BACTERIAL INFECTIONS

Bacterial infections of the skin, soft :tissues and bones

- Most infections of the skin, soft tissues and bone are caused by either staphylococci (mainly *Staph. aureus) or* streptococci (mainly *Strep. pyogenes)*.

:Staphylococcal infections

- Staphylococci are usually found colonising the anterior nares and skin.
- Traditionally, staphylococci were divided into two groups according to their ability to produce coagulase, an enzyme that converts fibrinogen to fibrin in rabbit plasma, causing it to clot.
- *Staph. aureus* is coagulase-positive, and most other species coagulase-negative.

- The coagulase test is now less commonly undertaken, with identification of *Staph. aureus* often achieved by other methods.

- *Staph. aureus* is the main cause of staphylococcal infections.
- *Staph. intermedius* is another coagulase-positive staphylococcus, which causes infection following dog bites.
- Among coagulase-negative organisms, *Staph. epidermidis* is the predominant commensal organism of the skin, and can cause severe infections in those with central venous catheters or implanted prosthetic materials.

- *Staph. saprophyticus* is part of the normal vaginal flora and causes urinary tract infections in sexually active young women.
- Others implicated in human infections include *Staph. lugdunensis, Staph. schleiferi, Staph. haemolyticus* and *Staph. caprae.*
- Coagulase-negative staphylococci are not usually identified to species level.

- Staphylococci are particularly dangerous if they gain access to the blood stream, having the potential to cause disease in many sites.

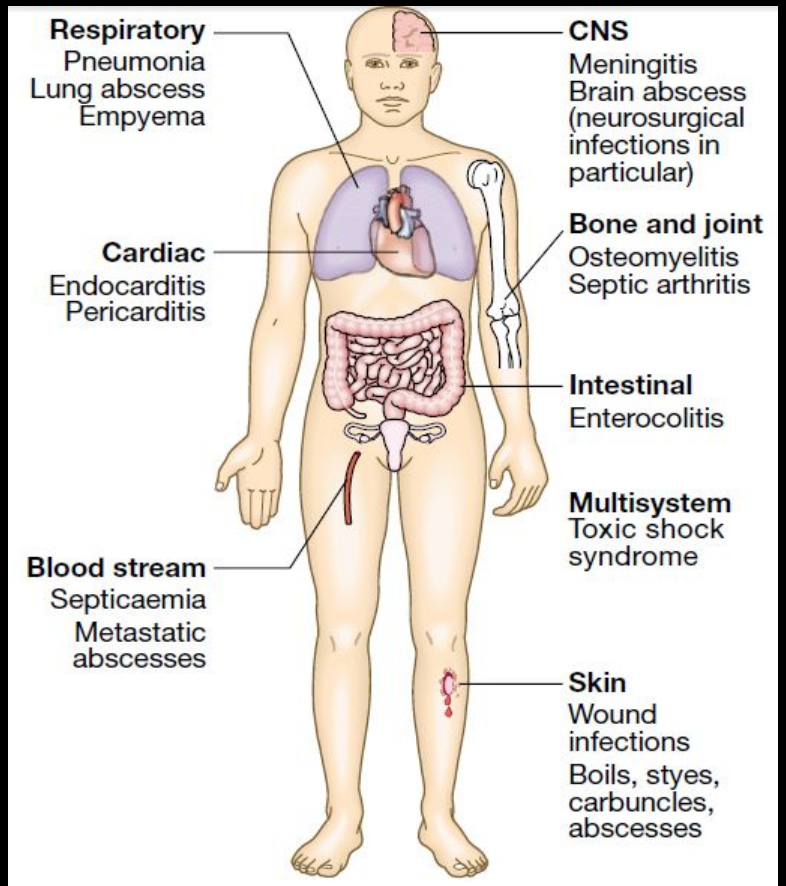

Fig. 13.15 Infections caused by *Staphylococcus aureus*.

- In any patient with staphylococcal bacteraemia, especially injection drug-users, the possibility of endocarditis must be considered.
- Growth of *Staph. aureus* in blood cultures should not be dismissed as a 'contaminant' unless all possible underlying sources have been excluded and repeated blood culture is negative.

- Any evidence of spreading cellulitis indicates the urgent need for an antistaphylococcal antibiotic such as flucloxacillin.
- This is particularly true for mid-facial cellulitis, which can result in cavernous sinus thrombophlebitis.

- In addition, *Staph. aureus* can cause severe systemic disease due to the effects of toxin produced at superficial sites in the absence of tissue invasion by bacteria.

:Skin infections

- Staphylococcal infections cause ecthyma, folliculitis, furuncles, carbuncles, bullous impetigo and the scalded skin syndrome.
- They may also be involved in necrotising infections of the skin and subcutaneous tissues.

:Wound infections

- Many wound infections are caused by staphylococci and may significantly prolong hospital stays in otherwise uncomplicated surgery.
- Prevention involves paying careful attention to hand hygiene, skin preparation and aspetic technique, and the use of topical and systemic antibiotic prophylaxis.

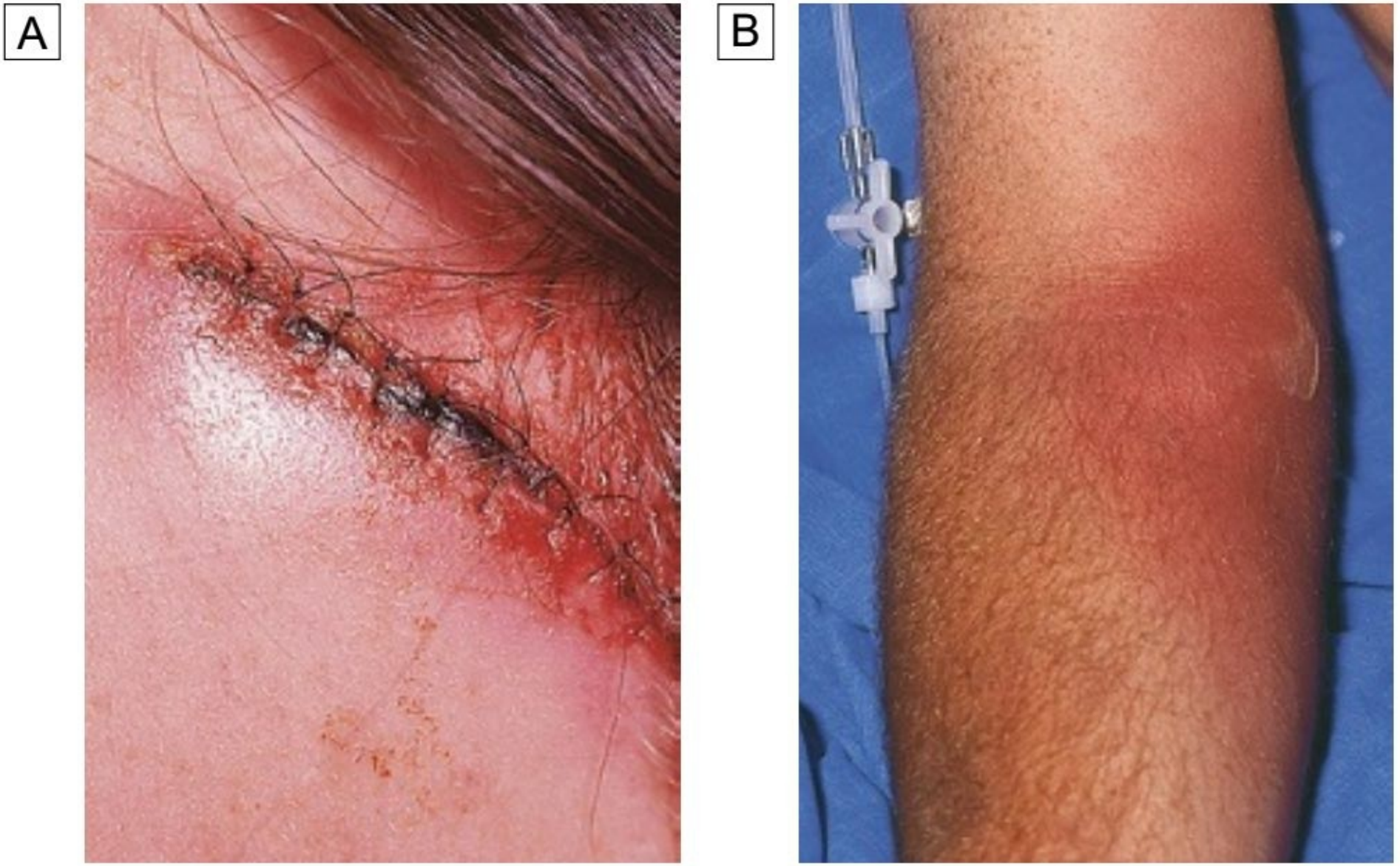

Fig. 13.16 Manifestations of skin infection with *Staph. aureus*.
A Wound infection. **B** Cannula-related infection.

- Treatment is by drainage of any abscesses plus adequate dosage of antistaphylococcal antibiotics.
- These should be instituted early, particularly if prosthetic implants of any kind have been inserted.

:Cannula-related infection

- Staphylococcal infection associated with cannula sepsis and thrombophlebitis is an important and, unfortunately, extremely common reason for morbidity following hospital admission.

- The Visual Infusion Phlebitis (VIP) score is a useful way of monitoring cannulae:

13.39 How to assess an i.v. cannula using the Visual Infusion Phlebitis score (VIP)

Clinical features	Score	Assessment and management
I.v. site appears healthy	0	**No signs of phlebitis** Observe cannula
One of the following is evident: Slight pain near i.v. site Slight redness near i.v. site	1	**Possible first signs of phlebitis** Observe cannula
Two of the following are evident: Pain near i.v. site Erythema Swelling	2	**Early stage of phlebitis** Resite cannula
ALL of the following are evident and extensive: Pain along path of cannula Erythema Induration	3	**Medium stage of phlebitis** Resite cannula Consider treatment
ALL of the following are evident and extensive: Pain along path of cannula Erythema Induration Palpable venous cord	4	**Advanced stage of phlebitis or start of thrombophlebitis** Resite cannula Consider treatment
ALL of the following are evident: Pain along path of cannula Erythema Induration Palpable venous cord Pyrexia	5	**Advanced stage of thrombophlebitis** Initiate treatment Resite cannula

*Adapted from Jackson A, Nursing Times 1997; 94:68–71.

- Staphylococci have a predilection for plastic, rapidly forming a biofilm which remains as a source of bacteraemia as long as the plastic is in situ.
- Local poultice application may relieve symptoms but cannula removal and antibiotic treatment with flucloxacillin (or a glycopeptide if MRSA is suspected) are necessary if there is any suggestion of spreading infection.

:Meticillin-resistant Staph. aureus (MRSA)

- Resistance to meticillin, due to a penicillin-binding protein mutation, has been recognised in *Staph. Aureus* for more than 30 years.
- The recent recognition of resistance to vancomycin/teicoplanin (glycopeptides) in either glycopeptide intermediate *Staph. aureus* (GISA) or, rarely, vancomycin-resistant (VRSA) strains threatens the ability to manage serious infections produced by such organisms.

- MRSA is now a major world-wide health care-acquired pathogen, accounting for up to 40% of staphylococcal bacteraemia in developed countries.
- Community-acquired MRSA (c-MRSA) currently accounts for 50% of all MRSA infections in the USA.

- These organisms have also acquired other virulence factors such as Panton–Valentine leukocidin (PVL), which can cause rapidly fatal infection in young people.
- Clinicians must be aware of the potential danger of these infections and be prepared to take whatever appropriate infection control measures are locally advised.

- Treatment should always be based on the results of antimicrobial susceptibility testing since resistance to all these agents occurs.
- Milder MRSA infections may be treated with clindamycin, tetracyclines or co-trimoxazole.

- Glycopeptides, linezolid and daptomycin are reserved for treatment of more severe infections.
- PVL-producing *Staph. aureus* infections should be treated with protein-inhibiting antibiotics (clindamycin, linezolid).

Staphylococcal toxic shock syndrome :(TSS)

- This serious and life-threatening disease is associated with infection by *Staph. aureus,* which produces a specific toxin (toxic shock syndrome toxin 1, TSST1).
- It was commonly seen in young women associated with the use of highly absorbent intravaginal tampons but can occur with any *Staph. aureus* infection involving a relevant toxin-producing strain.

- The toxin acts as a ‘superantigen’, triggering significant T-helper cell activation and massive cytokine release.
- TSS has an abrupt onset with high fever, generalised systemic upset (myalgia, headache, sore throat and vomiting), a generalised erythematous blanching rash resembling scarlet fever, and hypotension.

- It rapidly progresses over a matter of hours to multisystem involvement with cardiac, renal and hepatic compromise, leading to death in 10–20%.
- Recovery is accompanied at 7–10 days by desquamation.

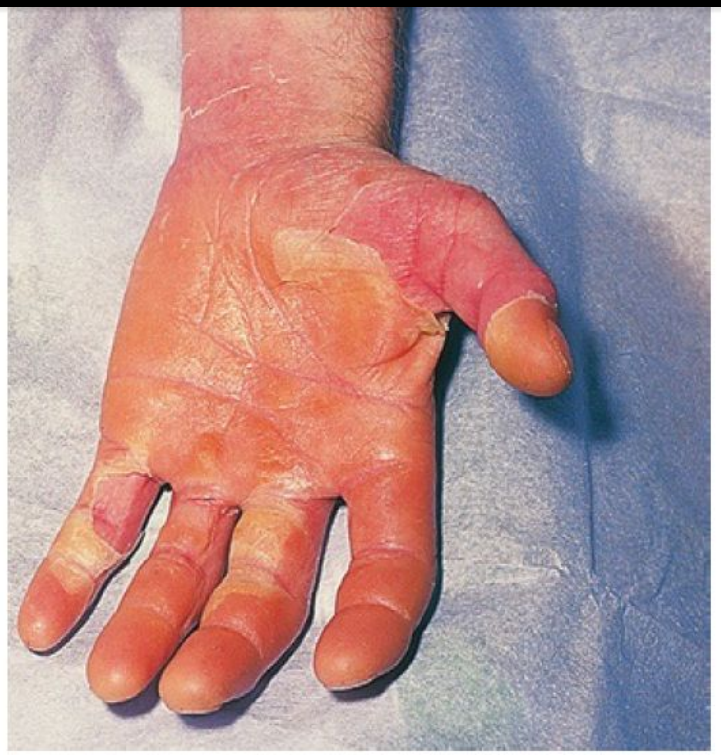

Fig. 13.17 Full-thickness desquamation after staphylococcal toxic shock syndrome.

- The diagnosis is clinical and may be confirmed in menstrual cases by vaginal examination, the finding of a retained tampon and microbiological examination by Gram stain demonstrating typical staphylococci.
- Subsequent culture and demonstration of toxin production are confirmatory.

:Management

- Treatment is with immediate and aggressive fluid resuscitation and an intravenous antistaphylococcal antibiotic (flucloxacillin or vancomycin), usually with the addition of a protein synthesis inhibitor (e.g. clindamycin) to inhibit toxin production.
- Intravenous immunoglobulin is occasionally added in the most severe cases on the basis of efficacy in streptococcal toxic shock.

- Women who recover should be advised not to use tampons for at least 1 year and should also be warned that, due to an inadequate antibody response to TSST1, the condition can recur.

:Streptococcal infections

- Streptococci are nasopharyngeal and gut commensals, which appear as Gram-positive cocci in chains.
- They are classified by the haemolysis they produce on blood agar and by their serotypes.
- Some streptococci (e.g. *milleri* group) defy simple classification.

13.40 Streptococcal and related infections

β-haemolytic group A (*Strep. pyogenes*)	
• Skin and soft tissue infection (including erysipelas, impetigo, necrotising fasciitis)	• Puerperal sepsis • Scarlet fever • Glomerulonephritis • Rheumatic fever
• Streptococcal toxic shock syndrome	• Bone and joint infection • Tonsillitis
β-haemolytic group B (*Strep. agalactiae*)	
• Neonatal infections, including meningitis • Septicaemia	• Female pelvic infections • Cellulitis
β-haemolytic group C (various zoonotic streptococci)	
• Septicaemia	• Cellulitis
α, β- or non-haemolytic group D enterococci (*E. faecalis/faecium*)	
• Endocarditis • Intra-abdominal infections	• Urinary tract infection
α, β- or non-haemolytic group D streptococci (*Strep. bovis*)	
• Septicaemia • Liver abscess	• Brain abscess
β-haemolytic group G streptococci	
• Septicaemia • Cellulitis	• Liver abscess
α-haemolytic viridans group (*Strep. mitis, sanguis, mutans, salivarius*)	
• Septicaemia in immunosuppressed	• Endocarditis
α-haemolytic optochin-sensitive (*Strep. pneumoniae*)	
• Pneumonia • Meningitis • Endocarditis • Otitis media	• Septicaemia • Spontaneous bacterial peritonitis
Anaerobic streptococci (*Peptostreptococcus* spp.)	
• Peritonitis • Dental infections	• Liver abscess • Pelvic inflammatory disease
N.B. All streptococci can cause septicaemia.	

Skin presentations of streptococcal :infections

- Group A streptococci (GAS) are the major cause of cellulitis, erysipelas and impetigo.
- Groups C and G streptococci cause cellulitis in particular in elderly, diabetic or immunocompromised patients.
- Group B streptococcal (GBS) infection is an increasing problem at the extremes of age.

:Streptococcal scarlet fever

- Group A (or occasionally groups C and G) streptococci causing pharyngitis, tonsillitis or other infection may lead to scarlet fever, if the infecting strain produces astreptococcal pyrogenic exotoxin.
- Common in schoolage children, scarlet fever can occur in young adults who have contact with young children.

- A diffuse erythematous rash occurs, which blanches on pressure, classically with circumoral pallor.
- The tongue, initially coated, becomes red and swollen (‘strawberry tongue’).
- The disease lasts about 7 days, the rash disappearing in 7–10 days followed by a fine desquamation.
- Residual petechial lesions in the antecubital fossa may be seen (‘Pastia’s sign’).

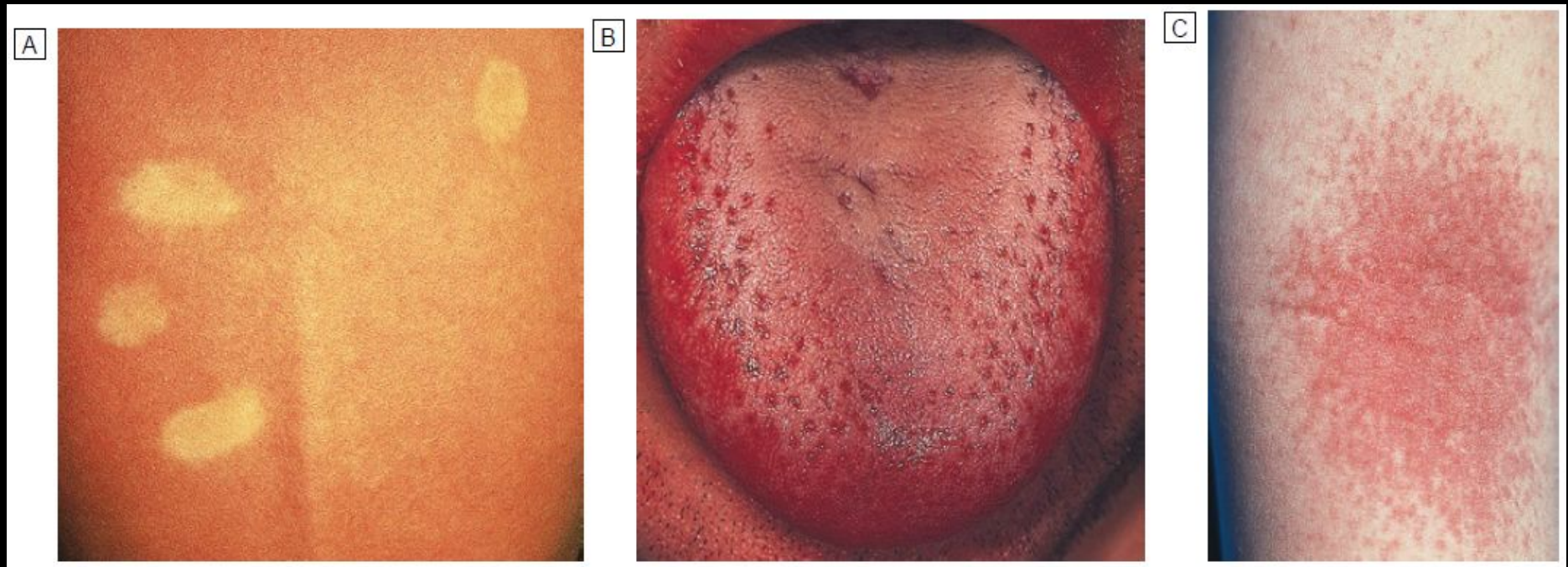

Fig. 13.18 Clinical features of scarlet fever. A Characteristic rash with blanching on pressure. B 'Strawberry tongue'. C Pastia's sign: a petechial rash in the cubital fossa.

- Treatment involves active therapy for the underlying infection (benzylpenicillin or orally available penicillin) plus symptomatic measures.

:Streptococcal toxic shock syndrome

- This is associated with severe group A (or occasionally group C or G) streptococcal skin infections producing one of a variety of toxins such as pyogenic exotoxin A.
- Like staphylococcal toxic shock syndrome toxin, these act as superantigens, stimulating T-helper cells and a dramatic cytokine response.

- Initially, an influenza-like illness occurs with, in 50% of cases, signs of localised infection, most often involving the skin and soft tissues.
- A faint erythematous rash, mainly on the chest, rapidly progresses to circulatory shock.
- Without aggressive management, multi-organ failure will develop.

- Fluid resuscitation must be undertaken, with parenteral antistreptococcal antibiotic therapy, usually with benzylpenicillin and a protein inhibitor such as clindamycin to inhibit toxin production.
- Intravenous immunoglobulin is usually administered in addition.
- If necrotising fasciitis is present, it should be treated with urgent débridement.

:Treponematoses

Endemic treponematoses:

Yaws:

- Yaws is a granulomatous disease, mainly involving the skin and bones, which is caused by *Treponema pertenue,* morphologically and serologically indistinguishable from the causative organisms of syphilis and pinta.

- It is important to establish the geographical origin and sexual history of patients to exclude a false-positive syphilis serology due to the endemic treponemal infections.

- WHO campaigns between 1950 and 1960 treated over 60 million people and eradicated yaws from many areas, but the disease has persisted patchily throughout the tropics; there was resurgence in the 1980s and 1990s in West and Central Africa and the South Pacific.

- Organisms are transmitted by bodily contact from a patient with infectious yaws through minor abrasions of the skin of another patient, usually a child.
- After an incubation period of 3–4 weeks, a proliferative granuloma containing numerous treponemes develops at the site of inoculation.
- This primary lesion is followed by secondary eruptions.

- In addition, there may be hypertrophic periosteal lesions of many bones, with underlying cortical rarefaction.
- Lesions of late yaws are characterised by destructive changes which closely resemble the osteitis and gummas of tertiary syphilis and which heal with much scarring and deformity.

13.41 Diagnosis and treatment of yaws, pinta and bejel

Diagnosis of early stages

- Detection of spirochaetes in exudate of lesions by dark ground microscopy

Diagnosis of latent and early stages

- Positive serological tests, as for syphilis (Box 15.7, p. 419)

Treatment of all stages

- Single intramuscular injection of 1.2 g long-acting (e.g. benzathine) benzylpenicillin

- The disease disappears with improved housing and cleanliness.
- In few fields of medicine have chemotherapy and improved hygiene achieved such dramatic success as in the control of yaws.

:Pinta and bejel

- These two treponemal infections occur in poor rural populations with low standards of domestic hygiene, but are found in separate parts of the world

- They have features in common, notably that they are transmitted by contact, usually within the family and not sexually, and in the case of bejel, through common eating and drinking utensils.
- Their diagnosis and management are as for yaws.

:Pinta

- Pinta is probably the oldest of the human treponemal infections.
- It is found only in South and Central America, where its incidence is declining.
- The infection is confined to the skin.
- The early lesions are scaly papules or dyschromic patches on the skin.
- The late lesions are often depigmented and disfiguring.

:Bejel

- Bejel is the Middle Eastern name for non-venereal syphilis, which has a patchy distribution across sub-Saharan Africa, the Middle East, Central Asia and Australia.
- It has been eradicated from Eastern Europe.

- Transmission is most commonly from the mouth of the mother or child and the primary mucosal lesion is seldom seen.
- The early and late lesions resemble those of secondary and tertiary syphilis but cardiovascular and neurological disease are rare.

:*Tropical ulcer*

- Tropical ulcer is due to a synergistic bacterial infection caused by a fusobacterium (*F. ulcerans*, an anaerobe*) and Treponema vincentii.*
- It is common in hot humid regions.
- The ulcer is most common on the lower legs and develops as a papule that rapidly breaks down to a sharply defined, painful ulcer.

- The base of the ulcer has a foul slough.
- Penicillin and metronidazole are useful in the early stages but rest, elevation and dressings are the mainstays of treatment.

:Buruli ulcer

- This ulcer is caused by *Mycobacterium ulcerans* and occurs widely in tropical rainforests.
- In 1999 a survey in Ghana found 6500 cases; there are an estimated 10 000 cases in West Africa as a whole.

- The initial lesion is a small subcutaneous nodule on the arm or leg.
- This breaks down to form a shallow, necrotic ulcer with deeply undermined edges which extends rapidly.
- Healing may occur after 6 months, but granuloma formation and the accompanying fibrosis cause contractures and deformity.

- Clumps of acid-fast bacilli can be detected in the ulcer floor.
- A combination of rifampicin and streptomycin can cure the infection.
- Infected tissue should be removed surgically.
- Health campaigns in Ghana have successfully focused on early removal of the small, pre-ulcerative nodules.

:Systemic bacterial infections

Brucellosis:

- Brucellosis is an enzootic infection (i.e. endemic in animals).

- Although six species of *Brucella* Gram-negative bacilli are known, only four are important to humans: *B. melitensis* (goats, sheep and camels in Europe, especially the Mediterranean basin, the Middle East, Africa, India, Central Asia and South America), *B. abortus* (cattle, mainly in Africa, Asia and South America), *B. suis* (pigs in South Asia) and *B. canis* (dogs).

- *B. melitensis* causes the most severe disease; *B. suis* is often associated with abscess formation.
- Infected animals may excrete *Brucella* spp. in their milk for prolonged periods and human infection is acquired by ingesting contaminated dairy products, uncooked meat or offal.

- Animal urine, faeces, vaginal discharge and uterine products may act as sources of infection through abraded skin or via splashes and aerosols to the respiratory tract and conjunctiva.

:*Clinical features*

- *Brucella* spp. are intracellular organisms that survive for long periods within the reticulo-endothelial system.
- This explains many of the clinical features, including the chronicity of disease and tendency to relapse even after antimicrobial therapy.
- Acute illness is characterised by a high swinging temperature, rigors, lethargy, headache, joint and muscle pains, and scrotal pain.

- Occasionally, there is delirium, abdominal pain and constipation.
- Physical signs are non-specific, e.g. enlarged lymph nodes.
- Enlargement of the spleen may lead to hypersplenism and thrombocytopenia.

- Localised infection, which occurs in about 30% of patients, is more likely if diagnosis and treatment are delayed.

13.42 Focal manifestations of brucellosis

Musculoskeletal	
• Suppurative arthritis; synovitis, bursitis	• Spinal spondylitis or sacro-iliitis
• Osteomyelitis	• Paravertebral or psoas abscess
Central nervous system	
• Meningitis	• Stroke
• Intracranial or subarachnoid haemorrhage	• Myelopathy
	• Radiculopathy
	• Cranial nerve palsies
Ocular	
• Uveitis	• Retinal thrombophlebitis
Cardiac	
• Myocarditis	• Endocarditis
Respiratory	
• Pneumonitis or abscesses	• Hilar adenopathy
Abdominal	
• Splenic abscesses or calcification	• Hepatitis
Genitourinary	
• Epididymo-orchitis	
Haematological	
• Pancytopenia	

:Diagnosis

- Definitive diagnosis of brucellosis depends on the isolation of the organism.
- Blood cultures are positive in 75–80% of infections caused by *B. melitensis* and 50% of those caused by *B. abortus*.
- Bone marrow culture should not be used routinely but may increase the diagnostic yield, particularly if antibiotics have been given before specimens are taken.

- CSF culture in neurobrucellosis is positive in about 30% of cases.
- The laboratory should be alerted to a suspected diagnosis of brucellosis, as the organism has a propensity for infecting laboratory workers and must be cultured at an enhanced containment level.

- Serum tests are also used to detect brucellosis antibodies.
- In endemic areas a single high titre of > 1/320 or a fourfold rise in titre is needed to support a diagnosis of acute infection.
- The test usually takes several weeks to become positive but should eventually detect 95% of acute infections.

:Management

- Aminoglycosides show synergistic activity with tetracyclines against brucellae; standard therapy in acute infection consists of doxycycline 100 mg 12-hourly for 6 weeks, with streptomycin 1 g i.m. daily for the first 2 weeks.
- The relapse rate with this treatment is about 5 %.

- An alternative oral regimen consists of doxycycline 100 mg 12-hourly plus rifampicin 900 mg (15 mg/kg) daily for 6 weeks, but failure and relapse rates are higher, particularly with spondylitis.
- Rifampicin may antagonise doxycycline activity by reducing serum levels through enzyme induction.

- Rifampicin and cotrimoxazole are potential agents to use in pregnancy.
- Endocarditis is often treated with three active drugs, usually doxycycline, rifampicin and streptomycin, but surgery is often required.
- Chronic illness or neurobrucellosis should be treated for a minimum of 3 months and many authorities would extend this to 6 months, depending upon the response.

:Borrelia infections

- *Borrelia* are flagellated spirochaetal bacteria which infect humans after bites from ticks or lice.
- They cause a variety of human infections world-wide.

13.43 Clinical diseases caused by *Borrelia* spp.

Species	Vector	Geographic distribution
Lyme disease		
B. burgdorferi sensu stricto	Tick: *Ixodes scapularis*	Northern and eastern USA
	I. pacificus	Western USA
B. afzelii	*I. ricinus*	Europe
	I. persulcatus	Asia
B. garinii	*I. ricinus*	Europe
	I. persulcatus	Asia
Louse-borne relapsing fever		
B. recurrentis	Human louse: *Pediculus humanus corporis*	World-wide
Tick-borne relapsing fever		
B. hermsii	Tick: *Ornithodoros hermsii*	Western North America
B. turicatae	*O. turicatae*	Southwestern North America and northern Mexico
B. venezuelensis	*O. rudis*	Central America and northern South America
B. hispanica	*O. erraticus*	Iberian peninsula and northwestern Africa
B. crocidurae	*O. erraticus*	North Africa and Mediterranean region
B. duttonii	*O. moubata*	Central, eastern and southern Africa
B. persica	*O. tholozani*	Western China, India, central Asia, Middle East
B. latyschewii	*O. tartakovskyi*	Tajikistan, Uzbekistan

:a. Lyme disease

- Lyme disease (named after the town of Old Lyme in Connecticut, USA) is caused by *B. burgdorferi,* which occurs in the USA, Europe, Russia, China, Japan and Australia.
- In Europe two additional genospecies are also encountered, *B. afzelii* and *B. garinii.*
- The reservoir of infection is ixodid (hard) ticks that feed on a variety of large mammals, particularly deer.
- Birds may spread ticks over a wide area.

- The organism is transmitted to humans via the bite of infected ticks; larval, nymphal and adult forms are all capable of spreading infection.
- Ehrlichiosis is a common co-infection with Lyme disease (*Anaplasma phagocytophila,* human granulocytic anaplasmosis (HGA); *Ehrlichia chaffeensis,* human monocytic ehrlichiosis (HME)).

:Clinical features

- There are three stages of disease.
- Progression may be arrested at any stage.

:Early localised disease

- The characteristic feature is a skin reaction around the site of the tick bite, known as erythema migrans.

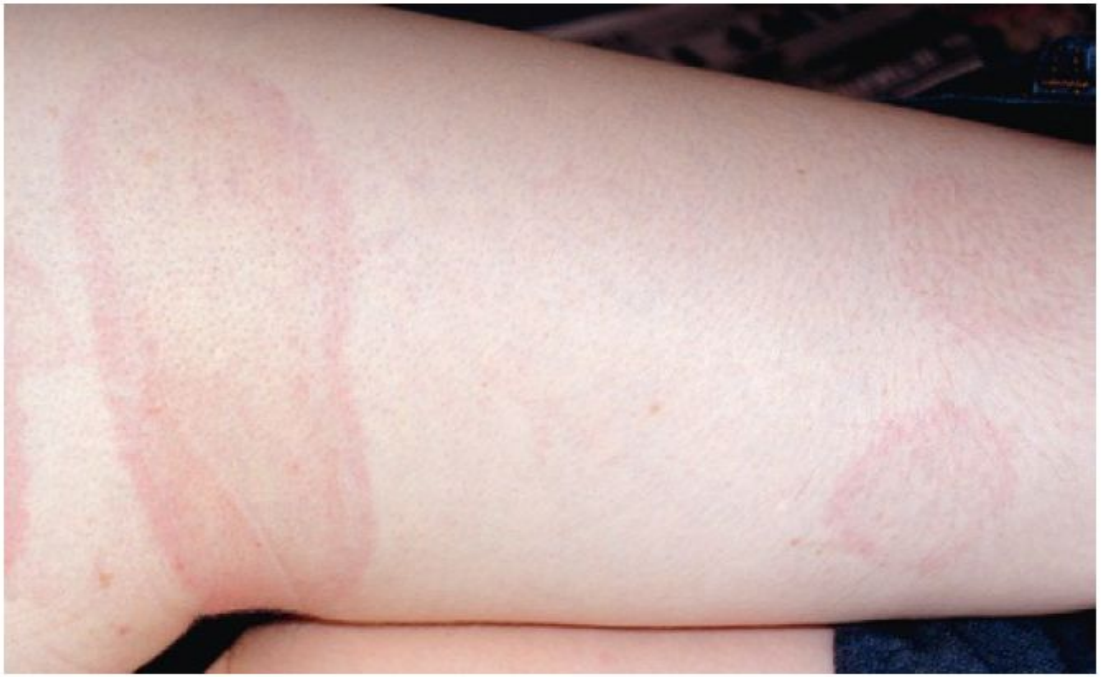

Fig. 13.19 Rash of erythema migrans in Lyme disease with metastatic secondary lesions.

- Initially, a red ‘bull’s eye’ macule or papule appears 2–30 days after the bite.
- It then enlarges peripherally with central clearing, and may persist for months.
- Atypical forms are fairly common.

- The lesion is not pathognomonic of Lyme disease since similar lesions can occur after tick bites in areas where Lyme disease does not occur.
- Other acute manifestations such as fever, headache and regional lymphadenopathy may develop with or without the rash.

:Early disseminated disease

- Dissemination occurs via the blood stream and lymphatics.
- There may be a systemic reaction with malaise, arthralgia, and occasionally metastatic areas of erythema migrans.
- Neurological involvement may follow weeks or months after infection.

- Common features include lymphocytic meningitis, cranial nerve palsies (especially unilateral or bilateral facial nerve palsy) and peripheral neuropathy.
- Radiculopathy, often painful, may present a year or more after initial infection.
- Carditis, sometimes accompanied by atrioventricular conduction defects, is not uncommon in the USA but appears to be rare in Europe.

:Late disease

- Late manifestations include arthritis, polyneuritis and encephalopathy.
- Prolonged arthritis, particularly affecting large joints, and brain parenchymal involvement causing neuropsychiatric abnormalities may occur, but are rare in the UK.
- Acrodermatitis chronica atrophicans is an uncommon late complication seen more frequently in Europe than North America.

- Doughy, patchy discoloration occurs on the peripheries, eventually leading to shiny atrophic skin.
- The lesions are easily mistaken for those of peripheral vascular disease.
- In patients from an endemic area or with risk factors, who have facial nerve palsy, Lyme disease should be considered.

:Diagnosis

- The diagnosis of early Lyme borreliosis is often clinical.
- Culture from biopsy material is not generally available, has a low yield, and may take longer than 6 weeks.
- Antibody detection is frequently negative early in the course of the disease, but sensitivity increases to 90–100% in disseminated or late disease.

- Immunofluorescence or ELISA can give false positive reactions in a number of conditions, including other spirochaetal infections, infectious mononucleosis, rheumatoid arthritis and systemic lupus erythematosus (SLE).

- Immunoblot (Western blot) techniques are more specific and, although technically demanding, should be used to confirm the diagnosis.
- Microorganism DNA detection by PCR has been applied to blood, urine, CSF, and biopsies of skin and synovium.

:Management

- Recent evidence suggests that asymptomatic patients with positive antibody tests should not be treated.
- However, erythema migrans always requires therapy because organisms may persist and cause progressive disease, even if the skin lesions resolve.
- Standard therapy consists of a 14-day course of doxycycline (200 mg daily) or amoxicillin (500 mg 8-hourly).

- Some 15% of patients with early disease will develop a mild Jarisch–Herxheimer reaction (JHR) during the first 24 hours of therapy.
- In pregnant women and small children, or in those allergic to amoxicillin and doxycycline, 14-day treatment with cefuroxime axetil (500 mg 12-hourly) or erythromycin (250 mg 6-hourly) may be used.

- Disseminated disease and arthritis require therapy for a minimum of 28 days.
- Arthritis may respond poorly, and prolonged or repeated courses may be necessary.
- Neuroborreliosis is treated with parenteral β-lactam antibiotics for 3–4 weeks; the cephalosporins may be superior to penicillin in this situation.

:*Prevention*

- Protective clothing and insect repellents should be used in tick-infested areas.
- Since the risk of borrelial transmission is lower in the first few hours of a blood feed, prompt removal of ticks is advisable.
- Unfortunately, larval and nymphal ticks are tiny and may not be noticed.

- Where risk of transmission is high, a single 200 mg dose of doxycycline, given within 72 hours of exposure, has been shown to prevent erythema migrans.
- A recombinant vaccine, OspA, in adjuvant was developed but withdrawn due to side-effects.

:b. *Louse-borne relapsing fever*

- The human body louse, *Pediculus humanus,* causes itching.
- Borreliae (*B. recurrentis)* are liberated from the infected lice when they are crushed during scratching, which also inoculates the borreliae into the skin.
- The disease occurs world-wide, with epidemic relapsing fever most often seen in Central and East Africa, and in South America.

- The borreliae multiply in the blood, where they are abundant in the febrile phases, and invade most tissues, especially the liver, spleen and meninges.
- Hepatitis and thrombocytopenia are common.

:Clinical features

- Onset is sudden with fever.
- The temperature rises to 39.5–40.5°C, accompanied by a tachycardia, headache, generalised aching, injected conjunctivae and, frequently, a petechial rash, epistaxis and herpes labialis.

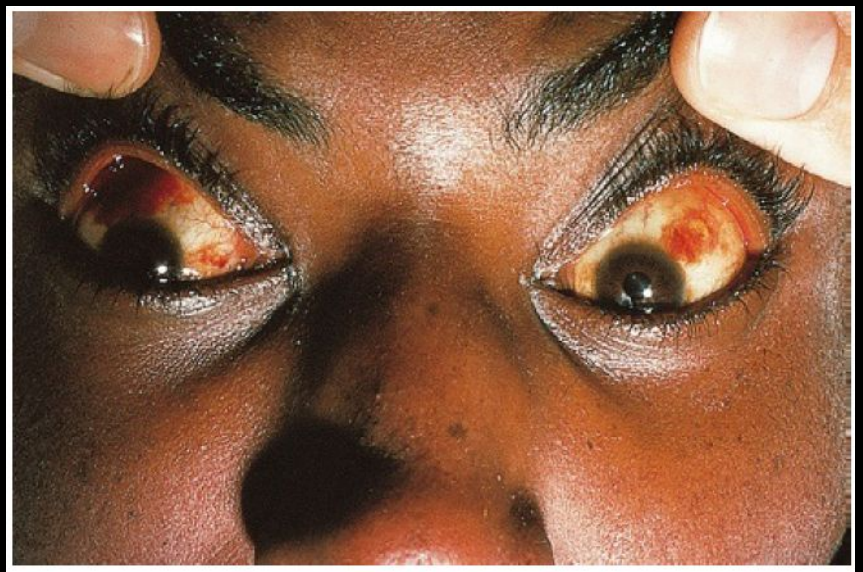

Fig. 13.20 Louse-borne relapsing fever. Injected conjunctivae.

- As the disease progresses, the liver and spleen frequently become tender and palpable, and jaundice is common.
- There may be severe serosal and intestinal haemorrhage, mental confusion and meningism.
- The fever ends in crisis between the 4th and 10th days, often associated with profuse sweating, hypotension, and circulatory and cardiac failure.

- There may be no further fever but, in a proportion of patients, after an afebrile period of about 7 days, there are one or more relapses, which are usually milder and less prolonged.
- In the absence of specific treatment, the mortality rate is up to 40%, especially among the elderly and malnourished.

:Investigations and management

- The organisms are demonstrated in the blood during fever either by dark ground microscopy of a wet film or by staining thick and thin films.
- The problems of treatment are to eradicate the organism, to minimise the severe Jarisch–Herxheimer reaction which inevitably follows successful chemotherapy, and to prevent relapses.

- The safest treatment is procaine penicillin 300 mg i.m., followed the next day by 0.5 g tetracycline.
- Tetracycline alone is effective and prevents relapse, but may give rise to a worse reaction.
- Doxycycline 200 mg once by mouth in place of tetracycline has the advantage of also being curative for typhus, which often accompanies epidemics of relapsing fever.

- JHR is best managed in a high-dependency unit with expert nursing and medical care.
- The patient, clothing and all contacts must be freed from lice as in epidemic typhus.

:c. *Tick-borne relapsing fever*

- Soft ticks (*Ornithodoros* spp.) transmit *B. duttoni* (and several other borrelia species) through saliva while feeding on their host.
- Those sleeping in mud houses are at risk, as the tick hides in crevices during the day and feeds on humans during the night.
- Rodents are the reservoir in all parts of the world except East Africa, where humans are the reservoir.

- Clinical manifestations are similar to the louse-borne disease but spirochaetes are detected in fewer patients on dark field microscopy.
- A 7-day course (due to a higher relapse rate than louse-borne relapsing fever) of treatment with either tetracycline (500 mg 6-hourly) or erythromycin (500 mg 6-hourly) is needed.

:Leptospirosis

Microbiology and epidemiology:

- Leptospirosis is one of the most common zoonotic diseases, favoured by a tropical climate and flooding during the monsoon but occurring world-wide.
- Leptospires are tightly coiled, thread-like organisms about 5–7 μm in length which are actively motile; each end is bent into a hook.

- *Leptospira interrogans* is pathogenic for humans.
- The genus can be separated into more than 200 serovars (subtypes) belonging to 23 serogroups.
- Leptospirosis appears to be ubiquitous in wildlife and in many domestic animals.
- The organisms persist indefinitely in the convoluted tubules of the kidney and are shed into the urine in massive numbers, but infection is asymptomatic in the host.

- The most frequent hosts are rodents, especially the common rat (*Rattus norvegicus).*
- Particular leptospiral serogroups are associated with characteristic animal hosts; *L. ictero-haemorrhagiae is the* classical parasite of rats, *L. canicola* of dogs, *L. hebdomadis* of cattle, and *L. pomona* of pigs.
- There is nevertheless considerable overlap in host–serogroup associations.

- Leptospires can enter their human hosts through intact skin or mucous membranes, but entry is facilitated by cuts and abrasions.
- Prolonged immersion in contaminated water will also favour invasion, as the spirochaete can survive in water for months.
- Leptospirosis is common in the tropics and also in freshwater sports enthusiasts.

:Clinical features

- After a relatively brief bacteraemia, invading organisms are distributed throughout the body, mainly in kidneys, liver, meninges and brain.
- The incubation period averages 1–2 weeks.
- Four main clinical syndromes can be discerned.

:a. *Bacteraemic leptospirosis*

- Bacteraemia with any serogroup can produce a non-specific illness with high fever, weakness, muscle pain and tenderness (especially of the calf and back), intense headache and photophobia, and sometimes diarrhoea and vomiting.
- Conjunctival congestion is the only notable physical sign.
- The illness comes to an end after about 1 week, or else merges into one of the other forms of infection.

:b. *Aseptic meningitis*

- Classically associated with *L. canicola* infection, this illness is very difficult to distinguish from viral meningitis.
- The conjunctivae may be congested but there are no other differentiating signs.
- Laboratory clues include a neutrophil leucocytosis, abnormal LFTs, and the occasional presence of albumin and casts in the urine.

:c. *Icteric leptospirosis (Weil's disease)*

- Less than 10% of symptomatic infections result in severe icteric illness.
- Weil's disease is a dramatic life-threatening event, characterised by fever, haemorrhages, jaundice and renal impairment.
- Conjunctival hyperaemia is a frequent feature.
- The patient may have a transient macular erythematous rash, but the characteristic skin changes are purpura and large areas of bruising.

- In severe cases there may be epistaxis, haematemesis and melaena, or bleeding into the pleural, pericardial or subarachnoid spaces.
- Thrombocytopenia, probably related to activation of endothelial cells with platelet adhesion and aggregation, is present in 50% of cases.
- Jaundice is deep and the liver is enlarged, but there is usually little evidence of hepatic failure or encephalopathy.

- Renal failure, primarily caused by impaired renal perfusion and acute tubular necrosis, manifests as oliguria or anuria, with the presence of albumin, blood and casts in the urine.
- Weil's disease may also be associated with myocarditis, encephalitis and aseptic meningitis.
- Uveitis and iritis may appear months after apparent clinical recovery.

:d. Pulmonary syndrome

- This syndrome has long been recognised in the Far East, and has been described during an outbreak of leptospirosis in Nicaragua.
- It is characterised by haemoptysis, patchy lung infiltrates on chest X-ray, and respiratory failure.
- Total bilateral lung consolidation and ARDS with multi-organ dysfunction may develop, with a high mortality (> 50%).

:Diagnosis

- A polymorphonuclear leucocytosis is accompanied in severe infection by thrombocytopenia and elevated blood levels of creatine kinase.
- In jaundiced patients there is mild hepatitis and the prothrombin time may be a little prolonged.
- The CSF in leptospiral meningitis shows a variable cellular response, a moderately elevated protein level and normal glucose content.

- In the tropics, dengue, malaria, typhoid fever, scrub typhus and hantavirus infection are important differential diagnoses.
- Definitive diagnosis of leptospirosis depends upon isolation of the organism, serological tests or the detection of specific DNA.

- Blood cultures are most likely to be positive if taken before the 10th day of illness. Special media are required and cultures may have to be incubated for several weeks.
- Leptospires appear in the urine during the 2nd week of illness, and in untreated patients may be recovered on culture for several months.

- Serological tests are diagnostic if seroconversion or a fourfold increase in titre is demonstrated. The microscopic agglutination test (MAT) is the test of choice and can become positive by the end of the first week. IgM ELISA and immunofluorescent techniques are, however, easier to perform, while rapid immunochromatographic tests are specific but of only moderate sensitivity in the 1st week of illness.

- Detection of leptospiral DNA by PCR is possible in blood in early symptomatic disease, and in urine from the 8th day of illness and for many months thereafter.

:Management and prevention

- The general care of the patient is critically important.
- Blood transfusion for haemorrhage and careful attention to renal failure, the usual cause of death, are especially important.
- Renal failure is potentially reversible with adequate support such as dialysis.
- The optimal antimicrobial regimen has not been established.
- Most infections are self-limiting.

- Therapy with either oral doxycycline (100 mg 12-hourly for 1 week) or intravenous penicillin (900 mg 6-hourly for 1 week) is effective but may not prevent the development of renal failure.
- Parenteral ceftriaxone (1 g daily) is as effective as penicillin.

- A Jarisch–Herxheimer reaction may occur during treatment but is usually mild.
- Uveitis is treated with a combination of systemic antibiotics and local corticosteroids.
- Trials in military personnel have shown that infection with *L. interrogans* can be prevented by taking prophylactic doxycycline 200 mg weekly.

:Plague

- Plague is caused by *Yersinia pestis*, a small Gram-negative bacillus that is spread between rodents by their fleas.
- If domestic rats become infected, infected fleas may bite humans.
- Hunters and trappers can contract plague from handling rodents.
- In the late stages of human plague, *Y. pestis* may be expectorated and spread between humans by droplets, causing ‘pneumonic plague’.

- Epidemics of plague, such as the ‘Black Death’, have occurred since ancient times.
- It is often said that the first sign of plague is the appearance of dead rats.
- Plague foci are widely distributed throughout the world, including the USA; human cases are reported from about ten countries per year.

Fig. 13.21 Foci of the transmission of plague.

- *Y. pestis* is a potential bioweapon because of its capacity for mass production and aerosol transmission, and the high fatality rate associated with pneumonic plague.

:Clinical features

- Organisms inoculated through the skin are taken rapidly to the draining lymph nodes, where they elicit a severe inflammatory response that may be haemorrhagic.
- If the infection is not contained, septicaemia ensues and necrotic, purulent or haemorrhagic lesions develop in many organs.

- Oliguria and shock follow, and disseminated intravascular coagulation may result in widespread haemorrhage. Inhalation of *Y. pestis* causes alveolitis.
- The incubation period is 3–6 days, but shorter in pneumonic plague.

:Bubonic plague

- In this, the most common form of the disease, onset is usually sudden, with a rigor, high fever, dry skin and severe headache.
- Soon, aching and swelling at the site of the affected lymph nodes begin.
- The groin is the most common site of this ‘bubo’, made up of the swollen lymph nodes and surrounding tissue.

- Some infections are relatively mild but in the majority of patients toxaemia quickly increases, with a rapid pulse, hypotension and mental confusion.
- The spleen is usually palpable.

:Septicaemic plague

- Those not exhibiting a bubo usually deteriorate rapidly and have a high mortality.
- The elderly are more prone to this form of illness.
- The patient is toxic and may have gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea.
- DIC may occur, manifested by bleeding from various orifices or puncture sites, along with ecchymoses.

- Hypotension, shock, renal failure and ARDS may lead to further deterioration.
- Meningitis, pneumonia and expectoration of blood-stained sputum containing *Y. pestis* may complicate septicaemic, or occasionally bubonic, plague.

:*Pneumonic plague*

- Following primary infection in the lung, the onset of disease is very sudden, with cough and dyspnoea.
- The patient soon expectorates copious blood-stained, frothy, highly infective sputum, becomes cyanosed and dies.
- Chest radiology reveals bilateral infiltrates which may be nodular and progress to an ARDS-like picture.

:Investigations

- The organism may be cultured from blood, sputum and bubo aspirates.
- For rapid diagnosis Gram, Giemsa and Wayson's stains (the latter containing methylene blue) are applied to smears from these sites.
- *Y. pestis* is seen as bipolar staining coccobacilli, sometimes referred to as having a 'safety pin' appearance.

- Smears are also subjected to antigen detection by immunofluorescence, using *Y. pestis* F1 antigen-specific antibodies.
- The diagnosis may be confirmed by seroconversion or a single high titre (> 128) of anti-F1 antibodies in serum.
- DNA detection by PCR is under evaluation.
- Plague is a notifiable disease under international health regulations.

:Management

- If the diagnosis is suspected on clinical and epidemiological grounds, treatment must be started as soon as, or even before, samples have been collected for laboratory diagnosis.
- Streptomycin (1 g 12-hourly) or gentamicin (1 mg/kg 8-hourly) is the drug of choice.
- Tetracycline (500 mg 6-hourly) and chloramphenicol (12.5 mg/kg 6-hourly) are alternatives.

- Fluoroquinolones (ciprofloxacin and levofloxacin) may be as effective, but there is less clinical experience.
- Treatment may also be needed for acute circulatory failure, DIC and hypoxia.

:Prevention and infection control

- Rats and fleas should be controlled.
- In endemic areas, people should avoid handling and skinning wild animals.
- The patient should be isolated for the first 48 hours or until clinical improvement begins.
- Attendants must wear gowns, masks and gloves.

- Exposed symptomatic or asymptomatic people who have been in close contact with a patient with pneumonic plague should receive post-exposure antibiotic prophylaxis (doxycycline 100 mg or ciprofloxacin 500 mg 12-hourly) for 7 days.

- A formalin-killed vaccine is available for those at occupational risk but offers little protection against pneumonic plague.
- A recombinant subunit vaccine (protein antigens F1 + V) is in development.

:Listeriosis

- *Listeria monocytogenes* is an environmental Gram-positive bacillus which can contaminate food.
- Outbreaks have been associated with raw vegetables, soft cheeses, undercooked chicken, fish, meat and pâtés.
- The bacterium demonstrates ‘cold enrichment’, outgrowing other contaminating bacteria during refrigeration.

- Although food-borne outbreaks of gastroenteritis have been reported in immunocompetent individuals, *Listeria* causes more significant invasive infection especially in pregnancy, the elderly and the immunocompromised.

- In pregnancy, in addition to systemic symptoms of fever and myalgia, listeriosis causes chorioamnionitis, fetal deaths, abortions and neonatal infection.
- In other susceptible individuals, it causes systemic illness due to bacteraemia without focal symptoms.

- Meningitis, similar to other bacterial meningitis but with normal CSF glucose, is the next most common presentation; CSF usually shows increased neutrophils but occasionally only the mononuclear cells are increased.

:Investigations and management

- Diagnosis is made by blood and CSF culture.
- The organism grows readily in culture media.
- The most effective regimen consists of a combination of an intravenous aminopenicillin (amoxicillin or ampicillin) plus an aminoglycoside.
- A sulfamethoxazole/trimethoprim combination can be used in those with penicillin allergy.

- Cephalosporins are of no use in this infection, as the organism is inherently resistant, an important consideration when empirically treating meningitis.
- Proper treatment of foods before eating is the key to preventing listeriosis.
- Pregnant women are advised to avoid high-risk products, including soft cheeses.