



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

KEY POINTS

- Increasing population mobility means that a wide range of infections is seen globally
- Infections are especially common in immunodeficient people

An enormous range of infections is recognized; many are prevalent in the tropics and developing countries, and some are fatal. Global travel and global warming increasingly bring contact with these infections to the rest of the world. Concern has been expressed about more than a dozen potentially fatal infections that appear to be increasing in their geographical range (Box 21.1).

Bacteria, viruses and fungi are common in the external and internal environment, however, and most cause problems only if they secrete noxious substances, become invasive or elicit inappropriate host defence responses. Protection against most bacteria involves largely B cells and plasma cell production of antibodies, together with phagocytes (neutrophils and macrophages). Protection against mycobacteria, viruses and fungi is largely via T lymphocytes.

EMERGING INFECTIONS

Emerging infections (see also Appendix 21.1 and Ch. 33) may be:

- a recognized infection spreading to new areas or populations
- a hitherto known disease that is discovered to be caused by infection
- a previously unrecognized infection appearing where the habitat is changing (e.g. deforestation)
- a new infection resulting from change(s) in pre-existing microorganisms
- a known infection re-emerging because it has become resistant to treatment, or because of a breakdown in public health measures.

Box 21.1 Possible fatal diseases increasing with global warming

- Avian flu
- Babesiosis
- Cholera
- Dengue fever
- Ebola fever
- Lyme disease
- Malaria
- Parasitic infections
- Plague
- Red tides
- Rift valley fever
- Sleeping sickness
- Tuberculosis
- West Nile fever
- Yellow fever

INFECTION CONTROL

Guidelines to prevent transmission of infections are found at <http://www.bda.org/dentists/advice/ba/ic.aspx> (accessed 30 September 2013).

DISEASE NOTIFICATION

Notification of a number of specified infectious diseases is required in UK under the Public Health (Infectious Diseases) 1988 Act and the Public Health (Control of Diseases) 1984 Act. New (amended) regulations for clinical notifications came into force on 6 April 2010 (Box 21.2). Registered general *medical* practitioners (GMPs) in England and Wales

Box 21.2 Notifiable diseases

UK

- Acute bacterial meningitis (urgent)
- Acute viral meningitis (not Scotland)
- Acute encephalitis (not Scotland)
- Acute infectious hepatitis (not Scotland, urgent)^a
- Acute poliomyelitis (urgent)
- Anthrax (urgent)
- Botulism (urgent)
- Brucellosis (urgent if UK-acquired)
- Cholera (urgent)
- Diphtheria (urgent)
- Enteric fever (typhoid or paratyphoid, urgent)
- Food poisoning (not Scotland, urgent if clusters or outbreaks)
- Haemolytic uraemic syndrome (urgent)
- Infectious bloody diarrhoea (not Scotland unless caused by *Escherichia coli* O157, urgent)
- Invasive group A streptococcal disease (Scotland any necrotizing fasciitis, urgent)
- Scarlet fever (not Scotland)
- Legionnaires' disease (not Scotland, urgent)
- Leprosy (not Scotland or Northern Ireland)
- Malaria (not Scotland, urgent if UK-acquired)
- Measles (urgent)
- Meningococcal septicaemia (urgent)
- Mumps
- Plague (urgent)
- Rabies (only urgent if seen at time of bite rather than with symptoms)
- Rubella
- Severe acute respiratory syndrome (SARS) (urgent)
- Smallpox (urgent)
- Tetanus (urgent if intravenous drug user)
- Tuberculosis (urgent if health worker, case cluster or multiple drug resistance)
- Typhus
- Viral haemorrhagic fever (urgent)
- Whooping cough (urgent in acute phase)
- Yellow fever (urgent if UK-acquired)

USA

- Anthrax
- Arboviral neuroinvasive and non-neuroinvasive diseases:
 - California serogroup virus disease
 - Eastern equine encephalitis virus disease
 - Powassan virus disease
 - St Louis encephalitis virus disease
 - West Nile virus disease
 - Western equine encephalitis virus disease
- Babesiosis
- Botulism:
 - Botulism, food-borne
 - Botulism, infant
 - Botulism, other (wound and unspecified)
- Brucellosis
- Chancroid
- Chlamydia trachomatis infection
- Cholera
- Coccidioidomycosis
- Cryptosporidiosis
- Cyclosporiasis
- Dengue:
 - Dengue fever
 - Dengue haemorrhagic fever
 - Dengue shock syndrome
- Diphtheria
- Ehrlichiosis/Anaplasmosis:
 - *Ehrlichia chaffeensis*
 - *Ehrlichia ewingii*
 - *Anaplasma phagocytophilum*
 - Undetermined
- Giardiasis
- Gonorrhoea
- Haemophilus influenzae, invasive disease
- Hansen disease (leprosy)
- Hantavirus pulmonary syndrome
- Haemolytic uremic syndrome, post-diarrhoeal
- Hepatitis:
 - Hepatitis A, acute
 - Hepatitis B, acute
 - Hepatitis B, chronic
 - Hepatitis B virus, perinatal infection
 - Hepatitis C, acute
 - Hepatitis C, past or present
- HIV infection:
 - HIV infection, adult/adolescent (age ≥ 13 y)
 - HIV infection, child (age ≥ 18 months and < 13 y)
 - HIV infection, paediatric (age < 18 months)
- Influenza-associated paediatric mortality
- Legionellosis
- Listeriosis
- Lyme disease
- Malaria
- Measles
- Meningococcal disease
- Mumps
- Novel influenza A virus infections
- Pertussis
- Plague
- Poliomyelitis, paralytic
- Poliovirus infection, non-paralytic
- Psittacosis
- Q fever:
 - Acute
 - Chronic
- Rabies:
 - Rabies, animal
 - Rabies, human
- Rubella
- Rubella, congenital syndrome
- Salmonellosis
- Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) disease
- Shiga toxin-producing *E. coli* (STEC)
- Shigellosis
- Smallpox
- Spotted fever rickettsiosis
- Streptococcal toxic shock syndrome
- *Streptococcus pneumoniae*, invasive disease
- Syphilis:
 - Primary
 - Secondary
 - Latent
 - Early latent
 - Late latent
 - Latent, unknown duration
 - Neurosyphilis
 - Late, non-neurological
 - Stillbirth
 - Congenital
- Tetanus
- Toxic shock syndrome (other than streptococcal)
- Trichinellosis (trichinosis)
- Tuberculosis
- Tularaemia
- Typhoid fever
- Vancomycin-intermediate *Staphylococcus aureus* (VISA)
- Vancomycin-resistant *Staph. aureus* (VRSA)
- Varicella (morbidity)
- Varicella (deaths only)
- Vibriosis
- Viral haemorrhagic fevers, due to:
 - Ebola virus
 - Marburg virus
 - Crimean–Congo haemorrhagic fever virus
 - Lassa virus
 - Lujo virus
 - New World arenaviruses (Guanarito, Machupo, Junin and Sabia viruses)
- Yellow fever

^aAcute infective hepatitis but not HIV is notifiable in the UK.

have ‘a statutory duty to notify a “proper officer” of the Local Authority of suspected cases of certain infectious diseases’ – usually the consultant in communicable disease control (CCDC). The GMP should fill out a notification certificate immediately on diagnosis without waiting for laboratory confirmation and ensure that it reaches the officer within 3 days (telephone if urgent). The proper officers are required weekly to inform the Health Protection Agency (HPA) Centre for Infections (CFI) of the details of each case of each disease that has been notified.

As well as notifications of the infectious diseases specified below, the 2010 regulations also require GMPs to notify cases of ‘other infections or of contamination which they believe present, or could present, a significant risk to human health’, e.g. emerging or new infections, or cases of contamination (such as with chemicals or radiation) – particularly if there is a risk of transmission to others. Diagnostic laboratories also have a requirement to notify the HPA of specified causative agents they identify in tests on human samples.

Notification requires completion of the appropriate form, but urgent cases should be notified by telephone as well (certainly within 24 hours of any suspicions arising).

The following details are required:

- Patient’s name, date of birth, sex and home address with postcode
- Patient’s National Health Service number
- Ethnicity (used to monitor health equalities)
- Occupation, and/or place of work or educational establishment if relevant
- Current residence (if it is not the home address)
- Contact telephone number
- Contact details of a parent (for children)
- The disease or infection, or nature of poisoning/contamination being reported
- Date of onset of symptoms and date of diagnosis
- Any relevant overseas travel history
- If in hospital, also:
hospital address
day admitted
whether the disease was contracted in hospital.

There is no fee payable for notification.

In Scotland, written notification should be undertaken electronically via the Scottish Care Information (SCI) Gateway (<http://www.hps.scot.nhs.uk/publichealthact/NotifiableInfectiousDiseaseData.aspx>; accessed 30 September 2013).

Diseases that are notifiable to the local authorities in the UK and USA are shown in **Box 21.2**. Incubation times are shown in Appendix 21.2.

Further information may be found at: http://www.hpa.org.uk/infections/topics_az/noids/archive.htm (accessed 30 September 2013).

BACTERIAL INFECTIONS

Bacterial infections and therapy are discussed here and in other chapters (**Table 21.1**) and in Appendices 21.3, 21.4 and 21.5.

Bacterial infections are common. Most are transient with few untoward sequelae but some can cause serious, recurrent, disseminated or persistent lesions – especially in immunocompromised persons (particularly in neutropenic patients, those with organ transplants, and those with human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS]) – or can be life-threatening immediately (e.g. meningococcal meningitis), less immediately (e.g. diphtheria) or in the longer term (e.g. tuberculosis, syphilis).

Bacterial infections are often diagnosed on clinical grounds, supported by smears, culture, testing for immune responses (serology) and, increasingly, examining for nucleic acids.

Antibacterial drugs can often be effective therapy (see Appendix 21.3) but drainage of pus is often more important. Antibiotic resistance is increasingly a serious problem (e.g. *Staphylococcus aureus*, *Clostridium difficile*, *Mycobacterium tuberculosis*) and is encouraged by unwarranted use of antibiotics. Uncommon bacterial infections

Table 21.1 Bacterial infections

Bacterial infection	Chapter location
<i>Bartonella</i> infections (<i>Rochalimaea</i>)	This chapter
Brucellosis	This chapter
<i>Chlamydia</i>	Ch. 32
Cholera	This chapter
Diphtheria	This chapter
Gonorrhoea	Ch. 32
Granuloma inguinale	Ch. 32
<i>Haemophilus</i>	This chapter
<i>Legionella</i>	Ch. 15
Leprosy	This chapter
Leptospirosis	This chapter
<i>Listeria</i>	This chapter
Lyme disease	This chapter
Meningococci	Ch. 13
Paratyphoid	This chapter
Pertussis	This chapter
Plague	This chapter
Pneumococci	This chapter
Q fever	This chapter
<i>Rickettsia</i>	This chapter
<i>Salmonella</i>	This chapter
Staphylococci	This chapter
Streptococci	This chapter
Syphilis	Ch. 32
Tetanus	This chapter
Trichomoniasis	Ch. 32
Tuberculosis	Ch. 15
Tularaemia	This chapter
Typhoid	This chapter
<i>Yersinia</i>	This chapter

are shown in Appendix 21.6. Immunization against various bacteria is available and should be taken up (Appendix 21.7).

A wide range of bacterial infections are recognized (see **Table 21.1**). This chapter discusses odontogenic and orofacial bacterial infections; most cause lesions of limited duration but some are life-threatening. Nosocomial infections (health-care associated infections; HCAs), tetanus, puncture wounds and bites, and other infections not discussed elsewhere are then summarized.

OROFACIAL AND ODONTOGENIC BACTERIAL INFECTIONS

PERIODONTAL INFECTIONS

Abscesses

A gingival abscess may arise from infection or a foreign body. A lateral periodontal abscess (parodontal abscess) is seen almost exclusively in patients with chronic periodontitis but may follow impaction of a foreign body or, rarely, can be related to a lateral root canal on a non-vital tooth.

Clinical features

Erythema and swelling are the main features. Lateral periodontal abscesses may be painful and eventually may discharge – either through the pocket or buccally, but more coronally than a periapical abscess.

General management

Drainage is needed, and sometimes antibiotics (Table 21.2).

Acute necrotizing ulcerative gingivitis

Acute necrotizing ulcerative gingivitis (ANUG) is a non-contagious anaerobic infection associated with proliferation of *Borrelia vincentii* and fusiform bacteria. It is typically an infection of young adults, found especially in institutions, the armed forces, etc., and predisposing factors include poor oral hygiene, smoking, viral respiratory infections and immune defects such as in HIV/AIDS.

Clinical features

Characteristic features of ANUG include profuse gingival bleeding, severe soreness from gingival ulceration, halitosis and a bad taste. Malaise, fever and cervical lymph node enlargement are rare.

General management

Diagnosis is usually clinical. Smears show fusospirochaetal bacteria and leukocytes. Occasionally, ANUG may be confused with acute leukaemia or herpetic stomatitis, and a full blood picture may be needed. HIV infection may need to be considered.

Management is by oral debridement, metronidazole (penicillin, if pregnant) and improved oral hygiene.

Noma (cancrum oris; gangrenous stomatitis)

Noma can result from ANUG in malnourished, debilitated or immunocompromised patients, especially in children in developing areas. Anaerobes have been implicated, particularly *Bacteroides* (*Porphyromonas*) species, *Fusobacterium necrophorum* (an animal pathogen), *Prevotella intermedia*, *Actinomyces* and alpha-haemolytic streptococci. In cases following ANUG, *Streptococcus anginosus* and *Abiotrophia* species are the predominant organisms. In early noma, predominant species include *Ochrobactrum anthropi*, *Stenotrophomonas maltophilia*, an uncharacterized species of *Dialister* and an uncultivated phylotype of *Leptotrichia*. A range of species or phylotypes

is found in advanced noma, including *Propionibacterium acnes*, *Staphylococcus* species, *Stenotrophomonas maltophilia*, *Ochrobactrum anthropi*, *Achromobacter* species, *Afipia* species, *Brevundimonas diminuta*, *Capnocytophaga* species, *Cardiobacterium* species, *Eikenella corrodens*, *Fusobacterium* species, *Gemella haemolysans* and *Neisseria* species. Phylotypes unique to noma infections include those in the genera *Eubacterium*, *Flavobacterium*, *Kocuria*, *Microbacterium* and *Porphyromonas*, and the related *Streptococcus salivarius* and genera *Sphingomonas* and *Treponema*. Spreading necrosis penetrates the buccal mucosa, leading to gangrene, an orocutaneous fistula and scarring.

Diagnosis is clinical; an immune defect should always be excluded. Management includes improving nutrition, systemic antibiotics (clindamycin, penicillin, tetracyclines or metronidazole) and plastic surgery.

Pericoronitis

Acute pericoronitis is inflammation of the operculum over an erupting or impacted tooth, usually a mandibular third molar. It appears in relation to the accumulation of plaque and trauma from the opposing tooth. A mixed flora with *Fusobacterium* and *Bacteroides* is recognized to be important. Immune defects may predispose.

Clinical features

Acute pericoronitis manifests with pain, trismus, swelling and halitosis. The operculum is swollen, red and often ulcerated, and there may be fever and regional lymphadenitis. Pus usually drains from beneath the operculum but, in a migratory abscess of the buccal sulcus, may track anteriorly.

General management

Diagnosis is from clinical features. Radiology is usually indicated to confirm the position and root formation of the underlying partially erupted tooth.

Initial management comprises local debridement and application of antiseptics such as chlorhexidine. Reduction of the occlusal surface (or extraction) of an opposing tooth may be helpful if there is local trauma. Pyrexia, trismus or cervical lymphadenopathy may be indications for use of systemic antibiotics, typically metronidazole. Long-term treatment may include extraction of the associated impacted tooth, particularly when this is a lower third molar.

Dental abscess (periapical abscess, odontogenic abscess)

General aspects

A dental abscess is often a sequel of pulpitis caused by dental caries, but may arise in relation to any non-vital tooth. A mixed bacterial flora, especially anaerobes such as *Fusobacterium* and *Bacteroides* (*Porphyromonas*), is implicated.

Clinical features

The causal tooth is non-vital but tender to palpation. Most dental abscesses produce an intraoral swelling, typically on the labial or buccal gingival; those on maxillary lateral incisors and those from palatal roots of the first molar tend to present palatally. Occasionally, abscesses track or discharge elsewhere; for example, lower incisors or molars may discharge extraorally, and maxillary premolars and molars may discharge into the maxillary sinus (Fig. 21.1). Pain and

Table 21.2 Antimicrobials for odontogenic and antral infections^a

Condition	In non-allergic individuals, antimicrobial for >3 days or until symptoms resolve	Comments
Acute necrotizing gingivitis	Metronidazole or amoxicillin	Only if systemic involvement
Bites	Co-amoxiclav	Ch. 24
Cellulitis	Benzyl penicillin plus flucloxacillin	–
Periapical abscess	Amoxicillin or metronidazole for 5 days	Only if systemic involvement or cellulitis
Pericoronitis	Metronidazole or amoxicillin	Only if systemic involvement or trismus
Periodontal abscess	Amoxicillin or metronidazole for 5 days	Only if systemic involvement or cellulitis
Periodontitis	Metronidazole or doxycycline	Only for severe disease
Sinusitis	Amoxicillin or doxycycline or erythromycin for 7 days	Only for symptoms >7 days

^aAfter British National Formulary 2009.

facial swelling are characteristic but, once the abscess discharges, the acute inflammation, pain and swelling resolve and a chronic abscess develops discharging from a sinus – usually buccally and intraorally. Acute periapical suppuration may track through the cortical plate and may be limited by fascial planes within anatomical spaces or spread beyond them, as in the case of Ludwig's angina. Spread may also be lymphatics to regional lymph nodes, or haematogenously leading to thrombophlebitis, bacteraemia or even septicaemia.

General management

Diagnosis is from clinical features plus imaging. Extraction or endodontic therapy of the affected tooth removes the source of infection. Analgesics may be indicated. Antimicrobials are required only in the circumstances outlined below.

ODONTOGENIC INFECTIONS

Odontogenic infections are mainly a consequence of pulpitis that leads initially to periapical infection and a dental abscess. Most odontogenic (and many orofacial) infections arise from the commensal oral mixed flora, with a substantial proportion of anaerobes. Most odontogenic and orofacial infections respond to drainage, by either endodontic treatment, incision or tooth extraction. A drain usually needs to stay in place for 24–48 hours until most/all of the pus has discharged. Analgesics also may be required. Antimicrobials may be indicated in a number of circumstances (Table 21.3).



Fig. 21.1 Odontogenic infection.

Table 21.3 Indications for antimicrobial therapy

Patient status	Infections
Any patient with:	Fascial space infections in the neck Necrotizing fasciitis Osteomyelitis; removal of affected tissue is mandatory
Ill or immunocompromised persons with:	Serious or life-threatening infections Acute sinusitis Acute ulcerative gingivitis Dental abscess Dry socket Oral surgery Pericoronitis

Most odontogenic infections respond well to penicillin or metronidazole, but increasing rates of resistance due to production of beta-lactamase (an enzyme that degrades penicillins) have lowered the usefulness of many penicillins. Amoxicillin (\pm metronidazole) is a common first choice: second choices include cefuroxime, erythromycin, or clindamycin. Co-amoxiclav plus clindamycin are increasingly used first-line because of their broad spectrum of activity and resistance to beta-lactamase.

Anaerobic infections

Most head and neck infections are endogenous and mixed, with anaerobes, two-thirds containing more than one anaerobic species. Predominant anaerobes include *Prevotella*, *Fusobacterium* species, *Actinomyces* species (about 50% are *Actinomyces odontolyticus*), anaerobic cocci and *Eubacterium* species. *Prevotella intermedia*, *Fusobacterium nucleatum*, *Prevotella melaninogenica* and the *Bacteroides fragilis* group are the most common Gram-negative anaerobic species. Microaerophilic streptococci are often associated with anaerobes. Gram-positive anaerobic cocci (GPAC) are detected in about 15% of specimens – *Finegoldia magna* accounting for about one-third. Among aerobic/facultative isolates are Gram-positive cocci, Gram-negative bacteria and *Candida* species.

Treatment involves surgical procedures and antibacterial agents, which should cover both aerobes and anaerobes. Resistance rates to some agents (such as ampicillin/sulbactam and clindamycin) have increased.

Group A streptococcus (GAS) infections

People may carry group A streptococci in the throat or on the skin without symptoms of illness. Streptococcal oral or head and neck infections are shown in Table 21.4 (see also Fig. 21.2). Most streptococci are highly susceptible to penicillin. Some pneumococci (mostly imported) are increasingly resistant. Few people who come in contact with GAS will develop invasive GAS disease, but people with chronic illnesses like cancer, diabetes and chronic heart or lung disease, and those on

Table 21.4 Streptococcal infections in the head and neck

Bacteria	Found in/on	May cause
<i>Streptococcus viridans</i>	Normal oral flora	Caries and, rarely, infective endocarditis
<i>Strep. pyogenes</i>	Skin and pharynx	Cellulitis, impetigo (Fig. 21.2), necrotizing fasciitis, pharyngitis, scarlet fever or erysipelas, rheumatic fever and carditis
<i>Strep. pneumoniae</i> (pneumococci)	Upper respiratory tract	Acute glomerulonephritis, meningitis, sinusitis, otitis media, bronchitis and pneumonia



Fig. 21.2 Impetigo can mimic herpes simplex infections.

immunosuppressive medications such as steroids, have a higher risk. Persons with skin lesions (such as cuts, chickenpox or surgical wounds), the elderly, and adults with a history of alcohol abuse or injection drug use also have a higher risk for disease. Infection with GAS can result in a range of symptoms ranging from mild illness (streptococcal throat or a skin infection such as impetigo) to severe disease (necrotizing fasciitis, streptococcal toxic shock syndrome [STSS]). About 25% of those with necrotizing fasciitis and more than 35% with STSS die (see below).

Staphylococcal infections

Staphylococcal oral or head and neck infections may be caused by *Staphylococcus aureus*; most are minor (such as furuncles and boils) and most can be treated without antibiotics, but *S. aureus* can also cause serious infections such as surgical wound infections, sinusitis, tonsillitis, otitis externa or media, tracheitis, cellulitis, necrotizing fasciitis and toxic shock syndrome (caused by a staphylococcal-produced toxin that has resulted from nasal packing, and by tampon use). Infection is characterized by fever, hypotension, flushing of the skin followed by desquamation, shock and sometimes death.

Up to 80% of the *S. aureus* isolates in the West are resistant to penicillin, primarily due to production of beta-lactamase, but these will usually respond to lactamase-stable antibiotics such as flucloxacillin and meticillin. Meticillin-resistant *S. aureus* (MRSA) is resistant to these, however, and often to other antibiotics. Culture is essential to guide treatment of MRSA infections.

SERIOUS SEQUELAE OF ODONTOGENIC OR OFACIAL INFECTIONS

Fatal dental or orofacial infections are rare unless there is an immune defect, but may include progression to mediastinitis, infective endocarditis, necrotizing fasciitis, brain abscess and disseminated intravascular coagulation. Patients with advanced infections need urgent admission for intravenous antibiotics and urgent surgery to remove the cause as well as for incision and drainage of tissue spaces involved. ICU may be needed until the airway is assured. Fiberoptic endotracheal intubation or occasionally emergency surgery (cricothyrotomy or tracheostomy) may be indicated.

Cellulitis

Cellulitis is usually an acute streptococcal or staphylococcal skin infection. It normally resolves on treatment with benzyl penicillin plus flucloxacillin or, if the patient is penicillin-allergic, clarithromycin, erythromycin, clindamycin or vancomycin/teicoplanin. Cellulitis can spread locally or systemically.

Buccal cellulitis is usually caused by *Haemophilus influenzae* type B, spread by bacteraemia, by lymphatics from, for example, otitis media, or more probably from direct invasion through the oral mucosa. It is an uncommon but distinctive infection, characterized by swelling, tenderness, induration and warmth of the cheek soft tissues in the absence of an adjacent oral or skin lesion; it almost invariably affects children under the age of 5 years. A minority develop meningitis. Blood and cerebrospinal fluid cultures should be taken and treatment with intravenous cefuroxime started.

Lymphangitis

Lymphangitis (inflammation of the lymphatics with pain and systemic symptoms) is commonly secondary to an acute streptococcal or staphylococcal cellulitis, or to an abscess in the skin or soft tissues. Lymphangitis may be confused with thrombophlebitis and suggests

that an infection is progressing, and may lead to bacteraemia, septicaemia and life-threatening infection.

Fascial space infections

Fascial space infections of the neck are dangerous, since they can embarrass the airway, erode the carotid vessels, cause toxicity, or spread to the mediastinum or intracranially. They usually arise from the oral flora and are polymicrobial, involving predominantly anaerobes, including Gram-positive cocci and bacilli, as well as Gram-negative bacilli.

Patients with fascial space infections must be admitted for hospital care, which may involve drainage and usually high-dose antibiotics.

Necrotizing fasciitis (Fournier gangrene, Melaney ulcer, postoperative progressive bacterial synergistic gangrene, flesh-eating bacteria, Cullen ulcer)

More information about necrotizing fasciitis is available at: <http://www.nnff.org/> (accessed 30 September 2013).

General aspects

Necrotizing fasciitis is a dangerous, rapidly progressive, and spreading infection in the deep fascia, with secondary necrosis of subcutaneous tissues, which destroys muscles, fat and skin. The speed of spread along the deep fascial plane is directly proportional to the thickness of the subcutaneous layer. Most patients are middle-aged or older but, though the condition has become more frequent because of an increase in immunocompromised patients with diabetes, cancer, alcoholism, vascular insufficiencies, transplants, neutropenia or HIV, few have such detectable underlying predisposing factors.

Group A haemolytic streptococci and *S. aureus*, alone or in synergism, are often the initiating causal bacteria, but other aerobic and anaerobic pathogens, such as *Bacteroides* (*Porphyromonas*), *Clostridium*, *Peptostreptococcus*, Enterobacteriaceae, coliforms, *Proteus*, *Prevotella*, *Pseudomonas*, *Klebsiella*, *Bacteroides fragilis*, *Fusobacterium necrophorum* and *Escherichia coli* may be present.

Some men who have sex with men (MSM) have suffered outbreaks of necrotizing fasciitis caused by community-associated MRSA – distinct from health-care-associated strains. Anaerobic streptococci, occasionally seen in drug users, cause many forms of non-clostridial myonecrosis. Necrotizing fasciitis can also be caused by *Vibrio vulnificus*, often following the consumption of raw seafood – especially in patients with chronic liver disease. There may also be a relationship between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the development of necrotizing fasciitis during varicella infections.

Clinical features

There is often a history of trauma or recent surgery to the area. Features of necrotizing fasciitis include the following:

- *Early* (usually within 24 hours):
Usually a minor trauma or other skin opening (the wound does not necessarily appear infected)
Pain in the general area of the injury, not necessarily at the site of the injury but in the same region or limb of the body; it is usually disproportionate to the injury and may start as something akin to a muscle pull, but becomes more and more painful
‘Flu-like’ symptoms, such as diarrhoea, nausea, fever, confusion, dizziness, weakness and malaise

Intense thirst

- **Advanced** (usually within 3–4 days):
Swelling of the limb or area of body experiencing pain, possibly accompanied by a purplish rash
Large, dark marks on the limb, which will become blisters filled with blackish fluid
Necrotic appearance of the wound, with a bluish, white or dark, mottled, flaky surface
- **Critical** (usually within 4–5 days):
Severe drop in blood pressure
Signs that the body is entering toxic shock
Unconsciousness.

The lesion begins with an area of thrombosis and skin necrosis, which is initially red, painful and oedematous. Erythema quickly spreads over hours to days, and rapidly turns purplish, dusky and then black, with gas and exudate, and pain disproportionate to the clinical appearance. The margins of the infection move into surrounding skin without being raised or sharply demarcated. Over the next several hours to days, despite severe pain, there may be cutaneous anaesthesia – an unusual combination, as the cutaneous nerves are damaged by the infection (hence anaesthesia) but the proximal stump is irritated (hence the pain). Multiple patches develop to produce a large area of gangrenous skin.

Early on, the patient may look deceptively well but, within 24–48 hours, fever appears with rapidly spreading tissue necrosis, so that the patient usually appears moderately to severely toxic.

General management

Necrotizing fasciitis is uncommon but potentially fatal; if from a dental source, it can also spread and may threaten the airway. The mortality can sometimes reach 30%.

The gas-forming organisms may release subcutaneous gas that may be seen on radiography. Absence of gadolinium contrast enhancement in magnetic resonance imaging (MRI) T1 images reliably detects fascial necrosis. Thoracic computed tomography (CT) may be required to detect mediastinal spread.

Necrotizing fasciitis requires early aggressive treatment. The patient should be admitted to hospital and intubated; the affected area is opened to drain, and necrotic tissue excised. High doses of penicillin or clindamycin are given, plus metronidazole or a cephalosporin, or gentamicin, combined with clindamycin or chloramphenicol. Hyperbaric oxygen, if available, should be given.

Streptococcal toxic shock syndrome (STSS) results in acute hypotension and organ (e.g. kidney, liver, lungs) failure. STSS is not the ‘toxic shock syndrome’, which is due to *S. aureus* associated with tampon usage.

Recommended therapy for necrotizing fasciitis and STSS is early aggressive surgery plus high-dose antimicrobials (penicillin plus clindamycin). Supportive care in an intensive care unit may also be needed.

Lemierre syndrome (post-anginal septicaemia)

Lemierre syndrome is a rare, potentially fatal, acute anaerobic oropharyngeal infection, the classical presentation of human necrobacillosis. The main pathogen is *Fusobacterium necrophorum*, an obligate anaerobic, pleomorphic, Gram-negative rod.

The primary infection is in the head in a young, previously healthy person, who subsequently develops persistent high fever and disseminated metastatic abscesses, frequently including septic thrombophlebitis of the internal jugular vein. Lemierre syndrome is often complicated by septic pulmonary emboli and distant metastatic infections.

Surgical drainage and intravenous antibiotics are indicated. *F. necrophorum* is typically susceptible to penicillin, cephalosporins, metronidazole,

clindamycin, tetracyclines and chloramphenicol. Some beta-lactamase-producing strains of *F. necrophorum* have been reported.

Septicaemia

Septicaemia can arise from odontogenic or orofacial infections, but more commonly from infections of the urinary tract, gallbladder or chest. Immunosuppressed patients are particularly susceptible and oral bacteria are sometimes responsible.

Blood, urine and sputum should be cultured and the patient started on ceftriaxone (a once-daily dose), or cefuroxime plus metronidazole if anaerobic sepsis is suspected.

Actinomycosis (lumpy jaw)

Actinomycosis is a rare chronic infection, usually of the face and neck. It is caused by *Actinomyces israelii*, a Gram-positive, non-contagious anaerobic bacillus with filamentous growth and mycelia-like colonies bearing a striking resemblance to fungi; it is primarily a commensal found in normal oral cavities, tonsillar crypts, dental plaque and carious teeth. There are three main presentations.

Cervicofacial actinomycosis is the most common and typically causes a red or purplish, somewhat indurated, subcutaneous mass of abscesses and open draining sinuses, usually in the submandibular area near the angle of the mandible, arising a few weeks after an antecedent local lesion (dental or periodontal infection or tooth extraction). Tenderness is slight or absent. Microscopic examination of drained fluid shows ‘sulphur granules’ and *Actinomyces*, and culture of the fluid or tissue shows *Actinomyces* species.

Pulmonary actinomycosis causes fever and general malaise, cough and purulent sputum. Cutaneous sinuses may form.

Abdominal actinomycosis may cause pain and a palpable mass in the abdomen.

Treatment of actinomycosis is at least 1–2 months of penicillin or tetracycline. Surgical drainage may be indicated.

Osteomyelitis

See Chapter 16.

ANTIMICROBIAL PROPHYLAXIS

Antimicrobial cover may be required for bites; for contact with certain infections (e.g. open tuberculosis, meningitis, *Haemophilus influenzae* B infections or group A streptococci); and for oral-health-care invasive procedures in people with sickle cell anaemia or asplenia (usually phenoxymethyl penicillin or erythromycin – plus relevant vaccinations). It is sometimes suggested for various procedures or in various other conditions, but otherwise is infrequently indicated (Box 21.3).

Box 21.3 Conditions in which antibiotic prophylaxis for oral health care is not usually considered essential

- Augmentation procedures (e.g. lips, breasts)
- Cardiac surgery
- Immunocompromising states unless severe
- Indwelling intraperitoneal catheters
- Intraocular lenses
- Pacemakers and other cardiac devices
- Penile prostheses
- Prosthetic joint implants
- Ventriculo-peritoneal shunts

HEALTH-CARE-ASSOCIATED (NOSOCOMIAL) INFECTIONS (HCAIs)

HCAIs are an increasing problem across the world (Box 21.4). Box 21.5 shows precautions against them. A number of microorganisms can be involved in HCAIs, usually bacteria, and many are antimicrobial-resistant ('super-bugs'). HCAIs may affect wounds (surgical site infections), the skin, the respiratory tract, the gastrointestinal tract, the urinary tract, catheters, ventilators or any implanted device. Central line-associated bloodstream infections, catheter-associated urinary tract infections and ventilator-associated pneumonia account for about two-thirds of all HCAIs that are not in surgical sites.

WOUND INFECTIONS (SURGICAL SITE INFECTIONS)

General aspects

Infections (surgical wound infections; surgical site infections, SSIs) can be a problem in terms of morbidity and mortality. Postoperative bacterial infection rates vary from 3% to 21%, with SSIs accounting for up to 34% of the total (probably underestimated since most wound infections start after the patient is discharged). SSIs have significant morbidity and mortality, accounting for approximately 77% of deaths of general surgical patients.

Surgical wounds have been classified as clean, clean-contaminated, contaminated and dirty-infected (Table 21.5). Most head and neck surgery involves class I or II wounds.

Most SSIs arise from the patient's own flora, from health-care workers and articles brought into the operative field, and from the operating room air. The usual pathogens on skin surfaces are Gram-positive aerobic cocci (mainly staphylococci), but anaerobes and Gram-negative aerobes may be involved. The normal oral flora is 90% anaerobes and 10% Gram-positive aerobic cocci. Gram-negative aerobes may be a problem in patients who have been hospitalized or treated with radiotherapy. Factors promoting wound infection include preoperative removal of hair, especially when there is skin abrasion, inadequate skin preparation with bactericidal solution, poor surgical technique, lengthy operation (over 2 hours), intraoperative contamination, prolonged stay in hospital,

Box 21.4 Main health-care-acquired infections (HCAIs)

- *Acinetobacter*
- *Burkholderia cepacia*
- *Clostridium difficile*
- *Clostridium sordellii*
- Enterobacteriaceae (carbapenem-resistant)
- *Escherichia coli*
- Glycopeptide-resistant enterococci (GRE)
- Hepatitis
- Human immunodeficiency virus (HIV)
- Influenza
- *Klebsiella*
- Meticillin-resistant *Staphylococcus aureus* (MRSA)
- *Mycobacterium abscessus*
- Norovirus
- Pencillin-resistant *Streptococcus pneumoniae* (PRSP)
- *Staphylococcus aureus*
- Tuberculosis
- Vancomycin-intermediate *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus*
- Vancomycin-resistant enterococci (VRE)

Box 21.5 Prevention of health-care-associated infection transmission

- Follow good hygiene and standard infection control procedures
- Avoid contact with wounds or material contaminated from wounds
- Use alcohol-based waterless antiseptic agents for routinely decontaminating hands, when hands are not visibly soiled
- Wash hands thoroughly with a non-antimicrobial soap and water, or an antimicrobial soap and water, when hands are visibly dirty or contaminated with proteinaceous material such as blood
- Keep cuts and abrasions clean and covered with a proper dressing until healed, when hands are cut or abraded
- Use a moisturizer to prevent skin cracking

Table 21.5 Surgical wound classification and subsequent risk of infection (no antibiotics used)

Classification	Oral or perioral example	Description	Infective risk (%)
Clean (Class I)	Excision of a facial skin lesion	Uninfected operative wound No acute inflammation Closed primarily Respiratory, gastrointestinal, biliary and urinary tracts not entered No break in aseptic technique Closed drainage used if necessary	<2
Clean-contaminated (Class II)	Parotid surgery	Elective entry into respiratory, biliary, gastrointestinal or urinary tracts and with minimal spillage No evidence of infection or major break in aseptic technique	<10
Contaminated (Class III)	Third molar surgical removal	Non-purulent inflammation present Spillage from gastrointestinal tract Penetrating traumatic wounds <4 h Major break in aseptic technique	About 20
Dirty-infected (Class IV)	Incision and drainage of a submandibular abscess	Purulent inflammation present Preoperative perforation of viscera Penetrating traumatic wounds >4 h	About 40

hypothermia, trauma, non-viable tissue in the wound, haematoma, foreign material (including drains and sutures), dead space, pre-existing sepsis (local or distant), immunocompromised or malnourished host, hypovolaemia, poor tissue perfusion or obesity, and delayed prophylaxis with, or incorrect choice of, antibiotics.

Prophylaxis

Prophylactic antibiotics are indicated for clean-contaminated and contaminated trauma, for clean procedures in which prosthetic devices are inserted and, more controversially, for clean procedures such as orthognathic surgery.

The concentration of prophylactic antibiotic should be at therapeutic levels by the time of incision, during the surgical procedure and for a few hours postoperatively, and this is achieved by intravenous administration of the antibiotic 30 minutes before incision (but not more than 2 hours before surgery). For head and neck surgery, *S. aureus*, streptococci, anaerobes and streptococci can be present in an oropharyngeal approach; examples of antibiotics shown to be effective in class II head and neck wound prophylaxis include cefazolin 1–2 g alone or in combination with metronidazole, or clindamycin alone or with gentamicin or amikacin, amoxicillin/clavulanate, ampicillin/sulbactam and ticarcillin/clavulanate.

Clinical features

SSI is suggested by features such as pus draining from the wound, the wound becoming excessively tender, progressive swelling starting about 48 hours after surgery, increasing redness around the wound (cellulitis), a red streak from the wound toward the heart (lymphangitis), lymphadenitis or fever. The wound may fail to heal within 10 days after the injury, the scab increases in size, and a pimple or yellow crust may form on the wound (impetigo).

General management

Treatment of SSI often involves antibiotics after opening the wound, evacuating pus and cleansing the wound – inspecting deeper tissues for integrity and for deep space infection or source. Dressing changes allow the tissues to granulate, and the wound heals by secondary intention over several weeks.

The antibiotic choice depends on the known or probable infecting microorganism, and factors such as severity of SSI, patient's age, hepatic and renal function, allergies and other medication(s). First choices are flucloxacillin in the absence of allergy if staphylococci or streptococci are implicated; metronidazole or clindamycin for anaerobic infections; cefuroxime for Gram-negative organisms; and amoxicillin or co-amoxiclav for enterococcal infection. For pain relief, paracetamol (acetaminophen), ibuprofen or an opioid is indicated.

CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTION (CLABSI)

CLABSI is a serious infection that may present with fever, skin erythema and soreness around the central line entry point. CLABSIs must be prevented in the following manner:

- Follow recommended central line insertion practices:
 - Hand hygiene
 - Skin antiseptic
 - Barrier precautions: sterile gloves, sterile gown, cap, mask, sterile drape.

- Once the central line is in place, wash hands with soap and water or an alcohol-based handrub before and after touching the line.
- Remove a central line as soon as it is no longer needed.

More than 50% of all *S. aureus* CLABSI isolates are MRSA but the incidence is decreasing. In contrast, *Klebsiella pneumoniae* and *E. coli* resistance to third-generation cephalosporins has increased significantly, as has imipenem and ceftazidime resistance in *Pseudomonas aeruginosa*, and *Candida* spp. are increasingly fluconazole-resistant.

Guidelines for the prevention of intravascular catheter-related infections are available at: <http://www.cdc.gov/hicpac/BSI/BSI-guidelines-2011.html> (accessed 30 September 2013).

ANTIBIOTIC-RESISTANT INFECTIONS

The main antibiotic-resistant infections are meticillin-resistant *S. aureus* (MRSA) and clindamycin-resistant *Clostridium difficile*, but there are several others; many of these arise as HCAs and the most important are discussed here, alphabetically. Six of these bacteria have been dubbed ESKAPE (*Enterococcus faecium*, *S. aureus*; *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species). Some of these infections are with multidrug-resistant organisms (MDROs); see http://www.cdc.gov/hicpac/mdro/mdro_toc.html (accessed 30 September 2013).

ACINETOBACTER

Acinetobacter are commonly found in soil and water. *Acinetobacter* infections in the community are rare and most strains are sensitive to antibiotics. Infections are usually HCAs and are typically found in intensive care units, in very ill patients and with resistant organisms. *A. baumannii* accounts for about 80% of reported infections and these include pneumonia, bacteraemia (bloodstream infection), wound infections and urinary tract infections. They are often resistant to antibiotics and are increasingly difficult to treat. *A. baumannii* wound infections have been found in US military personnel deployed to Iraq and Afghanistan. Of the beta-lactamase inhibitors, sulbactam possesses the greatest intrinsic bactericidal activity against *A. baumannii*. Carbapenems (imipenem, meropenem or doripenem) are the most important other options for serious infections caused by multidrug-resistant *A. baumannii*. Amikacin and tobramycin are aminoglycosides that appear to retain activity against *A. baumannii*. Other possibilities include polymyxin E, polymyxin B, colistin, minocycline and doxycycline. Tigecycline may be used, as may extended-infusion β -lactams, cefepime and piperacillin–tazobactam.

BURKHOLDERIA CEPACIA

Burkholderia cepacia is a group of bacteria found in soil and water; they are often resistant to common antibiotics but pose little risk to healthy people. However, *B. cepacia* can cause infections in people with immune defects or chronic lung disease (particularly cystic fibrosis/bronchiectasis). Treatment typically involves multiple antibiotics and may include ceftazidime, doxycycline, piperacillin, meropenem, chloramphenicol or co-trimoxazole.

CLOSTRIDIUM DIFFICILE

Clostridium difficile (also called *C. diff*) is the major organism linked with antibiotic-associated diarrhoea and colitis, usually caused by expanded-spectrum and broad-spectrum cephalosporins and clindamycin, though the role of fluoroquinolones is less clear. An HCAI that

mostly affects older patients with other underlying disorders in hospital environments, the disease usually develops after cross-infection from another patient, either through direct contact, or via health-care staff or via a contaminated environment. Community-acquired *C. difficile* infection (CDI) has also emerged.

Diagnosis is from the presence of *C. difficile* toxins in a faecal sample. The emergence and epidemic spread of a novel strain, known as PCR ribotype 027 (BI/NAP1/027), resistant to clindamycin, is an issue. Type 027 produces many more of the toxins than most other types.

Prevention and control of *C. difficile* is by reduction of the use of broad-spectrum antibiotics, isolation of patients with *C. difficile* diarrhoea, good infection control nursing (alcohol gel does not destroy the spores), and enhanced environmental cleaning using a chlorine-containing disinfectant. Metronidazole and vancomycin are the treatments of choice but some strains are now resistant. More information on epidemiology can be found by searching on *C. difficile* at <http://cmr.asm.org> (accessed September 2013).

CLOSTRIDIUM SORDELLII

Clostridium sordellii is a rare bacterial cause of pneumonia, endocarditis, arthritis, peritonitis and myonecrosis. *Cl. sordellii* bacteraemia and sepsis are usually seen in people with other health conditions – mostly after trauma, childbirth and gynaecological procedures – but they have recently been associated with medically induced abortions and injection drug use. Mortality is very high; *Cl. sordellii* is typically susceptible to beta-lactams, clindamycin, tetracycline and chloramphenicol but resistant to aminoglycosides and sulphonamides. Further details may be found at: <http://www.cdc.gov/hai/organisms/csordellii.html> (accessed September 2013).

EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCERS

Gram-negative enteric bacilli (Enterobacteriaceae) are producers of enzymes that destroy beta-lactam antibiotics and mediate resistance to extended-spectrum (third-generation) cephalosporins (e.g. ceftazidime, cefotaxime and ceftriaxone) and oxyimino-monobactams (e.g. aztreonam) but do not affect cephamycins (e.g. cefoxitin and cefotetan) or carbapenems (e.g. meropenem or imipenem). ESBL enzymes are most commonly produced by *E. coli* and *K. pneumoniae*, but other bacteria that may do so include *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Salmonella* species and *Proteus mirabilis*. *K. pneumoniae* most commonly produce *K. pneumoniae* carbapenemase (KPC). Resistance of *Enterobacter* species to third-generation cephalosporins is most typically caused by overproduction of AmpC beta-lactamases. Some *E. cloacae* strains are now ESBL- and AmpC-producers, conferring resistance to both third- and fourth-generation cephalosporins.

Quinolone resistance in Enterobacteriaceae is usually the result of chromosomal mutations leading to alterations in target enzymes or drug accumulation. More recently, however, plasmid-mediated quinolone resistance has been reported in *K. pneumoniae* and *E. coli*, associated with acquisition of the *qnr* gene. The vast majority of Enterobacteriaceae, including ESBL-producers, remain susceptible to carbapenems, which are considered the preferred empirical therapy for serious infections.

ESBL infection may stem from infected chicken meat and outbreaks have originated in hospitals and nursing homes, and increasingly in the community, typically with urinary tract infections and bacteraemia. Persistent oral carriage may be seen in immunocompromised persons, in

advanced age and in dry mouth. Until recently, the numbers of patients affected remained small and the problem showed little sign of growing. However, a new class of ESBL (CTX-M enzymes) has emerged and has been widely detected among hospital *E. coli* but also found in the community. These ESBL-*E. coli* are found most often in urinary tract infections and are resistant to penicillins and cephalosporins. Carbapenems, such as meropenem, are usually the effective treatment for ESBL. However, *carbapenem-resistant Enterobacteriaceae* (CRE; *glycopeptide-resistant enterococci* [GRE]) may arise in *Klebsiella* species and *E. coli*. CRE infections are most common in patients receiving treatment involving devices such as catheters or ventilators, and those who are on long antibiotic courses. New Delhi metallo-beta-lactamase (NDM-1), an enzyme that inactivates carbapenems, is most widespread in *Klebsiella* in the Indian subcontinent but has spread to the UK and elsewhere, often via patients previously treated in the subcontinent. Verona integron-encoded metallo-beta-lactamase (VIM) and imipenemase (IMP) metallo-beta-lactamases may also be seen.

CRE have been associated with high mortality rates (up to 40–50% in some studies). In addition to beta-lactam/carbapenem resistance, CRE often have high levels of resistance to many other antimicrobials. More information is available at: <http://www.cdc.gov/hai/organisms/cre/index.html> (accessed September 2013).

Most bacteria with NDM-1 remain susceptible to colistin and tigecycline. ‘Pan-resistant’ KPC-producing strains have been reported.

METICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Meticillin-resistant *Staphylococcus aureus* (MRSA) is resistant to beta-lactam antibiotics (meticcillin and other more common antibiotics, such as oxacillin, flucloxacillin, penicillin and amoxicillin). Most severe or potentially life-threatening MRSA infections occur among patients in health-care settings. The most common clones are E(pidemic)-MRSA 15 and E-MRSA16. Strains of *S. aureus* producing Panton–Valentine leukocidin (PVL) are especially virulent. About 1 in 3 people carry *S. aureus* on the skin surface or in the nose; if this enters the body through a break in the skin, it can cause infections such as abscesses or impetigo. MRSA is no more infectious than other types of *S. aureus* but infections are more difficult to treat, owing to their antibiotic resistance, and mortality is increased. The infection may simply require a much higher dose over a much longer period, or the use of an agent to which MRSA is not resistant.

MRSA is usually spread through person-to-person contact with someone who has an MRSA infection or who is colonized. It can also spread through contact with towels, sheets, clothes, dressings or other objects that have been used by someone with MRSA. *S. aureus* can also survive on objects or surfaces such as door handles, sinks, floors and cleaning equipment. MRSA infections are far more common in people who are in hospital; risk factors are shown in [Box 21.6](#).

Box 21.6 Risk factors for MRSA infection

- Immune incompetence (e.g. elderly, newborn babies, patients with diabetes, cancer or HIV/AIDS)
- Open wound, catheter or intravenous tube
- Severe skin condition (e.g. burn or cut, ulcer or psoriasis)
- Recent surgery
- Frequent courses of antibiotics
- Prolonged hospital stay
- Asymptomatic MRSA nasal carriage

Community-associated MRSA infections typically involve the skin, and are usually transmitted from people with active MRSA skin infections. The strains causing these infections, designated community-associated MRSA (CA-MRSA), are distinct from health-care-associated strains (HA-MRSA). Infection with multidrug-resistant USA300 MRSA has emerged among MSM. Infection most often involves the buttocks, genitals or perineum. The risk is independent of HIV infection but the infection might be sexually transmitted in this population.

Community-associated MRSA spreads especially to:

- intravenous drug users
- children in day care
- athletes
- military personnel
- prison inmates.

Clinical features

Symptoms depend on the type of infection. Most *S. aureus* infections involve the skin, and include boils, abscesses, styes, carbuncles, cellulitis and impetigo, but infections are also able to enter the bloodstream (bacteraemia); these can cause septicaemia, septic shock, septic arthritis, osteomyelitis, abscesses, meningitis, pneumonia and endocarditis, and can be fatal. *S. aureus* can also cause scalded skin syndrome and, very occasionally, toxic shock syndrome.

General management

Many hospitals now test all people being admitted to see if they are colonized; swabs from the skin and nose, and urine and blood samples may be tested. It can take 3–5 days for the results to become available. People colonized with MRSA may still be admitted to hospital but treated to reduce or remove it by using antibiotic cream applied to the skin or the inside of the nose, and washing skin and hair with antiseptic shampoo and lotion. Health-care workers should use fast-acting, special alcohol rubs or gels, and wear disposable gloves when there will be physical contact with open wounds: for example, when changing dressings, handling needles or inserting intravenous lines.

MRSA infections are diagnosed by testing blood, urine or a tissue sample for the presence of the organism. Patients who are only colonized with MRSA usually do not need treatment. Infections often require hospital treatment in isolation for several weeks. Frank MRSA infections can sometimes be treated without antibiotics by draining and, in reality, most are resistant to multiple antibiotics as well as to meticillin.

Agents used to treat MRSA infections include vancomycin, or quinupristin combined with dalfopristin or linezolid, but resistance has been reported. Linezolid can also cause cytopenias, including pancytopenia, and optic neuropathy, and acts as a monoamine oxidase inhibitor. Teicoplanin, rifampicin and streptogramin may be effective.

People more at risk of MRSA are best advised not to visit an infected person and all visitors must wash their hands thoroughly before and after visiting. Mandatory MRSA bacteraemia surveillance and better infection control practices, such as universal hand hygiene, contact precautions and admission screening, have seen a dramatic reduction in MRSA infection. The intensive care unit (ICU), an important reservoir for seeding MRSA, has been at the forefront of MRSA control programmes. Decolonization with agents such as chlorhexidine and mupirocin has an important role in reducing transmission. Chlorhexidine particularly is being recommended in the ICU

for an increasing number of indications, including decolonization, universal patient bathing, oropharyngeal antiseptics in ventilated patients and antiseptics at vascular catheter insertion sites.

MRSA has rarely been transmitted to dental patients but oral infections have now been reported.

PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* (PRSP)

Streptococcus pneumoniae (pneumococcus) is the major pathogen causing community-acquired infections such as acute otitis media, pneumonia, bacteraemia and meningitis. Penicillin resistance is seen in over 80%. The penicillin-resistant *S. pneumoniae* are usually also resistant to macrolides, tetracyclines, co-trimoxazole, chloramphenicol and clindamycin, and increasingly to fluoroquinolone. Treatment is generally with a third-generation cephalosporin, or vancomycin together with rifampicin for a serious infection such as meningitis.

STAPHYLOCOCCUS AUREUS

S. aureus is found on the skin and in the nose of about 30% of healthy individuals. Coagulase-positive (*S. aureus*) and coagulase-negative staphylococci are Gram-positive cocci – important causes of infection, primarily of the skin, bloodstream, native and prosthetic cardiac valves, and other implanted devices. Their progressively reduced susceptibility to penicillin, meticillin and glycopeptides makes treatment of staphylococcal infections difficult. Although the use of chlorhexidine-impregnated catheters has reduced catheter-related infections, chlorhexidine-resistant *S. aureus* has emerged. MRSA strains carrying the antiseptic resistance genes *qacA/B* can be clinically resistant to chlorhexidine.

The two most commonly used decolonization agents are mupirocin for nasal carriage and chlorhexidine for skin carriage, the latter applied either as a daily bath after dilution in water, where there is potential for variability in the applied concentration, or as disposable cloths saturated in 2% chlorhexidine. Triclosan, octenidine dihydrochloride and tea tree oil are alternatives to chlorhexidine.

Chlorhexidine is used for skin antiseptics prior to blood culture collection and the insertion of vascular catheters; applied to the catheter exit site in the form of impregnated sponges; impregnated into vascular catheters to prevent bloodstream infections; and for oropharyngeal antiseptics to prevent ventilator-associated pneumonias. Mupirocin resistance is well known, but chlorhexidine resistance is an emerging threat and of additional concern.

STENOTROPHOMONAS MALTOPHILIA ('STENO')

Stenotrophomonas (Pseudomonas) maltophilia is an aerobic, non-fermentative, Gram-negative bacterium of low virulence found in aquatic environments. It frequently colonizes fluids used in hospitals (e.g. irrigation solutions, intravenous fluids) and is found in patient secretions (e.g. secretions, urine, exudates).

S. maltophilia rarely causes disease in healthy hosts, unless invasive medical devices are present. Antimicrobial treatment is usually unnecessary and may be potentially harmful. Infections are, in any event, difficult to treat, but *S. maltophilia* is susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), meropenem, minocycline, quinolones and colistin/polymyxin B.

TUBERCULOSIS

See Chapter 15.

VANCOMYCIN-RESISTANT BACTERIA

Vancomycin-resistant enterococci (VRE)

Vancomycin-resistant enterococci (VRE) are often present in the normal intestinal flora and in the female genital tract, as well as in the environment. Some of the other antibiotics that fail include some types of penicillin, cephalosporins, clindamycin, aminoglycosides, macrolides (such as erythromycin), tetracycline, quinolones and others.

Most VRE infections occur in hospitals and are often acquired from other people or from contaminated food or water. Up to 66% carry enterococci in the mouth, especially patients undergoing endodontic treatment. VRE may be associated with endodontic failures. It can cause diarrhoea, wound infection, bacteraemia or urinary tract infections, mainly in immunocompromised and medically ill patients. It may also give rise to endocarditis. Most VRE infections can be treated with antibiotics other than vancomycin.

Vancomycin-intermediate *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus*

Vancomycin-resistant (VRSA) and reduced susceptibility (vancomycin-intermediate) *S. aureus* (VISA) infections are usually seen in people with underlying health conditions (e.g. diabetes, chronic kidney disease), devices (e.g. catheters), previous infections with MRSA, and recent exposure to vancomycin and other antimicrobials.

Quinupristin–dalfopristin, linezolid, tetracycline, trimethoprim–sulfamethoxazole (TMP–SMX), tigecycline and daptomycin have been used for treatment of VISA infections.

TETANUS, PUNCTURE WOUNDS AND BITES

TETANUS

General aspects

Tetanus is a non-communicable infection caused by wound contamination with *Clostridium tetani* spores; it has a mortality of up to 60%. The spores are ubiquitous in soil or dust, particularly where there is faecal contamination, as on agricultural land. Tetanus is most likely to follow contaminated deep wounds, such as puncture wounds, especially if there is tissue necrosis, but it may also follow trivial wounds, or even bites or burns. The elderly, particularly women, are at greatest risk. Neonates may develop tetanus from contamination of the umbilical stump, a condition only found in the developing world.

Clinical features

The incubation period is between 4 and 21 days, commonly about 10 days.

C. tetani produces a neurotoxin (tetanospasmin) that is responsible for violent muscular spasms; trismus (lockjaw) due to masseteric spasm is the single most common early sign. Facial spasm produces a so-called sardonic smile (risus sardonicus), in which the eyebrows are raised with eyes closed and the lips are drawn back over clenched teeth. Spinal muscle spasm produces arching of the back (opisthotonos), while laryngeal spasm can lead to asphyxiation. Autonomic dysfunction can cause cardiac arrhythmias and fluctuations in blood pressure. Death may follow within 10 days of the onset of tetanus, usually from asphyxia, autonomic dysfunction or bronchopneumonia.

General management

Patients who have contaminated wounds, such as those associated with maxillofacial injuries caused by road traffic or riding accidents, are at greatest risk from tetanus. Situations that are considered tetanus-prone include any wound or burn sustained more than 6 hours before surgical treatment of the injury, or that shows a significant degree of devitalized tissue; a puncture wound; contact with manure or soil; or clinical sepsis.

Management of wounds where tetanus is likely includes active immunization with tetanus toxoid but it is *not* good practice to give toxoid after every *minor* injury, as severe allergic reactions can occasionally follow (Table 21.6).

The diagnosis of tetanus is clinical. There are no immediate tests that will help the diagnosis. Patients with tetanus should be admitted to an ICU for protection of the airway (tracheostomy should be carried out if the airway is endangered) and to facilitate artificial respiration, should it become necessary. They should be given anti-tetanus immunoglobulin (early, as it is ineffective after the toxin has become bound to nervous tissue) – human anti-tetanus immunoglobulin (ATG; Humotet, 500 units or more); if this is not available, animal anti-tetanus serum (ATS) should be used, after testing for hypersensitivity and with adrenaline (epinephrine) and corticosteroids available in case a severe reaction develops. Control of muscle spasms should be achieved by heavy sedation or, in severe cases, using general anaesthesia, muscle relaxants and mechanical ventilation; wound debridement should also be carried out, the purpose being to remove the source of toxin, as antibiotics alone are ineffective. Metronidazole is usually given.

Survivors suffer no after-effects but should have active immunization with toxoid.

Prophylaxis

Prophylaxis is active immunization in childhood, given as a triple vaccine (diphtheria, pertussis and tetanus antigens) starting at the age of 12 weeks, followed by further injections 6–8 weeks later and then after a further 4–6 months. Booster immunization (diphtheria, tetanus, pertussis and polio) is given at 3 years 4 months, and tetanus, diphtheria and polio at around 14 years old. The duration of immunity after such an immunization schedule is not known but current practice is to boost it every 10 years. Groups at highest risk (e.g. farm workers) should be given boosters every 5 years. Most cases of tetanus in developed countries are now seen in those who were never immunized, or in those whose immunity has declined – hence the risk in the elderly.

Table 21.6 Management of wounded patients at risk from tetanus

Wound type	Immune status	Course of action ^a
Superficial wound or abrasion	Immune ^b	–
	Not known to be immune	Active immunization with toxoid. Full three-dose course or, if partially immune, a reinforcing dose
Deep wounds, puncture wounds, or bites or burns	Immune	Give toxoid booster ^c
	Not known to be immune	Give antibiotics (metronidazole or penicillin) and start immunization with toxoid and: (1) if seen after 4h, give 250–500 units HTIG i.m.; (2) if seen after 24h, give 500 units HTIG i.m.

^aWound debridement in all.

^bLast of three-dose course or reinforcing dose within past 10 y.

^cHuman tetanus immunoglobulin (HTIG; 250–500 units i.m.) should also be given if the wound is highly contaminated or there is any doubt about immune status.

Dental aspects

Trismus is usually caused by local irritation, such as pericoronitis or temporomandibular pain–dysfunction syndrome, but in the absence of a local cause, tetanus must always be considered. Such patients should therefore be asked whether they have had any recent wounds, particularly if they are farm workers or gardeners.

Dyskinesias due to phenothiazines include facial grimacing but rarely trismus – the mouth is usually opened forcefully.

PUNCTURE WOUNDS

A puncture wound is caused by an object *piercing* the skin and creating a small hole. Some punctures can be very deep, do not often result in obvious excessive bleeding and tend to close fairly quickly spontaneously. A puncture wound from a cause such as stepping on a nail can become infected. Treatment may be necessary to prevent tetanus or other infections. Most healthy people without signs of infection do not require antibiotics, but these may be given to people with diabetes, peripheral vascular disease, contaminated wounds or deep wounds to the foot.

BITES

Dogs and cats cause most animal bites. Dog bites may cause severe tissue injury, as well as infections. Cat bites are more frequently (approximately 50%) infected. Animal bite infections are usually bacterial – typically polymicrobial (staphylococci and anaerobes). Tetanus is rarely transmitted.

Bites from non-immunized domestic animals and wild animals may carry the risk of rabies, which is more common in raccoons, skunks, bats and foxes than in cats and dogs. Rabbits, squirrels and other rodents rarely carry rabies.

Human bites are discussed in Chapter 24. Bites from humans may carry the risk of blood-borne virus infections (e.g. hepatitis B or C, or HIV). Consideration of post-exposure prophylaxis is important.

Treatment of bites may include debridement; antimicrobial coverage for staphylococci (co-amoxiclav) and anaerobes; and consideration of the possibilities of tetanus, rabies and blood-borne viruses.

Cat scratch disease (CSD) is caused by a bacterium, *Bartonella henselae*, usually transmitted when a person is bitten or scratched by a cat. About 40% of cats carry *B. henselae* at some time in their lives but show no signs. Patients develop lymphadenopathy, especially around the head, neck and axilla, and may develop fever, headache, fatigue and anorexia. Immunocompromised people are more likely to have complications – bacillary angiomatosis and Parinaud oculoglandular syndrome.

FOOD POISONING

Food poisoning is common, especially where hygiene is lacking and in warmer climates. Prevention is by:

- washing hands thoroughly before preparing or eating food, particularly after using the bathroom, changing nappies or having contact with animals or their environments
- cooking meat, poultry and fish thoroughly, preferably using a thermometer
- preventing cross-contamination in food preparation areas by washing hands, working tops, cutting boards and utensils thoroughly – particularly after preparing raw meat
- avoiding unpasteurized dairy products and juices
- avoiding swallowing water when swimming or playing in lakes, ponds, streams, rivers or swimming pools.

CAMPYLOBACTER

Campylobacter is the commonest reported bacterial intestinal disease in the UK. Most infections are with *C. jejuni* or *C. coli*, which are found in the gastrointestinal tract of birds (particularly poultry), cattle and domestic pets. Raw or undercooked meat (especially poultry), unpasteurized milk, bird-pecked milk on doorsteps, untreated water, and domestic pets with diarrhoea are the usual sources. Occupational exposure when processing poultry in abattoirs has been implicated in some cases. However, most infections remain unexplained by recognized risk factors.

Clinical features and general management

After an incubation period of 1–11 days (usually 2–5 days), there is abdominal pain, profuse diarrhoea and malaise, but vomiting is uncommon.

Disease may be passed from person to person if personal hygiene is poor. The illness is contagious, and children must be kept at home until they have been clear of symptoms for at least 2 days. Treatment is with azithromycin.

ESCHERICHIA COLI

E. coli are bacteria that normally live in the intestines of humans and animals without causing problems. Some strains can cause food poisoning, however, and one (*E. coli* O157:H7) can cause severe food poisoning, releasing a verotoxin (verocytotoxic *E. coli* [VTEC]; enterohaemorrhagic *E. coli* [EHEC]; or ‘Shiga toxin-producing’ *E. coli* [STEC]) that binds to receptors on human kidney, brain and gut cells, damaging them.

STEC live in the guts of ruminant animals, including cattle, goats, sheep, deer and elk. The major source of human illnesses is cattle. STEC that cause human illness generally do not make animals sick. Other kinds of animals, including pigs and birds, sometimes pick up STEC from the environment and may spread it. Foods implicated can include unpasteurized (raw) milk, unpasteurized apple cider, and soft cheeses made from raw milk. Sometimes the contact is obvious (e.g. working with cows or changing nappies) but sometimes it is not (e.g. eating undercooked hamburger or contaminated lettuce). People have been infected by swallowing water while swimming, touching the environment in zoos, and eating food prepared by people who did not wash their hands well.

The strain of STEC O104:H4 that caused a large outbreak in Europe in 2011 was referred to as EHEC. The most common STEC in North America is *E. coli* O157:H7 (*E. coli* O157 or simply ‘O157’).

Other *E. coli* serogroups in the STEC group, including *E. coli* O145, are sometimes called ‘non-O157 STECs’. Some types of STEC frequently cause severe disease, including bloody diarrhoea and haemolytic uraemic syndrome (HUS).

Clinical features

After an incubation period of 3–4 days (1–10 days), abdominal pain or non-bloody diarrhoea appears and worsens over several days. While people can become infected at any age, very young children and older people are more likely to develop severe illness and HUS. The symptoms of STEC infections vary but often include severe stomach cramps, diarrhoea (often bloody) and vomiting. If there is fever, it usually is not very high (less than 38.5°C). Most people recover within 5–7 days.

Around 5–10% of those who are diagnosed with STEC infection develop HUS and manifest decreased frequency of urination, malaise and anorexia. HUS, if it occurs, develops an average 7 days after the first symptoms, when the diarrhoea is improving. Persons with HUS should be hospitalized because renal failure is possible.

General management

STEC infections are usually diagnosed through laboratory testing of faecal specimens. Non-specific supportive therapy, including hydration, is important. There is no evidence that treatment with antibiotics is helpful, and taking antibiotics may increase the risk of HUS. Antidiarrheal agents may also increase that risk.

STEC typically disappear from the faeces by the time the illness is clinically resolved but may be shed for several weeks, even after symptoms go away. Young children tend to carry STEC longer than adults. A few people keep shedding these bacteria for several months.

INVASIVE MENINGOCOCCAL DISEASE

Meningococcal infection is typically caused by *Neisseria meningitidis*. Of the 13 *N. meningitidis* serotypes, only A, B, C, W135 and Y are clinically important. *N. meningitidis* serogroups A, B and C account for up to 90% of disease worldwide. W135 has emerged in recent years in Africa and the Middle East. Serogroups B and C are responsible for most cases in Europe and the Americas, serogroups A and C in Asia and Africa. Worldwide, the highest rates of infection occur in the meningitis belt of sub-Saharan Africa – from Senegal in the west, to Ethiopia in the east.

High-risk groups for invasive meningococcal disease include:

- people living in dormitories
- microbiologists who are routinely exposed to isolates of *N. meningitidis*
- people visiting countries where *N. meningitidis* is hyperendemic or epidemic (e.g. for Hajj), particularly if contact with the local population is prolonged
- people who have terminal complement component deficiencies
- people who have asplenia.

The reservoir for *N. meningitidis* is exclusively human, the bacteria being carried in the nasopharynx. Transmission is via the respiratory route, from coughing and sneezing, during close contact with a carrier. Epidemics are seen during the winter–spring period in temperate areas and during the dry season in tropical areas.

Clinical features

Infection risk is highest in the first 7 days after exposure to an infected person and falls rapidly during the following week. The incubation period is 2–10 days. Meningococcal infection can cause mainly:

- meningitis (49% of cases)
- septicaemia (33%)
- pneumonia (9%).

Infection can have an abrupt onset, with a rapid disease course and a case fatality rate of up to 15%; up to 20% of survivors suffer serious sequelae, including deafness, neurological deficit or limb loss. Meningococcal meningitis usually presents with sudden onset of fever, intense headache, nausea and vomiting. Neck stiffness from meningeal irritation is characteristic. A non-blanching petechial or purpuric rash usually occurs with septicaemia. Delirium, coma and shock can ensue.

General management

Suspected meningococcal infection is a medical emergency. On admission to hospital, parenteral antibiotics should be commenced

immediately. Intensive care, monitoring and supportive treatment are necessary.

For practical purposes, a 7-day period is considered sufficient to identify close contacts for prophylaxis. The ideal protection is provided by simultaneous administration of an antimicrobial drug and quadrivalent meningococcal vaccine. This approach is particularly suitable for outbreaks because of prolonged risk of transmission.

Antibiotic prophylaxis should be given as soon as possible after diagnosis of the index case. The drug of choice is rifampicin 600 mg b.i.d. for 2 days, but a single dose of ciprofloxacin 500 mg or an intramuscular injection of ceftriaxone 250 mg may also be used. The protection lasts for several days to a few weeks. The risk for contacts is still significant after 2 weeks and may persist for 6 months or even longer. Therefore immunization should be considered.

There is no vaccine to protect against all forms of meningitis and associated diseases, including the most common in the UK – meningococcal group B and streptococcal group B. Routine UK immunization programme protects against *Haemophilus influenzae* b, meningitis C and, most recently, pneumococcal meningitis.

Quadrivalent A/C/W135/Y and bivalent A/C meningococcal vaccines are available in the UK. ACWY is needed for Hajj/Umrah pilgrims (http://www.nathnac.org/pro/factsheets/Hajj_Umrah.htm; accessed 30 September 2013). There are two quadrivalent vaccines available in the UK: ACWY Vax[®] and Menveo[®]. See also Chapter 33.

Information for health professionals is available at: <http://www.nathnac.org/pro/factsheets/index.htm> (accessed 30 September 2013).

OTHER BACTERIAL INFECTIONS

Many other infections are seen, especially in the developing world (see Appendix 21.5).

VIRAL INFECTIONS

Viral infections are often transmitted readily in saliva and other body fluids; where general hygiene is low and there is close contact with other persons or their secretions, infections are common. They thus mainly affect young children, who often thereby acquire immunity. In developed countries, children may not contract these infections and thus are non-immune, and may have a primary infection as adolescents and adults.

Rashes (exanthemata) are common in some viral infections (Table 21.7).

Most viral infections are transient with few untoward sequelae, though many cause malaise, fever and depression of the immune system. Some viral infections can be immediately life-threatening (e.g. severe acute respiratory syndrome; SARS), others can result in tumours (e.g. hepatitis C and B and liver cancer), and others can seriously damage the immune system (e.g. HIV/AIDS; Ch. 20). Many viral infections can cause severe, recurrent, disseminated or persistent lesions in immunocompromised persons, such as those with organ transplants or HIV/AIDS.

Viral infections are often diagnosed on clinical grounds, supported by testing for immune responses (serology) and, increasingly, by examining for viral nucleic acids.

Antiherpetic and antiretroviral drugs can be effective (see the Appendices in Ch. 21) but relatively few other effective antiviral agents are available. Immunization against various viruses is available and should be taken up.

A wide range of infections is recognized (Table 21.8). This chapter discusses the important common viral infections, alphabetically; see

Table 21.7 Common childhood infections with rashes (exanthemata)

	Name	Alternative term
First disease	Measles	Rubeola
Second disease	Scarlet fever	Streptococci
Third disease	German measles	Rubella
Fourth disease	Filatov–Dukes disease	Doubt exists over the existence of this
Fifth disease	Erythema infectiosum ('slapped cheek syndrome')	Parvovirus
Sixth disease	Herpesvirus 6 infection ('exanthem subitum')	Roseola infantum

Table 21.8 Viral infections

Viral infection	Chapter location
Arboviruses	This chapter
Arenaviruses	This chapter
Enteroviruses	This chapter
Hantaviruses	This chapter
Hepatitis viruses	Ch. 9
Herpesviruses	This chapter
Human immunodeficiency viruses	Ch. 20
Influenza	Ch. 15
Measles	This chapter
Molluscum contagiosum	This chapter
Mumps	This chapter
Papillomaviruses	This chapter
Parvovirus	This chapter
Poliomyelitis	Ch. 13
Rabies	This chapter
Rhabdoviruses	This chapter
Rubella	This chapter
Severe acute respiratory syndrome (SARS)	Ch. 15

Appendices 21.8 and 21.9 for serious life-threatening but fortunately uncommon viral infections.

CHIKUNGUNYA

This is a togavirus (RNA) transmitted by the Asian Tiger mosquito (*Aedes albopictus*), found mainly in areas in, and bordering, the Indian Ocean. Similar to dengue and O'nyong'nyong, the incubation is 2–4 days, and clinical features may include;

- Oral ulceration
- Rash; central maculopapular
- Headache, malaise
- Arthralgia
- Fever to 39 degrees.

There are neither cures nor antiviral drug treatments.

ENTEROVIRUSES

Enteroviruses multiply in the gut mucosa and are transmitted from person to person by the faecal–oral route. Most infections are in childhood, often as small epidemics. Enterovirus infections are usually



Fig. 21.3 Hand, foot and mouth disease.

transient but produce lifelong immunity to the strain. Clinical syndromes are generally mild but occasional infections may cause serious disease, such as paralytic poliomyelitis, meningitis or myocarditis.

Enterovirus diseases relevant to dentistry include hepatitis A (Ch. 9), poliomyelitis (Ch. 13), herpangina, and hand, foot and mouth disease.

HERPANGINA

Coxsackie viruses, usually A7 or B1, or echoviruses 9 or 17 cause infections, often subclinically. After an incubation of 2–9 days, clinical features may include mouth ulcers affecting the posterior mouth alone (soft palate and uvula) and causing sore throat, cervical lymphadenitis, fever, malaise, irritability, anorexia and sometimes vomiting. Diagnosis is from the clinical features. Management is symptomatic (see Herpes simplex).

HAND, FOOT AND MOUTH DISEASE

Picornaviruses (Coxsackie A and enterovirus [EV] 71) are responsible for most hand, foot and mouth disease (HFMD). Coxsackie (usually A16; rarely, A5 or 10) virus infections are often subclinical. However, the World Health Organization reported one outbreak in 2008 in China involving a total of 1884 cases, including 20 deaths, due to enterovirus EV-71.

Clinical features, after an incubation of 2–6 days, include mouth ulcers, resembling herpetic stomatitis, mild fever, malaise, anorexia and a rash. Red papules that evolve to superficial vesicles in a few days form mainly on the palms and soles (Fig. 21.3). Diagnosis is from the clinical features. Management is symptomatic (see Herpes simplex).

HERPESVIRUSES

The herpesviruses are DNA viruses, transmitted mainly in saliva and other body fluids (Table 21.9). They typically cause a short-lived primary clinical, or more often subclinical, infection, and remain latent thereafter. Reactivation is often because of immunosuppression and recrudescence can lead to protracted illness. Some herpesviruses can be oncogenic.

HERPES SIMPLEX VIRUS (HSV; HUMAN HERPESVIRUS TYPES 1 AND 2) INFECTIONS

General aspects

Type 1 herpes simplex virus (HSV) typically causes primary oral infection with acute gingivostomatitis but may cause primary pharyngeal or anogenital infection. Type 2 HSV typically causes anogenital

Table 21.9 The herpesviruses

Herpesvirus type	Standard nomenclature	Abbreviation
1	Herpes simplex type 1	HSV-1
2	Herpes simplex type 2	HSV-2
3	Herpes varicella zoster	VZV
4	Epstein–Barr virus	EBV
5	Cytomegalovirus	CMV
6	Human herpesvirus type 6	HHV-6
7	Human herpesvirus type 7	HHV-7
8	Human herpesvirus type 8 (Kaposi sarcoma herpesvirus)	HHV-8 (KSHV)



Fig. 21.4 Herpes simplex recurrent infection.



Fig. 21.5 Recurrent herpes labialis.

infections but may cause oral or oropharyngeal infections. HSV thereafter remains latent in the sensory ganglia but if reactivated may cause lesions. Recurrent infections typically affect the mucocutaneous junctions and are often precipitated by factors such as exposure to systemic infections, sunlight, trauma, stress, menstruation or immune incompetence (Figs 21.4 and 21.5).

Clinical features

Primary oral infection with HSV, usually type 1, typically causes acute gingivostomatitis, ulcers, fever, cervical lymph node enlargement and irritability. It is common in young children and sometimes misdiagnosed as 'teething', or may be subclinical. Primary herpetic gingivostomatitis is limited to the mouth and resolves within about 10 days but, in immunosuppressed patients or in those with eczema, disseminated infection may result.

Thereafter HSV remains latent, often in the trigeminal ganglia, but reactivates from time to time; it appears in the saliva and may cause



Fig. 21.6 Herpetic whitlow.

Table 21.10 Antiviral therapy considerations in common herpesvirus infections

Virus	Disease	Otherwise healthy patient	Immunocompromised patient
Herpes simplex	Primary	Consider oral aciclovir ^a 100–200 mg, five times daily as suspension (200 mg/5 mL) or tablets	Aciclovir 250 mg/m ² i.v. every 8 h
	Recurrent herpetic ulcers	Consider oral aciclovir ^a 100–200 mg, five times daily as suspension (200 mg/5 mL) or tablets	Consider aciclovir 250 mg/m ² i.v. every 8 h
	Recurrent herpes labialis	Penciclovir 1% cream or aciclovir 5% cream every 2 h	Consider aciclovir 250 mg/m ² i.v. every 8 h
Herpes varicella	Chickenpox	–	Aciclovir 500 mg/m ² (5 mg/kg) i.v. every 8 h
	Zoster (shingles)	3% aciclovir ophthalmic ointment for shingles of ophthalmic division of trigeminal	Aciclovir 500 mg/m ² (5 mg/kg) i.v. every 8 h or famciclovir 250 mg three times daily, or 750 mg daily

Aciclovir: systemic preparations, caution in renal disease and pregnancy, occasional rise in liver enzymes and urea, rashes, CNS effects. Famciclovir: caution in renal disease and pregnancy. Occasional nausea and headache.

^aIn neonate, treat as if immunocompromised.

lesions. The virus can be spread by saliva and occasionally causes painful whitlows in dental staff not previously exposed to it (Fig. 21.6). A growing number of oral or oropharyngeal infections appear to be caused by HSV-2, which otherwise causes genital infections. Diagnosis is typically clinical.

Aciclovir is effective against HSV but many patients present with disease that is too far advanced for there to be any real benefit. Aciclovir, famciclovir and other antivirals are essential to control infection in immunocompromised patients (Table 21.10). Treatment is supplemented with supportive care, such as adequate fluid intake, antipyretics and analgesics (usually paracetamol [acetaminophen]), and good oral hygiene by mouth cleansing and use of aqueous chlorhexidine mouthwashes.

Recurrent infections appear in up to 30% of patients, typically at the mucocutaneous junction of the lip (herpes labialis; cold sores) or nose, and are often precipitated by exposure to systemic infections, sunlight, trauma, stress or menstruation. These factors stimulate HSV to reactivate by more than one mechanism. One way is by direct induction of viral genes such as *ICP4* and *VPI6*. Heat can induce these viral genes either directly or via the by-products of heat. The activated viral gene products then overcome the effects of latent (LAT) RNAs. Another mechanism is an indirect one involving immunosuppression. Ultraviolet light is immunosuppressive and also induces cytokines that can trigger inflammation. These cytokines may affect dendrites that communicate the signal back to the neuron where the viral DNA is residing; *ICP4* and *VPI6* are viral genes critical for reactivation.

Diagnosis is clinical. Recurrent labial infections respond well to penciclovir or aciclovir cream applied early. A patch with hydrocolloid particles and zinc sulphate is an alternative.

Intraoral recurrences appear as ulcers and seem to be more likely after trauma, such as in the palate, or in immunocompromised patients (e.g. leukaemia or HIV/AIDS). Aciclovir may be indicated but HSV is now showing starting to show resistance. Fanciclovir, valaciclovir or even foscarnet may then be required.

Genital herpes

A person almost always contracts HSV-2 infection by sexual contact. HSV-1 infection of the genitals is almost always caused by oral–genital contact with a person who has oral HSV-1 infection. One out of five of the total adolescent and adult population in the USA are infected with HSV-2; the prevalence is rising but few have signs or symptoms. When signs of genital herpes do appear, they are typically as blisters on or around the genitals or rectum. The blisters break, leaving tender ulcers that may take 2–4 weeks to heal. It is important that women avoid contracting HSV-2 during pregnancy because a first episode during pregnancy causes a greater risk of transmission to the newborn. HSV-2 can cause potentially fatal infections in infants if the mother is shedding virus at the time of delivery. If a woman has active genital herpes at delivery, a Caesarean delivery is therefore usually performed.

Antiviral medications, such as aciclovir or fanciclovir, can shorten and prevent outbreaks during the period the medication is being taken.

VARICELLA ZOSTER VIRUS (VZV; HUMAN HERPESVIRUS 3)

Chickenpox

General aspects

Varicella (chickenpox) is a highly contagious disease caused by the varicella zoster virus (VZV), spread readily by droplets. VZV is an exclusively human pathogen. The primary infection typically occurs during childhood and causes varicella. Patients are infectious from 1–2 days before the rash, until the rash scabs and dries.

During viraemia, VZV enters epidermal cells, causing the typical varicella rash; it then enters sensory nerves in mucocutaneous sites and travels through retrograde axonal transport to the sensory dorsal root ganglia adjacent to the spinal cord, where the virus establishes permanent latency in neuronal cell bodies. VZV then remains latent within dorsal root ganglia and, if reactivated, as can happen in older or immunocompromised people, can lead to shingles (zoster) – a painful unilateral rash.

More information on varicella and other infectious diseases may be found at: <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/> (accessed September 2013).

Clinical features

Varicella is most common in children below the age of 10 years. There is fever, malaise and a centripetal rash (mainly on trunk and face), which passes through macular, papular, vesicular and pustular stages before scabbing. There are about 3–5 crops of lesions. There may be mouth ulcers.

Infants, adolescents, adults and immunocompromised persons are at higher risk for complications, such as disseminated or haemorrhagic varicella. Adults, especially those who are pregnant or who smoke, are at risk from fulminating varicella pneumonia. There is also a risk to the fetus and neonate if the mother contracts chickenpox. In the first 20 weeks of pregnancy, a congenital varicella syndrome with microcephaly, cataracts, growth retardation and limb hypoplasia may result, and the mortality rate is high. Later in pregnancy, chickenpox may result in zoster in an otherwise healthy infant. Chickenpox around the time of delivery may cause severe and even fatal infection of the neonate.

General management

Diagnosis is clinical. Varicella zoster immunoglobulin, or aciclovir, valaciclovir or fanciclovir, may be indicated for non-immune persons who are pregnant or immunocompromised. Varicella vaccine is effective in preventing illness or modifying varicella severity if used within 3 days, and possibly up to 5 days of exposure.

Zoster

General aspects

VZV remains latent within dorsal root ganglia and may be reactivated, especially in the elderly or immunocompromised, leading to shingles (zoster). In about 8–10%, zoster may reflect an underlying immunodeficiency state, sometimes as a result of HIV/AIDS or a neoplasm, particularly a lymphoma.

Latent VZV infects approximately 98% of the adult population and is non-infectious but it can reactivate to migrate to the skin through axons, spread from cell to cell, and penetrate the epidermis, causing pain; this is followed by a vesicular rash distributed across closely overlapping dermatomes of the involved sensory nerve roots. VZV reactivation triggers are unclear but cell-mediated immunity (CMI) is important in controlling the development of zoster. The CMI components are partially or substantially maintained by periodic ‘endogenous boosting’ in response to subclinical reactivation or to ‘exogenous boosting’ in response to VZV circulating in the population as chickenpox.

Age is the most important risk factor for development of zoster. Approximately 50% of persons who live to the age of 85 years will have experienced zoster.

The incidence of zoster is increased substantially in persons with haematological malignancies and solid tumours. Patients with Hodgkin’s disease are at particularly high risk for zoster. Zoster is common following haemopoietic stem cell transplantation (HSCT) and following solid organ transplants (renal, cardiac, liver and lung; 5–17%). Incidence is highest during the months immediately following the procedure, and the majority of zoster cases occur within a year of transplantation. The risk for zoster and its recurrence is elevated in persons infected with HIV.

The risk for zoster also appears to be higher in persons with inflammatory diseases. Zoster has been associated with systemic lupus erythematosus (SLE), rheumatoid arthritis, granulomatosis with polyangiitis (formerly called Wegener granulomatosis), Crohn disease and ulcerative colitis, and possibly diabetes mellitus and multiple sclerosis.

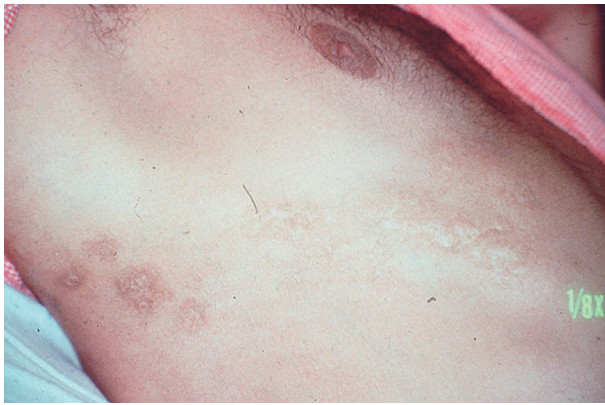


Fig. 21.7 Thoracic zoster.



Fig. 21.8 Ophthalmic zoster.

Zoster lesions contain high concentrations of VZV that can be spread, presumably by the airborne route, and cause primary varicella in exposed susceptible persons. Zoster is contagious after the rash erupts and until the lesions crust. It is less contagious than varicella, though transmission has been documented between patients or from patients to health-care personnel, but transmission from health-care personnel to patients has not been documented.

Clinical features

Zoster involves one or more contiguous sensory dermatomes, usually of the face or the chest, and causes severe pain and a rash similar to chickenpox but localized to the dermatome (Fig. 21.7). Trigeminal ophthalmic zoster may cause facial rash and pain, and ulcerate the cornea (Fig. 21.8). Zoster of the maxillary or mandibular divisions of the trigeminal nerve may cause facial rash and pain (sometimes simulating toothache) and oral ulceration – unilateral and in the nerve distribution.

Zoster is usually more severe in older adults, typically with a prodrome of headache, photophobia and malaise (Fig. 21.9). Abnormal skin sensations and aching, burning, stabbing or shock-like pain of varying severity are common and can precede the rash by days to weeks; rarely, they might constitute the only clinical manifestation (termed zoster sine herpette).

Zoster rash is typically unilateral and does not cross the midline, erupting in one or two adjacent dermatomes. Thoracic, cervical and ophthalmic involvement are most common. The rash is initially erythematous and maculopapular but progresses to coalescing clusters of clear vesicles over several days and then evolves through pustular, ulcer and crust stages over 7–10 days, with complete healing within 2–4 weeks.

A common consequence of zoster is post-herpetic neuralgia (PHN), a persistent pain after resolution of the rash. The duration of pain after



Fig. 21.9 Zoster in cervical nerves.

rash resolution, used to define PHN, ranges from at least 30 days to 6 months or more after rash onset. PHN can last for weeks or months and occasionally for many years, and varies from mild to excruciating in severity; it may be constant, intermittent, or triggered by trivial stimuli.

Zoster may be associated with other complications too: 10–25% have eye involvement, called herpes zoster ophthalmicus (HZO). Keratitis occurs in approximately two-thirds of patients with HZO, often causing corneal ulceration. Other sequelae include conjunctivitis, uveitis, episcleritis and scleritis, retinitis, choroiditis, optic neuritis, lid retraction, ptosis and glaucoma. Extraocular muscle palsies also occur. Ramsay Hunt syndrome is an uncommon complication, in which there is a peripheral facial nerve palsy accompanied by reactivation of VZV in the geniculate ganglion of the facial nerve with zoster vesicles on the ear, hard palate or tongue. Occasionally, zoster can cause motor weakness in non-cranial nerve distributions, called zoster paresis; this develops abruptly within 2–3 weeks of the rash and can involve upper or lower extremities. Diaphragmatic paralysis has also been described. Zoster can also result in autonomic dysfunction, causing urinary retention and colon pseudo-obstruction. Rarely, patients will experience acute focal neurological deficits weeks to months after resolution of the rash, with myelitis, aseptic meningitis, meningoencephalitis or Guillain–Barré syndrome.

In immunocompromised persons, the rash tends to be more severe and its duration prolonged; there may be dissemination and it is a marker for VZV viraemia that can seed the lungs, liver, gut and brain, and cause pneumonia, hepatitis, encephalitis and disseminated intravascular coagulopathy. Neurological zoster complications are increased in immunocompromised persons and can be aggressive and even fatal; they include myelitis, chronic encephalitis, ventriculitis, meningoencephalitis and cranial palsies.

General management

Diagnosis is clinical and might not be possible in the absence of a rash. VZV obtained from lesions can be identified using tissue culture, but this can take several days and false negative results occur because

viable virus is difficult to recover from cutaneous lesions. Direct fluorescent antibody (DFA) staining of VZV-infected cells in a scraping of cells from the base of the lesion is rapid and sensitive. DFA and other antigen-detection methods can also be used on biopsy material, and eosinophilic nuclear inclusions (Cowdry type A) are observed on histopathology. Polymerase chain reaction (PCR) techniques can be used to detect VZV DNA rapidly and sensitively.

Treatment of zoster is with aciclovir, valaciclovir or famciclovir by mouth, given within 3 days of the appearance of the rash. Intravenous administration is needed in immunodeficient patients, particularly in those with HIV/AIDS, for whom it can be a life-threatening disease.

An urgent ophthalmological opinion should be sought for patients with ophthalmic zoster. Aciclovir, famciclovir and valaciclovir are approved by the US Food and Drug Administration (FDA) for treatment of zoster; they reduce the duration of viral shedding and lesion formation, and decrease the time to rash healing, the severity and duration of acute pain from zoster, and the risk for progression to PHN. Even with antiviral treatment, fatality from dissemination is 5–15%, with most deaths attributable to pneumonia.

The pain of herpetic neuralgia may not respond well to analgesics but tricyclic antidepressants, carbamazepine or capsaicin may be of value. Other treatments for postherpetic pain include skin stimulation of the painful area by prolonged rubbing with a soft cloth; firm pressure with the flat of the hand or the ball of the thumb; massage; acupuncture; local heat; a cold spray; or transcutaneous electric nerve stimulation (TENS).

Immunization of children against VZV reduces the risk of zoster at a later age. However, if immunity wanes with age, there may be epidemics of chickenpox in the middle-aged, and if the middle-aged who have had chickenpox do not receive occasional boosts of their immunity by exposure to chickenpox (which has been prevented in children by vaccination), the incidence of shingles may rise. In immunocompromised patients who are exposed to VZV, it may be desirable to give zoster immunoglobulin or vaccine.

If a person susceptible to varicella infection has close exposure to a person with zoster, postexposure prophylaxis with varicella vaccine or VARIZIG™ should be considered. Zoster vaccine may be offered to older patients and is now offered in UK to those over 70.

EPSTEIN–BARR VIRUS (EBV; HUMAN HERPESVIRUS 4)

General aspects

Epstein–Barr virus (EBV) causes infectious mononucleosis (IM; classic glandular fever). EBV also has epidemiological associations with Burkitt and some other lymphomas, and with nasopharyngeal carcinoma. EBV may also cause sialadenitis (see later) and, in immunocompromised patients, may be associated with hairy leukoplakia (Ch. 20) or lymphomas.

Clinical features

EBV is found in saliva during IM and for several months thereafter. It is also often in the saliva of immunocompromised persons. Though infectivity is low, EBV appears to be spread by close oral contact, such as kissing.

Infection is common among young adults but is often subclinical or unrecognized, especially in children. IM mainly causes lymphadenopathy, sore throat and fever but is protean in its manifestations (glandular fever). Glandular fever is a syndrome in which fever, malaise and lymph node enlargement are the main features; though typically

Box 21.7 Causes of glandular fever syndromes

- Cytomegalovirus infection
- Epstein–Barr virus infection (infectious mononucleosis)
- HIV infection
- Human herpesvirus 6 infection
- Infectious lymphocytosis (babesiosis; *Bordetella pertussis*; brucellosis; cat scratch disease; Coxsackie, hepatitis, influenza, mumps, rubella, syphilis, TB; varicella)
- Toxoplasmosis
- Rarely: acute leukaemia; drug-induced hypersensitivity syndrome (DIHS; drug reaction with eosinophilia and systemic symptoms [DRESS] syndrome)



Fig. 21.10 Infectious mononucleosis.

caused by EBV, other infectious agents are occasionally responsible (Box 21.7).

IM can appear in many forms:

- *Febrile type IM* – high fever with rubelliform rashes and occasionally jaundice
- *Anginose type IM* – sore throat with soft palate petechiae and a whitish exudate confined to the tonsils, and pharyngeal oedema that may threaten the airway (to be distinguished from diphtheria) and petechiae on the palate. The latter are occasionally seen in other viral infections, such as rubella and HIV. Occasionally, there is mouth ulceration
- *Glandular type IM* – generalized, especially cervical lymph node enlargement and splenomegaly. IM is an important cause of enlarged cervical lymph nodes. Unfortunately, the lymph node histopathological changes closely resemble those in lymphomas and an expert opinion is needed.

Complications of IM include persistent fatigue, mild liver dysfunction, ECG changes, depression, neurological syndromes and, rarely, nephritis, pancreatitis or lung infiltration. Ampicillin and amoxicillin frequently cause a maculopapular rash (which is not an allergy), affecting the extensor surfaces of limbs (Fig. 21.10).

General management

Characteristic blood changes of IM are an excess of atypical lymphocytes (mononucleosis); these may cause confusion with leukaemia – but

for the absence of anaemia. Occasionally, there is also mild neutropenia or thrombocytopenia.

Serological tests for IM include heterophile antibodies and EBV antibodies. Heterophile antibodies are immunoglobulin M (IgM) antibodies that agglutinate sheep and horse red blood cells. The Paul–Bunnell heterophile antibody test uses sheep erythrocytes, but a more rapid method identifies heterophile antibodies (to horse red blood cells) by detecting agglutination on a glass slide (Monospot test). Heterophile antibodies usually develop during the first or second week of the illness (60% of patients), and by 4 weeks up to 90% of patients have a titre before absorption of 224, which then declines and disappears over 3–6 months.

EBV-specific laboratory tests on a single acute-phase serum sample can help determine whether a person is susceptible to EBV, has had recent infection, has had past infection, or has reactivated EBV infection (Table 21.11).

When the Monospot (Paul–Bunnell) test is negative, the best testing combination is of:

- IgM and IgG to viral capsid antigen (VCA): IgM appears early in infection and disappears within 4–6 weeks. IgG to VCA appears in the acute phase, peaking at 2–4 weeks after onset, declining slightly and then persisting for life
- IgM to early antigen (EA), and IgG to EA: these appear in the acute phase and generally fall to undetectable levels after 3–6 months
- antibody to EBV nuclear antigen (EBNA): this slowly appears 2–4 months after onset and persists for life. Some EBNA enzyme immunoassays can detect antibody sooner.

However, even when EBV antibody tests suggest that reactivated infection is present, this does not necessarily indicate that the current illness is caused by EBV infection, since a number of healthy people continue to have antibodies to EBV EA for years. There may be a false positive Wassermann reaction.

Infection with EBV is usually acute and self-limiting, and no reliably effective specific treatment is available. As malaise and fatigue are frequent accompaniments, however, the patient may benefit from bed rest. Systemic corticosteroids are required if there is severe pharyngeal oedema that poses a hazard to the airway. Nearly 20% of patients have concurrent beta-haemolytic streptococcal pharyngeal infection, for which penicillin may be given. Tinidazole may improve the sore throat.

Burkitt lymphoma

Burkitt lymphoma, found predominantly in Africa in children below 12 years of age, presents with massive swellings that affect the mandible in particular; there is pain, paraesthesia and bone destruction, causing tooth mobility, jaw radiolucencies and destruction of the lamina dura. It appears to be related to EBV in association with malaria.

Burkitt lymphoma may also be seen outside of Africa and can be a complication of HIV/AIDS. Chemotherapy is remarkably effective but relapse is common.

Hairy leukoplakia in HIV/AIDS

See Chapter 20.

Lymphomas

See Chapter 8.

Nasopharyngeal carcinoma

See Chapters 14 and 22.

CYTOMEGALOVIRUS (CMV; HUMAN HERPESVIRUS 5)

Cytomegalovirus (CMV) is a ubiquitous herpesvirus found in large quantities in the saliva and urine of infected persons.

Primary infections are mostly asymptomatic but some cause a glandular fever-like illness. Thereafter CMV remains latent in oropharyngeal and other epithelial cells, and may be reactivated by immunosuppression and other factors. Under these circumstances, disseminated infection can cause CMV retinitis in particular, often leading to blindness. CMV infection is a particular problem in HIV/AIDS (Ch. 20).

The other main problem identified in relation to CMV is its potential to cause fetal damage. A range of infections of the pregnant mother, especially in the first trimester, can cause fetal damage, that can sometimes be fatal. These include toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (TORCH syndrome). When less severe, they may cause mild hearing loss; alternatively, they may result in learning disability, pneumonitis, cardiac malformations, microphthalmia, microcephaly, jaundice and low birth weight. CMV is thereafter excreted by the neonate in urine and saliva for many months.

Antiviral therapy for CMV includes ganciclovir or foscarnet.

HUMAN HERPESVIRUS 6

Human herpesvirus 6 (HHV-6) is a T-cell lymphotropic herpesvirus that is almost invariably contracted via oropharyngeal secretions within the first 2 years of life.

HHV-6 causes a febrile illness, sometimes with a macular or papular rash on the face and/or trunk (exanthema subitum; roseola infantum; sixth disease), mild diarrhoea, cough, oedematous eyelids and occasionally sialadenitis, hepatitis, meningitis or meningo-encephalitis or blood dyscrasias (particularly granulocytopenia). Erythematous papules (Nagayama spots) may appear on the soft palate and uvula and pharynx. Cervical lymphadenopathy is detectable in about one-third of patients. HHV-6 infection in later life may produce a glandular fever syndrome, persistent lymphadenopathy, chronic fatigue syndrome or hepatitis.

Thereafter, HHV-6 remains latent. Immunocompromised patients may suffer reactivation of HHV-6 with pneumonitis, retinitis, encephalitis or bone marrow failure, and it may have a cofactorial role in HIV infection. There are suggested but certainly unproven associations with multiple sclerosis and various neoplasms.

HHV-6 is inhibited by ganciclovir, foscarnet (phosphonoformate, PFA) and phosphonoacetic acid (PAA) but is relatively resistant to aciclovir.

HUMAN HERPESVIRUS 7

Human herpesvirus 7 (HHV-7) is T-lymphotropic; it is not known to be related to any human disease but might be a cofactor in HHV-6-related syndromes and may cause rashes.

Table 21.11 Diagnosis in Epstein–Barr virus (EBV) infection

EBV nuclear antigen (EBNA) antibody	Other EBV antibodies	Interpretation
Absent	Viral capsid antigen (VCA) antibodies absent	Susceptible
Absent	VCA immunoglobulin M (IgM) antibody present VCA IgG antibody rising or high	Primary infection
Present	VCA antibodies present	Past infection
Present	Early antigen (EA) antibodies present	Reactivation

HUMAN HERPESVIRUS 8

Human herpesvirus 8 (HHV-8; Kaposi sarcoma herpesvirus, KSHV) is a B-lymphotropic DNA virus, transmitted mainly by sexual contact. It is strongly associated with Kaposi sarcoma and body cavity-based lymphomas. It is present in saliva but there are as yet no documented cases of nosocomial transmission to health-care workers. There is no specific effective treatment but ART (Ch. 20) may play an indirect role in clearing HHV-8 from HIV-infected patients.

HUMAN IMMUNODEFICIENCY VIRUSES

See Chapter 20.

MEASLES

Measles is an acute infection with the measles virus, transmitted by droplet infection, with an incubation period of about 10–14 days. Whitish spots in the buccal mucosa (Koplik spots) herald the onset. The illness consists of fever, coryza, conjunctivitis and a maculopapular rash. Complications include bronchitis, pneumonia, otitis media, convulsions and encephalitis (which has a mortality of 15% – highest in infants – and leaves a neurological deficit in up to 40%). Subacute sclerosing panencephalitis (SSPE) is a late complication.

Immunization is indicated in early childhood (Appendix 21.7) and had almost abolished measles, until the recent decline over concerns about immunization.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a viral infection that spreads easily among children; in adults, it may be sexually transmitted and is common in HIV/AIDS. Characteristic umbilicated papules may be seen on the face and elsewhere. Local application of trichloroacetic acid effectively burns the lesions off.

MUMPS

Mumps was a common infection, usually caused by the mumps virus and spread by droplet infection; it is now mostly eliminated by vaccination. Of 101 specimens in a recent study on mumps, 38 were positive for a single virus: Epstein-Barr virus (in 23), human herpesvirus (HHV)-6B (10), human parainfluenza virus (HPIV)-2 (3), HPIV-3 (1), and human bocavirus (1). Mumps virus itself, enteroviruses (including human parechovirus), HHV-6A, HPIV-1, and adenoviruses were not detected. Mumps-like illnesses are occasionally caused by adenoviruses or echoviruses.

The incubation period is 14–21 days and mumps is transmissible from 2 or 3 days before parotitis appears until several days afterwards. Mumps causes swellings involving particularly the major salivary glands, usually the parotids (Fig. 21.11). One or both parotids become enlarged and tender (parotitis) with trismus, and oedema and erythema of the orifice of the parotid duct (papillitis). The other major salivary glands may also be affected but rarely in the absence of parotitis. Mumps should always be considered in the differential diagnosis of acute swellings of salivary glands, particularly in the young. Complications of mumps are uncommon but include deafness, pancreatitis, meningo-encephalitis, orchitis and oophoritis in particular. The latter conditions rarely cause sterility, even if bilateral.



Fig. 21.11 Mumps.



Fig. 21.12 Human papillomavirus infection: common warts.

There is no antiviral agent available for use against mumps. Mumps immunization is carried out in childhood.

PAPILLOMAVIRUSES (HUMAN PAPILLOMAVIRUSES; HPVS)

Human papillomaviruses (HPVs) are ubiquitous DNA viruses. Over 100 HPV types are recognized; they are transmissible and mostly cause benign warts and other epithelial lesions affecting skin and mucosae, including mouth and genitals. Skin warts (*verruca vulgaris*) are common (Figs 21.12 and 21.13), especially in children, and spread mainly from close contact or in wet environments such as changing rooms. Genital warts (*condylomata acuminata*) are caused by HPV and may be found on the penis, vulva or vagina or perianally, or may be unseen in the urethral meatus or cervix. Around one-third of young American women have genital HPV infection. About 65% of sexual contacts of patients with genital warts develop warts after an incubation period that may exceed 2 years.

Some HPVs cause oral warts (*verruca vulgaris*) and papillomas. Heck disease (focal epithelial hyperplasia) is an unusual oral condition caused by specific HPV (types 13 and 32), mainly in ethnic groups such as Inuits and American Indians.

Some HPVs are closely associated with malignant disease; for example, HPV-16, 18 and 33 appear to be associated with cervical carcinoma. HPVs may also be associated with some oropharyngeal carcinomas.

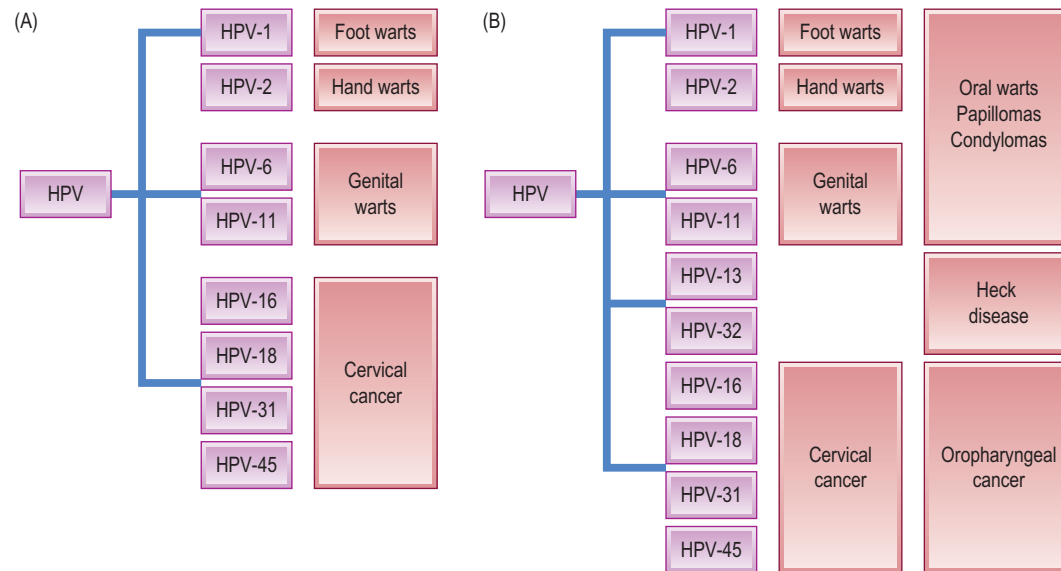


Fig. 21.13 Human papillomavirus infections.

Local surgery or podophyllum resin has been the usual treatments for non-malignant HPV-related lesions. Immune stimulators such as interferon-alpha and imiquimod are now available.

HPV vaccines protect against the types of HPV that cause most cervical cancers. There are two vaccines, both of which are safe and are usually given as a three-shot series:

- Cervarix: recommended for females from 10 to 25 years of age, and protects against HPV 16 and 18.
- Gardasil: recommended for 11–26-year-old females and also for 9- to 26-year-old males to protect against some genital warts. This vaccine protects against HPV 6, 11, 16 and 18.

There is no statistically significant increased risk for stroke, thromboembolism, appendicitis, seizures, syncope, allergic reactions, Guillain-Barré syndrome and anaphylaxis but the most common adverse events reported from vaccination have been:

- syncope – common, especially in pre-teens and teens
- local pain and redness at the site of immunization
- dizziness
- nausea
- headache
- venous thromboembolism – 90% had a known other risk factor, such as smoking, obesity or hormonal contraceptives.

PARVOVIRUSES

Parvoviruses are among the smallest, simplest DNA viruses and cause infections in a variety of birds and mammals. The only known human parvovirus is B19, which is transmitted by droplets, touch and occasionally in blood, and usually has an incubation period of 4–14 days. Parvoviruses tend to infect rapidly dividing tissues, most commonly the fetus, the intestinal epithelium or the haemopoietic system. A total of 70–90% of most adult populations is seropositive for B19.

Parvovirus commonly causes fifth disease (erythema infectiosum; slapped cheek syndrome), a mild illness with a lace-like rash on the face, trunk and extremities, usually in children. In approximately 80% of patients, there is also arthropathy – temporary arthritis-like joint involvement (particularly in adults). Since the vaccination-induced disappearance of rubella, parvovirus is the commonest cause of infection-related transitory arthritis, particularly if it affects the hands.

B19 also causes acute depression of red blood cell production, a transient event of little clinical significance, except in patients with other haematological diseases, particularly sickle cell disease, when haemolytic crises may be precipitated. B19 infection in pregnancy is associated with early fetal loss, although the probability of this appears to be low (less than 10%). There is no specific therapy for parvoviruses.

RUBELLA (GERMAN MEASLES)

ACQUIRED RUBELLA

Rubella, caused by rubella virus, is a highly infectious but usually mild disease, spread by droplet infection, with an incubation period of about 14–21 days.

In children, rubella causes a minor macular rash, starting on the face and behind the ears, mild fever, sore throat and enlarged lymph nodes (including the posterior auricular and suboccipital posterior cervical nodes). In adults, rubella may cause arthritis or arthralgia.

No antiviral treatment is available for rubella. Immunization is available and indicated for health-care workers. After rubella immunization, immunity is long-lasting.

CONGENITAL RUBELLA

Rubella infection during the first trimester of pregnancy can damage the fetus, causing problems ranging from deafness to death. If the fetus survives, learning disability, retinopathy and cataracts, cardiac malformations and deafness may result (major rubella syndrome). The infant may also have liver damage, bone defects and thrombocytopenic purpura. The virus is excreted, particularly in the urine, for months after birth (see TORCH syndrome). Pregnant females should thus consider whether or not they are immune to rubella. Rashes resembling rubella (rubelliform rashes) are also common in enterovirus and other infections, and thus a *clinical* diagnosis of rubella may not always be accurate unless confirmed serologically. Females who believe they have had rubella (and thus think they are immune) may in fact be non-immune and they and any fetus may be at risk. Antibody titres should be assayed to determine their actual immune status.

Rubella immunization of non-immune pre-pubertal females is the most effective prophylaxis and should be given to female health-care staff who are not known to be immune, who are seronegative, and who

Table 21.12 Confirmation of diagnosis of rubella

Suspected rubella infection of patient	Suspected rubella contact
1. Test acute serum for haemagglutination inhibition (HAI) antibody to rubella	1. Test acute serum for HAI antibody to rubella
2. If HAI-positive in acute serum, reassure. If HAI continues negative, reassure	2. Test serum of the contact for rubella. If HAI-negative, reassure
3. If HAI-negative but then rises, offer termination or rubella immunoglobulin	3. If pregnant woman has rubella antibodies already, reassure
	4. If pregnant woman has no immunity and contact is, or is suspected of being, rubella-positive, retest patient's sera for HAI. If HAI continues negative, reassure. If HAI becomes positive, offer termination or rubella immunoglobulin

are not pregnant and are unlikely to become pregnant within the following 2 months. Rubella immunization should also be given to males who, as health-care workers, may come into contact with pregnant women.

Because of the danger to the fetus, pregnant patients exposed to, or developing, rubella or a similar rash should have serological investigation. The haemagglutination inhibition (HAI) test for rubella antibodies is rapid and reliable; antibody titre rises within 48 hours of illness or immunization, persists for years, and is useful for differentiating past infection from acute illness. Serum should be obtained within 2 days of the onset of the illness or within 2 weeks of exposure to the virus. If this acute serum is not available, complement fixation tests or assay of rubella-specific IgM antibody is required (Table 21.12).

OTHER VIRAL INFECTIONS

See Appendix 21.9.

MYCOSES (FUNGAL INFECTIONS)

Fungi are widespread and sometimes commensals, but infections may occur where general hygiene is low, where suitable local conditions (humid sites) are present and where people are immunocompromised, such as those with organ transplants or HIV/AIDS.

Fungal infections (Table 21.13) are often diagnosed on clinical grounds, supported by culture. Antifungal drugs can be effective therapy but resistance may arise, especially in long-term use or HIV/AIDS (Appendix 21.10). Most fungal infections have few untoward sequelae in otherwise healthy people but some can cause severe, recurrent, disseminated or persistent lesions in immunocompromised persons (Appendix 21.11).

SUPERFICIAL MYCOSES

The common superficial mycoses are candidosis and tinea.

CANDIDOSIS

Candidosis (candidiasis) is infection with *Candida* species, usually *Candida albicans*. Candidosis can produce a variety of clinical pictures but thrush is the best-known type. Thrush was aptly described in the nineteenth century as a 'disease of the diseased', and candidosis can

Table 21.13 Fungal infections

Fungal infection	Chapter location
Aspergillosis	This chapter
Blastomycosis (North American blastomycosis)	This chapter
Candidosis	This chapter
Coccidioidomycosis	This chapter
Cryptococcosis	This chapter
Histoplasmosis	This chapter
Mucormycosis (zygomycosis)	This chapter
Paracoccidioidomycosis (South American blastomycosis)	This chapter
Pneumocystosis	This chapter
Rhinosporidiosis	This chapter
Sporotrichosis	This chapter
Tinea	This chapter



Fig. 21.14 Candidosis.



Fig. 21.15 Candidosis.

undoubtedly be a reflection of impaired immune responses. This has become particularly evident since HIV/AIDS was first recognized. *Candida* is one of many other fungi that can cause severe, recurrent, disseminated or persistent lesions in immunocompromised persons, such as those with AIDS (Figs 21.14 and 21.15).

Candida species other than *C. albicans* can cause candidosis (Table 21.14), particularly in immunocompromised individuals, and some, especially *C. krusei*, are resistant to conventional antifungal agents. Correction of any underlying local cause, and use of antifungals, is the usual treatment for candidosis. Topical gentian violet is now rarely used as an antifungal. Topical nystatin or an azole such as miconazole or fluconazole are the usual treatments. Nystatin is available as a suspension, miconazole as a gel or gingival muco-adhesive tablet.

Table 21.14 *Candida* species

Most common	Less common
<i>Candida albicans</i>	<i>Candida zeylanoides</i>
<i>Candida tropicalis</i>	<i>Candida viswanathii</i>
<i>Candida glabrata</i>	<i>Candida rugosa</i>
<i>Candida parapsilosis</i>	<i>Candida lambica</i>
<i>Candida krusei</i>	<i>Candida norvegensis</i>
<i>Candida lusitanae</i>	<i>Candida lipolytica</i>
<i>Candida kefyr</i>	<i>Candida famata</i>
<i>Candida guilliermondii</i>	<i>Candida ciferrii</i>
<i>Candida dubliniensis</i>	

Table 21.15 Factors predisposing to mycoses

Predisposing factor	Aetiological agent(s)
Cell-mediated immune defects	<i>Candida</i> spp., <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Coccidioides immitis</i> <i>Paracoccidioides brasiliensis</i> , <i>Blastomyces dermatitidis</i>
Chronic granulomatous disease	<i>Aspergillus</i> spp., <i>Candida albicans</i> , <i>Torulopsis glabrata</i>
Desferrioxamine therapy	Agents of zygomycosis
Intravenous drug abuse	<i>Candida</i> spp., agents of zygomycosis
Ketoacidosis	Agents of zygomycosis
Malnutrition	<i>Candida</i> spp., agents of zygomycosis
Moisture	<i>Trichophyton</i> spp.
Neutropenia	<i>Candida</i> spp., <i>Aspergillus</i> spp., agents of zygomycosis, <i>Pseudallescheria boydii</i> , <i>Trichosporon</i> spp., <i>Fusarium</i> spp.
Traumatized skin	<i>Candida</i> spp., <i>Torulopsis glabrata</i> , <i>Malassezia furfur</i>

Thrush

General aspects and clinical features

Thrush produces a highly characteristic picture of soft, creamy-coloured, slightly raised patches that *can be wiped off the mucosa*, leaving red areas. These lesions may form isolated flecks or large confluent areas. Typical sites are the vagina or mouth.

Thrush is common in the newborn, in whom it does not usually indicate any immunodeficiency and may resolve spontaneously or in response to topical antifungal treatment. In adults, unless they are known to be having immunosuppressive treatment, thrush is rare and should prompt investigation for an underlying cause. Thrush in a young or middle-aged adult must be regarded as a possible sign of HIV infection until proved otherwise. The other main predisposing factors are antibiotic treatment, anaemia, diabetes mellitus or an immunological defect, as shown in Table 21.15.

General management

The diagnosis is usually clinical but can be readily confirmed by taking a Gram-stained smear, which shows long tangled masses of candidal hyphae.

Superficial fungal infections often respond readily to topical treatment but deep-seated infections often require protracted systemic therapy. In addition to treatment of any underlying disorder, localized thrush should be manageable with topical antifungal drugs such as nystatin or amphotericin. Alternatively, a nystatin suspension or systemic fluconazole or suspension may be indicated.

Erythematous candidosis

General aspects and clinical features

Erythematous candidosis appears as mucosal erythema, in the mouth due to coverage of the mucosa with a denture (denture-related stomatitis; denture sore mouth), antibiotic treatment, xerostomia or immunodeficiency. Denture-related stomatitis (denture-associated stomatitis) is a common infection secondary to long-standing occlusion of part of the oral mucosa by a denture. Denture-related stomatitis typically develops beneath a well-fitting upper denture, which effectively cuts off the mucous membrane from the normal oral defence mechanisms. It is not seen under a lower denture, in spite of the fact that the latter is a common cause of trauma. The characteristic feature is uniform bright erythema of the whole of the upper denture-bearing area, limited by the denture margin. Occasionally, the erythema is patchy or there may be flecks of thrush. Symptoms are typically absent but occasionally there is soreness. Angular stomatitis is frequently associated. The vast majority of patients are healthy, as local factors alone determine the pathogenesis. Occasionally, patients may be anaemic but less frequently than might be expected from the fact that angular stomatitis is often regarded as a typical sign of iron deficiency. Other occasional contributory factors are dry mouth, diabetes mellitus or immune defects. It is, however, unjustifiable to screen all patients with denture-related stomatitis but investigation should be considered if the patient has any other complaints suggestive of such disorders or if the infection is particularly severe or intractable. Treatment includes leaving dentures out of the mouth at night and storing them in hypochlorite to clear the fungus from the denture surface. Topical antifungals should also be used, as suggested above, or the fitting surface of the denture can be coated with miconazole.

Antibiotic stomatitis occasionally follows the use of broad-spectrum antibiotics, particularly tetracycline used topically in the mouth. The whole of the oral mucosa is then typically red, oedematous and sore. One or two flecks of thrush may be found in protected situations, such as the posterior upper buccal sulcus. A similar picture of generalized redness and soreness of the oral mucosa is the typical manifestation of candidosis related to xerostomia. As with any other type of candidosis, angular stomatitis may be associated.

Xerostomia may also underlie erythematous candidosis. In HIV infection a patch of erythematous candidosis is sometimes seen on the palate or tongue.

General management

The treatment of erythematous candidosis is to deal with the underlying problem, if feasible, and to give antifungal drugs as described earlier.

Angular stomatitis

General and clinical aspects

Angular stomatitis (angular cheilitis; cheilosis) is most frequently seen as a complication of denture-related stomatitis but can be associated with any type of intraoral candidosis; in addition, it is a 'classic' sign of a deficiency anaemia.

General management

It is important to consider the possibility of underlying systemic disease, and treat it where possible.

Clearance of intraoral candidosis with adequate antifungal treatment typically leads to healing of the lesions at the angles of the mouth without any local treatment, but miconazole cream applied to

the lesion may be useful. Occasionally, bacteriological examination may be necessary, as the cause may be staphylococcal, but imidazoles such as miconazole or clotrimazole also have antibacterial activity and may be effective.

Candidal leukoplakia

General aspects and clinical features

Candidal leukoplakia (chronic hyperplastic candidosis) appears as white plaques clinically indistinguishable from other types of keratotic lesion, though they may be speckled, tough and firmly adherent; they are seen mainly in men of middle age or over, many of whom are heavy smokers. Typical sites are the buccal mucosa just within the commissures, or the dorsum or edges of the tongue. Long-standing angular stomatitis and occasionally also denture-related stomatitis may be associated. Patients are usually otherwise well.

Candidal leukoplakia may account for up to 10% of leukoplakias and several reports of malignant transformation have appeared. However, the prevalence of candidal leukoplakia and its potentialities remain uncertain.

General management

Diagnosis depends on biopsy, showing *C. albicans* hyphae and a characteristic inflammatory reaction in the superficial epithelial plaque. Investigations should include a family history and haematological examination. Investigations for cell-mediated responses to *C. albicans* may be needed to exclude one of the rare mucocutaneous candidosis syndromes that show similar oral lesions, as described below, but in most cases no abnormality is detectable.

Treatment is difficult, since the response to topical antifungal drugs such as nystatin or amphotericin is poor, and excision is also followed by recurrence. Antifungals like miconazole topically or ketoconazole or fluconazole systemically appear to be more effective.

Persistent candidosis

General aspects and clinical features

Persistent candidosis is a well-recognized complication of defective cell-mediated immunity (Box 21.8).

Both thrush and herpetic infection may be present together and produce confluent lesions.

General management

Candidal infection usually responds eventually to antifungal drugs but sometimes immunosuppressive treatment has to be moderated for a time. Patients on long-term corticosteroid treatment for any of the immunologically mediated diseases are also susceptible to oral candidosis but not often as a serious complication.

Box 21.8 Causes of persistent candidosis

- HIV infection
- Primary immunodeficiencies, especially severe combined (Swiss) type or DiGeorge syndrome
- Chronic mucocutaneous candidosis (CMCC)
- Intense immunosuppression, particularly for organ grafts
- Resistant *Candida* species

Chronic mucocutaneous candidosis (CMC or CMCC)

See Chapter 20.

'Chronic candidiasis syndrome'

Many normal persons, around half the population, harbour *C. albicans* as part of their normal microflora. This finding has been exploited as a supposed explanation of such symptoms as headaches, fatigue and lassitude, rashes and gastrointestinal symptoms, but this so-called syndrome has absolutely no scientific basis, and there is no evidence that antifungal treatment is warranted. A controlled trial has shown that it has no effect on the symptoms.

TINEA

General aspects and clinical features

Tinea is a term for a range of common skin infections seen worldwide; they are caused by dermatophytes, usually *Trichophyton* (Table 21.16; Figs 21.16 and 21.17). Dermatophytes, specifically *Trichophyton*, *Epidermophyton* and *Microsporum* species, are responsible for most superficial fungal infections. Fungal transmission occurs through direct contact with infected persons, animals, soil or fomites.

General management

Treatment of tinea is with topical clotrimazole, miconazole or terbinafine, or oral fluconazole, itraconazole or terbinafine.

Dental aspects

Terbinafine may disturb taste. Azoles may enhance the effects of warfarin (Ch. 8).

Table 21.16 Forms of tinea

Tinea	Features	Organisms
Barbae	Beard area	<i>Trichophyton verrucosum</i>
Capitis ('ringworm')	Head; itchy, red areas, leaving bald patches	<i>Trichophyton tonsurans</i> <i>Microsporum andouinii</i> <i>Microsporum canis</i>
Corporis	Red spots growing into large rings on arms, legs or chest	<i>Trichophyton rubrum</i> <i>M. canis</i> <i>T. tonsurans</i> <i>T. verrucosum</i>
Cruris	Itchy erythema in moist, warm areas, e.g. the groin ('jock itch') or beneath the breasts (Fig. 21.16). Second most common tinea	<i>T. rubrum</i> <i>Epidermophyton floccosum</i>
Pedis (athlete's foot)	Most common tinea. Itchy and red moist skin between toes (Fig. 21.17), with a white, wet surface. Infection may spread to the toenails (tinea unguium – from Latin for nail). Toenails become thick and crumbly	<i>T. rubrum</i> <i>Trichophyton mentagrophytes</i> var. <i>interdigitale</i> <i>E. floccosum</i>
Versicolor	Patchy skin discolouration. Areas of infected face, for example, may appear lighter in colour (hypopigmented). Seen primarily in young adults	<i>Malassezia furfur</i>



Fig. 21.16 Tinea cruris.



Fig. 21.17 Tinea pedis.

SYSTEMIC MYCOSES (DEEP MYCOSES)

Healthy individuals in endemic areas (often in the developing world) are often infected with fungi, typically involving the lungs but often asymptomatic. In otherwise healthy persons, even acute pulmonary and primary mucocutaneous symptomatic mycotic lesions may resolve spontaneously. Chronic pulmonary infections tend to progress and disseminated infections can be fatal. Immunocompromised persons are at particular risk from clinical disease. Equally, clinical infection with mycoses may be an indication of an underlying immune defect. Severe, recurrent, disseminated or persistent lesions appear in immunocompromised persons, particularly those with HIV/AIDS, organ transplants, leukaemia, leukopenia, solid tumours or burns, and in premature infants.

The proliferation of mycoses in immunocompromised persons includes 'new' opportunists such as new *Candida* species, *Torulopsis glabrata*, *Fusarium* and *Trichosporon beigeli*.

Orofacial lesions caused by the main systemic mycoses may occasionally be seen in isolation but they are typically associated with lesions elsewhere, often in the respiratory tract. The diagnosis may be suggested by a tumour-like nodule or mass, chronic oral ulceration, chronic sinus infection or bizarre mouth lesions, especially in immunocompromised patients or in those who have been in endemic areas, or where there is granuloma formation found on biopsy. Investigations

include smear, biopsy, culture, sometimes serology, physical examination and chest radiography. Tissue forms of the fungus may be visible but special stains are often required.

Patients should be managed in consultation with a physician with appropriate expertise, usually with systemic antimycotics. Most systemic mycoses can be treated with systemic amphotericin given orally, liposomally or slowly intravenously, or with azoles. Adverse effects from intravenous amphotericin include thrombophlebitis, nephrotoxicity, chills, nausea, anaemia and hypokalaemia. The azoles are less toxic but the cost is prohibitive where they are most needed – in the developing world. Given orally, the adverse effects of ketoconazole include nausea, gynaecomastia and liver damage. The main adverse effects of miconazole include thrombophlebitis and ventricular tachycardia. Fluconazole and itraconazole are therefore now being used but fluconazole resistance can be a significant problem.

SYSTEMIC CANDIDOSIS

Candidosis is typically a superficial mycosis but, nevertheless, increasingly often causes invasion of deep organs, particularly in immunocompromised persons. Many *Candida* species are now responsible; some are resistant to fluconazole but voriconazole or caspofungin may be effective.

PNEUMOCYSTIS JIROVECI (CARINII)

General aspects and clinical features

Pneumocystis jiroveci (*carinii*) is now recognized to be a fungus rather than a protozoan. Some of the first patients recognized in the HIV epidemic were revealed because of *Pneumocystis* pneumonia (PCP); it is a common infection in AIDS and other severely immunocompromised patients.

General management

Treatment is with co-trimoxazole, inhaled pentamidine isetionate or atovaquone.

ASPERGILLOSIS

General aspects and clinical features

Aspergillus species are the most common environmental fungi and are prolific saprophytes in soil and decaying vegetation.

Aspergillosis is found worldwide; it is increasing in frequency and is the most prevalent mycosis after candidosis. Inhalation of *Aspergillus* spores and colonization of the respiratory tract are common but disease is rare. Types of aspergillosis include the following:

- *Allergic bronchopulmonary aspergillosis* – the most common disease
- *Invasive aspergillosis* – a rare lung infection that may spread to brain, bone or endocardium. Invasive sinus aspergillosis affects mainly immunocompromised hosts, though it is also seen in some apparently healthy individuals in subtropical countries, such as Sudan, Saudi Arabia or India
- *Aspergillus fumigatus* – the usual cause of invasive sinus aspergillosis, although *A. flavus* appears to predominate in immunocompromised patients. There is destruction of the antral wall and often antral pain, swelling or sequelae from orbital invasion (impaired ocular motility, exophthalmos or impaired vision) or intracranial extension (headaches, meningism)

- *Aspergillomas* – fungus balls that grow in pre-existing cavities, such as tuberculous lung cavities. Aspergilloma of the maxillary antrum is uncommon, typically appearing in a healthy host as a hyphal ball in a chronically obstructed sinus
- *Chronic sinus aspergillosis* – an uncommon cause of a diffusely radio-opaque antrum, sometimes with dense punctate radio-opacities. It is unresponsive to treatment used for bacterial sinusitis. Occasional cases of sinus aspergillosis are a result of metastasis from pulmonary aspergillosis or are iatrogenic, following dental procedures such as extractions
- *Allergic fungal sinusitis* – an uncommon problem, usually due to fungi other than *Aspergillus*.

General management

Diagnosis of antral aspergillosis is supported by MRI and CT (which are more sensitive than conventional radiography in detecting bone erosion) and confirmed by smear and lesional microscopy, staining with periodic acid–Schiff (PAS) or Gomori methenamine silver. Immunostains may help definitive diagnosis.

Prolonged conservative therapy may worsen the prognosis. Topical ketoconazole or clotrimazole may clear superficial infections. If there is no resolution in 72 hours, a course of systemic amphotericin should be tried. Miconazole is not active and ketoconazole is not particularly active against *Aspergillus*, but itraconazole may have a place in treatment. Fluconazole is under trial.

Non-invasive antral forms usually need treatment by antral debridement and drainage. Corticosteroids may also be indicated in allergic sinusitis.

Invasive aspergillosis should be treated by surgical debridement supplemented with amphotericin and, possibly, hyperbaric oxygen.

BLASTOMYCOSES

General aspects and clinical features

Blastomyces dermatitidis causes North American blastomycosis, seen predominantly in the USA and Canada. *Paracoccidioides brasiliensis* causes the South American form, seen especially in Brazil. Inhalation of spores, found in soil, leads to subclinical infection in up to 90% of the population in endemic areas. Outdoor workers are particularly affected.

Clinical illness is typically pulmonary. HIV infection and other immunocompromising states predispose to pulmonary and disseminated disease.

General management

Diagnosis is based on biopsy, smear or culture. Amphotericin, ketoconazole, miconazole, itraconazole and voriconazole can be effective.

COCCIDIOIDOMYCOSIS

General aspects and clinical features

Coccidioidomycosis is seen mainly in hot dry areas of the south-west USA, Mexico, Central America and parts of South America. Inhalation of spores of *Coccidioides immitis*, found in soil, produces subclinical infection in up to 90% of the population. Clinical illness is typically acute pulmonary disease and fever (San Joaquin valley fever). Chronic pulmonary disease is less common but pregnant women, blacks, Filipinos, Mexicans and immunocompromised persons are susceptible.

General management

Diagnosis is mainly by history and examination, supported by histology and the spherulin or coccidioidin skin tests. Management is with systemic amphotericin, sometimes supplemented with ketoconazole, itraconazole, fluconazole or voriconazole.

CRYPTOCOCCOSIS

General aspects and clinical features

Cryptococcosis is seen worldwide. Aspiration of spores of *Cryptococcus neoformans*, a yeast found especially in pigeon faeces and soil, may lead to infection. In healthy persons, infection is typically pulmonary and subclinical. Immunocompromised persons are liable to dissemination of infection to meninges, heart, spleen, pancreas, adrenals, ovaries, muscles, bones, liver and gastrointestinal tract. Most patients with disseminated cryptococcosis have meningoencephalitis and, untreated, this is fatal in over 70%.

Cryptococcosis is the most common systemic mycosis in AIDS.

General management

Diagnosis is confirmed by microscopy, culture and assay of serum or cerebrospinal fluid for capsular antigen and antibody. Systemic amphotericin is effective, best supplemented with flucytosine. Ketoconazole and itraconazole may be effective.

HISTOPLASMOSIS

General aspects and clinical features

Histoplasmosis is found worldwide and is the most frequent systemic mycosis in the USA. *Histoplasma capsulatum* is present especially in bird and bat faeces and is a soil saprophyte found particularly in the Ohio and Mississippi valleys, Latin America, India, the Far East and Australia. In endemic areas, over 70% of adults are infected, typically subclinically, by inhaling spores. Clinical histoplasmosis includes acute and chronic pulmonary and cutaneous forms. Disseminated and potentially fatal histoplasmosis, which can affect the reticuloendothelial system, lungs, kidneys and gastrointestinal tract, is rare and seen typically in immunocompromised patients, especially in HIV/AIDS.

General management

Diagnosis is confirmed by microscopy, culture and serotests. Amphotericin is the first line for treatment, followed by ketoconazole, fluconazole, itraconazole or voriconazole.

MUCORMYCOSIS (ZYGOMYCOSIS; PHYCOMYCOSIS)

General aspects and clinical features

Mucorales are responsible for most mucormycosis. *Mucor*, *Rhizopus* and many other species of the class Zygomycetes can be responsible and therefore the condition is probably better termed zygomycosis. These fungi are ubiquitous worldwide in soil, manure and decaying organic matter, and can commonly be cultured from the nose, throat, mouth and faeces of healthy individuals.

Immunocompromising conditions underlie most zygomycosis; diabetes mellitus and leukaemia are the most important underlying causes but

cases are now appearing in HIV/AIDS and malnutrition. Rhinocerebral and pulmonary zygomycoses are the most common forms.

Rhinocerebral zygomycosis is usually caused by *Rhizopus oryzae*; it typically starts in the nasal cavity or paranasal sinuses with pain and nasal discharge, accompanied by fever, and may then invade the palate, orbit or skull. Orbital invasion may cause orbital cellulitis, impaired ocular movements, proptosis and ptosis. Intracranial invasion follows penetration of ophthalmic vessels or the cribriform plate.

General management

Zygomycosis used to be almost uniformly fatal and still has a mortality approaching 20%. Radiography or MRI typically shows thickening of the antral mucosa with patchy destruction of the walls, and may define the extent of the lesion.

Diagnosis is confirmed by smears and histological demonstration of tissue invasion by hyphae. Control of underlying disease is essential, if at all possible, together with systemic amphotericin and surgical debridement.

RHINOSPORIDIOSIS

Rhinosporidium seeberi can infect the nasal and other mucosae. It is particularly common in India and Sri Lanka, but also found in Latin America, Africa and South-East Asia. Mouth lesions are usually proliferative lumps on the palate. Diagnosis is by biopsy. Surgery is required for treatment.

SPOROTRICHOSIS

Sporothrix schenckii is found throughout the world, mainly as a saprophyte on plants and shrubs. Disease is seen almost exclusively in visitors to tropical and subtropical countries. Infection follows an injury to the epithelium resulting in a primary lesion – a sporotrichotic chancre. Lesions may then spread by the lymphatics. Pulmonary and disseminated sporotrichoses are rare and of uncertain origin.

Diagnosis is confirmed by histology and culture. Potassium iodide is effective treatment for superficial sporotrichosis, itraconazole or amphotericin for other forms.

CRYPTOSPORIDIOSIS ('CRYPTO')

Cryptosporidiosis is a diarrhoeal disease spread in animal and human faeces; it is one of the most frequent causes of water-borne disease among humans and can be spread by drinking and recreational water. *Cryptosporidium* is a parasite found throughout the world in soil, food, water or surfaces that have been contaminated with faeces from infected humans or animals. *Cryptosporidium* survives outside the body for long periods of time, and is resistant to chlorine disinfection. It is not spread by contact with blood but exposure to human faeces through sexual contact may transmit infection. People who are most likely to become infected with *Cryptosporidium* include:

- children who attend day-care centres
- child-care workers
- people who take care of others with cryptosporidiosis
- international travellers
- backpackers, hikers and campers who drink unfiltered, untreated water

- people who drink from untreated shallow, unprotected wells
- people, including swimmers, who swallow water from contaminated sources
- people who handle infected cattle
- people exposed to human faeces through sexual contact.

Although cryptosporidiosis can infect anyone, young children, pregnant women and the immunocompromised are likely to develop more serious illness.

Clinical features

The incubation period is 2–10 days (average 7 days). Some people with cryptosporidiosis have no symptoms but the most common symptom is watery diarrhoea. Other features include:

- abdominal pain
- nausea
- vomiting
- dehydration
- fever
- weight loss.

General management

Treatment for cryptosporidiosis is nitazoxanide.

INFESTATIONS

Parasitic infestations are endemic in the tropics and developing world, and are seen increasingly frequently in developed countries, in travellers or immigrants; infection is usually acquired from animals (zoonotic parasites), water or improperly prepared food. Common parasitic infestations include fleas, lice, mites and ticks, all transmitted between humans, particularly in conditions of poor hygiene and close-living and in war areas; sometimes disease can be fatal. Serious parasitic infections are shown in [Box 21.9](#) and [Appendix 21.12](#).

Since the appearance of the HIV/AIDS pandemic, parasitic infestations, especially toxoplasmosis and leishmaniasis, are now being recognized in HIV-infected patients.

Many parasitic infestations can be prevented by avoidance of insect bites (avoiding areas of high prevalence, maintaining good hand and food hygiene, and using protective clothing and insect repellents), especially at high-risk times (dusk is the worst time for many mosquitoes, though dengue is transmitted by mosquitoes that bite during the day). Many parasitic infestations are difficult to diagnose unless there is a high index of suspicion. Clinicians and pathologists should therefore

Box 21.9 Main parasitic infestations

- Amoebiasis – common in the developing world; causes gastrointestinal disease
- Giardiasis – common worldwide; causes gastrointestinal disease
- Leishmaniasis – common in the tropics and around the Mediterranean; may cause skin lesions
- Malaria – one of the more serious infestations worldwide; common in the tropics, where anopheline mosquitoes survive; causes haemolysis
- Toxoplasmosis – one of the more serious infestations worldwide; endemic in the developing world, relatively common in the developed world; causes eye and CNS disease
- Worms, fleas, lice, ticks, mites and maggots (Ch. 33)

be vigilant, especially when examining lesions in travellers or immigrants. Treatments include a range of medications, and patients should be managed in consultation with a specialist physician.

AMOEBIASIS

General aspects and clinical features

Entamoeba histolytica can cause amoebic dysentery or amoebic liver abscesses.

General management

Metronidazole is used. Diloxanide furoate clears cysts from symptomless patients.

GIARDIASIS

General aspects and clinical features

Giardia lamblia is a protozoon, cysts of which may be found in unfiltered drinking and recreational waters contaminated by faeces of humans or animals in many parts of the world. Features include anorexia, chronic diarrhoea, abdominal cramps, bloating, frequent loose greasy stools, fatigue and weight loss.

General management

Treatment is with metronidazole, tinidazole or mepacrine.

LEISHMANIASIS

General aspects and clinical features

A blood-sucking sandfly is the intermediate host; humans or other vertebrates, including dogs and cats, are the definitive hosts. The developmental stage is the amastigote in the vertebrate host and promastigote in the arthropod host. After inoculation into the skin, leishmanias multiply within histiocytes. Leishmaniasis is one of the most common HIV/AIDS-associated opportunistic infections in Spain. Human *Leishmania* species, although similar in morphology and life cycle to one another, produce different types of infection.

Mucocutaneous leishmaniasis usually has an incubation period of 2–8 weeks but it can be as long as 3 years. An itching papule at the site of the sandfly bite (usually on the face) becomes surrounded by gradually spreading erythema and induration. In a few days, the surface crusts, then breaks down to form a slowly extending ulcer that discharges fluid. Healing usually begins in 3–12 months, leaving a scar. Secondary lesions develop at the mucocutaneous junctions many years after the primary infection and are destructive. The nose is the site of predilection.

Visceral leishmaniasis causes fever, splenomegaly, anaemia, wasting, cough and diarrhea, and is potentially fatal.

General management

Clinical and serological tests are useful diagnostically but the demonstration of the parasite in biopsies or smears is definitive. A leishmanin skin test is also available. Mucocutaneous leishmaniasis may heal spontaneously but, since there can be extensive destruction of tissue, chemotherapy is indicated.

Pentavalent antimony as sodium stibogluconate or meglumine antimonate is usually effective. Alternatives are amphotericin or pentamidine isetionate. Miltefosine is the only available oral treatment for visceral, cutaneous, and mucosal leishmaniasis.

MALARIA

General aspects and clinical features

Malaria is the most serious and common parasitic infection worldwide; it still infects over 100 million persons, mainly in tropical areas of Africa, Latin America and Asia. It is transmitted by mosquito bites and is potentially fatal.

There are four main species of the protozoon, usually *Plasmodium falciparum* or *P. vivax*, sometimes *P. ovale* or *P. malariae*. In highly endemic areas, the patient may become infected with one, two or even more species of the malarial parasite. In India, 4–8% of cases are due to mixed infection. The plasmodium infects erythrocytes and damages them, causing haemolysis, as well as fever, myalgia, headaches and, in some cases, cerebral involvement. Infection with *P. falciparum* is the most dangerous (Table 21.17) and often fatal (malignant malaria) due to haemolysis and sludging in intracerebral vessels. Infection with *P. vivax*, *P. ovale* or *P. malariae* is usually benign.

Typical features of malaria are incapacitating episodes of hyperrexia, rigors and chills, sometimes recurring for years.

Table 21.17 Malaria

<i>Plasmodium</i>	Comments	Chloroquine resistance
<i>falciparum</i>	Widespread. Results in the most severe infections and responsible for nearly all malaria-related deaths. 'Severe' and 'complicated' are the terms used more frequently than 'malignant' to describe this type of malaria	Chloroquine-resistant strains found in South America, Central America east of the Panama Canal, the Western Pacific, East Asia and sub-Saharan Africa. Resistance to combination of pyrimethamine and sulfadoxine in South-East Asia, Amazon Basin and sub-Saharan Africa. Variable degrees of resistance to quinine and quinidine in South-East Asia and Oceania, and in sub-Saharan Africa
<i>malariae</i>	Restricted distribution in India and responsible for less than 1% of infections	No chloroquine resistance
<i>ovale</i>	A rare parasite of humans; mostly confined to tropical Africa	No chloroquine resistance
<i>vivax</i>	The widest geographical distribution throughout the world. Causes much debilitating but relatively mild disease, which is seldom fatal. Also called benign or uncomplicated malaria	High levels of chloroquine resistance in Indonesia and Papua New Guinea, also Solomon Islands, Myanmar, Brazil, Colombia. Resistance to pyrimethamine and sulfadoxine, particularly in South-East Asia

General management

Diagnosis is made from the history of travel to a malarial area and from clinical features, confirmed by demonstrating the parasite in a blood smear. Repeated smears may be required.

Treatment of *P. malariae* disease is usually chloroquine; that of *P. ovale* and *P. vivax* malaria is usually chloroquine followed by primaquine; and that of *P. falciparum* infections (which are often drug-resistant, particularly in Asia and Latin America) is currently with quinine, mefloquine or artesunate or artemether or artemether with lumefantrine.

Prophylaxis

Specialist advice should always be sought before travel to the tropics. Disease is transmitted by the bite of an infected mosquito, and clothing, insect repellents and nets reduce the risk. Prophylactic chemotherapy does not guarantee total protection but may be life-saving. It may be with chloroquine and/or proguanil, but mefloquine or doxycycline or proguanil plus atovaquone is recommended where the malaria risk is high and chloroquine resistance likely; it should commence well before entering the malarial area and continue for 6 weeks after leaving.

TOXOPLASMOSIS

General aspects and clinical features

Toxoplasma gondii is a common intestinal parasite of many animals, particularly cats. Infection is contracted mainly from the ingestion of cysts, either from animal faeces or in inadequately cooked food (up to 10% of lamb and pork contains cysts). *Toxoplasma* may also be transmitted occasionally in infected blood or blood products.

T. gondii may cause a glandular fever-type of illness with fever and cervical lymphadenopathy, sometimes with rash, hepatosplenomegaly, myalgia and other minor features. Some patients may develop chorioretinitis, which threatens sight, severe pneumonia, necrotizing encephalitis or myocarditis, but such untoward sequelae are seen mainly if the patient is immunocompromised. Central nervous system (CNS) involvement is common, and can cause changes in mental status, headache, neurological defects and epilepsy. CT or MRI scans may demonstrate the lesions.

Toxoplasmosis in pregnancy may lead to chorioretinitis, or transplacental spread and fetal infection, with resultant congenital defects and blindness (TORCH syndrome; Fig. 21.18).



Fig. 21.18 Congenital toxoplasmosis causing learning impairment with visual and hearing defects.

General management

Toxoplasmosis is confirmed serologically by the Sabin–Feldman dye test, enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test or indirect haemagglutination test. The organism may be demonstrable in tissue sections or smears. Treatment is *not* usually required for asymptomatic healthy infected persons who are not pregnant. For immunocompromised patients with toxoplasmosis, treatment is a combination of pyrimethamine and sulfadiazine, together with folic acid (pyrimethamine is a folate antagonist), continued for at least 1 month after clinical resolution. Weekly full blood counts are essential.

For pregnant patients with toxoplasmosis, sulfadiazine alone is used since pyrimethamine may be teratogenic. Clindamycin, clarithromycin and azithromycin are alternatives.

WORMS

A range of helminths can occasionally infect humans (Table 21.18).

CYSTICERCOSIS

Cysticercus cellulosae (encysted larva of *Taenia solium*) can cause cysticercosis, which prevails in regions of poverty and where hygiene is insufficient, particularly Africa, the Far East, India, Latin America, Eastern Europe and the Iberian peninsula. It is rare in Jews and Muslims since they avoid pork.

General aspects and clinical features

The adult *T. solium* lives in the intestine of humans, the only definitive host. The stools release eggs, which, if they contaminate the ground,

Table 21.18 Worms (helminths)

Usual helminth	Geographical distribution	Therapy
Cestodes		
<i>Cysticercus cellulosae</i> (<i>Taenia solium</i> larvae)	Worldwide	Niclosamide Praziquantel
<i>Echinococcus granulosus</i>	Middle East, North and East Africa, Asia, Latin America, Australasia	Albendazole
Nematodes		
<i>Ancylostoma duodenale</i>	Mediterranean littoral, Middle East, China, India, South America	Mebendazole
<i>Ascaris lumbricoides</i>	Worldwide	Mebendazole Levamisole
<i>Filariae</i>	South-East Asia, India, East Africa, South America	Diethylcarbamazine Ivermectin
<i>Gnathostoma spinigerum</i>	South-East Asia	Albendazole Ivermectin
<i>Gongylonema pulchrum</i>	Former USSR, China, Sri Lanka	Albendazole
<i>Onchocerca volvulus</i>	Africa, Central America	Ivermectin Diethylcarbamazine
<i>Schistosoma mansonii</i> , <i>S. haematobium</i> or <i>S. japonicum</i>	Middle and Far East, Latin America, sub-Saharan Africa	Praziquantel
<i>Trichinella spiralis</i>	Worldwide	Mebendazole
<i>Trichuris trichiura</i>	South-East Asia	Mebendazole

can be swallowed by pigs. The eggs hatch in the pig's intestine, releasing oncospheres that enter the bloodstream and become encysted as cysticerci in muscle. Pork is then the intermediate host. The life cycle is completed when humans ingest inadequately cooked pork containing cysticerci (measly pork), which, upon reaching the human intestine, release the oncospheres. Oncospheres also penetrate the gut mucosa and are distributed to various tissues and organs, particularly muscles; here they develop into cysticerci, most commonly in the brain and eye, striated muscles in the tongue, neck and trunk, and skin and subcutaneous tissues.

General management

Prevention relies on thorough cooking of pork meat and good hygiene.

Diagnosis usually relies upon identification of the parasite. The appearance of the translucent membrane, with its central milky spot, is characteristic.

Praziquantel plus prednisolone (prednisone), or albendazole, or niclosamide can be curative. Single or even multiple parasites may be excised from tissues and organs.

ECHINOCOCCOSIS (ECHINOCOCCIASIS)

Echinococcosis (hydatid disease) is caused most often by larvae (cestodes) of the tapeworm *Echinococcus granulosus*. Echinococcosis has been a serious problem in many sheep-raising regions, most prevalently in Australia, New Zealand, South, East and North Africa, Mediterranean countries and parts of the Russian Federation, Middle East and Americas.

General aspects and clinical features

The adult tapeworm *E. granulosus* lives in the small intestine of sheep mainly, though many mammals can serve as intermediate hosts. The eggs hatch in the sheep's intestine, releasing oncospheres that penetrate the intestinal mucosa, enter the bloodstream and develop into hydatid cysts in various organs, particularly the liver and the lungs. Daughter cysts pass in the faeces. Dogs and wolves are infected by eating the discarded offal of sheep and deposit eggs in their faeces. Humans are an accidental intermediate host, usually infected by ingestion of eggs from the faeces of dogs, typically from improper hand-washing and, less often, by ingestion of contaminated water or food such as lamb or mutton containing cysts or eggs. The incubation is from 10 to 30 years. Only the larval stage, the hydatid cyst, develops in humans and there are no specific clinical signs until a cyst becomes large enough to act as a space-occupying lesion, causing compression of adjacent structures. Typically, the liver and sometimes the lungs, bone or brain are affected.

General management

A skin test (Casoni test) is available but not specific. Serology may be helpful. Eosinophilia is merely suggestive of a parasitic disease and not specific. The hydatid cyst can sometimes be demonstrated radiographically or by MRI or ultrasound, but a definitive diagnosis is often made only by identifying it at operation.

Prevention relies on protecting definitive hosts (dogs), as well as intermediate hosts (sheep), from contamination. Thorough hand-washing, washing of vegetables and wild berries located close to the ground, and elimination of contact with potentially contaminated dogs are the best measures. High doses of albendazole, mebendazole or flubendazole interfere with larval growth but are not curative. Only surgery is curative.

FILARIASIS

General aspects and clinical features

Filariae are helminths transmitted by the bite of blood-sucking insects, usually mosquitoes or black flies, whose adult and larval forms are found in humans. The main filariasis is onchocerciasis, seen mainly in tropical Africa but also in Saudi Arabia, Yemen and Latin America. It may involve the face, and eye lesions remain a major problem in Africa (river blindness). The diagnosis is made by identifying the worm in biopsies. Treatment is with ivermectin.

Lymphatic filariasis is infestation, particularly by *Wuchereria bancrofti* or *Brugia malayi*, transmitted by blood-sucking mosquitoes and most common in India, South-East Asia, the South Pacific, Latin America, East Africa and Egypt. The lymphatics are affected, causing obstructive oedema or elephantiasis. Diagnosis is from blood examination for filariae. Diethylcarbamazine is the treatment of choice.

GNATHOSTOMIASIS

Gnathostomiasis is a rare benign infestation, seen mainly in South and South-East Asia; it is caused by larvae of the nematode *Gnathostoma spinigerum*, harboured in chicken, snails or fish. The worm may cause swellings in the skin or mouth, or occasionally bleeding. Skin tests and serology help the diagnosis. Metronidazole, albendazole or ivermectin may be of some benefit or the worm can be excised.

LARVA MIGRANS

General aspects and clinical features

Adult hookworms live mainly in animal intestines and release ova into the faeces, which are then found in sand or soil contaminated by the animals. The ova hatch into infective larvae, which can infect human skin; here they fail to develop fully but may wander in the tissues, causing 'larva migrans'. Larva migrans is common in tropical climates, along the US coast from southern New Jersey to Florida, around the Caribbean and around the Mediterranean. It is seen especially in those working or playing in warm, moist, shaded sandy places.

There are two types of larva migrans:

- *Visceral larva migrans* is synonymous with toxocariasis – infection by larvae from roundworms of dogs, cats or wild carnivores
- *Cutaneous larva migrans* (creeping eruption) is caused by hookworms of dogs, cats and other mammals and characterized by itching serpiginous tracks, mainly on the feet, hands or buttocks.

Larva migrans is self-limiting but nearly 50% of patients can develop transient migratory pulmonary infiltrates with eosinophilia (Loeffler syndrome).

General management

Larva migrans can be prevented by stopping dogs, cats and other animals contaminating play areas. Treatments include thiabendazole, albendazole, ivermectin or mebendazole. Local application of 10% thiabendazole, ethyl chloride, chloroform, electrocoagulation and cryotherapy have been tried for cutaneous lesions.

THREADWORMS

General aspects and clinical features

Threadworms (*Enterobius vermicularis*; pinworms) are common infestations worldwide. The ova are swallowed and worms develop when

exposed to digestive juices of the upper gastrointestinal tract. Female worms lay ova on the anal skin, which cause intense peri-anal itching.

General management

Treatment must involve the whole family and includes mebendazole (or piperazine) and improved hygiene.

TRICHINOSIS

General aspects

Trichinosis is the most frequent roundworm infestation to affect muscles.

Trichinella spiralis is a nematode acquired through the ingestion of contaminated meat, usually pork products. Trichinosis is more prevalent in Central Europe and North America, where pork is widely consumed, than in Islamic or Jewish cultures or tropical countries. Both larval and adult forms of *T. spiralis* can parasitize humans as the definitive host but later they become the intermediate host when the larvae are established in the muscles. The same host sustains the adult worm temporarily, but the larvae for a long period of time. After ingestion of infected meat, the larvae mature to adult forms in the intestine in approximately 1 week. Adult female nematodes then deposit larvae in the gastrointestinal mucosa. The larvae penetrate and subsequently enter the bloodstream and pass to muscles such as the tongue, masseter, gastrocnemius, deltoid and diaphragm, where they grow and develop, and become encapsulated. Many infestations are subclinical but they can calcify and appear as radio-opaque nodules.

Clinical features

In mild infections, symptoms are often vague and transient. Acute trichinosis is characterized by myalgia, facial and palpebral oedema, and fever with eosinophilia. Myocarditis is present in up to 20% and there may be involvement of lungs, kidneys, pancreas and CNS.

General management

The diagnosis is clinical, supported by a history of ingestion of poorly cooked meat and by investigations. There is eosinophilic leukocytosis, serodiagnosis is feasible after the third week, and serum levels of muscle enzymes (such as creatine phosphokinase) are also raised. However, definitive diagnosis relies on biopsies from affected muscle or blind biopsies from the deltoid or gastrocnemius muscles.

Treatment is mebendazole or thiabendazole. Prevention requires meat to be cooked throughout at a temperature above 65°C.

TRICHURIASIS

General aspects and clinical features

Trichuriasis, infestation of the large intestine by the whipworm *Trichuris trichiura*, is common in the Caribbean and South-East Asia, especially in children, who contract the condition by ingesting eggs from contaminated soil.

General management

Trichuriasis is diagnosed by faecal examination for the worms. Treatment is mebendazole or albendazole.

MITES

General aspects and clinical features

Scabies is a common infestation with the mite *Sarcoptes scabiei*, which is transmitted by close contact, particularly in bed. The mite burrows into the superficial skin and lays eggs, which excite an inflammatory response and an itchy rash, typically interdigitally and on the wrists.

General management

Patient and family/partners need improved hygiene and treatment with malathion or permethrin.

MAGGOTS

General aspects and clinical features

Myiasis is the condition when fly maggots invade living tissue, most commonly the nose, or when they are harboured in the intestine or any part of the body and feed on the host's organs. Human myiasis is most common in the tropics.

Various flies can cause human myiasis; most troublesome in the New World is *Cochliomyia hominivorax* (screwworm). *Chrysomya bez-ziana* is seen in Africa, Asia, the Pacific Islands and the Old World.

Larvae burrow through tissue and may produce a type of larva migrans creeping eruption (see earlier); when they mature, they migrate out of the host in an effort to reach soil to pupate, and may then be visible.

General management

A few drops of turpentine or 15% chloroform in light vegetable oil should be instilled in the lesion and larvae should be removed with blunt tweezers.

PRION INFECTIONS

See Chapter 13.

KEY WEBSITES

(Accessed 29 May 2013)
Centers for Disease Control and Prevention. <<http://www.cdc.gov/parasites/bedbugs/>>.
National Center for Infectious Diseases. <<http://www.cdc.gov/ncidod/diseases/eid/index.htm>>.
National Institutes of Health: National Center for Biotechnology Information. <<http://www.ncbi.nlm.nih.gov/books/NBK20370/>>.
NHS Choices. <<http://www.nhs.uk/conditions/Head-lice/Pages/Introduction.aspx>>.
NHS Direct. <<http://www.nhsdirect.nhs.uk/FemaleSexualHealthSelfCare/Worms>>.

USEFUL WEBSITES

(Accessed 29 May 2013)
Centers for Disease Control and Prevention. <<http://www.cdc.gov/Diseasesconditions/>>.
Department of Health's consultation draft of HTM 01-05 on Decontamination in primary care dental facilities. <<https://www.gov.uk/government/publications/decontamination-in-primary-care-dental-practices>>.
fitfortravel. <<http://www.fitfortravel.nhs.uk/home.aspx>>.
Medline Plus. <<http://www.nlm.nih.gov/medlineplus/>>.
Merck Manual Home Health Handbook for Patients & Caregivers. <<http://www.merckmanuals.com/home/index.html>>.

FURTHER READING

- Almeida, O.D.P., et al. 2003. Paracoccidioidomycosis of the mouth: an emerging deep mycosis. *Crit. Rev. Oral Biol. Med.* 14, 377.
- Barskey A.E., Juieng P., Whitaker B.L., Erdman D.D., Oberste M.S., Chern S.W., et al. Viruses detected among sporadic cases of parotitis, United States, 2009–2011. *J. Infect. Dis.* 2013;208(12):1979–1986. 10.1093/infdis/jit408. Epub 2013 Aug 9. PubMed PMID: 23935203.
- Bedi, R., Scully, C., 2009. Tropical oral health. In: Cook, G.C., Zumla, A. (Eds.), *Manson's tropical diseases* (22nd ed.). WB Saunders/Elsevier, Edinburgh, pp. 499.
- Berman, J., 2003. Current treatment approaches to leishmaniasis. *Curr. Opin. Infect. Dis.* 16, 397.
- Beyari, M.M., et al. 2003. Multiple human herpesvirus-8 infection. *J. Infect. Dis.* 188, 678.
- Bez, C., et al. 2000. Genoprevalence of TT virus among clinical and auxiliary UK dental health care workers: a pilot study. *Br. Dent. J.* 189, 554.
- Boyanova, L., et al. 2006. Anaerobic bacteria in 118 patients with deep-space head and neck infections from the University Hospital of Maxillofacial Surgery, Sofia, Bulgaria. *J. Med. Microbiol.* 55, 1759.
- Centers for Disease Control and Prevention, 2003. Guidelines for infection control in dental health care settings. *MMWR* 52, 10.
- Cleveland, J.L., Cardo, D.M., 2003. Occupational exposures to human immunodeficiency virus, hepatitis B virus, and hepatitis C virus: risk, prevention and management. *Dent. Clin. N. Am.* 47, 681.
- Cousin, G.C., 2002. Potentially fatal oro-facial infections: five cautionary tales. *J. R. Coll. Surg. Edinb.* 47, 585.
- Cruse, P.J., 1970. Surgical wound sepsis. *Can. Med. Assoc. J.* 102, 251.
- Cruse, P.J., Foord, R., 1980. The epidemiology of wound infection: a 10-year prospective study of 62,939 wounds. *Surg. Clin. North Am.* 60, 27.
- Dawson, M.P., Smith, A.J., 2006. Superbugs and the dentist: an update. *Dent. Update* 33, 198.
- Epstein, J.B., et al. 2003. Oral candidiasis in hematopoietic cell transplantation patients: an outcome-based analysis. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 96, 154.
- Fishbain, J., Peleg, A.Y., 2010. Treatment of *Acinetobacter* infections. *Clin. Infect. Dis.* 51 (1), 79.
- Garcia-Pola, M.J., et al. 2002. Submaxillary adenopathy as sole manifestation of toxoplasmosis: case report and literature review. *J. Otolaryngol.* 31, 122.
- Groll, A.H., 2002. Itraconazole – perspectives for the management of invasive aspergillosis. *Mycoses* 45 (Suppl. 3), 48.
- Gupta, A.K., Tomas, E., 2003. New antifungal agents. *Dermatol. Clin.* 21, 565.
- Hay, R.J., 2003. Antifungal drugs used for systemic mycoses. *Dermatol. Clin.* 21, 577.
- Hegarty, A.M., et al. 2008. Oral health care for HIV-infected patients: an international perspective. *Expert Opin. Pharmacother.* 9, 387.
- Hodgson, T.A., Rachanis, C.C., 2002. Oral fungal and bacterial infections in HIV-infected individuals: an overview in Africa. *Oral Dis.* 8 (Suppl. 2), 80.
- Holmstrup, P., et al. 2003. Oral infections and systemic diseases. *Dent. Clin. North Am.* 47, 575.
- Karlsmark T., Goodman J.J., Drouault Y., Lufrano L., Pledger G.W. Cold Sore Study Group; Randomized clinical study comparing Compeed cold sore patch to acyclovir cream 5% in the treatment of herpes simplex labialis. *J. Eur. Acad. Dermatol. Venereol.* 2008;22(10):1184–1192.
- Knouse, M.C., et al. 2002. *Pseudomonas aeruginosa* causing a right carotid artery mycotic aneurysm after a dental extraction procedure. *Mayo Clin. Proc.* 77, 1125.
- Martin, S., 2001. Congenital toxoplasmosis. *Neonatal. Netw.* 20, 23.
- Martins, M.D., et al. 2007. Orofacial lesions in treated southeast Brazilian leprosy patients: a cross-sectional study. *Oral Dis.* 13, 270.
- Milian, M.A., et al. 2002. Oral leishmaniasis in an HIV-positive patient: report of a case involving the palate. *Oral Dis.* 8, 59.
- Moraru, R.A., Grossman, M.E., 2000. Palatal necrosis in an AIDS patient: a case of mucormycosis. *Cutis* 66, 15.
- Motta, A.C.F., et al. 2007. Oral leishmaniasis: a clinicopathological study of 11 cases. *Oral Dis.* 13, 335.
- Nakamura, S., et al. 2002. Clostridial deep neck infection developed after extraction of a tooth: a case report and review of the literature in Japan. *Oral Dis.* 8, 224.
- Nunez-Marti, J.M., et al. 2004. Leprosy: dental and periodontal status of the anterior maxilla in 76 patients. *Oral Dis.* 10, 19.
- Ochandiano, S., 2000. Leprosy. *Med. Oral* 5, 316.
- Phelan, J.A., 2003. Viruses and neoplastic growth. *Dent. Clin. North Am.* 47, 533.
- Reichert, P.A., et al. 2002. High oral prevalence of *Candida krusei* in leprosy patients in northern Thailand. *J. Clin. Microbiol.* 40, 4479.
- Reichert, P.A., et al. 2007. Prevalence of oral *Candida* species in leprosy patients from Cambodia and Thailand. *J. Oral Pathol. Med.* 36, 342.
- Scott, L.A., Stone, M.S., 2003. Viral exanthems. *Dermatol. Online J.* 9, 4.
- Silverman, S., Scully, C., 2000. Infectious diseases. In: Millard, D., Mason, D.K. (Eds.), 3rd World workshop in oral medicine. University of Michigan Press, Ann Arbor.
- Sitheeque, M.A., Samaranayake, L.P., 2003. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). *Crit. Rev. Oral. Biol. Med.* 14, 253.
- Vargas, P.A., et al. 2003. Parotid gland involvement in advanced AIDS. *Oral Dis.* 9, 55.
- Witherow, H., Swinson, B.D., Amin, M., Kalavrezos, N., Newman, L., 2004. Management of oral and maxillofacial infection. *Hosp. Med.* 65, 28–33.

APPENDIX 21.1 EMERGING INFECTIONS

Infection	Comments	Distributions
Acquired immunodeficiency syndrome (AIDS); human immunodeficiency virus (HIV)	Recognized in 1980s	Worldwide
Bovine spongiform encephalopathy (BSE; 'mad cow disease'). Cholera new strain: 0139	Prion disease first recognized in mid-1980s Appeared in 1992 in south-eastern India	UK mainly India, into western China, Thailand and other parts of South-East Asia
Cryptosporidiosis Diphtheria	Came to prominence in AIDs epidemic Epidemics since 1980s following lax vaccinations	Worldwide Russian Federation and other former republics of the USSR
Ebola	Recorded in Zaire and Sudan in 1976; struck in Côte d'Ivoire in 1994 and 1995, Liberia in 1995, and again in Zaire in 1995	Africa, Asia, USA and Latin America
Enterococci strains <i>Escherichia coli</i> O157:H7 strain Hantavirus pulmonary syndrome	Outbreaks resistant to the main groups of antibiotics, such as the beta-lactams and the aminoglycosides Appeared in 1982 First recognized in USA in 1993	USA and other countries Hantavirus infection has been detected in more than 20 US states, and has also surfaced in Argentina and Brazil. Other hantaviruses have been recognized for many years in Asia
Influenza pandemics Resistant tuberculosis, malaria, cholera, dysentery, pneumonia, staphylococci, streptococci	– –	Worldwide Worldwide
<i>Salmonella typhi</i> , resistance to antibiotics <i>Salmonella typhimurium</i> isolated from cattle is paralleled by increasing resistance among strains of human origin <i>Shigella dysenteriae</i>	– – –	Resistance to multiple drugs is common in South-East Asia India and Pakistan in recent years Thailand Central and southern Africa

APPENDIX 21.2 SOME INFECTIOUS DISEASES: INCUBATION TIMES AND PERIOD OF INFECTIVITY

Incubation period	Disease	Incubation period	Period of infectivity
<1 week	Diphtheria	2–5 days	Until treated ^a
	Gonorrhoea	2–5 days	Until treated ^a
	Influenza	1–2 days	Until fever gone
	Scarlet fever	1–3 days	3 weeks after onset of rash
	Hand, foot and mouth	3–6 days	Until rash gone
1–2 weeks	Herpes	2–12 days	Until lesions gone ^a
	Measles	7–14 days	4 days after onset of rash
	Pertussis	7–10 days	21 days after onset of symptoms
2–3 weeks	Chickenpox	14–21 days	Until all lesions scab ^a
	Mumps	12–21 days	7 days after onset of sialadenitis
	Rubella	14–21 days	7 days after onset of rash
>3 weeks	Hepatitis A	2–6 weeks	Usually non-infective at diagnosis
	Hepatitis B	2–6 months	3 months after jaundice resolves ^a
	Hepatitis C	2–26 weeks	3 months after jaundice resolves ^a
	Human immunodeficiency virus (HIV)	Up to 5 y	Persists. ^a Average time from infection to acquired immunodeficiency syndrome (AIDS) is 10 y in the untreated
	Human papillomavirus (HPV)	30–180 days	While lesions present
	Infectious mononucleosis (Epstein–Barr virus)	30–50 days	Until fever resolved. ^a Once infected, patients intermittently excrete the virus asymptotically for the rest of their lives. Thus most people who develop infectious mononucleosis have not had contact with someone who has had a recent illness
	Syphilis	10–90 days	Until treated ^a
Tuberculosis	14–70 days	Until treated ^a	

^aCarrier states exist.

APPENDIX 21.3 SOME ANTIBACTERIALS

Antibacterial	Group	Examples	
Aminoglycosides	–	Amikacin Gentamicin Neomycin Streptomycin Tobramycin	
Beta-lactams	Penicillin	Benzyl penicillin Phenoxymethyl penicillin	
	Penicillinase-resistant penicillins	Flucloxacillin Temocillin	
	Broad-spectrum penicillins	Amoxicillin Ampicillin Co-amoxiclav Co-fluampicil	
	Anti-pseudomonal penicillins	Piperacillin Ticarcillin	
	Mecillinams	Pivmecillinam	
	Cephalosporins	First-generation (cephalosporin) Second-generation (cefuroxime, cefamandole) Third-generation (cefotaxime, ceftazidime, ceftriaxone)	
	Carbapenems	Imipenem–cilastatin Doripenem Ertapenem Meropenem	
	Monobactams	Aztreonam	
	Glycopeptides	–	Teicoplanin Vancomycin
	Lincosamides	–	Clindamycin

(Continued)

Antibacterial	Group	Examples
Macrolides	–	Azithromycin Clarithromycin Erythromycin Spiramycin Telithromycin
Nitroimidazoles	–	Metronidazole
Oxazolidinones	–	Linezolid
Quinolones (fluoroquinolones; 4-quinolones)	–	Ciprofloxacin Norfloxacin Ofloxacin
Sulphonamides and trimethoprim	–	Co-trimoxazole
Tetracyclines	–	Doxycycline Minocycline Tetracycline Tigecycline is related

APPENDIX 21.4 SUMMARY OF THE MAIN ANTIBACTERIAL AGENTS USED IN DENTISTRY

Antibacterial	Comments	Cautions and contraindications
<u>Penicillins</u>		
Amoxicillin	Given by mouth (absorption better than ampicillin) Broad-spectrum (effective against many Gram-negative bacilli) <i>Staphylococcus aureus</i> often resistant Not resistant to penicillinase	Contraindicated in penicillin allergy Rashes, particularly in infectious mononucleosis, lymphoid leukaemia, or during allopurinol treatment May cause diarrhoea
Ampicillin	Less well absorbed than amoxicillin, otherwise similar (many analogues, such as bacampicillin and pivampicillin – but few advantages) Available with cloxacillin (Ampiclox) or flucloxacillin (co-fluampicil)	Contraindicated in penicillin allergy. Causes transient rashes if given to patients with glandular fever, leukaemia or cytomegalovirus infection
Benzyl penicillin	Given i.m. or i.v. Most effective penicillin when organism is sensitive Not resistant to penicillinase	Contraindicated in penicillin allergy Large doses may cause K ⁺ to fall, Na ⁺ to rise
Co-amoxiclav	Mixture of amoxicillin and potassium clavulanate Inhibits some penicillinases (beta-lactamases) and therefore active against most <i>Staph. aureus</i> ; also active against some Gram-negative bacilli	Contraindicated in penicillin allergy May cause cholestatic jaundice
Flucloxacillin	Given by mouth Effective against most penicillin-resistant staphylococci	Contraindicated in penicillin allergy Treatment in elderly, or for more than 2 weeks, may result in cholestatic jaundice
Phenoxyethyl penicillin (penicillin V)	Given by mouth Not resistant to penicillinase Used for prophylaxis of rheumatic fever, in sickle cell disease, and after splenectomy	Contraindicated in penicillin allergy
Procaine penicillin	Depot penicillin Not resistant to penicillinase	Contraindicated in penicillin allergy Rarely, psychotic reaction due to procaine
Temocillin	Given by i.m. or i.v. injection Active against penicillinase-producing Gram-negative bacteria	Contraindicated in penicillin allergy
Tripopen	Depot penicillin (benzyl penicillin 300 mg, procaine penicillin 250 mg, and benethamine penicillin 475 mg) Not resistant to penicillinase	Contraindicated in penicillin allergy
<u>Tetracyclines</u>		
Tetracyclines	Very broad antibacterial spectrum. Little to choose between the many preparations, but doxycycline and minocycline (see later) are safer for patients with renal failure Given by mouth	Absorption impaired by iron, antacids, milk, etc. May predispose to candidosis

(Continued)

Antibacterial	Comments	Cautions and contraindications
	Many bacteria now resistant but still useful for infections with <i>Chlamydia</i> , <i>Rickettsia</i> , <i>Brucella</i> , Lyme disease, acne, leptospirosis, <i>Haemophilus influenzae</i> , methicillin-resistant <i>Staph. aureus</i> (MRSA)	Contraindicated in pregnancy and children up to at least 7 y (tooth discolouration)
Doxycycline	Given by mouth in a single daily dose	Dose reduced in renal failure, liver disease and elderly Frequent mild gastrointestinal upsets May rarely cause intracranial hypertension Contraindicated in pregnancy and children up to at least 7 y (tooth discolouration)
Minocycline	Given by mouth Active against some meningococci Absorption not reduced by milk	Safer than other tetracyclines in renal failure; may rarely cause intracranial hypertension Reduce dose in liver disease and elderly Mild gastrointestinal effects Safer than tetracycline in renal disease May cause dizziness and vertigo Contraindicated in pregnancy and children up to at least 7 y (tooth discolouration) May also cause bone pigmentation
<u>Macrolides</u>		
Azithromycin	Slightly less active than erythromycin against Gram-positive bacteria Long half-life (single daily dose) Fewer gastrointestinal effects than erythromycin	Reduced dose indicated in liver disease and long QT syndrome With terfenadine and pimozone may cause arrhythmias
Erythromycin	Given by mouth but absorption erratic and unpredictable Similar antibacterial spectrum to penicillin Avoid erythromycin estolate, which may cause liver disturbance Useful in those hypersensitive to penicillin Effective against some staphylococci and most streptococci May cause nausea or hearing loss in large doses Rapid development of resistance	Interacts with theophylline and lithium Caution in pregnancy Reduced dose indicated in liver disease and long QT syndrome With terfenadine and pimozone may cause arrhythmias Interacts with theophylline and lithium Caution in pregnancy
Clarithromycin	Fewer gastrointestinal effects than with erythromycin	Reduced dose indicated in liver disease and long QT syndrome With terfenadine and pimozone may cause arrhythmias Interacts with theophylline and lithium Caution in pregnancy
<u>Others</u>		
Cephalosporins cephamycins and other beta-lactams	Rarely needed in dentistry; expensive	May cross-react with penicillins, causing hypersensitivity reactions in those allergic to penicillins
Clindamycin	Given by mouth Very reliably absorbed	Caution in pregnancy Cross-resistance with erythromycin Mild diarrhoea common Repeated doses may cause pseudomembranous colitis (antibiotic-associated colitis), especially in the elderly and in combination with other drugs
Gentamicin	Reserved for serious infections	Caution in pregnancy Can cause vestibular and renal damage
Metronidazole	Given by mouth Effective only against anaerobes Available as i.v. preparation but expensive	Contraindicated in pregnancy and myasthenia gravis Use only for 7 days (or peripheral neuropathy may develop, particularly in patients with liver disease) Avoid alcohol (disulfiram-type reaction) May increase warfarin effect Avoid in pregnancy
Rifampicin	Reserved mainly for treatment of tuberculosis May be used in prophylaxis of meningitis after head injury since <i>Neisseria meningitidis</i> and <i>Staph. aureus</i> are frequently resistant to sulphonamides	May interfere with oral contraception Occasional rashes, jaundice or blood dyscrasias
Sulphonamides	Main indication is for prophylaxis of post-traumatic meningitis but meningococci are increasingly resistant	Safe and effective but resistance rapidly develops Body secretions turn red Contraindicated in pregnancy and in renal disease

(Continued)

Antibacterial	Comments	Cautions and contraindications
Teicoplanin	Adequate hydration essential to prevent (rare) crystalluria Other adverse reactions include rashes, erythema multiforme and blood dyscrasias Reserved mainly for endocarditis and serious <i>Staph. aureus</i> infections, including some MRSA Occasional rashes, nausea, fever, anaphylaxis May cause hearing loss or tinnitus	Reduce dose in renal failure and elderly
Vancomycin	Reserved for serious infections (including MRSA) Given by slow (100-min) i.v. infusion	Contraindicated in renal disease or deafness May cause nausea, rashes, 'red man syndrome', tinnitus, deafness when given intravenously
Quinolones	Extravenous extravasation causes necrosis and phlebitis Effective by mouth for pseudomembranous colitis Can induce fits Can cause tendon damage	Contraindicated in patients with tendonitis, the elderly or those on steroids; epilepsy; diabetes; pregnancy; myasthenia gravis

Warn patients taking an oral contraceptive to use additional precautions if on antimicrobials for more than a single dose.

APPENDIX 21.5 BACTERIAL INFECTIONS SEEN MAINLY IN PEOPLE FROM THE DEVELOPING WORLD

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Anthrax	<i>Bacillus anthracis</i> (Central Asia and worldwide)	Contact with contaminated products or soil infected by animals (mainly cattle, goats, sheep). Spores survive for decades	Untreated infections may spread to regional lymph nodes and bloodstream, and may be fatal	Avoidance of direct contact with soil and products of animal origin (e.g. souvenirs made from animal skins). Vaccine available for people at high risk	Isolation from blood, skin or respiratory secretions	Ciprofloxacin, doxycycline or erythromycin
<i>Bartonella</i>	<i>Bartonella (Rochalimaea) henselae</i> , Gram-negative bacilli that appear to be transmitted by ectoparasites (worldwide)	Contact with cats	Cat scratch disease lymphadenitis Most common in children, in the cervical region; the typical case presents with a tender papule about 3–10 days after contact with the animal, and this is followed by cervical lymphadenopathy after up to 6 weeks Systemic features vary from none to a mild 'flu-like illness and only very rarely are there more serious sequelae such as encephalitis <i>B. henselae</i> or sometimes <i>B. quintana</i> in immunodeficient patients may cause epithelioid (bacillary) angiomatosis; clinical resemblance of the lesions to Kaposi sarcoma, but they are benign	Avoidance of cats	Warthin–Starry silver stain may show causal organisms, or they may be identified by in vitro DNA amplification or serological testing	Treatment, if required, involves use of tetracyclines, doxycycline or chloramphenicol, or erythromycin or other macrolides

(Continued)

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Brucellosis	<i>B. bacilliformis</i> (in some valleys of Colombia, Ecuador and Peru)	Transmitted by sandflies	Carrion disease is either acute with severe infectious haemolytic anaemia (or Oroya fever), or appears as benign cutaneous tumours (verruca peruana). Healthy blood carriers of the bacterium exist	Avoidance of sandflies		
	<i>B. quintana</i> (worldwide)	Bacterial reservoir is in humans only Transmitted by body louse	Trench fever, first described during the First World War, is a non-fatal disease of recurrent attacks of fever and bone pains. Can also cause endocarditis, bacillary angiomatosis and chronic or recurrent bacteraemia	Avoidance of lice		
	<i>Brucella</i> species (worldwide, mainly in developing countries and around the Mediterranean)	Humans seem to be the reservoir of <i>B. quintana</i> From cattle (<i>B. abortus</i>), dogs (<i>B. canis</i>), pigs (<i>B. suis</i>), or sheep and goats (<i>B. melitensis</i>), by direct contact with animals, skin or unpasteurized milk or cheese	Continuous or intermittent fever and malaise <i>Acute form</i> , symptoms are non-specific and 'flu-like, particularly fever, sweats, malaise, anorexia, headache, myalgia and back pain <i>Undulant form</i> (<1 y from illness onset), symptoms include undulant fevers, arthritis and epididymo-orchitis in males. Neurological symptoms may develop rapidly in up to 5% <i>Chronic form</i> (>1 y from onset), symptoms may include chronic fatigue syndrome-like depressive episodes and arthritis Brucellosis may be associated with chronic or intermittent lymphadenopathy	Avoidance of unpasteurized milk and milk products, and direct contact with animals, particularly cattle, goats and sheep	Blood or bone marrow culture and serology are required for diagnosis	Doxycycline and rifampicin are used in combination for 6 weeks to prevent recurring infection
Cholera	<i>Vibrio cholerae</i> , serogroups O1 and O139 from contaminated water, occasionally from food (developing countries, particularly in Africa and Asia, and to a lesser extent in Central and South America; endemic in Bangladesh and common throughout the tropics, currently in South America, the Middle East, Africa and Asia)	Ingestion of food or water contaminated directly or indirectly by faeces or vomitus of infected persons	Acute enteric disease varying in severity	Oral cholera vaccines gave little protection and have been abandoned	Stool culture	Treatment is with electrolyte-containing solutions and, if necessary, ciprofloxacin

(Continued)

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Diphtheria	<i>Corynebacterium diphtheriae</i> (where immunization has been neglected, diphtheria continues to re-emerge, as in Eastern Europe, e.g. Ukraine 2008)	Human-to-human transmission by droplet infection and fomites	Can cause massive diarrhoea with depletion of water and electrolytes, and can be fatal	All care should be taken to avoid consumption of potentially contaminated food, drink and drinking water	Swabs should be taken for bacterial culture and for Gram and Kenyon staining	Antibiotics (usually penicillin or erythromycin) immediately
			<i>C. diphtheriae</i> multiplies mainly on the nasal, pharyngeal or laryngeal mucous membranes to cause inflammation, surface necrosis and exudate (pseudomembrane)	Diphtheria immunization carried out in early childhood		
			Mild sore throat but disproportionate cervical lymph node enlargement, which in severe cases produces a bull neck. Nasal, laryngeal or tracheal diphtheria are variants			
		Patients infectious for up to 4 weeks but carriers may shed for longer	Exotoxin causes potentially fatal myocardial, adrenal and neurological damage			Household contacts may need immunization
		Three biotypes – <i>gravis</i> , <i>intermedius</i> and <i>mitis</i> , the most severe disease being caused by the <i>gravis</i> biotype, but any strain may produce neurotoxin	Palatal paralysis is a possible manifestation			
<i>Haemophilus meningitis</i>	<i>Haemophilus influenzae</i> type b (Hib) (worldwide where vaccination against Hib is not practised)	Direct contact with infected person	Meningitis in infants and young children; may also cause epiglottitis, osteomyelitis, pneumonia, sepsis and septic arthritis	Vaccination against Hib	White cell count	
Leprosy	<i>Mycobacterium leprae</i> (India alone accounts for 78% of new cases detected worldwide; endemic in tropical and subtropical areas of Asia, Africa and Latin America; also seen occasionally around the Mediterranean and Black Sea and in southern Europe)	<i>M. leprae</i> transmitted by direct contact and via the respiratory tract	Outcome of infection highly dependent upon cell-mediated immune reactions; if these are intact, infection results in localized form (tuberculoid leprosy); if deficient, generalized (lepromatous) leprosy	Hygiene	Hib culture from blood	Multidrug therapy (MDT) with clofazimine, rifampicin and prothionamide over 2 or more years; second-line drugs include ofloxacin, minocycline and clarithromycin
			<i>Tuberculoid leprosy</i> : a benign form and causes thickening of cutaneous nerves, flat and hypopigmented or raised and erythematous skin lesions, and enlarged lymph nodes		Based on one or more of three cardinal signs: hypopigmented or reddish hypo- or anaesthetic skin lesion(s); peripheral nerve involvement; and a positive smear from an open lesion, or biopsy, for acid-fast bacilli	

(Continued)

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Leptospirosis	Spirochaetes of the genus <i>Leptospira</i> worldwide (most common in tropics)	Contact between the skin or mucosae and water, wet soil or vegetation contaminated by animal urine, notably rats and foxes	<i>Lepromatous leprosy</i> : affects nerves (with hypoaesthesia); skin with macules progressing to papules and nodules or infiltration; lymph nodes; and other tissues, including bones, eyes, testes, kidneys and bone marrow Sudden fever, headache, myalgia, chills, conjunctival suffusion and rash. May progress to meningitis, haemolytic anaemia, jaundice, haemorrhages and hepatorenal failure	Avoidance of contact with rodents and contaminated waters, including canals, ponds, rivers, streams and swamps	Serological diagnostic tests capable of identifying and allowing treatment of early-stage leprosy are appearing Enzyme-linked immunosorbent assay (ELISA) serology	Doxycycline, penicillin
Listeriosis	<i>Listeria monocytogenes</i> (worldwide)	<i>Listeria</i> multiplies readily in refrigerated foods that have been contaminated (e.g. unpasteurized milk, soft cheeses, vegetables and prepared meat products)	Newborn infants, pregnant women, older and immunocompromised individuals are particularly susceptible. In pregnancy, causes fever and abortion. Meningoencephalitis and/or septicaemia in adults and newborn infants. In others, disease may be limited to a mild acute febrile episode	Avoidance of unpasteurized milk and milk products	Culture blood, urine, cerebrospinal fluid or amniotic fluid	Ampicillin plus gentamicin
Lyme disease	<i>Borrelia burgdorferi</i> (first recognized in 1977 when arthritis was noted in children in and around Lyme, Connecticut, USA)	Bite of infected deer ticks, which have become infected by feeding on small rodents, such as white-footed mice	Some individuals have subclinical infection but presentation is most often with a 'bull's-eye' rash (erythema migrans) and non-specific features, e.g. fever, malaise, fatigue, headache, muscle aches (myalgia) and joint aches (arthralgia)	Avoidance of areas where there could be deer	Serological testing initially with a sensitive ELISA or indirect fluorescent antibody (IFA) test, followed by testing with the more specific Western immunoblot (WB), which is confirmatory	Doxycycline or amoxicillin for 3–4 weeks
	British Lyme disease differs from the USA version, in having fewer complications	Spirochaetes disseminate from the tick bite via lymphatics and blood to nervous or musculoskeletal systems, or heart	Rash usually appears 7–14 days after tick exposure Early neurological manifestations may include lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis Musculoskeletal manifestations may include migratory joint and muscle pains Cardiac manifestations rare but may include myocarditis and transient atrioventricular blocks			Cefuroxime or erythromycin for persons allergic to penicillin
Meningococcal disease	<i>Neisseria meningitidis</i> (epidemics in Saudi Arabia during Haj)	Humans	Meningitis	Hygiene		

(Continued)

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Paratyphoid	<i>Salmonella paratyphi</i> , <i>S. cholerae-suis</i> or <i>S. enteritidis</i>	Poultry, eggs, dairy products, other foods	Similar to typhoid but usually less severe	Vaccination is indicated Hygiene	Culture stool	Supportive therapy
Pertussis	<i>Bartonella pertussis</i>	Nasopharyngeal secretions	Catarrh, recurrent cough	Hygiene	Culture nasopharyngeal swab	Erythromycin, azithromycin
Plague	<i>Yersinia pestis</i> (Asia, Africa, South America; epidemics)	<i>Xenopsylla cheopis</i> (oriental rat flea) is primary vector Other routes of spread include direct contact with infected tissues or fluids from handling sick or dead animals or by droplets from cats Direct person- to-person transmission only in pneumonic plague	<i>Bubonic plague</i> : lymphadenitis with swelling and suppuration – buboes. Untreated bubonic plague is often fatal <i>Septicaemic plague</i> : may develop from bubonic plague or occur in the absence of lymphadenitis. Dissemination of infection in bloodstream causes meningitis, endotoxic shock and disseminated intravascular coagulation <i>Pneumonic plague</i> : results from secondary infection of lungs following dissemination from other sites. Direct infection of others may result. Untreated septicaemic and pneumonic plague are invariably fatal	Avoidance of contact with rodents Antibiotics for prophylaxis with tetracyclines or sulphonamides	Immunostain smear from affected tissues serology	Aminoglycosides, e.g. streptomycin and gentamicin
Q fever	<i>Coxiella burnetii</i> (worldwide)	Excreta or milk of cattle, sheep and goats Ticks	Fever, headache, malaise, myalgia, sore throat, chills, sweats, cough, nausea, vomiting, diarrhoea, abdominal and chest pain	Avoidance of contact with excreta or unpasteurized milk	Serology	Tetracycline, doxycycline
Salmonellosis	<i>Salmonella</i> serotype <i>typhimurium</i> and <i>Salmonella</i> serotype <i>enteritidis</i> (outbreaks in developing world mainly, e.g. Kenya 2008, but also in developed world, e.g. USA 2008)	Contaminated foods are often of animal origin, such as beef, poultry, milk or eggs, but any food, including vegetables, may become contaminated	Diarrhoea, fever or abdominal cramps	Avoidance of contact with uncooked food and not eating raw or undercooked eggs, poultry or meat Thorough cooking kills <i>Salmonella</i> Reptiles (turtles, iguanas, lizards, snakes) may harbour <i>Salmonella</i> . Chicks and birds may carry <i>Salmonella</i> in their faeces Hands should be washed immediately after handling reptiles or birds	Laboratory tests that identify <i>Salmonella</i> in the stool of an infected person	Usually resolves in 5–7 days and often does not require treatment other than oral fluids Persons with severe diarrhoea may require rehydration with intravenous fluids Antibiotics, e.g. ampicillin, trimethoprim– sulfamethoxazole or ciprofloxacin, are not usually necessary

(Continued)

Disease	Microorganism or parasite (areas of greatest risk)	Infection via	Possible outcomes	Prevention	Diagnostic aids	Management
Sodoku	<i>Spirillum minus</i> (Asia mainly)	From rat bites or scratches	High fever, headache and regionally swollen lymph nodes	Avoidance of rats, mice or squirrels	Darkfield microscopy	Penicillin
Tularaemia	<i>Francisella tularensis</i> (USA and other countries)	From ticks, water contaminated by rats, undercooked meat from an infected animal such as rabbit, and also from contaminated soil	High fever, generalized aching and swollen lymph nodes	Avoidance of rats	Serology	Aminoglycosides (e.g. gentamicin and streptomycin), chloramphenicol, fluoroquinolones and tetracyclines
Typhoid fever	<i>Salmonella typhi</i> (worldwide, especially North and West Africa, South Asia and Peru)	Contaminated water or food	Fever, rash, splenomegaly and leukopenia, and intestinal bleeding or perforation	Vaccination	Culture blood, vomit and stool	Chloramphenicol effective but toxic. <i>S. typhi</i> may be resistant in India, Middle East and South-East Asia, where ciprofloxacin is indicated
		A strict human pathogen, typhoid is always acquired from a human. Contact tracing is important		Hygiene		
Typhus fever (epidemic louse-borne typhus)	<i>Rickettsia prowazekii</i> (colder, i.e. mountainous, regions of Central and East Africa, Central and South America, and Asia. In recent years, most outbreaks have taken place in Burundi, Ethiopia and Rwanda)	Human body louse, rat or cat flea	Sudden fever, headache, chills, prostration, coughing and muscular pains	Avoidance of contaminated water or food Avoidance of infestation by body lice	Serology after the first week	Doxycycline, azithromycin, rifampicin
			After 5–6 days, a macular skin eruption (dark spots) on the upper trunk and then rest of the body, except face, palms or soles Case fatality rate up to 40%		Polymerase chain reaction (PCR)	
Yersiniosis	<i>Y. enterocolitica</i> (worldwide)	Eating contaminated food, especially raw or undercooked pork products	Features typically develop 4–7 days after exposure and may last 1–3 weeks or longer Fever, abdominal pain, bloody diarrhoea and sometimes cervical lymphadenopathy	Hygiene	Culture stool or body fluids	Uncomplicated cases usually resolve spontaneously In severe or complicated infections, use aminoglycosides, doxycycline, trimethoprim–sulfamethoxazole or fluoroquinolones

APPENDIX 21.6 UNCOMMON BACTERIAL INFECTIONS THAT MAY HAVE IMPLICATIONS IN DENTISTRY

Organism	Main features	Orofacial lesions	Treatments
<i>Bacillus anthracis</i>	Anthrax	Painful or ulcerated swellings, mainly on palate	Penicillin
<i>Brucella melitensis, suis and abortus</i>	Brucellosis	Rare infections or cranial nerve palsies	Tetracycline with streptomycin
<i>Clostridium botulinum</i>	Botulism	Xerostomia, parotitis Muscle weakness	Antitoxin
<i>Clostridium perfringens</i> (C. <i>welchii</i>), C. <i>sporogenes</i> , C. <i>oedematiens</i> and C. <i>septicum</i>	Gas gangrene	Gas gangrene	Antitoxin
<i>Escherichia coli</i>	Enteric infections, mainly	Found in some oral infections, especially in denture wearers and immunocompromised	Penicillin Surgery Ampicillin
	Also urinary tract, wound and other infection		Cefalexin Cefalotin Co-trimoxazole Streptomycin
<i>Francisella tularensis</i>	Tularaemia	Pharyngitis Stomatitis (often ulcerative) Faucial membrane Cervical lymphadenopathy	Tetracyclines
<i>Mycoplasma hominis</i> and <i>pneumoniae</i>	Pneumonia	Rare infections or cranial nerve palsies? Reiter syndrome	Erythromycins Penicillin
<i>Neisseria meningitidis</i>	Meningitis	Petechiae	Co-trimoxazole
	Septicaemia	Occasionally, herpes labialis Facial palsy	
<i>Nocardia asteroides, brasiliensis</i> and <i>caviae</i>	Nocardiosis	Ulceration	Ciprofloxacin Sulfadiazine Aminoglycosides
<i>Proteus vulgaris</i>	Urinary tract and wounds	Cheek or gingivae Occasional infections	Penicillin Cephalosporins Tetracyclines
<i>Pseudomonas aeruginosa</i>	Skin and lungs	Opportunistic infections	
<i>Pseudomonas mallei</i>	Glanders (acute pneumonia)	Ulceration from nasal glanders Ulcers	Tetracyclines
<i>Pseudomonas pseudomallei</i>	Melioidosis (lung or other localized infections or septicaemia)	Oral abscesses, or other infections	
<i>Rickettsia rickettsiae</i>	Rocky mountain spotted fever	Parotitis Faucial gangrene	Tetracyclines
<i>Rickettsia akari</i>	Rickettsial pox	Vesicles	Tetracyclines
<i>Salmonellae typhi, paratyphi, cholerae, suis</i> and <i>enteritidis</i>	Typhoid and paratyphoid fever	Occasional infections	Co-trimoxazole Ampicillin

APPENDIX 21.7 IMMUNIZATION SCHEDULES (UK)^a

When to immunize	Diseases protected against	Vaccine
2 months old	Diphtheria, tetanus, pertussis, polio and <i>Haemophilus influenzae</i> type b (Hib)	DTaP/IPV/Hib (Pediaceal)
	Pneumococcal disease	PCV (Prevenar 13)
	Rotavirus	Rotavirus (Rotarix)
3 months old	Diphtheria, tetanus, pertussis, polio and Hib	DTaP/IPV/Hib (Pediaceal)
	Meningococcal group C disease (MenC)	MenC (Neisvac-C or Menjugate)
	Rotavirus	Rotavirus (Rotarix)
4 months old	Diphtheria, tetanus, pertussis, polio and Hib	DTaP/IPV/Hib (Pediaceal)
	Pneumococcal disease	PCV (Prevenar 13)
Between 12 and 13 months old – within a month of the first birthday	Hib/MenC	Hib/MenC (Menitorix)

(Continued)

When to immunize	Diseases protected against	Vaccine
2 and 3 years old	Pneumococcal disease Measles, mumps and rubella Influenza	PCV (Prevenar 13) MMR (Priorix or MMR VaxPRO) Flu nasal spray (Fluenz; annual) If Fluenz unsuitable, use inactivated flu vaccine
3 years 4 months old or soon after	Diphtheria, tetanus, pertussis and polio	dTap/IPV (Repevax) or DTaP/IPV (Infanrix-IPV)
Girls aged 12–13 years	Measles, mumps and rubella Cervical cancer caused by human papillomavirus types 16 and 18 (and genital warts caused by types 6 and 11)	MMR (Priorix or MMR VaxPRO; check first dose has been given) HPV (Gardasil)
Around 14 years old	Tetanus, diphtheria and polio MenC	Td/IPV (Revaxis), and check MMR status MenC (Meningitec, Menjugate or NeisVac-C)
65 years old	Pneumococcal disease	PPV Pneumococcal polysaccharide vaccine (Pneumovax II)
65 years of age and older	Influenza	Flu injection (annual)
70 years old	Shingles	Shingles (Zostavax)
Immunizations for those at risk		
At birth, 1 month old, 2 months old and 12 months old	Hepatitis B	Hep B
At birth	Tuberculosis	BCG
6 months up to 2 years	Influenza	Inactivated flu vaccine (annual)
2 years up to under 65 years	Pneumococcal disease	PPV Pneumococcal polysaccharide vaccine (Pneumovax II)
Over 2 up to less than 18 years	Influenza	Flu nasal spray (Fluenz; annual) If Fluenz unsuitable, use inactivated flu vaccine
18 up to under 65 years	Influenza	Inactivated flu vaccine (annual)
From 28 weeks of pregnancy	Pertussis	dTap/IPV (Repevax)

^aSource: <https://www.gov.uk/government/publications/the-complete-routine-immunisation-schedule-201314> (accessed 30 September 2013).

APPENDIX 21.8 COMMON VIRAL INFECTIONS THAT MAY HAVE IMPLICATIONS IN DENTISTRY^a

Virus	Infection mainly in	Orofacial consequences	Antivirals that may have a role
Cytomegalovirus	Immunocompromised persons	Ulcers	Ganciclovir Foscarnet Valganciclovir
Epstein–Barr virus	Any	Ulcers	–
	Immunocompromised persons	Ulcers Hairy leukoplakia Lymphomas	Ganciclovir Aciclovir
Hepatitis B	Any	–	Usually none. Interferon-alpha 2b, adefovir, entecavir, lamivudine, telbivudine or tenofovir
	Chronic infection or immunocompromised persons	–	Interferon-alpha 2b, adefovir, entecavir, lamivudine, telbivudine or tenofovir
Hepatitis C	Any	Lichenoid lesions/lichen planus	Usually none. Interferon-alpha 2b and ribivirin. A protease inhibitor (e.g. boceprevir or telaprevir) may also be given
	Chronic infection or immunocompromised persons	Sicca syndrome	
Herpes simplex	Primary infections	Gingivostomatitis	Aciclovir
	Secondary infections (labial or orogenital)	Blistering	Aciclovir Penciclovir
	Secondary infections (oral)	Ulceration Erythema multiforme Bell palsy	Aciclovir
HIV	Encephalitis See Ch. 20	–	Aciclovir
Influenza	Older or immunocompromised persons	–	Amantadine Oseltamivir

(Continued)

Virus	Infection mainly in	Orofacial consequences	Antivirals that may have a role
Papillomaviruses	Any	Warty lesions Oropharyngeal carcinoma	Rimantadine Zanamivir Interferon-alpha 2b Imiquimod
Respiratory syncytial virus	Young or immunocompromised persons	–	Ribavirin
Severe acute respiratory syndrome corona virus	Older or immunocompromised persons	–	Ribavirin
Varicella zoster virus	Chickenpox; any patient	Ulcers	Aciclovir
	Zoster; any patient	Pain Ulcers	Famciclovir Valaciclovir
	Zoster in immunocompromised	Pain Ulcers	Aciclovir

^aSee Table 21.10.

APPENDIX 21.9 VIRAL INFECTIONS PREVALENT MAINLY IN THE DEVELOPING WORLD

Disease	Virus	Infection via	Consequences	Epicentres of greatest risk	Prevention
Arboviruses	Many different arboviruses	Transmitted to humans by arthropods, mostly mosquitoes, sandflies or ticks	Fever with rashes, arthralgias, lymphadenopathy, CNS involvement or haemorrhagic features	Worldwide, especially Latin America, the southern USA, South-East Asia and Africa	Avoid insect bites (wear protective clothing and use insect repellants) and use prophylactic measures such as vaccination
Chikungunya	Togavirus	Mosquito	Similar to dengue; fever and joint pain, muscle pain, headache, nausea, fatigue and rash	Around Indian Ocean	Avoid mosquito bites
Dengue	Dengue virus – a flavivirus	<i>Aedes aegypti</i> mosquito, which bites during the day. There is no direct person-to-person transmission. Monkeys act as a reservoir host in South-East Asia and West Africa	Dengue fever – an acute febrile illness, macular skin rash and muscle pains ('breakbone fever')	Tropical and subtropical regions of Central and South America, South and South-East Asia, and Africa below 600 m	Avoid mosquito bites
Ebola fever	See Haemorrhagic fevers		Dengue haemorrhagic fever Dengue shock syndrome		
Encephalitis viruses	Togaviridae or flaviviruses	Mosquito bites	Aseptic meningitis or encephalitis. Infections range from mild 'flu-like illness to frank encephalitis, coma and death, leaving mild to severe neurological deficits in survivors	Worldwide	Avoid bites of mosquitoes. A vaccine against tick-borne encephalitis is available for those walking or camping in forests in areas at risk
				<i>Tick-borne encephalitis</i> is seen in forested areas of Austria, northern Europe and Scandinavia <i>Japanese encephalitis</i> virus is a flavivirus <i>St Louis encephalitis</i> virus is a flavivirus seen in the southern USA and Caribbean	

(Continued)

Disease	Virus	Infection via	Consequences	Epicentres of greatest risk	Prevention
Haemorrhagic fevers: Crimean–Congo haemorrhagic fever (CCHF), dengue, Ebola and Marburg haemorrhagic fevers, Lassa fever, Rift Valley fever (RVF) and yellow fever	Most haemorrhagic fevers, including dengue and yellow fever, caused by flaviviruses	Most viruses transmitted by mosquitoes	Sudden onset of fever, malaise, headache and myalgia followed by pharyngitis, vomiting, diarrhoea, rash and haemorrhages, including from the mouth. Fatal in over 50%	Tropics and subtropical regions	Avoid mosquitoes, ticks and rodents
	Ebola and Marburg caused by filoviruses, CCHF by bunyavirus, Lassa fever by arenavirus, RVF by phlebovirus	Ebola or Marburg viruses acquired from bats or monkeys or direct contact with body fluids of infected patients		Ebola and Marburg haemorrhagic fevers in sub-Saharan Africa. Marburg virus has been of concern since first reports in 1967 in persons working with monkeys in Germany and Yugoslavia	Filoviruses have very high transmissibility, morbidity and mortality
		CCHF transmitted by a tick bite		Lassa fever, the most infamous arenavirus, is named after the Nigerian town where infection was first recorded in 1969. Cases since reported from Liberia, Sierra Leone and Uganda	
		Lassa fever virus carried by rodents and transmitted by excreta, either as aerosol or direct contact		CCHF in steppe regions of Central Asia and Central Europe (including Greece and Turkey in 2008), as well as in tropical and southern Africa	
		RVF acquired either by mosquito bite or by direct contact with blood or tissues of infected animals		RVF in Africa and Saudi Arabia	
				Other viral haemorrhagic fevers in Central and South America	
				Other arenavirus infections include Korean, Argentinian and Bolivian fevers	
Hantavirus diseases – haemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS)	Hantaviruses – family bunyaviruses. HPS caused by sin nombre virus (SNV)	Direct contact with the faeces, saliva or urine of infected rodents such as deer, mice or by inhalation of the virus	Vascular endothelium is damaged, leading to vascular permeability, hypotension, haemorrhages and shock Impaired renal function with oliguria characterizes HFRS; fatal in up to 15% Respiratory distress due to pulmonary oedema in HPS; fatal in up to 50%	Worldwide. New World hantaviruses with distinct rodent hosts. A pan-American zoonosis, with an expanding clinical spectrum. Seen also in Europe	Avoid exposure to rodents and their excreta
Hepatitis viruses	Ch. 9				
Human immunodeficiency virus (HIV)	Ch. 20				
Influenza	Ch. 15				

(Continued)

Disease	Virus	Infection via	Consequences	Epicentres of greatest risk	Prevention
Japanese encephalitis	Japanese encephalitis (JE) virus – a flavivirus	Various mosquitoes of the genus <i>Culex</i> . Infects pigs and wild birds as well as humans	Fever, headache or aseptic meningitis. Severe cases rapid onset with headache, high fever and meningeal signs. May be neurological sequelae. Approximately 50% of severe cases are fatal	Asia, especially monsoon areas of South-East Asia	Vaccination. Avoid mosquito bites
Lassa fever	See Haemorrhagic fevers				
Marburg virus	See Haemorrhagic fevers				
Nipah and Hendra viruses	Paramyxoviruses	Animals (Nipah from fruit bats and pigs; Hendra from horses)		Nipah- Malaysia, Bangladesh; Hendra- Australia	Avoid excreta
Poliomyelitis	Ch. 13				
Rabies	Rhabdovirus of genus Lyssavirus	Bite of an infected animal such as a dog, fox or bat	Acute encephalomyelitis, which is almost invariably fatal. Initial signs include sense of apprehension, headache, fever, malaise and sensory changes around bite site. Excitability, hallucinations and aerophobia are common, followed in some cases by fear of water (hydrophobia) due to spasms of swallowing muscles, progressing to delirium, convulsions and death	Worldwide, especially in developing countries	Avoid contact with both wild and domestic animals, including dogs and cats. Vaccination
Severe acute respiratory syndrome (SARS)	Ch. 15				
Tick-borne encephalitis (spring-summer encephalitis)	Tick-borne encephalitis (TBE) virus – a flavivirus	Bite of infected ticks	Influenza-like illness, with a second phase of fever in 10% of cases. Encephalitis develops during the second phase and may result in paralysis or death	Below 1000 m in Eastern Europe, particularly Austria, Baltic States, Czech Republic, Hungary and Russian Federation	Avoid bites by ticks by wearing long trousers and closed footwear when hiking or camping in endemic areas
West Nile fever	West Nile virus (WNV)	Bite of an infected mosquito, and can infect people, horses, many types of birds and some other animals The virus can be transmitted through contact with the blood or other tissues of infected animals	Rarely, severe or sometimes fatal encephalitis	Africa, USA, southern Europe	Avoid mosquito bites Avoid handling WNV-infected tissues or fluids from animals
Yellow fever	Yellow fever virus – an arbovirus of the Flavivirus genus	Bite of <i>Aedes aegypti</i> mosquitoes Yellow fever virus infects humans and monkeys	Acute illness characterized initially by fever, chills, headache, muscular pain, anorexia, nausea and/or vomiting, with bradycardia. About 15% progress to second phase, with fever resurgence, jaundice, abdominal pain, vomiting and haemorrhages. 50% die after 10–14 days	Tropical areas of Africa and Central and South America below 2500 m	Vaccination. Avoid mosquito bites during the day, as well as at night

^aSee also Appendix 21.8 for the more common viral infections.

APPENDIX 21.10 MAIN ANTIFUNGAL DRUGS

Group	Examples	Comments	Oral dose
Polyenes	Amphotericin ^a	Active topically. Negligible absorption from gastrointestinal tract. Given i.v. for deep mycoses	10–100 mg 6-hourly
	Nystatin ^a	Active topically. Negligible absorption from gastrointestinal tract. Pastilles taste better than lozenges	500 000 unit lozenge, 100 000 unit pastille or 100 000 unit per mL of suspension 6-hourly
Imidazoles	Ketoconazole	Absorbed from gastrointestinal tract. Useful in intractable candidosis. Contraindicated in pregnancy and liver disease. May cause nausea, rashes, pruritus and liver damage. Interacts with anticoagulants, terfenadine, cisapride and astemizole	200–400 mg once daily with meal, for 14 days
	Miconazole ^a	Active topically. Also has antibacterial activity. Absorption from gastrointestinal tract. Theoretically the best antifungal to treat angular stomatitis. Interacts with anticoagulants, terfenadine, cisapride and astemizole. Avoid in pregnancy and porphyria	250 mg tablet 6-hourly or 25 mg/mL gel used as 5 mL 6-hourly, for 14 days
Triazoles	Fluconazole	Absorbed from gastrointestinal tract. Useful in intractable candidosis. Contraindicated in pregnancy and lactation, and liver and renal disease. Interacts with anticoagulants, terfenadine, cisapride and astemizole	50–100 mg daily for 14 days
	Itraconazole	Absorbed from gastrointestinal tract. Useful in intractable candidosis. May cause nausea, neuropathy, diarrhea and rash. In high dose, or in older people or those with cardiac disease or on calcium channel blockers, it may cause cardiac failure. Contraindicated in heart disease, pregnancy, liver disease. Interacts with terfenadine, cisapride and astemizole	100 mg daily for 14 days
	Posaconazole	Caution with cardiac patients. Contraindicated in porphyria	400 mg b.d.
	Voriconazole	Caution with cardiac patients, and liver or renal disease. Contraindicated in porphyria and breast-feeding	200 mg b.d.

^aDissolve in mouth slowly.

APPENDIX 21.11 IMPORTANT SYSTEMIC (DEEP) MYCOSES

Disease	Organism	Source	Main endemic areas	Clinical forms	Prognosis
Aspergillosis	<i>Aspergillus fumigatus</i> , <i>A. flavus</i> , <i>A. niger</i> and other <i>Aspergillus</i> spp.	Ubiquitous	Worldwide	Allergic bronchopulmonary, pulmonary, disseminated, aspergilloma	Variable
Blastomycosis	<i>Blastomyces dermatitidis</i>	Soil	Mississippi and Ohio valleys in USA, Canada, North Africa and Venezuela	Cavitary, pulmonary, disseminated, others	Often good, except in disseminated form
Coccidioidomycosis	<i>Coccidioides immitis</i>	Soil	South-western USA, Mexico, Latin America	Acute pulmonary, disseminated, chronic pulmonary, meningitis	Often good, except in disseminated or meningeal form
Cryptococcosis	<i>Cryptococcus neoformans</i>	Soil, pigeon droppings	Worldwide	Pneumonia, meningitis, disseminated, cryptococcoma	Poor in disseminated form
Histoplasmosis	<i>Histoplasma capsulatum</i>	Soil, bird and bat droppings	Mississippi and Ohio valleys in USA, Latin America, Africa, India, Far East, Australia	Benign pulmonary, disseminated, chronic pulmonary, cutaneous	Often good, except in disseminated form
Mucormycosis	<i>Mucor</i> , <i>Rhizopus</i> and <i>Absidia</i>	Ubiquitous	Worldwide	Rhinocerebral, pulmonary, gastrointestinal	Variable
Paracoccidioidomycosis (South American blastomycosis)	<i>Paracoccidioides brasiliensis</i>	Soil	South America, especially Brazil	Pulmonary, disseminated	Good in young patients
Pneumocystosis	<i>Pneumocystis jiroveci</i> (<i>carinii</i>)	Ubiquitous	Worldwide	Pulmonary, disseminated	Variable
Sporotrichosis	<i>Sporothrix schenckii</i>	Associated with thorny plants, wood, sphagnum moss	Worldwide	Lymphocutaneous, localized cutaneous, pulmonary, disseminated	Good

APPENDIX 21.12 MAIN PARASITIC INFESTATIONS^a

Disease	Microorganism or parasite	Infection via	Consequence	Areas of greatest risk	Prevention	Treatment
Angiostrongyliasis	<i>Angiostrongylus cantonensis</i>	Rat lungworm	Eosinophilic meningitis	Asia, Africa, Caribbean, Hawaii and other Pacific islands	Avoid eating undercooked or raw snails and slugs. Fish do not spread this parasite	None
Filariasis	Nematodes (roundworms) of family Filarioidea	Lymphatic filariasis transmitted through bite of mosquitoes Onchocerciasis transmitted through bite of blackflies	Lymphatic filariasis and onchocerciasis (river blindness)	Lymphatic filariasis throughout sub-Saharan Africa and South-East Asia Onchocerciasis in western and Central Africa, Central and South America	Avoid bites of mosquitoes and/or blackflies	Diethylcarbamazine, ivermectin
Giardiasis	Protozoan parasite <i>Giardia lamblia</i>	Ingestion of <i>Giardia</i> cysts in water (unfiltered drinking and recreational waters) contaminated by faeces of humans or animals	Anorexia, chronic diarrhoea, abdominal cramps, bloating, frequent loose greasy stools, fatigue and weight loss	Worldwide	Avoid ingesting any potentially contaminated (i.e. unfiltered) drinking water or recreational water	Metronidazole
Leishmaniasis	See text					
Malaria	See text					
Schistosomiasis (bilharziasis)	Parasitic blood flukes (trematodes), of which the most important are <i>Schistosoma mansoni</i> , <i>S. japonicum</i> and <i>S. haematobium</i>	Infection occurs in fresh water containing larval forms (cercariae) of schistosomes, which develop in snails infected as a result of excretion of eggs in human urine or faeces. The free-swimming larvae enter the skin of individuals swimming or wading in water	<i>S. mansoni</i> and <i>S. japonicum</i> cause hepatic and intestinal signs <i>S. haematobium</i> causes urinary dysfunction	<i>S. mansoni</i> in sub-Saharan Africa, Arabian peninsula, Brazil, Surinam and Venezuela <i>S. japonicum</i> in China, Indonesia and Philippines (not Japan) <i>S. haematobium</i> in sub-Saharan Africa and eastern Mediterranean areas	Avoid swimming or wading in fresh water in endemic areas	Praziquantel
Strongyloidiasis	<i>Strongyloides stercoralis</i> , <i>Strongyloides fuelleborni</i>	Infection acquired by walking barefoot in contaminated soil. Larvae enter the body by burrowing into the skin	At entry site, larvae petechial haemorrhages and intense pruritus. Larvae migrate into pulmonary circulation via lymphatic system and venules, produce haemorrhages and alveolar inflammatory response with eosinophilic infiltration (pneumonitis). Larvae migrate up pulmonary tree, are swallowed and reach gastrointestinal system, where they embed and can produce inflammatory reaction and malabsorption syndrome	<i>Strongyloides</i> spp. distributed worldwide but endemic in tropical and subtropical regions. Most prevalent in South-East Asia, Sahara Desert, Colombia and tropical Brazil. Infection rates in these areas can be 60%	Avoid walking barefoot	Albendazole

(Continued)

Disease	Microorganism or parasite	Infection via	Consequence	Areas of greatest risk	Prevention	Treatment
Trypanosomiasis:	Protozoan parasites <i>Trypanosoma brucei</i> (<i>T. b.</i>) <i>gambiense</i> and <i>T. b. rhodesiense</i>	Humans are principal host. Dogs, cats and other mammals too Bite of infected tsetse flies	<i>T. b. gambiense</i> causes chronic illness after prolonged incubation period of weeks or months	<i>T. b. gambiense</i> present in foci in tropical countries of western and central Africa	Persons in household contact not at risk for infection Proper disposal of human excreta reduces prevalence Avoid contact with tsetse flies – bites are difficult to avoid because tsetse flies bite during day, can penetrate clothing and are not deterred by insect repellents	Tiabendazole Consult experts
African trypanosomiasis (sleeping sickness)			<i>T. b. rhodesiense</i> causes more acute illness, with onset a few days or weeks after infected bite; often, a striking inoculation chancre. Initial signs include headache, insomnia, enlarged lymph nodes, anaemia and rash. In late stages, there is loss of weight and involvement of CNS. Without treatment, invariably fatal	<i>T. b. rhodesiense</i> in East Africa, extending south as far as Botswana		
Trypanosomiasis: American trypanosomiasis (Chagas disease)	Protozoan parasite <i>Trypanosoma cruzi</i>	Blood-sucking triatomine bugs ('kissing bugs'). Also by transfusion if blood is from infected donor	Chronic illness, progressive myocardial damage leading to cardiac arrhythmias and dilatation, and mega-oesophagus and megacolon	Mexico, Central and South America (to central Argentina and Chile)	Avoid exposure to blood-sucking bugs. Use bednets in houses and camps	Consult experts

^aA more comprehensive list is available at: <http://www.cdc.gov/parasites/az/index.html> (accessed 30 September 2013).