; in scrub typhus the cardiovascular system and lungs in particular are attacked.

- An eschar, a black necrotic crusted sore, is often found in tick- and mite-borne typhus.
- This is due to vasculitis following immunological recognition of the inoculated organism.
- Regional lymph nodes often enlarge.

:*Spotted fever group*

Rocky Mountain spotted fever:

- *Rickettsia rickettsii* is transmitted by tick bites.
- It is widely distributed and increasing in western and south-eastern states of the USA and also in Central and South America.
- The incubation period is about 7 days.

- The rash appears on about the 3rd or 4th day of illness, looking at first like measles, but in a few hours a typical maculopapular eruption develops.
- The rash spreads in 24–48 hours from wrists, forearms and ankles to the back, limbs and chest, and then to the abdomen, where it is least pronounced.
- Larger cutaneous and subcutaneous haemorrhages may appear in severe cases.
- The liver and spleen become palpable.
- At the extremes of life the mortality is 2–12%.

:*Other spotted fevers*

- *R. conorii* (boutonneuse fever) and *R. africae* (African tick fever) cause Mediterranean and African tick typhus, which also occurs on the Indian subcontinent.
- The incubation period is approximately 7 days.
- Infected ticks may be picked up by walking on grasslands or dogs may bring ticks into the house.

- Careful examination might reveal a diagnostic eschar, and the maculopapular rash on the trunk, limbs, palms and soles.
- There may be delirium and meningeal signs in severe infections but recovery is usual.
- *R. africae* can be associated with multiple eschars.
- Some cases, particularly those with *R. africae,* present without rash (‘spotless spotted fever’).

:*Typhus group*

Scrub typhus fever:

- Scrub typhus is caused by *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*), transmitted by mites.
- It occurs in the Far East, Myanmar, Pakistan, Bangladesh, India, Indonesia, the South Pacific islands and Queensland, particularly where patches of forest cleared for plantations have attracted rats and mites.

- In many patients one eschar or more develops, surrounded by an area of cellulitis and enlargement of regional lymph nodes.
- The incubation period is about 9 days.
- Mild or subclinical cases are common.
- The onset of symptoms is usually sudden, with headache (often retro-orbital), fever, malaise, weakness and cough.

- In severe illness the general symptoms increase, with apathy and prostration.
- An erythematous maculopapular rash often appears on about the 5th–7th day and spreads to the trunk, face and limbs, including the palms and soles, with generalised painless lymphadenopathy. The rash fades by the 14th day.

- The temperature rises rapidly and continues as a remittent fever (i.e. the difference between maximum and minimum temperature exceeds 1˚C) remaining above normal with sweating until it falls on the 12th–18th day.

- In severe infection the patient is prostrate with cough, pneumonia, confusion and deafness.
- Cardiac failure, renal failure and haemorrhage may develop.
- Convalescence is often slow and tachycardia may persist for some weeks.

:Epidemic (louse-borne) typhus

- Epidemic typhus is caused by *R. prowazekii* and is transmitted by infected faeces of the human body louse, usually through scratching the skin.
- Patients suffering from epidemic typhus infect the lice, which leave when the patient is febrile.
- In conditions of overcrowding the disease spreads rapidly.

- It is prevalent in parts of Africa, especially Ethiopia and Rwanda, and in the South American Andes and Afghanistan. Large epidemics have occurred in Europe, usually as a sequel to war.
- The incubation period is usually 12–14 days.

- There may be a few days of malaise but the onset is more often sudden with rigors, fever, frontal headaches, pains in the back and limbs, constipation and bronchitis.
- The face is flushed and cyanotic, the eyes are congested and the patient becomes confused.

- The rash appears on the 4th–6th day. In its early stages it disappears on pressure but soon becomes petechial with subcutaneous mottling.
- It appears first on the anterior folds of the axillae, sides of the abdomen or backs of hands, then on the trunk and forearms. The neck and face are seldom affected.

- During the 2nd week symptoms increase in severity. Sores develop on the lips. The tongue becomes dry, brown, shrunken and tremulous.
- The spleen is palpable, the pulse feeble and the patient stuporous and delirious.
- The temperature falls rapidly at the end of the 2nd week and the patient recovers gradually.
- In fatal cases the patient usually dies in the 2nd week from toxaemia, cardiac or renal failure, or pneumonia.

:Endemic (flea-borne) typhus

- Flea-borne or ‘endemic’ typhus caused by *R. typhi* is endemic world-wide.
- Humans are infected when the faeces or contents of a crushed flea, which has fed on an infected rat, are introduced into the skin.
- The incubation period is 8–14 days.
- The symptoms resemble those of a mild louse-borne typhus.
- The rash may be scanty and transient.

:Investigation of rickettsial infection

- Routine blood investigations are not diagnostic but malaria must be excluded by blood film examination in most cases, and there is usually hepatitis and thrombocytopenia.
- Diagnosis is made on clinical grounds and response to treatment.

- Species-specific antibodies may be detected in specialised laboratories.
- Differential diagnoses include malaria, typhoid, meningococcal sepsis and leptospirosis.

:Management of rickettsial fevers

- The different rickettsial fevers vary greatly in severity but all respond to tetracycline 500 mg 6-hourly, doxycycline 200 mg daily or chloramphenicol 500 mg 6-hourly for 7 days.
- Louse-borne typhus and scrub typhus can be treated with a single dose of 200 mg doxycycline, repeated for 2–3 days to prevent relapse.

- Chloramphenicol and doxycycline-resistant strains of *O. tsutsugamushi* have been reported from Thailand and patients here may need treatment with rifampicin.

- Nursing care is important, especially in epidemic typhus.
- Sedation may be required for delirium and blood transfusion for haemorrhage.
- Relapsing fever and typhoid are common intercurrent infections in epidemic typhus, and pneumonia in scrub typhus. They must be sought and treated.
- Convalescence is usually protracted, especially in older people.
- To prevent rickettsial infection, lice, fleas, ticks and mites need to be controlled with insecticides.

:Q fever

- Q fever occurs world-wide and is caused by the rickettsia- like organism *Coxiella burnetii*, an obligate intracellular organism that can survive in the extracellular environment.
- Cattle, sheep and goats are important reservoirs and the organism is transmitted by inhalation of aerosolised particles.

- An important characteristic of *C. burnetii* is its antigenic variation, called phase variation, due to a change of lipopolysaccharide (LPS).
- When isolated from animals or humans, *C. burnetii* express phase I antigen and are very infectious (a single bacterium is sufficient to infect a human).

- In culture there is an antigenic shift to the phase II form, which is not infectious.
- This antigenic shift can be measured and is valuable for the differentiation of acute and chronic Q fever.

:Clinical features

- The incubation period is 3–4 weeks.
- The initial symptoms are non-specific with fever, headache and chills; in 20% of cases a maculopapular rash occurs.
- Other presentations include pneumonia and hepatitis.
- Chronic Q fever may present with osteomyelitis, encephalitis and endocarditis.

:Investigations and management

- Diagnosis is usually serological and the stage of the infection can be distinguished by isotype tests and phase-specific antigens.
- Phase I and II IgM titres peak at 4–6 weeks.
- In chronic infections IgG titres to phase I and II antigens may be raised.

- Prompt treatment of acute Q fever with doxycycline reduces fever duration.
- Treatment of Q fever endocarditis is problematic, requiring prolonged therapy with doxycycline and rifampicin or ciprofloxacin; even then, organisms are not always eradicated. Valve surgery is often required.

:Bartonellosis

- This group of diseases are caused by intracellular Gram-negative bacilli closely related to the rickettsiae and have been found to be important causes of ‘culture-negative’ endocarditis.
- They are found in many domestic pets, such as cats, although for several the host is ill defined.
- The principal human pathogens are *Bartonella quintana, B. henselae* and *B. bacilliformis*.

13.54 Clinical diseases caused by bartonellosis

Reservoir	Vector	Organism	Disease
Cats	Flea	*B. henselae*	**Cat scratch disease, bacillary angiomatosis, endocarditis**
Undefined	Lice	*B. quintana*	**Trench fever, bacillary angiomatosis, endocarditis**
Undefined	Sandfly	*B. bacilliformis*	**Carrion's disease: Oroya fever and verruga peruana**
Undefined	Flea	*B. rochalimae*	**Fever, rash, anaemia, splenomegaly**

Bartonella infections are associated with the following clinical :conditions

- **Trench fever**: This is a relapsing fever with severe leg pain and is due to *B. quintana*. The disease is not fatal but is very debilitating.
- **Bacteraemia and endocarditis in the homeless**: The endocarditis due to *B. quintana* or *henselae* is associated with severe damage to the heart valves.

- **Cat scratch disease**: *B. henselae* causes this common benign lymphadenopathy in children and young adults. A vesicle or papule develops on the head, neck or arms after a cat scratch. The lesion resolves spontaneously but there may be regional lymphadenopathy that persists for up to 4 months before also resolving spontaneously.
- **Bacillary angiomatosis**: This is an HIV-associated disease due to *B. quintana* or *henselae.*

- **Oroya fever and verruga peruana (Carrion's disease):** This is endemic in areas of Peru. It is a biphasic disease caused by *B. bacilliformis* and is transmitted by sandflies of the genus *Phlebotomus*. Fever, haemolytic anaemia and microvascular thrombosis with end-organ ischaemia are features. It is frequently fatal if untreated.

:Investigations and management

- Bartonellae can be grown from the blood but this requires prolonged incubation using enriched media.
- Serum antibody detection is possible.
- *Bartonella* species are susceptible to β-lactams, rifampicin, erythromycin and tetracyclines.
- Antibiotic use is guided by clinical need.
- Cat scratch disease usually resolves spontaneously but *Bartonella* endocarditis requires valve replacement and combination antibiotic therapy.

:Chlamydial infections

13.55 Chlamydial infections

Organism	Disease caused
Chlamydia trachomatis	Trachoma Lymphogranuloma venereum (Box 15.11, p. 422) Cervicitis, urethritis, proctitis (pp. 421–422)
Chlamydia psittaci	Psittacosis (Box 19.43, p. 682)
Chlamydophila (Chlamydia) pneumoniae	Atypical pneumonia (Box 19.43, p. 682) Acute/chronic sinusitis

:Trachoma

- Trachoma is a chronic keratoconjunctivitis caused by *Chlamydia trachomatis*, and is the most common cause of avoidable blindness.
- The classic trachoma environment is dry and dirty, causing children to have eye and nose discharges.
- Transmission occurs through flies, on fingers and within families.
- In endemic areas the disease is most common in children.

:Pathology and clinical features

- The onset is usually insidious and infection may be asymptomatic.
- The infection lasts for years, may be latent over long periods and may recrudesce.
- The conjunctiva of the upper lid is first affected with vascularisation and cellular infiltration.
- Early symptoms include conjunctival irritation and blepharospasm.

- The early follicles of trachoma are characteristic, but clinical differentiation from conjunctivitis due to other viruses may be difficult.

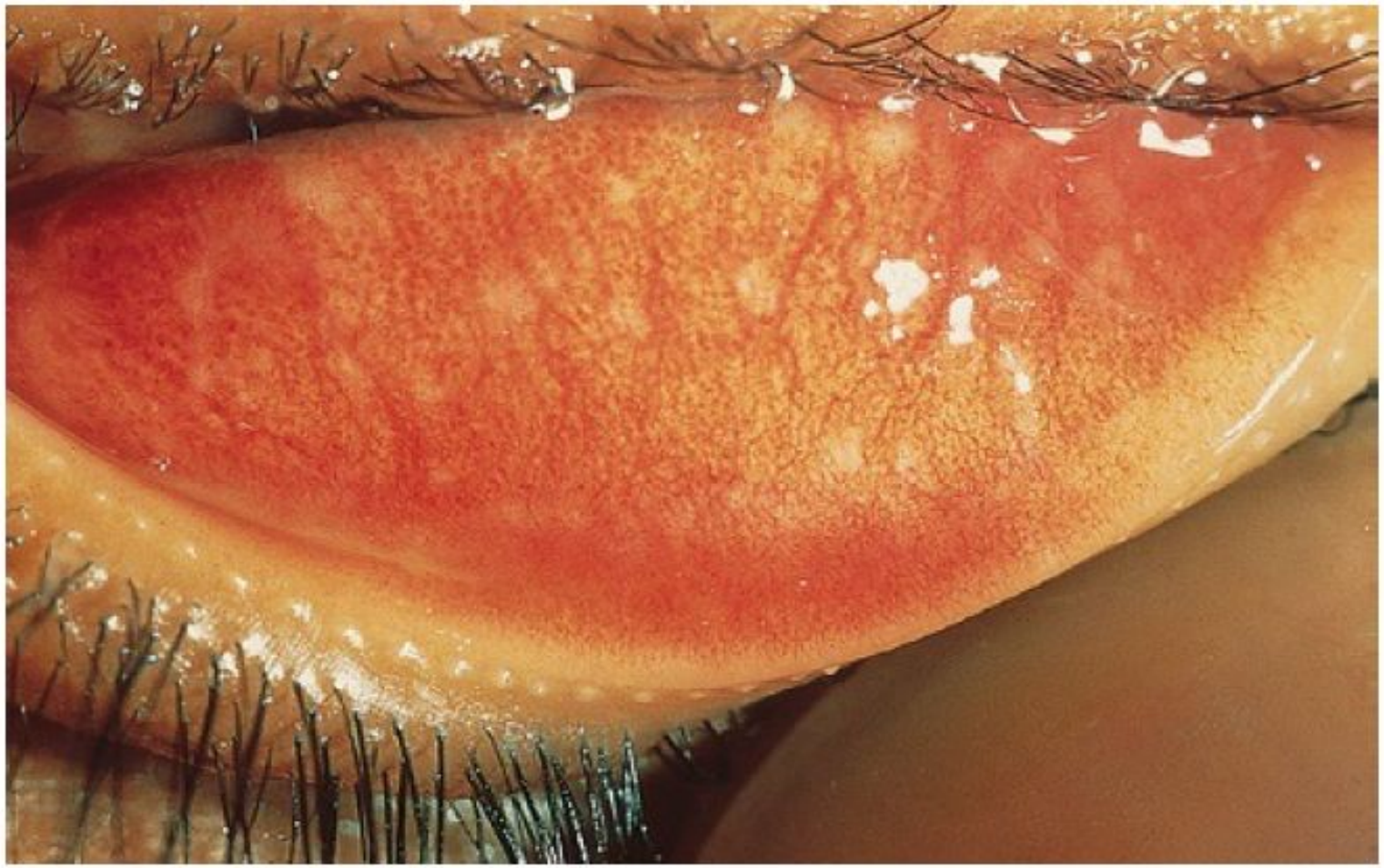

Fig. 13.27 Trachoma. Trachoma is characterised by hyperaemia and numerous pale follicles.

- Scarring causes inversion of the lids (entropion) so that the lashes rub against the cornea (trichiasis). The cornea becomes vascularised and opaque. The problem may not be detected until vision begins to fail.

:Investigations and management

- Intracellular inclusions may be demonstrated in conjunctival scrapings by staining with iodine or immunofluorescence.
- Chlamydia may be isolated in chick embryo or cell culture.

- A single dose of azithromycin (20 mg/kg) has been shown to be superior to 6 weeks of 12-hourly tetracycline eye ointment for individuals in mass treatment programmes.
- Deformity and scarring of the lids, and corneal opacities, ulceration and scarring require surgical treatment after control of local infection.

:Prevention

- Personal and family cleanliness should be improved.
- Proper care of the eyes of newborn and young children is essential.
- Family contacts should be examined.
- The WHO is promoting the **SAFE** strategy for trachoma control (**surgery, antibiotics, facial cleanliness and environmental improvement**).

THE END