

Upper Respiratory Tract Infections

6

Introduction, 117

Conjunctivitis and keratoconjunctivitis, 117

Introduction, 117
Organism list, 118
Diagnosis of conjunctivitis, 118
Management, 119
Adenoviruses, 119
Herpes simplex keratitis (dendritic ulcer), 119
Bacterial conjunctivitis, 119
Neonatal conjunctivitis, 120
Chlamydial conjunctivitis and trachoma, 120
Amoebic keratoconjunctivitis, 121

Infections of the middle ear, 121

Acute otitis media, 121
Paranasal sinusitis, 122

Viral infections of the throat and mouth, 122

Organism list, 122
The common cold (coryza), 122
Enteroviral pharyngitis, 123
Adenoviral sore throats and pharyngoconjunctival fever, 124
Infectious mononucleosis, 125

Bacterial throat infections, 128

Organism list, 128
Streptococcal tonsillitis, 128
Acute epiglottitis, 132
Diphtheria, 133
Ludwig's angina, 136
Retropharyngeal abscess, 137
Vincent's angina, 137

Introduction

The upper respiratory tract comprises the conjunctiva, nose, paranasal sinuses, middle ear, nasopharynx, oropharynx and laryngopharynx. It is largely covered with ciliated columnar epithelium. Exceptions are the oropharynx, vocal cords, upper posterior epiglottis and mastoid antrum of the middle ear, which are lined with stratified squamous epithelium. The conjunctiva is also composed of stratified squamous epithelium, continuous with and similar to the epithelium of the cornea.

The adenoids and tonsils are important structures of the upper respiratory tract. They are lymphoid organs whose surfaces are marked by many deep clefts, both macroscopic and microscopic.

The whole upper respiratory tract is colonized by a variety of normal flora.

Normal upper respiratory tract flora

- 1 *Streptococcus pneumoniae*.
- 2 Anaerobic and microaerophilic streptococci.
- 3 *S. 'milleri'* group of streptococci (found in the sinuses).
- 4 *Haemophilus influenzae*.
- 5 Other *Haemophilus* species.
- 6 Diphtheroids.
- 7 Coagulase-negative staphylococci.
- 8 *Staphylococcus aureus*.
- 9 *Moraxella catarrhalis* and *Neisseria* spp.
- 10 *Prevotella melaninogenica* and related species.

Temporary colonization of the pharynx, nose or eye by potential pathogens is also common, and may provide an important reservoir of infection, for instance with *Neisseria meningitidis* or *Corynebacterium diphtheriae*. Similarly, highly transmissible viruses, such as rhinoviruses, paramyxoviruses, enteroviruses, adenoviruses and myxoviruses, can infect the nasopharynx, mildly or asymptotically.

Latent viruses may be intermittently shed from the pharynx. Herpes simplex virus, other human herpesviruses, such as HHV-6, Epstein–Barr and cytomegalovirus virus are the most important of these.

The environment of the upper respiratory tract is varied, and different areas are susceptible to infection with different pathogens. While most infections are of surfaces, the middle ear and the paranasal sinuses are hollow structures with narrow outlets (the ostia of the sinuses and the Eustachian tubes of the middle ears) whose obstruction leads to loculated infection and abscess formation. The soft tissues of the fauces, surrounding the tonsils, are susceptible to abscess formation if severely inflamed.

Conjunctivitis and keratoconjunctivitis

Introduction

The conjunctiva is often inflamed during infections of the

respiratory tract, such as colds, influenza and measles. It is exposed to many air-borne infections, but the washing action of the tears discourages the establishment of infection. Tears contain a number of substances, including lysozymes and immunoglobulins, that inhibit pathogens. Nevertheless, a number of organisms commonly cause primary conjunctivitis. Conjunctival infections are easily transmitted directly from eye to eye by fingers, by fomites such as ophthalmological instruments, or shared face towels and, in conditions of poor hygiene, by flies. When the cornea is involved, the condition is called keratitis or keratoconjunctivitis.

Occlusion of the conjunctiva by contact lenses increases the likelihood of infection, and poor lens hygiene can lead to severe pseudomonal or amoebic infections with the risk of severe corneal damage.

Organism list

- Adenoviruses
- Enteroviruses (especially type 30)
- Herpes simplex virus
- *Staphylococcus aureus*
- *Moraxella lacunata*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Neisseria gonorrhoeae* and *N. meningitidis*
- *Chlamydia trachomatis*
- *Pseudomonas aeruginosa**
- *Acanthamoeba* spp.*
- *Naegleria* spp.*

*These organisms are particularly associated with contact lens use.

Clinical features

The eye feels sore and itchy, and there is a discharge of watery, mucoid or purulent material, which may dry, especially during sleep, and glue the eyelids together. Severe infection may cause swelling of the eyelids, which further inhibits eye-opening and drainage of secretions.

The conjunctiva appears red, often with a thin, clear outline surrounding the iris. Occasionally marked swelling causes it to bulge through the palpebral fissure.

Contact lenses exacerbate the inflammation, and may increase susceptibility to conjunctival and corneal infections, especially if not hygienically maintained. Soft or hydrophilic contact lenses may interfere with the access of drops to the eye, and can be damaged by the chemicals in eye drops. Their use should be discontinued during treatment for eye infections.

Childhood conjunctivitis

Childhood conjunctivitis (pink eye) mainly affects small children, and easily spreads in families and school com-



Figure 6.1 Conjunctivitis, showing red eye with sparing of an area around the cornea. (Courtesy of Dr K. Dansingani, Royal Free Hospital.)

munities. It begins unilaterally and often spreads to the other eye, but is usually mild, with a natural history of a few days. Respiratory strains of adenovirus (often type 3 or 7) are the common causes (Fig. 6.1).

'Shipyards eye'

Shipyards eye is acute keratoconjunctivitis spread by ophthalmological equipment. Often caused by adenovirus type 8, 19 or 37, it was once common in occupational settings such as shipyards, where minor eye trauma and frequent clinic visits occurred. Hand-washing by staff, and use of sterile or disposable equipment, control its spread in modern clinics.

Haemorrhagic conjunctivitis

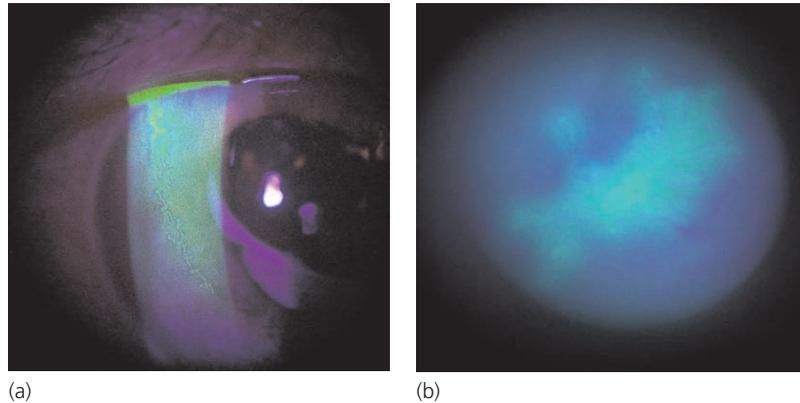
Haemorrhagic conjunctivitis caused many epidemics worldwide in the early 1980s. The agent was enterovirus type 30. The disease was abrupt in onset, moderate to severe, and associated with intense, haemorrhagic inflammation of the conjunctiva.

Diagnosis of conjunctivitis

The clinical diagnosis is usually evident. Important differential diagnoses for a red, painful eye include herpes simplex keratitis (dendritic ulcer: see below) and acute glaucoma. Both of these can be sight-threatening, and should be considered when a red eye is severely painful.

In infants the lacrimal sac may drain poorly, causing swelling and a mucus discharge at the inner canthus. The condition is non-infectious, harmless and self-limiting. Lacrimal sac drainage by digital compression abolishes the 'sticky eye' and can be discontinued after 1 or 2 weeks.

Figure 6.2 (a) Dendritic ulcer viewed by slit lamp with fluorescent contrast: the linear, meandering ulcer is seen at the edge of the cornea. (b) Large dendritic ulcer with many linear branches, occurring in an immunosuppressed patient. (Courtesy of Dr K. Dansingani, Royal Free Hospital.)



Management

Viral conjunctivitis usually resolves spontaneously in a few days. Failure to respond should prompt investigation with swabs for bacterial and viral culture, a search for chlamydial infection, and arrangements for slit-lamp examination with and without fluorescein staining, to exclude herpetic keratitis.



Cautions

- 1** A red eye unresponsive to antibiotic treatment should not be treated with corticosteroids until the possibility of herpes simplex keratitis has been ruled out.
- 2** A red eye accompanied by severe pain or headache could indicate acute glaucoma: seek an ophthalmological opinion without delay.

Adenoviruses

Adenoviruses are double-stranded linear DNA viruses (70 nm) that are classified into five subgenera and at least 51 serotypes. Infection can produce either a lytic cycle, with cell destruction and release of infectious virus, or latent or chronic infection, usually in tonsillar or lymphoid tissue. Alternatively, in 'oncogenic transformation' only the early replicative stages occur and the viral DNA is integrated into host cell DNA without production of infectious virions. Replication-incompetent adenoviruses are used in research as vectors for gene insertion.

Herpes simplex keratitis (dendritic ulcer)

This is a progressive infection of the corneal epithelium that presents as a red, painful eye. It produces an ulcer, which is often complex or branching.

The diagnosis is suggested by a persistently red eye, unresponsive to topical antibiotic treatment *and that progresses rapidly if treated with topical corticosteroids*. The linear, meandering ulcer can be seen on slit-lamp ex-

amination, or by inspection after the instillation of fluorescein drops (Fig. 6.2). Untreated herpes simplex ulcers erode the corneal epithelium, leading to scarring (Fig. 6.3) and visual impairment. Diagnosis is confirmed by demonstration of herpes simplex virus antigen (by direct fluorescence staining) or DNA (by polymerase chain reaction, PCR) in corneal scrapings, or by viral culture.

The treatment of choice is topical aciclovir ointment. Treatment is continued until healing is complete. Follow-up by an ophthalmologist is important, both to monitor healing and to detect residual corneal scarring.

Treatment of herpes simplex keratitis

- 1** Topical aciclovir 3% eye ointment five times daily (continue for at least 3 days after complete healing) or
- 2** Topical ganciclovir 0.15% in gel basis, five times daily until complete corneal re-epithelialization, then three times daily for 7 days.

Bacterial conjunctivitis

Bacterial conjunctivitis may occur alone, or complicate

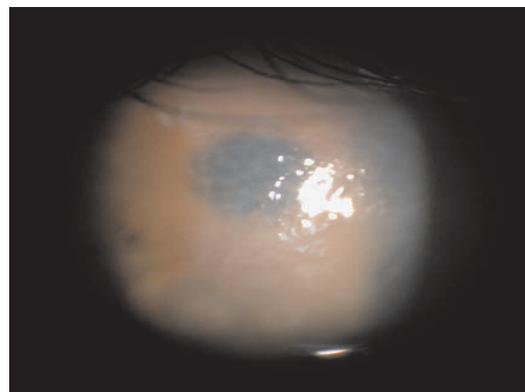


Figure 6.3 Loss of corneal epithelium, and scarring following herpes simplex keratitis. (Courtesy of Dr K. Dansingani, Royal Free Hospital.)

upper respiratory infections; common causes are *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae*. Purulent exudate is produced, often forming crusts at the inner canthus. The condition is usually mild and often self-limiting.

Unusual bacteria affecting the conjunctiva include *Moraxella lacunata*, which causes indolent or subacute infections (often in outbreaks where spread is by fomites or unwashed hands), and *H. aegyptius*, more common in tropical climates: this causes an aggressive infection and may also spread by the droplet route. *Pseudomonas aeruginosa* can cause keratoconjunctivitis, with blurred vision, in contact lens wearers. Infection is derived from unsterile cleaning fluids or from inappropriate use of stored tap water.

Chloramphenicol eye drops are the treatment of choice for mild and moderate bacterial conjunctivitis. Chloramphenicol ointment can be used at night. The course should rarely be longer than a week. The risk of agranulocytosis from topical use is now thought to be negligible. Specific bacterial infections may be treated with other appropriate antibiotics, for instance, *Pseudomonas* infections with ciprofloxacin drops, or staphylococci with fusidic acid. Gentamicin drops are also available for treating *Pseudomonas* conjunctivitis.

Severe, unresponsive or ulcerating eye infections require specialist management, which may include subconjunctivally injected and/or parenteral antibiotics.

Treatment of bacterial conjunctivitis

- 1 Chloramphenicol 0.5% eye drops at least 2-hourly, then four times daily when infection is controlled. Continue for 48 h after healing. Chloramphenicol 1% eye ointment may be used instead of drops at night, or alone in a dose of three or four times daily.
- 2 For staphylococcal infections: fusidic acid 1% drops in a gel basis twice daily.
- 3 For *Pseudomonas* infections: ciprofloxacin 0.3% or ofloxacin 0.3%, eye drops, in the same regimen as for chloramphenicol drops (for corneal ulcer, use ciprofloxacin every 15 min for 6 h, then every 30 min for that day, every hour the second day, then every four hours for days 3–14, maximum course: 21 days).
- 4 Alternatives for superficial conjunctivitis: gentamicin 0.3%, neomycin 0.5%, or framycetin 0.5%, may be used in the same regimen as for chloramphenicol or lomefloxacin 0.3%, every 5 minutes for five doses, then twice daily.

 **Caution:** Ciprofloxacin, ofloxacin and lomefloxacin are well-absorbed: in pregnancy their safety is not established; they should be used only if an expert risk assessment has been made.

Neonatal conjunctivitis

Neonatal conjunctivitis is an intrapartum infection, derived from the colonized or infected maternal birth canal.

Causes of neonatal conjunctivitis

- Onset at 2 to 4 days: *Neisseria gonorrhoeae*.
- Onset at 3 to 10 days (often unilateral): *Chlamydia trachomatis*.
- Onset at 2 to 16 days: herpes simplex.

Although these infections will respond to topical treatment, there may be coexisting infection of the respiratory, alimentary or genital tracts of the infant (see Chapter 17). Chlamydial pneumonia commonly occurs in neonates presenting with chlamydial conjunctivitis. Systemic treatment is therefore given.

Prophylaxis of neonatal bacterial conjunctivitis is possible, using chlortetracycline or chloramphenicol eye ointment, in a single application.

Treatment of neonatal conjunctivitis (see also Chapter 17)

- 1 Gonococcal: ceftriaxone 25–50 mg/kg; single intravenous dose.
- 2 Chlamydial: erythromycin 50 mg/kg daily, orally, in four divided doses for 14 days.
- 3 Herpes simplex: aciclovir 50–100 mg orally four times daily for 5 to 10 days (may be supplemented by topical treatment; then use lower oral dose).

 In all cases, both parents should be offered investigation and treatment for urogenital infections.

Chlamydial conjunctivitis and trachoma

Oculogenital strains of *Chlamydia trachomatis* commonly cause conjunctivitis, as well as colonizing the genital tract. Subacute conjunctivitis, unresponsive to chloramphenicol treatment, spreads between sexual contacts and from eye to eye. A rapid diagnosis is made from eye swabs, either by detecting chlamydial lipopolysaccharide (LPS) group antigen, using enzyme immunoassay (EIA), or detecting chlamydial DNA by PCR or ligase chain reaction. *Chlamydia trachomatis* inclusion bodies can be seen by microscopy of epithelial cells in conjunctival scrapings, but this is now rarely done. Oculogenital chlamydiae can be distinguished from one another and from the serotypes that cause trachoma and lymphogranuloma venereum, by serotyping. This is based on outer membrane proteins, nowadays identified by molecular methods.

Chlortetracycline eye ointment is the treatment of choice. Oral treatment, e.g. erythromycin or tetracycline, may be added. Investigation and treatment of the patient

and sexual partner for genital infection are also necessary (see Chapter 15).

Trachoma

Trachoma is a disease of crowding and poor hygiene that predominantly affects poor, marginalized and displaced communities. It is precipitated by persisting or repeated infection with *C. trachomatis*, spread from eye to eye by unwashed hands, and possibly by flies. Untreated infection and repeated super-infections may lead to the formation of a plaque of vascular inflammatory tissue (pannus), which deforms the eyelid. Scarring, leading to entropion and trichiasis, is an important cause of corneal damage, scarring and blindness.

For the treatment of trachoma, community wide application of single dose oral azithromycin has been found as effective as 6 weeks of once- or twice-daily tetracycline eye ointment administered under supervision. Azithromycin is therefore more likely to be effective, if the use of tetracycline eye ointment cannot be supervised.

World Health Organization (WHO) SAFE strategy for combating trachoma

Surgery for in-turned lids.

Antibiotics for active disease.

Face washing.

Environmental improvement, to reduce transmission.

Amoebic keratoconjunctivitis

Amoebic keratoconjunctivitis is a rare condition associated with using contact lenses or with environmental exposure (e.g. to water in hot springs). Contact lens cleaning fluid can become colonized by free-living amoebae, usually *Acanthamoeba*, but occasionally *Nae-gleria* spp., which are then repeatedly inoculated into the eye. The resulting severe, ulcerating keratitis is difficult to treat and often damages vision. The treatment of choice is propamidine isetionate (Brolene) 0.1% eye drops four times daily or 0.15% dibromopropamidine isetionate ointment once or twice daily. These may be used in combination with chlorhexidine and neomycin eye drops (specialist supervision required). Control is by the use of only sterile cleaning fluids, which are discarded after use.

Infections of the middle ear

Acute otitis media

Organism list

- Many respiratory viruses
- *Streptococcus pneumoniae*

- *Haemophilus influenzae*
- *S. pyogenes*
- *Staphylococcus aureus*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*
- *Moraxella catarrhalis*

Introduction

Childhood otitis media

Infection of the cavity of the middle ear (otitis media, or OM), is a common condition in small children. It causes pain, reddening and opacification of the tympanic membrane, sometimes with mild fever. Many cases of OM are probably viral. *Chlamydia pneumoniae* is also recognized as a cause. Symptomatic treatment with simple analgesics, such as paracetamol, is usually adequate, as the disorder resolves spontaneously in 48 to 72 hours. Several studies have shown that the time to recovery is rarely shortened by antibiotic treatment. Myringotomy and culture of middle ear contents do not lead to more effective treatment, and are not recommended.

Acute suppurative otitis media

Acute suppurative otitis media (ASOM) can affect individuals of any age. It is an aggressive infection, with fever, livid inflammation of the eardrum, a visible, whitish fluid level, or early tympanic rupture and frankly purulent discharge. It may be spontaneous, but often complicates a respiratory infection, in which respiratory tract organisms ascend the Eustachian tube to infect the obstructed or virus-inflamed cavity. ASOM is a common complication of influenza, and a major complication of measles. Causative organisms include *Streptococcus pneumoniae*, *H. influenzae*, *S. pyogenes* and *Staphylococcus aureus*. Swabs should be obtained of any discharge from the ear. Antibiotic therapy should be commenced without delay, to minimize damage and scarring of the eardrum.

Management of otitis media

- 1 For mild pain and reddening of drum, with no fluid level or other features, or with general upper respiratory symptoms: analgesics, and decongestant if indicated. Review if persistent or worsening.
- 2 Evidence of *C. pneumoniae* or *M. pneumoniae* infection (see Chapter 7): systemic erythromycin (or tetracycline in an adult) may be beneficial.
- 3 ASOM, with severe pain, discharge or important precursor such as measles or influenza: ideally, obtain pus for bacterial culture; oral antibiotic treatment should include an antistaphylococcal spectrum. Co-amoxiclav, cephradine, clarithromycin or azithromycin are appropriate. Analgesia is essential.

Complications

Mastoiditis

Mastoiditis is the extension of pyogenic middle ear infec-

tion into the mastoid antrum. If treated early with antibiotics this may resolve, but loculated pus in the air cells of the antrum makes the infection difficult to eradicate. There is severe pain behind and within the ear, and often a high fever. Surgical treatment, with opening and debridement of the air cells (mastoidectomy) is curative and removes the risk of advancing intracranial infection.

Attic infection

Attic infection involves the high roof of the middle ear cavity, which includes the course of the facial nerve. It is more common in chronic or neglected ear infections. A cholesteatoma (tumour of waxy inflammatory tissue) may form, and can erode the temporal bone, predisposing to intracranial infection. Treatment of cholesteatoma is surgical. Rare cases of chronic middle ear infection can be complicated by the presence of anaerobic pathogens.

Paranasal sinusitis

In this condition the paranasal sinuses fill with exudate, and the draining ostia become blocked. Like otitis media, it is often secondary to a catarrhal infection and may be caused by *S. pneumoniae*, *H. influenzae*, *S. 'milleri'*, anaerobes or *S. aureus*.

Clinical features are pain and tenderness over the affected sinus, usually a maxillary or frontal sinus. There is a loss of transillumination, and X-rays show thickening of the soft-tissue wall of the cavity, often with a fluid level (see Fig. 1.8).

Treatment includes elevation of the head, and decongestants to aid drainage. An oral broad-spectrum antibiotic such as co-amoxiclav, cefuroxime axetil or tetracycline will reduce the purulent exudate. In relapsing or chronic cases, the ostia of the frontal sinuses can be surgically enlarged, or false ostia can be made to drain the maxillary sinuses to the buccal cavity.

Complications of sinusitis

The ethmoid sinus has thin lateral and superior walls, which can rupture if infection causes raised pressure in the sinus cavity. Lateral spread of infection causes orbital cellulitis, while superior spread may lead to meningitis.

Cavernous sinus thrombosis is a grave complication of severe, untreated sphenoid sinusitis, or posterior extension from ethmoid sinusitis. Warning signs are high fever, severe headache, periorbital oedema and sometimes altered consciousness. It is best diagnosed by computed tomography or magnetic resonance scan. High-dose parenteral antibiotic treatment is mandatory. A third-generation cephalosporin, such as ceftriaxone, 2–4 g daily by intravenous infusion, should be given. Flucloxacillin 1.5–2.0 g 6-hourly may be added to improve antistaphylococcal cover. Clindamycin 600–900 mg 6-hourly by intravenous infu-

sion provides antistaphylococcal and anti-anaerobe cover with excellent tissue penetration.

Viral infections of the throat and mouth

Organism list

- Rhinoviruses
- Coronaviruses
- Enteroviruses
- Adenoviruses
- Epstein–Barr virus
- Herpes simplex virus

The common cold (coryza)

Introduction

The common cold is caused by numerous strains of rhinoviruses and sometimes by coronaviruses or other respiratory virus infections. Colds are extremely infectious by the droplet route, and are also transmitted by contaminated hands or fingers. Mild fever, swelling of the mucosae of the nose, throat and conjunctiva, and often sore throat are followed by a copious mucoid nasal exudate. Otitis media in children and sinusitis in adults are common complications.

Virology and pathogenesis of common colds

Rhinoviruses are members of the Picornaviridae and exist in over 100 different serotypes. They are small RNA viruses (28–34 nm), possessing a single, approximately 7.2 kb strand of positive RNA and expressing icosahedral symmetry. A single polypeptide is produced and cleaved. There are four capsid proteins, VP1–4. The viral shell consists of 60 capsids organized as 12 pentamers. These each contain a distinct valley, within which is a 'pocket', which is thought to play an important role after attachment, leading to release of viral RNA. In most strains this contains a strongly hydrophobic molecule known as pocket factor. This pocket is a potential site for specific inhibitors of the virus. The virus binds via its VP1 protein to host cell intercellular adhesion molecule 1 (ICAM-1) to gain attachment and entry. A single point mutation confers protection from virus neutralization, but new serotypes of rhinovirus are not emerging rapidly.

Coronavirus is the only genus in the family Coronaviridae. It is a pleomorphic, non-enveloped, positive sense, single-strand RNA virus of variable size (60 to 220 nm). The virus has characteristic club-shaped surface projections 20 nm in length (Fig. 6.4). These are composed of a high-molecular-weight glycoprotein (180 kDa) and dis-

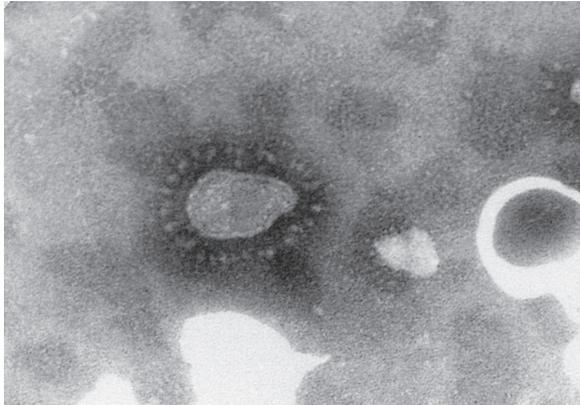


Figure 6.4 Negatively stained electron micrograph of a coronavirus.

play strain-specific antigens. They are readily removed by protease activity. The three main structural proteins are the nucleocapsid proteins, which are species-specific, the surface projection protein and the transmembrane (matrix) protein. These coronaviruses differ from the SARS coronavirus, which is discussed in more detail in Chapter 26.

The main mechanism of pathogenesis is probably a direct cytotoxic effect on respiratory epithelial cells.

Laboratory diagnosis

The principal approach to respiratory virus diagnosis is the identification of viral RNA by RT-PCR. Cell culture is rarely attempted due to the frequency and trivial nature of the infection. Nasal washings may be inoculated into human embryonic lung fibroblasts. An enterovirus-like cytopathic effect (CPE) often develops within 8 days but may require a second passage to become evident. Serotype-specific antibodies can be detected, but serological tests are too cumbersome for routine use.

Coronaviruses are difficult to isolate, and serological investigations are not readily available. Virus can be isolated from nasal and throat swabs and nasopharyngeal aspirates by inoculation in human embryonic lung fibroblasts. The CPE consists of small granular round cells in the monolayer. RT-PCR provides the simplest approach to diagnosis (see Chapter 3).

Management

Treatment is symptomatic and includes antipyretic analgesics, mild decongestants such as pseudoephedrine tablets, and bed rest in severe cases.

Enteroviral pharyngitis

Epidemiology

Enteroviral pharyngitis is common, with an annual epi-

demio peak in summer and autumn. Echovirus strains and Coxsackie type A10 are most often implicated. Humans are the only known reservoir of infection and transmission occurs by direct contact or droplet spread. Epidemics frequently affect young children in nurseries, playgroups and schools. Crowding and poor hygiene increase the risk of transmission.

Virology and pathogenesis of enteroviral infections

Enteroviruses all belong to the family Picornaviridae, which comprises four genera – of which rhinoviruses and enteroviruses cause disease in humans. More than 70 enterovirus serotypes have been isolated from human sources, and these belong to five main groups:

- 1 polioviruses;
- 2 group A Coxsackieviruses;
- 3 group B Coxsackieviruses;
- 4 ECHO (enteric cytopathogenic human orphan) viruses; and
- 5 five recently characterized human enteroviruses types 68–72 (type 72 is hepatitis A virus).

Each of these has different tissue tropisms (see also Chapter 13).

The viruses are 30 nm in diameter, with icosahedral symmetry. The virion contains four proteins: VP1–4. The genome is a single strand of positive-sense RNA. Variations in VP1–VP3 are responsible for serological diversity; antibodies generated by infection neutralize only the homologous virus strain. VP4 mediates binding to host cell receptor sites: different tissue tropisms among enteroviruses probably depend on the specificity of these receptors. The VP4 protein structure of two poliovirus serotypes has been fully identified. Both possess a deep cleft through which the virus binds to the host cell membrane.

Groups of enteroviruses

- 1 Polioviruses.
- 2 Coxsackieviruses group A.
- 3 Coxsackieviruses group B.
- 4 Echoviruses.
- 5 Other recently characterized human enteroviruses.

Pathology

Enteroviruses enter the body through the pharynx and alimentary tract. The virus multiplies in the tonsils, Peyer's patches and other bowel-associated lymphoid tissue. Viraemia often occurs, and may be followed by disease in different organs, for example meninges, myocytes, brain or skin. In poliomyelitis the virus multiplies in the anterior horn cells and the resulting cell damage leads to flaccid paralysis (see Chapter 13).

Clinical features

The incubation period of about 1 week is followed by sore

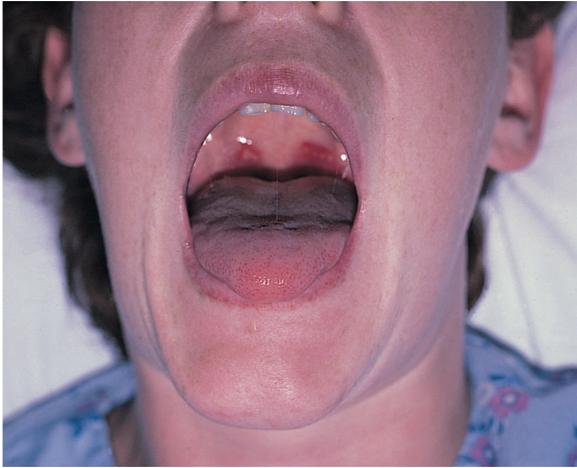


Figure 6.5 Faucial blisters in a case of herpangina.

throat and fever, whose severity and duration vary greatly. In severe cases, headache, stiff neck or meningism may occur. Symptoms rarely last more than 5–7 days.

Reddening of the fauces is usual, but does not parallel the intensity of symptoms. Groups of moderately enlarged lymph nodes are often palpable in the anterior and posterior triangles of the neck. Rarely, both echovirus and Coxsackievirus infections produce a rash of sparse macules or small papules, concentrated on the cheeks and trunk.

Coxsackie A infections may cause a pharyngeal rash of blisters with inflamed haloes (herpangina; Fig. 6.5). Hand, foot and mouth disease of toddlers causes similar lesions in the mouth, accompanied by blisters on the palms and soles, and a papular rash on the buttocks (see Chapter 5).

Coxsackie B infections can cause pleurodynia (Bornholm disease), with high fever, sore throat and tender, painful orchitis and, rarely, myocarditis.

Management

There is no specific antiviral treatment for enteroviral pharyngitis. Analgesics, especially non-steroidal anti-inflammatory agents, are helpful. In patients over the age of 16 years, soluble aspirin gargles may help, and can be swallowed for their systemic effects.

Laboratory diagnosis

Detection of enteroviral RNA by RT-PCR is a useful rapid test for the diagnosis of enteroviral meningitis or encephalitis. By culture, enteroviruses are most easily recovered from faeces, but throat swabs and cerebrospinal fluid should also be examined in cases of meningitis. Culture of an enterovirus from a sterile site is diagnostic, whereas isolation from faeces is less certainly so. Infected human embryonic lung (HeLu) cells become rounded and refrac-

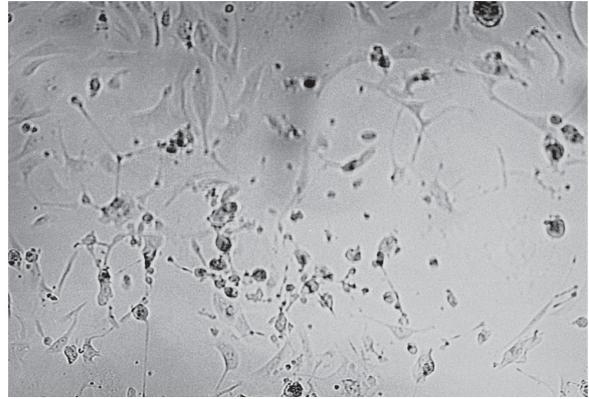


Figure 6.6 Cytopathic effect of enteroviruses, showing rounding, shrinkage and loss of contiguousness of the cell monolayer. Courtesy of Dr M. Zambon, HPA Centre for Infections.

tile before separating from the monolayer (Fig. 6.6). Isolates are typed by neutralization using pooled antisera.

Coxsackie group A viruses grow poorly in cell cultures, but can be replicated by intracerebral inoculation of mice. Serodiagnosis is available using immunoglobulin M (IgM) antibody capture methods.

Complications

The spectrum of enteroviral infections includes lymphocytic meningitis, myositis, pericarditis and acute myocarditis. Patients with significant meningism, precordial pain, dysrhythmias or heart failure require further investigation.

Adenoviral sore throats and pharyngoconjunctival fever

Introduction and pathology

Adenoviruses of types 1–10 are capable of infecting the respiratory tract. Typically, they cause severe, inflamed sore throat, high fever and painful enlargement of cervical lymph nodes. Some also infect the conjunctiva (leading to pharyngoconjunctival fever), or the lower respiratory tract. The illness may last 7–10 days and is often followed by debility in the convalescent period. Neonates and immunocompromised patients may suffer severe pneumonia (types 1–7), urethritis (type 37) and hepatitis in liver allografts.

Pathology of adenovirus infections

Human adenoviruses are unenveloped, icosahedral viruses with a double-stranded DNA genome of approximately 35kDa. They belong to the genus Mastadenovirus, from the family Adenoviridae. Forty-two adenovirus sero-

types are recognized, divided into subgenera A–F. Group A strains cause asymptomatic enteric infection, groups B and C respiratory disease, group D keratoconjunctivitis, group E conjunctivitis and respiratory disease, and group F infantile diarrhoea. These infections occur throughout the year. They are transmitted by the faecal–oral or drop-let routes. Eye infections are also transmitted by hand–eye contact, particularly in crowded swimming pools. Epidemic keratoconjunctivitis is highly infectious.

Adenoviruses multiply inside the nuclei of epithelial cells. They are cytopathic for human cells, and this is probably the mechanism of tissue damage associated with infection. Different target specificity of serotype-specific surface ‘fibres’ contributes to the different tissue tropisms. A toxin-like activity has been associated with the vertex capsomeres.

Clinical syndromes associated with adenovirus serotypes

- acute febrile pharyngitis: (serotypes 1–7).
- pharyngoconjunctival fever (serotypes 3, 7).
- acute respiratory infection and pneumonia (serotypes 3, 4*, 7*).
- pertussis-like syndrome (serotype 5).
- conjunctivitis (serotypes 3, 7).
- epidemic keratoconjunctivitis (serotypes 8, 19, 37).
- gastroenteritis (serotypes 40, 41).
- acute haemorrhagic cystitis (serotypes 11, 21).



A bivalent adenovirus type 4 and 7 vaccine is available for prevention of acute respiratory syndromes (see Chapter 7).

Laboratory diagnosis

Adenovirus is most easily isolated from stool but can be recovered from conjunctival swabs, nasopharyngeal aspirates and cerebrospinal fluid. Human cell lines, e.g. Hep-2, are suitable for virus isolation. A cytopathic effect, seen in 48 h, is characterized by rounded-up cells with refractile intranuclear inclusion bodies. The identification can be confirmed by electron microscopy. In patient’s serum, antibodies to a group-specific antigen are detected by complement fixation test or EIA. PCR diagnosis is available.

Management

There are currently no specific anti-adenoviral drugs. Treatment of adenoviral infections is therefore supportive and includes adequate fluid intake, analgesia and rest.

Infectious mononucleosis

Introduction

Infectious mononucleosis is caused by primary Epstein–Barr virus (EBV) infection. It is a systemic disease, but in

most clinically detected cases it presents as a sore throat, so that the differential diagnosis and main complications fall into this chapter. However, 15% present as hepatitis and 10% as fever alone (see Chapters 9 and 20).

Clinical presentations of Epstein–Barr virus infection

- 1 Sore throat (anginose infectious mononucleosis) 75%.
- 2 Hepatitis 15%.
- 3 Fever alone 10%.
- 4 Rare: viral-type meningitis, mononeuritis or polyneuritis, perisplenic pain.

Although primary disease can cause considerable morbidity, late effects of infection may also be important. Both Burkitt’s lymphoma and nasopharyngeal tumours are consequences of EBV infection in early infancy. Cofactors such as early infection with malaria, or ingestion of toxins in, for example, preserved vegetables, may also be important. In the immunosuppressed, EBV infection can cause interstitial pneumonitis, precipitate a haemophagocytic syndrome or trigger EBV-driven B-cell lymphomas.

Epidemiology

EBV is shed in pharyngeal secretions, and transmission occurs via close oral contact, shared eating utensils or, in some cultures, by a mother chewing food for her infant.

Seroconversion is commonest in young children, when it is usually asymptomatic. Clinical disease affects mainly teenagers and young adults. The estimated annual incidence of clinical disease in the UK, based on the last 20 years’ statistics from the Royal College of General Practitioners’, is 1.6 per 100 000 population.

Virology and pathogenesis of EBV infections

EBV was first identified in Burkitt’s lymphoma tissue. It is morphologically identical to other herpesviruses, with icosahedral symmetry and an envelope derived from the host-cell plasma membrane. The double-stranded DNA is 172 kb: large enough to code for 100–200 proteins. These include the latent membrane protein (LMP), the terminal protein, the membrane antigen complex, the early antigen (EA) complex, the viral capsid antigen (VCA) and the Epstein–Barr nuclear antigen (EBNA) complex. The EBNA complex contains at least six proteins, probably important in maintaining the virus in the infected cell. EBNA-1 antigen is expressed on all infected cells but may be lost as infected cells die. The early antigen (EA) complex depends on genes encoding thymidine kinase, DNA polymerase and late structural genes including viral capsid antigens, and marks cells that have entered a lytic phase. Host antibodies to EBNA and EA appear early in infection and are transient. Antibodies to capsid antigens appear in IgM by the onset of illness, and may persist for weeks or months.

IgG anti-capsid antibodies indicate immunity, and persist throughout life.

Virus binds to the CD21 receptor of host B-cells (the receptor for the C3d component of complement) via the major viral glycoprotein gp350/220. Adherence is followed by endocytosis, fusion of virus with the endocytotic vesicle membrane via viral gp85, and viral release into the cytoplasm. Another viral antigen, gp42, binds the major histocompatibility complex class II molecules, which serve as co-receptors for B-cells.

During viral latency, EBV DNA persists in host cells as double-stranded episomes, organized into nucleosomes similar to chromosomal DNA: 10% of EBV genes are expressed including six EBNA (1, 2, 3A, 3B, 3C and LP). The function of these genes in latency and in the immortalization of infected cells is now known. For example, LMP-1 mimics the growth and survival signals given to B cells by CD4 T cells. It mediates EBV-induced transformation, and is found in many EBV-related lymphomas.

Virus first invades pharyngeal cells, from where B lymphocytes become infected and carry the virus throughout the body. EBV-mediated activation and immortalization of infected B cells is the probable pathogenic mechanism for the many 'immunological' effects and complications of infection.

Clinical features

After 6–8 weeks' incubation, fever, sore throat and widespread lymphadenopathy develop more or less simultaneously. A white creamy exudate appears on the tonsils, and becomes confluent within 24–36 h. The exudate may become bulky but is rarely discoloured and it does not involve the pharyngeal mucosa (Fig. 6.7). The pharyngeal, conjunctival and nasal mucosae are congested and swollen. Gross pharyngeal swelling may make it impossible to swallow saliva and can threaten the airway.



Figure 6.7 Exudative tonsillitis with marked cervical lymphadenopathy in a case of infectious mononucleosis.

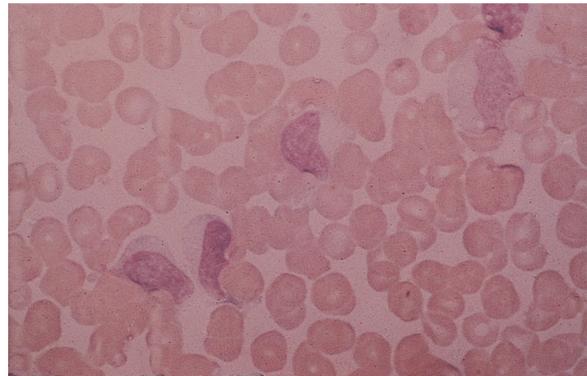


Figure 6.8 Atypical mononuclear cells in the peripheral blood of a case of infectious mononucleosis.

The spleen is palpable in 25–40% of cases; the liver edge is often palpable. Chest X-ray occasionally shows enlarged mediastinal lymph nodes and, surprisingly, as many as 20–25% of patients have a lung opacity suggesting segmental pneumonitis. These abnormalities resolve spontaneously as the fever abates.

Infected B cells remain within reticuloendothelial tissues, while numerous activated T cells appear in the bloodstream. These are seen as 'atypical mononuclear cells' and may constitute 40% or more of the total lymphocyte count during the acute infection (Fig. 6.8).

The liver function tests show raised transaminases, usually in the range of 60–500 IU/ml. The alkaline phosphatase may rise during convalescence, sometimes approaching 1000 IU/ml, but this usually resolves uneventfully.

The activated B cells produce various antibodies, including the diagnostic 'heterophile antibodies', which agglutinate horse and sheep red blood cells. Others include haemolysins, platelet antibodies, anti-nuclear antibodies, rheumatoid factors and anti-cardiolipin antibodies. These antibodies are occasionally associated with immune cytopenias or autoimmune-like diseases, but this affects fewer than 1 in 20 000–30 000 clinical cases.

The duration of fever and exudative pharyngitis varies from a few days to 3 weeks or more. Most patients subsequently convalesce steadily, but a minority suffer prolonged post-infectious fatigue. Persisting chronic fatigue syndrome (CFS) is a rare complication of EBV infection.

Diagnosis

The clinical picture is often sufficient for diagnosis. The exudate seen in streptococcal pharyngitis is follicular and rarely confluent. The pseudomembrane of diphtheria is sometimes confluent, but it is discoloured, and tends to spread beyond the tonsillar margin. In both bacterial diseases there is a low-grade neutrophilia, unlike the atypical lymphocytosis of EBV infection.

The Monospot slide agglutination test demonstrates the presence of heterophile antibody, utilizing horse red cell agglutination, and is positive in about 90% of patients at presentation. Children below age 5 years, however, do not produce high levels of heterophile antibodies, and about 50% of these patients have a negative test. PCR is emerging as a sensitive method of detecting EBV infection.

IgM anti-EBV capsid antibodies are detectable by ELISA at presentation, and are diagnostic of acute infection. Rising IgG titres to VCA cannot be detected, as concentrations are already high when the patient presents. Although EBV can be cultivated, this approach is not used as cultures are likely to be positive in specimens from latently infected asymptomatic individuals.

Management

There is no specific treatment; most cases recover eventually. In older children and adults soluble aspirin in standard doses may be gargled and swallowed. In the under-16s paediatric formulations of ibuprofen are useful if paracetamol is not effective. Stronger analgesics may be indicated if pharyngeal pain is severe.

Complications

Threatened respiratory obstruction

Threatened respiratory obstruction is the commonest reason for hospital admission. It often improves with elevation of the head (to encourage drainage of oedema from the pharyngeal tissues) and anti-inflammatory analgesics. Danger signs are inability to swallow saliva and a rapidly increasing pulse rate; increasing respiratory rate and cyanosis occur later. Obstructing pharyngeal oedema can often be reduced by intravenous treatment with a bolus of 100–200 mg hydrocortisone. This is effective within 20–30 minutes. As in corticosteroid treatment of croup and bronchiolitis, adverse effects are rare and dosing can be repeated if non-steroidal anti-inflammatory agents do not maintain the improvement. Emergency intubation or tracheostomy are rarely necessary.

Corticosteroid treatment does not affect the duration of symptoms.

Effects of abnormal antibodies

Effects of abnormal antibodies are rarely clinically important. Thrombocytopenia is the least uncommon, followed by haemolytic anaemia. A handful of cases of systemic lupus erythematosus-like disease are reported, with joint pains, and with anti-DNA positive antibodies, which may persist for some months. Symptoms resolve during convalescence when B-lymphocyte activation ceases and the antibodies disappear.

Suppurative complications

Peritonsillar abscess, pharyngeal abscess, ethmoiditis,

infection of other intracranial sinuses and periorbital cellulitis, sometimes with severe sepsis, can result from secondary infection of inflamed mucosae and obstructed sinuses. Severe pain and swelling affecting these sites should be actively investigated and appropriately treated.

Rupture of the spleen

Rupture of the spleen is extremely rare. It may present with left upper quadrant and shoulder pain during acute disease or be precipitated by apparently trivial trauma, such as a blow during play, a sudden movement or a cough. A peritoneal tap may yield blood-stained fluid. Imaging studies may demonstrate free fluid in the peritoneal cavity, or disrupted splenic anatomy. Prompt surgical intervention is needed to terminate bleeding. Contact sports or combat sports should be avoided until lymphadenopathy (and therefore splenomegaly) have subsided.

Neurological complications

Neurological complications include lymphocytic meningitis, mononeuritis or brachial plexitis (Fig. 6.9). These are benign and self-limiting. Occasional cases of encephalopathy are reported, of which some are progressive or even fatal.

Haemophagocytic syndrome

Haemophagocytic syndrome is a rare, life-threatening complication, with a high case-fatality rate. It results from inability to terminate EBV viral replication in activated lymphocytes. It is commonest in individuals with recognized disorders of cell-mediated immune (CMI) responses. However, some apparently normal young people develop the disorder, probably due to a subtle cell-mediated immunodeficiency that only becomes apparent when they contract EBV infection. Management should be undertaken by an expert clinical immunologist, and may

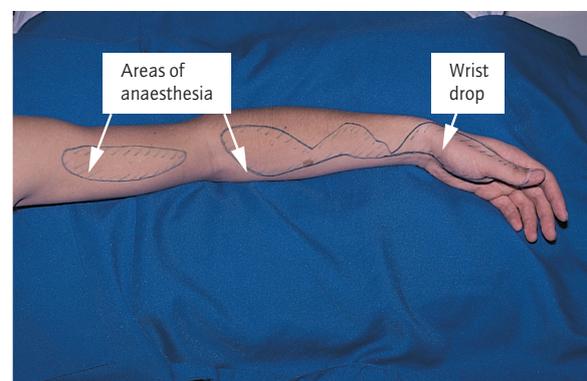


Figure 6.9 Brachial plexitis complicating infectious mononucleosis: complete recovery occurred within 3 weeks.

include the use of antiviral drugs, etoposide or other immunosuppressive regimens.

Bacterial throat infections

Organism list

- *Streptococcus pyogenes*
- *Haemophilus influenzae*
- *Corynebacterium diphtheriae*
- Other bacteria, including *Neisseria meningitidis*, *H. haemolyticum*, *Chlamydia pneumoniae* and *Staphylococcus aureus*.

Streptococcal tonsillitis

Introduction

Streptococcal tonsillitis is caused by *S. pyogenes* (group A streptococcus, or GAS). It is common worldwide, and can affect both adults and children. It causes considerable short- and medium-term morbidity, and can be recurrent, as *S. pyogenes* is a tenacious colonist of the throat, and exists in many serotypes. It is important because streptococcal throat infections can be complicated by scarlet fever, post-streptococcal nephritis, post-streptococcal reactive arthritis or rheumatic fever (see Chapter 21).

Epidemiology

Streptococcal pharyngitis is common in temperate climates, occurring mainly in the winter. Transmission is mainly by direct contact with respiratory secretions, and less commonly by air-borne droplets or indirect contact by hands. Rarely, outbreaks have resulted from consumption of contaminated food and milk.

The infection presents mainly in children, up to 20% of whom may be asymptomatic carriers. Disease is commoner in crowded settings such as children's homes and military camps.

The incidence and severity of scarlet fever (and other manifestations of group A streptococcal infection) have declined steadily over the past 50 years. In 1936, when yearly notifications began, there were 104 862 notifications and 440 deaths from scarlet fever in England and Wales; a case fatality ratio of 0.42 per 100. By 1986, this had dropped to 6888 notifications and 3 deaths (0.05 per 100). The incidence (but not the case fatality ratio) increased during 1988 and 1989, but has subsequently declined to around 2000 cases per annum. A similar fall was seen in the USA; however, a resurgence of severe infections complicated by rheumatic fever occurred in the late 1980s, associated with mucoid strains of *S. pyogenes*.

Pathogenesis of *S. pyogenes* infections (Fig. 6.10)

Inhibition of host defences

The M protein of *S. pyogenes* is a fibrillar protein possessing conserved and variable domains. It binds complement control proteins. It also binds fibrinogen, which inhibits alternative complement binding and reduces the ability of neutrophils to recognize and phagocytose GAS. The organism has multiple M types and several M protein homologues that bind IgG, IgA and other host proteins, all contributing to avoidance of phagocytosis. The polysaccharide capsule, a hyaluronic acid polymer, is a poor immunogen and also contributes to inhibiting phagocytes. Surface expression of C5a- and immunoglobulin-binding proteins may interfere with chemotaxis and humoral immune responses.

Host attachment

S. pyogenes expresses at least 17 adhesion molecules including fibronectin, vitronectin, collagen binding proteins and lipoteichoic acid.

Tissue damaging toxins

Streptolysin S is critically important in the pathogenesis of necrotizing fasciitis. Streptolysin O activates complement and destroys neutrophils, lymphocytes and tissue cells by inserting pores into the plasma membrane. C5a peptidase, encoded by *scpA*, destroys C5a, the complement component that recruits neutrophils to the site of infection. Hyaluronidase and collagenase may aid tissue invasion by breaking down collagen and hyaluronic acid in connective tissue. Streptokinase acts as a plasminogen activator, producing clot lysis, possibly enhancing spread of the organism. Surface-expressed enolase is a metabolic enzyme that acts as a plasminogen activator and enhances invasiveness across tissue boundaries. Other lytic enzymes include four serologically different DNases (A–D).

The ability to disrupt connective tissues, kill cells and reduce tissue redox potential is probably important in the pathogenesis of synergistic gangrene, mixed infection with Gram-positive cocci, including *S. pyogenes* and/or *Staphylococcus aureus*, and obligate anaerobes, which can invade and destroy tissue planes.

Three streptococcal pyrogenic exotoxins (SPEs) have been identified: A, B and C. A and C are structurally similar: they cause the rash of scarlet fever (erythrogenic toxins). They are superantigens, closely homologous with some *Staphylococcus aureus* exotoxins. They stimulate the production of tumour necrosis factor, a major mediator of sepsis, and are thought to mediate the shock syndrome in severe GAS infections.

SPE B has a different structure. It is secreted as a zymogen and converted to a proteinase that is mitogenic and cardiotoxic.

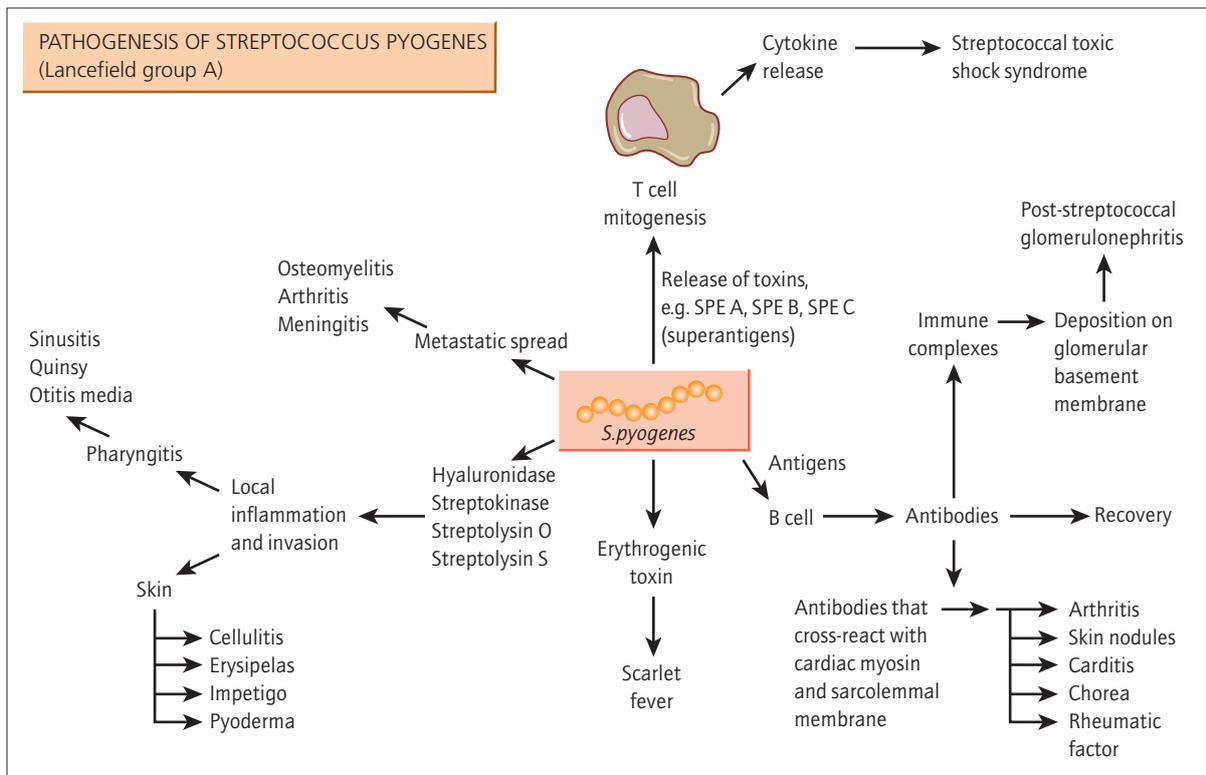


Figure 6.10 Pathogenicity of *Streptococcus pyogenes*.

Intracellular survival

Some strains of *S. pyogenes* that possess the *PRTF1* gene encoding fibronectin binding protein, are able to invade epithelial cells. They can survive within cells of the respiratory tract, possibly explaining why beta-lactam antibiotics cannot eradicate carriage.

Inappropriate immune responses

Through as yet uncharacterized cross-reacting antigens, *Streptococcus pyogenes* may trigger rheumatic fever and acute glomerulonephritis.

Pathogenicity factors for *Streptococcus pyogenes*

- 1 M proteins.
- 2 Streptolysin S.
- 3 Streptolysin O.
- 4 Hyaluronidase.
- 5 Collagenase.
- 6 DNAase.
- 7 Streptokinase.
- 8 Pyogenic exotoxins A, (B) and C.
- 9 Fibronectin binding protein.
- 10 Cross-reacting antigens.
- 11 Enolase.

Clinical features

The usual features are fever, pain in the throat, enlargement of the tonsils and tender swelling of the tonsillar lymph nodes at the angles of the jaw. The severity of the symptoms is variable; some patients with severe pain have only mild pharyngeal inflammation, while some with moderate pain have alarming tonsillar enlargement.

The classical appearance is of follicular tonsillitis, in which enlarged, red tonsils are dotted with patches of soft white exudate (Fig. 6.11). The throat is painful, rather than sore, and a large, tender lymph node swells downwards from beneath the angle of the jaw. One tonsil may be predominantly affected, with proportionately greater swelling of the lymph node on that side.

Scarlet fever

Scarlet fever is a hypersensitivity response to SPE produced by the infecting *Streptococcus pyogenes*. It presents with severe malaise and often vomiting, followed by the appearance of erythema, first on the chest but quickly becoming generalized. Erythema is increased in the folds and valleys of the skin (Pastia's sign). The papillae of the skin are swollen, forming tiny conical papules, and roughening the skin ('punctate' erythema). There may be a less affected area around the mouth or 'snout' area, but this is neither a constant nor a diagnostic feature (Fig. 6.12).



Figure 6.11 Typical appearance of follicular tonsillitis.



Figure 6.12 Typical rash of scarlet fever.

Initially the tongue is furred and white (white strawberry tongue). Over about 3 days this clears from the tip backwards, leaving a reddened (red strawberry tongue) appearance (Fig. 6.13).



Figure 6.13 Red strawberry tongue of scarlet fever.

Streptococcal toxic shock syndrome

This is a severe version of scarlet fever, with shock, thrombocytopenia and multisystem involvement. Pleural and peritoneal effusions are common, and renal failure is often seen but haemorrhage is rare.

Diagnosis

Mild streptococcal tonsillitis is clinically anonymous and often self-limiting. Follicular tonsillitis with tender enlargement of tonsillar lymph nodes is typical of severe *S. pyogenes* infection, and is clinically diagnostic. Neutrophilia, in cases of sore throat, is a predictor of bacterial aetiology (with a sensitivity of 75%), and supports a decision to give antibiotic treatment. Recovery of *S. pyogenes* from throat swabs supports the diagnosis, but streptococcal colonization can coexist with viral and other sore throats. Also, *S. pyogenes* does not transfer well from swab to culture, so that there is a 20–30% false negativity rate in the results of swab cultures.

S. pyogenes is fastidious, growing only on rich nutrient media, which usually contain blood. Haemolytic toxins produce the characteristic zone of complete (beta) haemolysis, revealing suspect colonies for identification. Both growth and haemolysis are enhanced by incubation in an anaerobic atmosphere. For screening multiple specimens, selective media can be used. They may contain antibiotics such as ofloxacin or nalidixic acid, or dyes such as crystal violet, which inhibit Gram-negative and Gram-positive commensal organisms, respectively.

For routine laboratories, identification of *S. pyogenes* is based on colonial morphology (large clear colonies surrounded by a zone of beta haemolysis) and identification of the group A Lancefield antigen. Antigen is extracted from a bacteria suspension with an enzyme and detected by latex agglutination, using particles coated with an-

Table 6.1 Species of beta-haemolytic streptococci and their pathogenicity

Group	Species	Diseases caused
A	<i>Streptococcus pyogenes</i> <i>S. 'milleri'</i> (minute colony)	Acute pharyngitis, quinsy, otitis media, erysipelas, synergistic gangrene, rheumatic fever, post-streptococcal glomerulonephritis, puerperal fever Metastatic suppurative infection
B	<i>S. agalactiae</i>	Neonatal septicaemia, meningitis and pneumonia
C	<i>S. dysgalactiae</i> <i>S. equi</i> <i>S. equisimilis</i> <i>S. zooepidemicus</i>	Rare cause of skin sepsis and endocarditis. Post-infectious glomerulonephritis has been reported
D	<i>S. bovis</i>	Endocarditis and bacteraemia associated with colonic neoplasm
F	<i>S. 'milleri'</i>	Metastatic suppurative disease, dental sepsis

tibodies to the different Lancefield antigens. Lancefield grouping is useful, as it relates to streptococcal species and pathogenicity (Table 6.1). Rapid diagnostic tests exist, based on latex agglutination of throat-swab material, and can be used in a general practitioner surgery. They are highly specific but of variable sensitivity (as low as 55% in some studies).

Laboratory identification of *Streptococcus pyogenes*

- 1 Chains of Gram-positive cocci, growing on blood agar, plus beta haemolysis, plus Lancefield group A antigen.
- 2 Rapid antigen detection in throat swabs.
- 3 Antibody detection: high or rising titres of anti-streptolysin O, anti-hyaluronidase and/or anti-DNAse.

Management

The treatment of choice is penicillin. Early and mild cases often respond to oral ampicillin, but severe infections require inpatient treatment with intravenous benzylpenicillin. Suitable alternative drugs are erythromycin, azithromycin or clindamycin. However, a small proportion of highly virulent strains are resistant to macrolides, and fail to respond to these drugs.

S. pyogenes is difficult to eradicate from the throat. Research shows that 2 weeks of vigorous (often parenteral)

penicillin therapy is needed and erythromycin treatment is unreliable. This is important in dormitory- or barracks-associated outbreaks of streptococcal sore throat, especially those associated with rheumatic fever. In a domiciliary setting a course of a least 7–10 days' treatment is probably advisable.

Treatment of streptococcal sore throat

- 1 Early and mild cases: oral ampicillin 250–500 mg 6-hourly for 10 days, or erythromycin in the same dosage and schedule.
- 2 Severe cases: benzylpenicillin 1.2–2.4 g 4–6-hourly (child over 1 month, 150–300 mg/kg daily in 4 to 6 divided doses); *alternative*: clindamycin 600–900 mg 6-hourly by IV infusion (child over 1 month 20–40 mg/kg daily in 3 or 4 divided doses).

Complications

Peritonsillar abscess

Peritonsillar abscess (quinsy) is a common complication of tonsillar sepsis. The fauces and soft palate on the affected side become oedematous and pendulous, and may completely envelope the tonsil. The throat, and the draining lymph node, are intensely painful and tender. A small proportion of cases have bilateral quinsy, which carries a high risk of airway obstruction (Fig. 6.14).

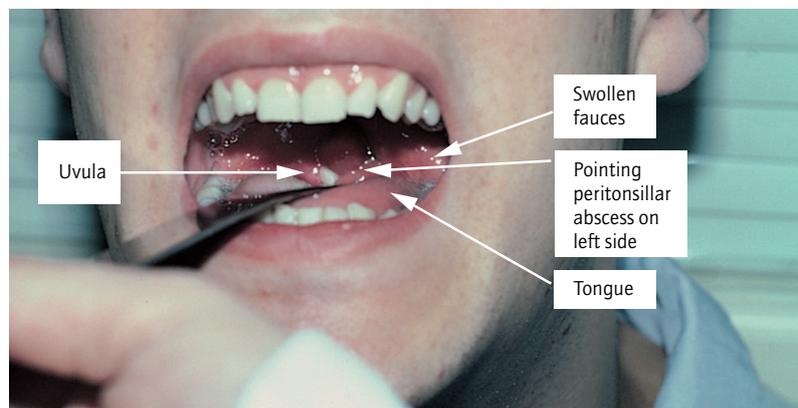


Figure 6.14 Bilateral quinsies (peritonsillar abscesses).

Prompt, vigorous treatment can avert the need for surgical drainage. The addition of metronidazole to high-dose penicillin therapy, or the substitution of clindamycin, which readily penetrate oedematous tissue, may speed improvement by inhibiting streptococcal growth in this rather anaerobic environment. In an emergency, oedema can be rapidly reduced by giving an intravenous bolus of 100–200 mg hydrocortisone. Many early abscesses will resolve; others drain into the throat, with rapid relief of symptoms. A few progress and enlarge, requiring urgent surgical drainage.

Streptococcal bacteraemia

Streptococcal bacteraemia is a rare complication, with a mortality rate reaching 25–30%. Warning signs are high fever, extreme pain (rarely, even suppuration or sloughing) in the draining lymph nodes (Fig. 6.15) or the appearance of erysipelas-like lesions on the skin. Patients with these features should be treated intravenously while blood culture results are awaited (see Chapter 19).

Post-streptococcal disorders

Post-streptococcal disorders include rheumatic fever, reactive arthritis, nephritis, erythema multiforme and erythema nodosum. These are discussed in Chapter 21.

Acute epiglottitis

Introduction and epidemiology

This is a severe throat infection that causes massive oedema of the epiglottis and threatens the airway. It is a rare but important disease. Before vaccination against *H. influenzae* type b (Hib) was included in national programmes (see Chapter 13), Hib caused many cases of epiglottitis in pre-school children. Most cases nowadays are caused by *S. pyogenes*, and affect mainly adults. The disease must be considered in cases of severe sore throat with stridor or



Figure 6.15 Suppuration of cervical lymph node following tonsillitis (300 ml of pus was drained at surgery).

inability to swallow saliva. The airway is vulnerable in this condition; respiratory obstruction can develop suddenly, or be precipitated by throat examination.

Clinical features

Illness develops rapidly, with high fever, severe throat pain, swelling and tenderness of the neck and hyoid region, and great difficulty in swallowing. As epiglottic swelling increases the patient drools and then develops stridor. The tonsillar lymph nodes may be tender and enlarged.

On examining the throat with the tongue depressed, the red, swollen epiglottis can be seen protruding upwards like a cherry. However, manipulation of the throat can precipitate complete respiratory obstruction and should be avoided if urgent X-ray diagnosis is available. The swollen epiglottis is visible on a lateral X-ray of the soft tissues of the neck, in which it looks like the rounded tip of the thumb, filling the lower oropharynx (Fig. 6.16). The blood count often shows a neutrophilia, with a total white count of $12\text{--}16 \times 10^9/\text{l}$.

Diagnosis

The diagnosis should be considered in any patient with severe throat pain, features of sepsis, and drooling or stridor. Diagnosis is often delayed because epiglottitis is not considered.

Confirmation is provided by a lateral X-ray of the soft tissues of the neck, or by direct inspection of the throat if there is no alternative. Blood culture should be obtained for microbiological diagnosis. Throat swabs should be deferred until the airway is secure.

Differential diagnoses

Differential diagnoses include infectious mononucleosis, bilateral peritonsillar abscesses, diphtheria, retropharyngeal abscess and Ludwig's angina. A differential white count and heterophile antibody test will exclude infectious mononucleosis (PCR or IgM antibody tests for EBV are more reliable in small children). Cautious examination of the mouth and fauces, avoiding the use of a tongue depressor, helps to exclude the gross sublingual swelling of Ludwig's angina, faucial swelling of quinsy and the membrane of diphtheria. It may be delayed until emergency measures have secured the airway. The X-ray will show the site of swelling within, rather than behind, the pharynx.

Management

Acute epiglottitis is a medical emergency. The patient should be allowed to sit up, which helps to keep the airway open. High-dose antibiotic treatment should be begun immediately. The treatment of choice is a broad-spectrum cephalosporin such as cefotaxime or ceftriaxone. This can be changed to penicillin if *S. pyogenes* infection is confirmed. A course of 10 days is adequate for most cases.

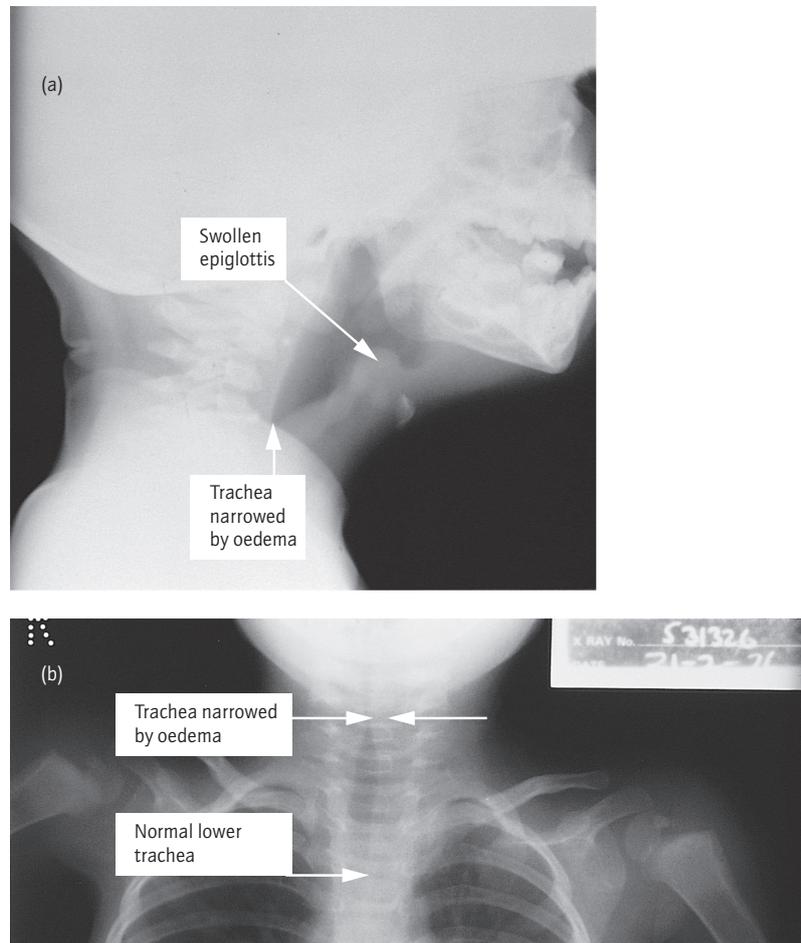


Figure 6.16 Acute epiglottitis: (a) enlarged epiglottis demonstrated by lateral X-ray of the soft tissues of the neck; (b) oedema tracking downwards narrows the trachea.

If the airway is critically obstructed, oxygen should be given by mask while urgent tracheostomy is considered. An intravenous bolus dose of hydrocortisone, 100 to 200 mg, may reduce oedema and avoid the need for tracheostomy. It will not compromise the response to treatment. Many ear, nose and throat departments keep a supply of heliox (80% helium and 20% oxygen), which has an extremely low viscosity and will pass much better than pure oxygen through a tiny airway or a small cannula in the trachea.

Treatment of acute epiglottitis

First choice: cefotaxime – child i.v. 150–250 mg/kg daily in two to four divided doses; adult 2–4 g 8-hourly, or ceftriaxone – child 50 mg/kg as a single daily dose; adult 2–4 g as a single daily dose. Treatment continued for 10 days.



Consider a bolus dose of corticosteroid to reduce epiglottic oedema.

Complications

Once the patient reaches medical care the mortality is low

and the complications are mainly those of intubation and ventilation: hypostatic lung infections, pneumothorax and infected tracheostomy sites.

Prevention and control

Many cases are prevented by childhood immunization against *H. influenzae* type b.

Diphtheria

Introduction

Diphtheria is a rare infection of the respiratory mucosa, and sometimes of broken skin, caused by toxigenic *Corynebacterium diphtheriae*. Although controlled in most communities by immunization, elderly unvaccinated travellers, or refugees and immigrants from rural areas may suffer from the disease or carry the organism in the nose and throat. Vaccine-induced immunity declines in adult life. In tropical countries where hygiene is poor, diphtheria is still common. *C. ulcerans* infection from unpasteurized milk occasionally presents as classical diphtheria. Areas

where diphtheria is transmitted include former USSR, the Indian subcontinent, south east Asia and south America. Western tourists may unwittingly pass through endemic areas, and be unexpectedly infected.

Epidemiology

Humans are the only reservoir of infection. The disease is spread by direct contact with cases or carriers. Patients with cutaneous diphtheria are more infectious than those with other forms, though the less extensive lesions of cutaneous disease may confer immunity without causing severe toxic illness. Nasal diphtheria also tends to be mild, but the infected discharge is important in the spread of disease among children. Between the introduction of routine immunization in Britain in 1942, and the 1960s, diphtheria was almost eliminated. Since 1985, one death has been reported. Sporadic cases, sometimes with limited indigenous transmission, occur occasionally.

Non-toxicogenic *C. diphtheriae* isolates are reported in about 10 cases per year, mostly in adults who were infected abroad. There has been a recent resurgence of these strains in European regions, isolated from cases of pharyngitis, septic arthritis, endocarditis and other conditions.

Pathogenesis of diphtheria

The consequences of infection with *C. diphtheriae* are twofold: the effects of the potent exotoxin; and obstruction of the airway by necrotic debris, which forms a tough pseudomembrane on infected respiratory mucosa (Fig. 6.17).

Diphtheria toxin is the major pathogenicity determinant of *C. diphtheriae*. Its genetic code resides on a beta-phage. Bacteria not infected by the phage are non-

toxigenic and do not cause diphtheria. The protein toxin possesses three domains. A receptor portion binds to the target cell, and the central portion, which is highly hydrophobic, dissolves in the cell membrane, carrying the toxin portion into the cell. The toxin itself is an adenosine diphosphate ribosylase, which ribosylates an amino acid diphthamide present in elongation factor 2. Elongation factor 2 is essential for protein synthesis in the host cell, and its inhibition leads to cell death.

Clinical features

After 3–5 days incubation, the infected site becomes inflamed and gradually acquires a spreading, tough, adherent slough (often called the membrane). The toxic effects of diphtheria are proportional to the extent of the membrane.

Pharyngeal diphtheria is the commonest respiratory form. This presents with fever, sore throat and marked oedema of the cervical lymph nodes, which may produce a bull-neck appearance (Fig. 6.18). The membrane may affect the tonsils but, unlike the exudate of infectious mono-

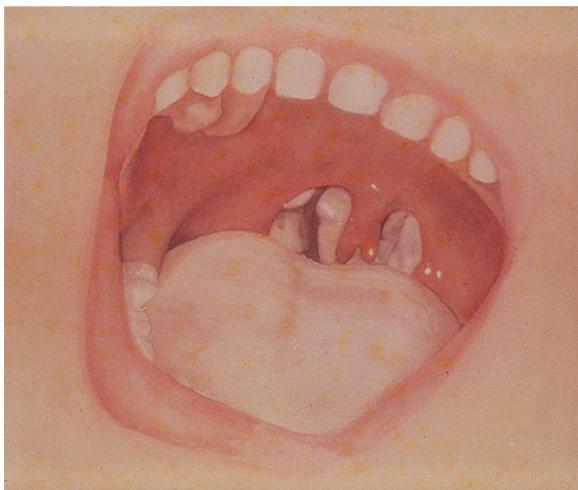


Figure 6.17 Diphtheria: the off-white, smooth pseudomembrane affects the tonsils and pharynx.



Figure 6.18 Diphtheria: bull-neck appearance and tracheostomy. Courtesy of the World Health Organization.

nucleosis, also spreads across the pharyngeal mucosa. It is off-white or greyish and semitransparent, opacified where it contains areas of altered blood, and sometimes blackened and necrotic. Attempts to scrape it away cause pain and bleeding. Diphtheria can also affect the larynx and trachea, and then presents as croup. The true diagnosis is often suspected late in such cases, as the membrane is not visible in the pharynx.

Threatened airway obstruction causes stridor. Children often assume a characteristic posture, leaning forward with the neck extended, to hold the airway open.

When diphtheria affects the nares, the conjunctiva or skin abrasions or ulcers, infected sites are inflamed, often produce a serosanguineous exudate and may have small adherent patches of membrane. *C. diphtheriae* can colonize sites of other infections and has been found in impetigo, cellulitis and broken chickenpox lesions.

During acute diphtheria there is a modest fever, but disproportionate prostration. There is a neutrophilia in the peripheral blood, but minimal disturbance of renal and liver function.

Effects of diphtheria toxin

The diphtheria toxin causes cardiac damage in the first week. Heart failure and conduction defects are common, and profound heart block is a risk, but the myocardium recovers completely when convalescence is established.

The neurological damage appears from the second week. It is caused by demyelination, and occurs earliest and most severely near to the site of the membrane. Palatal and ocular palsies are common after throat infections. After 3 or 4 weeks some patients develop a generalized weakness or paralysis similar to Guillain–Barré syndrome, but this also is fully reversible.

In rare cases a late nephritis causes impaired renal function.

Fatalities are usually due to irreversible heart failure. Intrabronchial or tracheal membrane can cause respiratory obstruction, which is difficult to treat if it cannot be by-passed by tracheostomy. In the recovery phase, these membranes may be sloughed, and can lodge in the trachea

and bronchi. Very severe cases occasionally die from a Waterhouse–Friderichsen syndrome of adrenal failure and haemorrhagic features.

Diagnosis

Clinical suspicion should be aroused by severe throat or pharyngeal swelling, typical membrane, and modest fever with severe prostration and neutrophilia.

Laboratory diagnosis

Specimens from the throat, larynx, nose or skin may be examined. Swabs are adequate. It is very important to inform the laboratory that diphtheria is suspected, otherwise special media will not be inoculated and the pathogen may be discarded as a diphtheroid. On tellurite media, corynebacteria reduce tellurite to metallic tellurium. The colonies have a black shiny appearance, aiding selection for identification. The Loeffler's slope contains a rich serum medium on which organisms grow rapidly. Sufficient growth is usually available after 6 h to allow staining by Albert's method, which demonstrates the volutin granules found in this species. The organism should then be subcultured on to blood agar for biochemical confirmation using sugar tests adapted for corynebacteria (Table 6.2).

Confirmation of toxigenicity is made by polymerase chain amplification, which allows rapid detection of the toxin gene in *C. diphtheriae* isolates.

The laboratory's role is to confirm the presence of toxigenic *C. diphtheriae* and to alert the public health services. The identification of non-toxigenic *C. diphtheriae* requires no public health control measures.

Management

Antibiotic treatment

Intravenous benzylpenicillin is the treatment of choice. Erythromycin or a cephalosporin are alternatives. As inflammation subsides in 24–36 h the membrane loosens. Casts of the upper airway or bronchi may be shed, sometimes needing assisted removal by suction or bronchoscopy.

Table 6.2 *Corynebacterium diphtheriae*: tests to identify and distinguish *gravis*, *intermedius* and *mitis* biotypes

Organism	Sucrose hydrolysis	Mannitol hydrolysis	Starch hydrolysis	Glycogen hydrolysis	Urease	Nitrate production	D toxin	Cp toxin	Both toxins
<i>C. diphtheriae</i> var. <i>gravis</i>	+	+	+	+		+	+		
<i>C. diphtheriae</i> var. <i>intermedius</i>	–	+	–	–		+	+		
<i>C. diphtheriae</i> var. <i>mitis</i>	+	+	–	–		+	+		
<i>C. ulcerans</i>	–		+		+	–	+	+	+

D, diphtheria toxin; Cp, toxin produced only by the animal pathogen *C. pseudotuberculosis* and by *C. ulcerans*.

Table 6.3 Antitoxin treatment of diphtheria

Type of diphtheria	Dose (units)	Route
Nasal	10 000–20 000	Intramuscular
Tonsillar	15 000–25 000	Intramuscular or intravenous
Pharyngeal or laryngeal	20 000–40 000	Intramuscular or intravenous
Combined sites or late diagnosis	40 000–60 000	Intravenous
Cutaneous disease	Not widely recommended: wound toilet and antibiotics preferred	

Antitoxin

Antitoxin is given to neutralize circulating toxin and prevent further damage to myocardium and myelin. Dosage ranges from 10 000 IU for nasal disease to 120 000 IU for aggressive nasolaryngeal diphtheria.

Antitoxin treatment in diphtheria

See Table 6.3.



Human immunoglobulin is not effective, so diphtheria antitoxin is prepared from horse serum. Precede full dose by subcutaneous test dose of anti-toxin, e.g. 50–100 U, 30 min before main dose.

(From WHO (1994) Manual for the Management and Control of Diphtheria in the European Region. World Health Organization.)

Elective tracheostomy

Elective tracheostomy avoids possible emergency tracheostomy, which is difficult when the tissues are very oedematous. It also provides airway protection in case palatal palsy develops later.

Follow up

Diphtheria cases require prolonged observation to detect cardiographic changes, rhythm disturbances and late neurological complications, which may require airway protection or other support. When patients have recovered, they are likely to be carriers of *C. diphtheriae*. Carriage is difficult to eradicate, often requiring two 14-day cycles of oral erythromycin.

Clinical diphtheria does not always induce effective levels of antitoxin. Patients should therefore be immunized or receive reinforcement 'booster' immunization after recovery with a diphtheria toxoid vaccine appropriate to their age.

Prevention and control

All forms of diphtheria, including cutaneous disease, are notifiable in Britain, and many other countries.

Cases and carriers of toxigenic *C. diphtheriae* should remain isolated until two consecutive nose and throat cultures, taken 24–48 hours apart, have proved negative. Cultures may be taken from 24 hours after completion of

antibiotic courses (or at least 2 weeks after, for cutaneous diphtheria).

Household, healthcare and other close contacts of cases should have surveillance swabs taken, have a complete or booster course of vaccination, as appropriate, and should be offered chemoprophylaxis.

Chemoprophylaxis of diphtheria

- 1 Oral erythromycin 500 mg 6-hourly for 7 days; child up to 2 years: 125 mg 6-hourly; 2–8 years: 250 mg 6-hourly.
- 2 Bacteriological clearance is confirmed by two consecutive negative nose and throat swabs, the first at least 24 hours after completion of chemoprophylaxis.



If surveillance swabs are positive, continue treatment for a further 10 days.

Diphtheria vaccine is a formalin-inactivated toxoid preparation. A standard paediatric dose contains at least 30 IU of antigen. In adults and children over 10 years a low-dose (1.5 IU) vaccine is used because of the risk of hypersensitivity reactions. Three doses of vaccine, given at monthly intervals, starting at 2 months of age, are recommended for primary immunization in the UK, with a booster dose 3 years later and again before leaving school (see Chapter 26). Nowadays over 95% of children in the UK receive a full course of vaccine. Adults born before 1942, when routine immunization was introduced, have only naturally acquired immunity. Up to 25% of people in this age group have no measurable antibody.

Measuring immunity to diphtheria by antitoxin concentration

- 1 < 0.01 IU/ml: no protection.
- 2 0.01–0.10 IU/ml: partial protection.
- 3 > 0.10 IU/ml: reliable protection.

Ludwig's angina

This is a suppurative infection of the hypoglossal tissue planes. It can become an emergency because the oedema and exudate push the tongue upwards and backwards, potentially threatening the airway.

The origins of the infection are probably the mouth and teeth. Most infections are polymicrobial. Typical implicated organisms include *Streptococcus pyogenes*, *Staphylococcus aureus*, oral streptococci and 'mouth' anaerobes such as *Prevotella melaninogenica* and *Fusobacterium* spp.

Clinical features develop rapidly. They include pain, fever, difficulty in swallowing and increasing stridor. Examination shows a bull-neck appearance with tenderness of the neck and throat. It is difficult to open the mouth and, when it is open, the tongue is elevated so that its underside is visible above the lower teeth. The fauces may also be swollen.

Treatment should be prompt. Antibiotics should include one active against *S. aureus*. Satisfactory therapy includes penicillin plus flucloxacillin, or a cephalosporin such as cefuroxime or cefotaxime. Although these agents are effective against mouth anaerobes, metronidazole penetrates oedematous tissues well and may be useful additional treatment. Treatment should usually last for about 10 days.

Oedema may be reduced medically with a bolus dose of corticosteroid, e.g. 200 mg hydrocortisone or 10 mg dexamethasone, intravenously. If this does not provide relief, drainage of pus from the sublingual space may be effective. This is performed by passing perforated drains through the floor of the mouth and out through the skin anterior to the hyoid bone.

Retropharyngeal abscess

This is a suppurative infection in the tissue spaces behind the pharynx. Normally there is only a narrow space between the posterior pharyngeal wall and the anterior ligaments of the spinal column. If oedema and pus expand this space, the posterior pharyngeal wall is pushed forwards, obstructing the airway.

The abnormal position of the pharyngeal wall is difficult to see on inspection, especially if the abscess is low in the throat. Many patients therefore present as emergencies, with neck or throat pain and difficulty in breathing. The diagnosis can be revealed by showing a wide soft-tissue space between the vertebrae and the air-filled pharynx on a lateral X-ray of the neck.

Emergency tracheostomy may be life-saving in urgent cases. Medical treatment is identical to that for Ludwig's angina, as the infection is almost always of mouth origin (and only rarely from a spinal infection). Pus can be released by incising the posterior pharyngeal wall. Spinal infection should be excluded by appropriate imaging of the spinal tissues. Rare cases of retropharyngeal abscess result from cervical infection with tuberculosis or (in endemic areas) brucellosis, so pus should be obtained for culture if the spine is involved.

Vincent's angina

This is a synergistic infection of the mouth that particularly affects the gums. It is associated with poor dental health and poor oral hygiene. The patient presents with extreme soreness of the mouth and gums, accompanied by an offensive halitosis.

The microbial cause is the synergistic action of the mouth spirochaete *Borrelia vincenti* and the anaerobe *Fusiformis* spp. If laboratory confirmation of the diagnosis is needed, the organisms can be demonstrated in large numbers by making a Gram stain of the material on a mouth swab.

Treatment with metronidazole will quickly eradicate the anaerobic organisms. Penicillin or ampicillin is also effective. Improved mouth care may be needed to avoid recurrence.