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Streptococcus and enterococcus

Pharyngitis; scarlet fever; skin and soft tissue infections; streptococcal toxic shock syndrome; pneumonia; meningitis; urinary tract infections; rheumatic fever; post-streptococcal glomerulonephritis

M. Kilian

Streptococci is the general term for a diverse collection of Gram-positive cocci that typically grow as chains or pairs (from the Greek *streptos*, pliant or chain; and *coccus*, a grain or berry) (Fig. 16.1). Virtually all the streptococci that are important in human medicine and dentistry fall into the genera *Streptococcus* and *Enterococcus*. Occasional opportunistic infections are associated with other genera of streptococci such as *Peptostreptococcus* (p. 340) and *Abiotrophia* ('nutritionally variant streptococci').

Streptococci are generally strong fermenters of carbohydrates, resulting in the production of lactic acid, a property used in the dairy industry. Most are facultative anaerobes, but peptostreptococci are obligate anaerobes. Streptococci do not produce spores and are non-motile. They are catalase-negative.

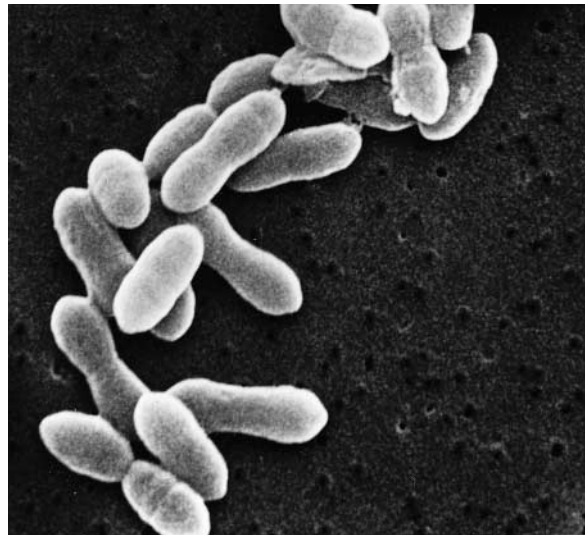
CLASSIFICATION

The genus *Streptococcus* includes important pathogens and commensals of mucosal membranes of the upper respiratory tract and, for some species, the intestines. The genus *Enterococcus*, which is also an intestinal commensal, is related to the other streptococci, but is classified separately.

The genus *Streptococcus* includes nearly 40 species. With few exceptions, the individual species are exclusively associated, either as pathogens or commensals, with man or a particular animal. The genus consists of six clusters of species (Table 16.1), each of which is characterized by distinct pathogenic potential and other properties.



a



b

Fig. 16.1 Scanning electron micrograph of **a** *Str. pyogenes* showing typical chain formation (2000 × magnification), and **b** *Str. pneumoniae* showing typical diplococcus formation (7000 × magnification). (By courtesy of A P Shelton, Nottingham Public Health Laboratory.)

Table 16.1 *Streptococcus* species of clinical importance

Phylogenetic group	Species	Lancefield group	Type of haemolysis ^a
Pyogenic group	<i>Str. pyogenes</i>	A	β
	<i>Str. agalactiae</i>	B	β
	<i>Str. equisimilis</i>	C	β
Mitis group	<i>Str. pneumoniae</i>	O	α
	<i>Str. mitis</i>	O	α
	<i>Str. oralis</i>	Not identified	α
	<i>Str. sanguis</i>	H	α
	<i>Str. gordonii</i>	H	α
Anginosus group	<i>Str. anginosus</i>	G, F (and A)	α
	<i>Str. intermedius</i>		α
Salivarius group	<i>Str. salivarius</i>	K	None
Bovis group	<i>Str. bovis</i>	D	α or none
Mutans group	<i>Str. mutans</i>	Not designated	None
	<i>Str. sobrinus</i>	Not designated	None

^a On horse blood agar.

- The *pyogenic* group includes most species that are overt pathogens of man and animals.
- The *mitis* group includes commensals of the human oral cavity and pharynx, although one of the species, *Streptococcus pneumoniae*, is also an important human pathogen.
- The *anginosus* group and the *salivarius* group are part of the commensal microflora of the oral cavity and pharynx.
- The *bovis* group belongs in the colon.
- The *mutans* group of streptococci colonizes exclusively tooth surfaces of man and some animals; some species belonging to this cluster are involved in the development of dental caries.

Virtually all the commensal species, including the enterococci, are opportunistic pathogens, primarily if they gain access to the bloodstream from the oral cavity or from the gut.

Haemolytic activity

Early attempts to distinguish between pathogenic and commensal streptococci recognized different types of haemolysis around colonies on blood agar plates. Colonies of streptococci belonging to the pyogenic group are generally surrounded by a clear zone, usually several millimetres in diameter, caused by lysis of red blood cells in the agar medium induced by bacterial haemolysins. This is called *β*-haemolysis and constitutes the principal

marker for potentially pathogenic streptococci in cultures of throat swabs or other clinical samples.

In contrast, most commensal streptococci give rise to a green discoloration around colonies on blood agar. This phenomenon is termed *α*-haemolysis. The factor causing the green discoloration is not a haemolysin, but hydrogen peroxide, which oxidizes haemoglobin to the green methaemoglobin.

Collectively, commensal streptococci are often called '*viridans streptococci*' which refers to their *α*-haemolytic property (*viridis* = green). Not quite logically, this term also includes the few streptococci (e.g. the *salivarius* and *mutans* groups of streptococci) that induce neither *α*- nor *β*-haemolysis. Moreover, in common usage, the term excludes *Str. pneumoniae*, although this species is also *α*-haemolytic.

Lancefield grouping

An important method of distinguishing between pyogenic streptococci is the serological classification pioneered by the American bacteriologist Rebecca Lancefield, who detected different versions of the major cell wall polysaccharide among the pyogenic streptococci.

This polysaccharide can be extracted from streptococci with hot hydrochloric acid and the different forms can be distinguished by precipitation with specific antibodies raised in rabbits. The polysaccharide is referred to as the group polysaccharide and identifies a number of different groups labelled by capital letters (Lancefield groups A, B, C etc.).

Among the pyogenic streptococci the individual serological groups are, with few exceptions, identical to distinct species (Table 16.1). Subsequently, serological grouping has been applied also to *viridans* streptococci and to enterococci, and the number of serological groups has been extended to a total of 21 (A–H and K–W). However, this has limited practical significance because there is no direct correlation between individual serogroups of *viridans* streptococci or enterococci and species.

STREPTOCOCCUS PYOGENES

This species, which consists of Lancefield group A streptococci, is among the most prevalent of human bacterial pathogens. It is exclusively associated with infections in man. It causes a wide range of suppurative infections in the respiratory tract and skin, life-threatening soft tissue infections, and certain types of toxin-associated reactions. Some of these infections may, in addition, result in severe non-suppurative sequelae due to adverse immunological reactions induced by the infecting streptococci.

The spectrum of infections caused by *Str. pyogenes* resembles that of *Staphylococcus aureus*, but the clinical characteristics associated with these two groups of pyogenic cocci are often distinct. Similarities and differences can be explained by the virulence factors expressed by the two species.

Pathogenesis

Virulence factors

Strains of *Str. pyogenes* express a large arsenal of virulence factors and, hence, their pathogenicity and the clinical signs that they induce are very diverse. The virulence factors are involved in adherence, evasion of host immunity and tissue damage (Fig. 16.2). While some factors are expressed by all clinical isolates, others are variably present among *Str. pyogenes* strains. This variation is due to the horizontal transfer of virulence genes among strains, primarily by transduction (see p. 66), and probably explains the temporal variations in the prevalence of severe infections and sequelae. It furthermore

explains differences in virulence of individual strains and the different clinical pictures that may be associated with infections due to *Str. pyogenes*. Many of the virulence factors of *Str. pyogenes* are also expressed by some of the other species of pyogenic streptococci. In some species pathogenic for animals the corresponding virulence factors are expressed in a form specifically adapted to interact with their particular host.

Adhesion. Interaction with host fibronectin, a matrix protein on eukaryotic cells, is considered the principal mechanism by which *Str. pyogenes* binds to epithelial cells of the pharynx and skin. The structure that recognizes host fibronectin is located on the F protein, which is one of the many proteins expressed on the surface of *Str. pyogenes* (Fig. 16.2). The interaction between the streptococcal F protein and host cell fibronectin also mediates internalization of the bacteria into host cells.

In addition to the F protein, surface-exposed lipoteichoic acid and M proteins appear to be involved in adherence to mucosal and skin epithelial cells.

M proteins. The ability of *Str. pyogenes* to resist phagocytosis by polymorphonuclear leucocytes is to a

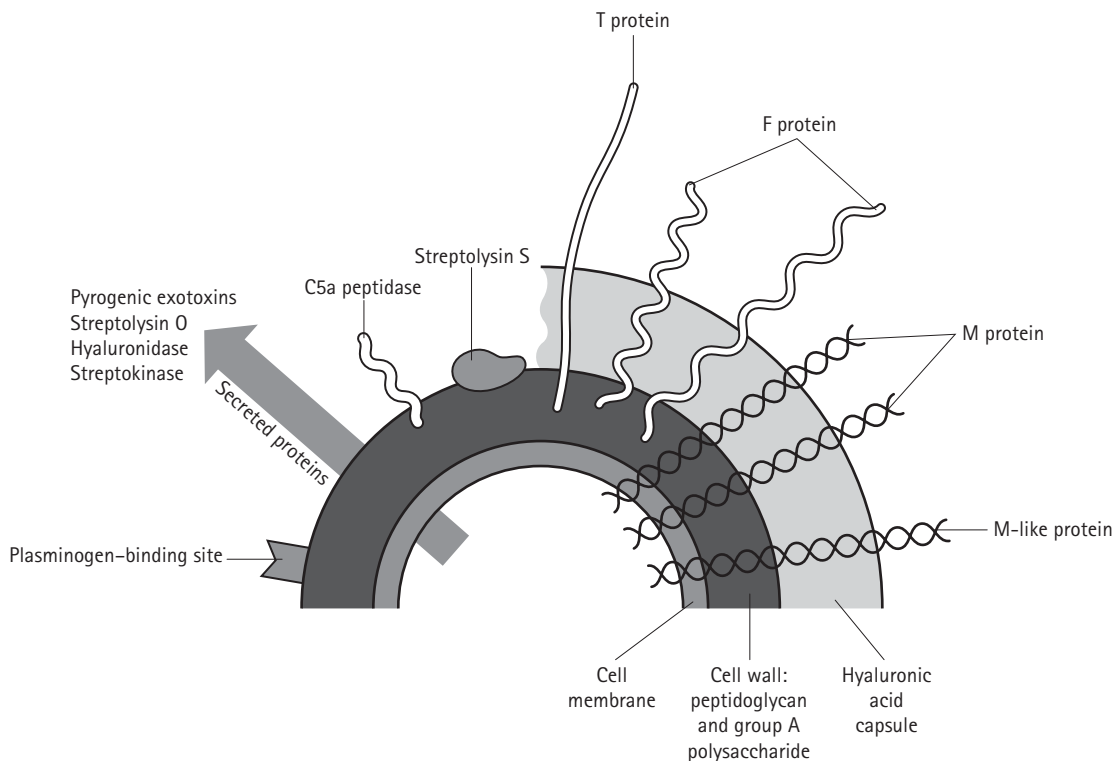


Fig. 16.2 Schematic diagram showing the location of virulence-associated products of *Str. pyogenes*.

high degree due to the cell surface-exposed M protein. The M protein is anchored in the cytoplasmic membrane, spans the entire cell wall, and protrudes from the cell surface as fibrils (Fig. 16.2). Acquired resistance to infection by *Str. pyogenes* is the result of antibodies in secretions and sera to the M protein molecule. However, as a result of genetic polymorphism in the gene encoding the M protein, the most distal part of the protein shows extensive variability among strains. As a consequence, individuals may suffer from recurrent *Str. pyogenes* infections with strains expressing different versions of the M protein. More than 80 different types of M protein have been identified by serological means.

Some strains produce two different M proteins with antiphagocytic activity and some, in addition, a structurally related M-like protein. All these proteins can bind various serum proteins of the host, including fibrinogen, plasminogen, albumin, IgG, IgA, the proteinase inhibitor α 2-macroglobulin, and some regulatory factors from the complement system (factor H and C4b-binding protein). As well as masking the bacterial surface with host proteins some of these affinities are probably responsible for the ability of M proteins to resist phagocytosis. Thus, factor H is capable of destabilizing the important opsonin C3b when deposited on the bacterial surface. Likewise, the C4b-binding protein inhibits surface complement deposition by stimulating degradation of both C4b and C3b.

Capsule. Some strains of *Str. pyogenes* form a capsule composed of hyaluronic acid. Such strains grow as mucoid colonies on blood agar and are highly virulent in animal models. While capsule production is rare among isolates from uncomplicated pharyngitis, a significant proportion of isolates from severe infections have a capsule. Like other bacterial capsules it has an antiphagocytic effect. The relative significance of the M protein and the capsule as antiphagocytic factors differs among strains.

The capsule is identical to the hyaluronic acid of the connective tissue of the host and is not immunogenic. The bacteria may, in this way, disguise themselves with an immunological 'self' substance.

C5a peptidase. The C5a peptidase, which is found also in human pathogenic strains of *Str. agalactiae*, is presented on the surface of all strains of *Str. pyogenes*. It specifically cleaves, and thereby inactivates, human C5a, one of the principal chemoattractants of phagocytic cells.

Streptolysins. *Str. pyogenes* produces two distinct haemolysins, termed streptolysins O (oxygen-labile) and S (serum-soluble), both of which lyse erythrocytes, polymorphonuclear leucocytes and platelets by forming pores in their cell membrane.

Streptolysin O belongs to a family of haemolysins found in many pathogenic bacteria. Intravenous injection

into experimental animals causes death within seconds, as the result of an acute toxic action on the heart. Streptolysin O may play a role in the pathogenesis of post-streptococcal rheumatic fever. Serum antibodies can be demonstrated after streptococcal infection, particularly after severe infections.

Streptolysin S is responsible for the β -haemolysis around colonies on blood agar plates. It can also induce the release of lysosomal contents with subsequent cell death after engulfment by phagocytes. In contrast to streptolysin O it is not immunogenic.

Pyrogenic exotoxins. Most strains of *Str. pyogenes* produce one or more toxins that are called *pyrogenic exotoxins* because of their ability to induce fever. Three, SPE A, SPE B and SPE C, have been extensively characterized, but there are several others. Purified SPE A causes death when injected into rabbits, and is the most toxic of the three, but SPE B also causes myocardial necrosis and death in experimental animals.

The genes for SPE A and SPE C are transmitted between strains by bacteriophage, and stable production depends on lysogenic conversion in a manner analogous to toxin production by *Corynebacterium diphtheriae* (p. 67). Even among strains that possess the genes the quantity of toxin secreted varies dramatically.

SPE A and SPE C are also called erythrogenic toxins, as they are responsible for the rash observed in patients with scarlatina. They are genetically related to *Staph. aureus* enterotoxins and, like these, have superantigen activity. By cross-linking MHC class II molecules and the V β -domain of the antigen receptor on a subset of T lymphocytes, these toxins cause comprehensive (antigen-independent) activation of helper T lymphocytes. The result is substantial release of interleukins IL-1 and IL-2, tumour necrosis factor- α (TNF- α) and interferon- γ . These cytokines may cause a variety of clinical signs, including inflammation, shock and organ failure characteristically seen in patients with severe streptococcal disease.

Unlike SPE A and SPE C, all strains of *Str. pyogenes* produce SPE B, which is a potent cysteine proteinase capable of cleaving many host proteins.

None of the three pyrogenic exotoxins is unambiguously associated with any of the clinical syndromes caused by *Str. pyogenes*. However, most isolates from episodes of severe invasive disease and toxic shock-like syndrome produce SPE A, and the protease SPE B appears to be responsible for the extensive tissue destruction observed in many patients with severe invasive infections, including toxic shock-like syndrome.

Hyaluronidase. *Str. pyogenes* and several other pyrogenic streptococci use a secreted hyaluronidase to degrade hyaluronic acid, the ground substance of host connective tissue. This property may facilitate the

spread of infection along fascial planes. During infections, particularly those involving the skin, serum antibody titres to hyaluronidase show a significant rise.

Streptokinase. Streptokinase, also known as fibrinolysin, is another spreading factor. It is expressed by all strains of *Str. pyogenes* and co-operates with a surface-expressed plasminogen-binding site on the bacteria. Once host plasminogen is bound to the bacterial surface, it is activated to plasmin by streptokinase. Thus, in contrast to *Staph. aureus*, which aims at hiding behind a wall of coagulated plasma (fibrin), *Str. pyogenes* employs host plasmin to hinder build-up of fibrin barriers. As a result, soft tissue infections due to *Str. pyogenes* are more diffuse, and often rapidly spreading, in contrast to the well localized abscesses that typify staphylococcal infections.

Lipoproteinase. This enzyme is also called *opacity factor*, as it induces opalescence in growth media containing serum. The exact biological significance is not known but there is a strong correlation between the production of this enzyme and particular M types, and it is produced mainly by strains causing skin infections.

Deoxyribonucleases (DNAases). At least four distinct forms of DNAases, designated A, B, C and D, are produced by *Str. pyogenes*. DNAase B is the most common form. The enzymes hydrolyse nucleic acids and may play a role as spreading factors by liquefying viscous exudates.

Clinical features

While a general decrease in the prevalence of serious infections with *Str. pyogenes* has occurred since the mid 19th century, a resurgence in severe streptococcal infections and increased mortality due to streptococcal sepsis has been observed since the early 1980s.

The most common route of entry of *Str. pyogenes* is the upper respiratory tract, which is usually the primary site of infection and also serves as a focus for other types of infections. Spread from person to person is by respiratory droplets or by direct contact with infected wounds or sores on the skin. Not all individuals colonized by *Str. pyogenes* in the upper respiratory tract develop clinical signs of infection.

After an acute upper respiratory tract infection, the convalescent patient may carry the infecting streptococci for some weeks. Only a few healthy adults carry *Str. pyogenes* in the respiratory tract, but the carriage rate in young school children is just over 10%. It may be considerably higher before or during an epidemic.

Non-invasive streptococcal disease

The most common infections caused by *Str. pyogenes* are relatively mild and non-invasive infections of the

upper respiratory tract (*pharyngitis*) and skin (*impetigo*). In the USA more than 10 million cases of non-invasive *Str. pyogenes* infection are estimated to occur annually.

Pharyngitis. This is the most common infection caused by *Str. pyogenes*. Clinical signs such as abrupt onset of sore throat, fever, malaise and headache generally develop 2–4 days after exposure to the pathogen. The posterior pharynx is usually diffusely reddened, with enlarged tonsils that may show patches of grey-white exudate on their surface and, sometimes, accumulations of pus in the crypts. The local inflammation results in swelling of cervical lymph nodes. Occasionally, tonsillar abscesses develop; this is a very painful condition and potentially dangerous as the pathogen may spread to neighbouring regions and to the bloodstream.

Despite the significant symptoms and clinical signs, differentiating streptococcal pharyngitis ('*strep throat*') from viral pharyngitis is impossible without microbiological or serological examination. Culture studies have demonstrated that 20–30% of cases of pharyngitis are associated with *Str. pyogenes*.

Occasional cases of streptococcal sore throat are caused by species belonging to Lancefield groups C and G.

Scarlet fever. Pharyngitis caused by certain pyrogenic exotoxin-producing strains of *Str. pyogenes* may be associated with a diffuse erythematous rash of the skin and mucous membranes. The condition is known as *scarlet fever* or *scarlatina*. The rash develops within 1–2 days after the first symptoms of pharyngitis and initially appears on the upper chest and then spreads to the extremities. After an initial phase with a yellowish-white coating the tongue becomes red and denuded ('*strawberry tongue*').

Between 1860 and 1870 the mean annual death rate from scarlet fever in England and Wales was close to 2500 per million of the population. Since then a steady decline in the incidence has been observed. The total number of scarlet fever cases in 1999 in England and Wales was 25 per million — the lowest annual total ever recorded — and death is now extremely rare.

Skin infections. *Str. pyogenes* may cause several types of skin infection, sometimes in association with *Staph. aureus*. The superficial and localized skin infection, known as *impetigo* or *pyoderma*, occurs mainly in children (Fig. 16.3). It primarily affects exposed areas on the face, arms or legs. The skin becomes colonized after contact with an infected person and the bacteria enter the skin through small defects. Initially, clear vesicles develop, which within a few days become pus-filled. Secondary spread is often seen as a result of scratching.

Potentially more severe is the acute skin infection *erysipelas* (*erythros*, red; *pell*a, skin). It occurs in the



Fig. 16.3 Impetigo. (Photograph courtesy of Dr L G Millard, Queen's Medical Centre, Nottingham.)

superficial layers of the skin (cellulitis) and involves the lymphatics. The infection is characterized by diffuse redness of the skin and the patients experience local pain, enlargement of regional lymph nodes and fever. Untreated, the infection may spread to the bloodstream, and was often fatal before antibiotics became available.

Invasive soft tissue infections

Severe, sometimes life-threatening *Str. pyogenes* infections may occur when the bacteria get into normally sterile parts of the body. The most severe forms of invasive infections are *necrotizing fasciitis*, *streptococcal toxic shock syndrome* and *puerperal fever*, all of which are associated with bacteraemia.

Worldwide, rates of invasive infections increased from the mid 1980s to the early 1990s. In 1999, nearly 10 000 cases of invasive *Str. pyogenes* infection occurred in the USA. Although these infections may occur in previously healthy individuals, patients with chronic illnesses like cancer and diabetes, and those on kidney dialysis or receiving steroids have a higher risk. Even with antibiotic treatment death occurs in 10–13% of all invasive cases: 45% of patients with toxic shock syndrome and 25% of patients with necrotizing fasciitis.

Necrotizing fasciitis. This infection progresses very rapidly, destroying fat and fascia. Although *Str. pyogenes* gains entry to these tissues through the skin after trauma, often of a minor nature, the skin itself may show only minimal signs of infection and may indeed be

spared. Systemic shock and general deterioration occur very quickly. The disease affects the fit, young person with no obvious underlying pathology, as well as the immunocompromised.

The clinical diagnosis may be difficult because *Staph. aureus* and anaerobes such as *Clostridium perfringens* can produce a similar clinical picture. Streptococci can be isolated from the blood, blister fluid and from cultures of the infected area.

Streptococcal myositis. This rare infection mimics necrotizing fasciitis clinically, although at operation they look quite different. As a breach of the skin or soft tissue damage is unusual, the source is considered to be the throat, with bacteraemic spread to the muscle. The infection may be precipitated by trauma or muscle strain.

Streptococcal toxic shock syndrome. Patients with invasive and bacteraemic *Str. pyogenes* infections, and in particular necrotizing fasciitis, may develop streptococcal toxic shock syndrome. The disease, which was first described in the late 1980s, is the result of the release of streptococcal toxins to the bloodstream. A striking feature of this acute fulminating disease is severe pain at the site of initial infection, usually the soft tissues. The additional clinical signs resemble those of staphylococcal toxic shock syndrome (p. 169) and include fever, malaise, nausea, vomiting and diarrhoea, dizziness, confusion, and a flat rash over large parts of the body. Without treatment, the disease progresses to shock and general organ failure.

Other suppurative infections. Historically, *Str. pyogenes* has been an important cause of puerperal sepsis. However, after the introduction of antibiotic therapy this and other suppurative infections such as lymphangitis, pneumonia and meningitis are relatively rare.

Bacteraemia. *Str. pyogenes* is the second most common (after *Str. agalactiae*) of the pyogenic streptococci isolated from blood cultures. Bacteraemia is regularly seen in patients with necrotizing fasciitis and toxic shock syndrome, but rarely as a complication to pharyngitis and local skin infections. Once in the blood, *Str. pyogenes* multiplies with incredible speed (doubling time, 18 min), and the mortality rate approaches 40%. The potential complications include acute endocarditis leading to heart failure.

Non-suppurative sequelae

Two serious diseases may develop as sequelae to *Str. pyogenes* infections:

- *Rheumatic fever*, a potential sequela to pharyngitis (including scarlatina).
- *Acute glomerulonephritis*, which is primarily, but not exclusively, associated with skin infections.

Both are caused by immune reactions induced by the streptococcal infection. The first clinical signs appear 1–5 weeks after the infection and at a time when the bacteria may have been eradicated by the immune system or as a result of antibiotic therapy.

Clinical correlations suggest that *psoriasis* may also be triggered by *Str. pyogenes* throat infection. Preliminary evidence supports the hypothesis that some streptococcal superantigens cause disruption of immunological tolerance of a CD8+ T cell subset that recognizes cross-reactive epitopes on M proteins and skin keratin.

Rheumatic fever. This manifests as an inflammation of the joints (arthritis), heart (carditis), central nervous system (chorea), skin (erythema marginatum), and/or subcutaneous nodules. Polyarticular arthritis is the most common manifestation, whereas carditis is the most serious as it leads to permanent damage, particularly of the heart valves.

Rheumatic fever is a major cause of acquired heart disease in young people throughout the world. The incidence of rheumatic heart disease worldwide ranges from 0.5 to 11 per 1000 of the population. New cases are relatively rare in most of Europe, but increased incidences have been observed among the aboriginal populations of Australia and New Zealand, and in Hawaii and Sri Lanka. Outbreaks of rheumatic fever have also been seen in the USA.

The disease is autoimmune in nature and is believed to result from the production of autoreactive (and polyspecific) antibodies and T lymphocytes induced by cross-reactive components of the bacteria and host tissues. Therefore, repeated episodes of *Str. pyogenes* infection increase the severity of the disease. The major antigens involved are myosin, tropomyosin, laminin and keratin in the human tissues and the group A antigen (a polymer of *N*-acetylglucosamine) in the *Str. pyogenes* cell wall in addition to epitopes on some variants of surface M proteins.

Acute post-streptococcal glomerulonephritis. The clinical manifestations include:

- coffee-coloured urine caused by haematuria
- oedema of the face and extremities
- circulatory congestion caused by renal impairment.

Unlike rheumatic disease, outbreaks of post-streptococcal acute glomerulonephritis have continued to decline in most parts of the world. Regions that still exhibit a high incidence of this disease include Africa, the Caribbean, South America, New Zealand and Kuwait.

Post-streptococcal glomerulonephritis is usually referred to as an immune complex-mediated disease. However, the exact pathogenesis is not clear. Several mechanisms have been proposed, including:

- immune complex deposition in the glomeruli
- reaction of antibodies cross-reactive with streptococcal and glomerular antigens
- alterations of glomerular tissues by streptococcal products such as streptokinase
- direct complement activation by streptococcal components that have a direct affinity for glomerular tissues.

Disease is associated with a limited number of M types of *Str. pyogenes*, and there is evidence that particular variants of streptokinase are crucial nephritogenic factors.

Unlike rheumatic fever there is a general absence of individual recurrences which suggests that antibodies to nephritogenic factors protect against disease rather than the opposite.

STREPTOCOCCUS AGALACTIAE

Str. agalactiae belongs to Lancefield group B. Its primary human habitat is the colon. It may be carried in the throat and, importantly, 10–40% of women intermittently carry *Str. agalactiae* in the vagina.

Previously, *Str. agalactiae* was recognized primarily as a cause of bovine mastitis (*agalactia*, want of milk). However, since 1960 it has become the leading cause of neonatal infections in industrialized countries and is also an important cause of morbidity among peripartum women and non-pregnant adults with chronic medical conditions. Among β -haemolytic streptococci, *Str. agalactiae* is the most frequent isolate from blood cultures.

Pathogenesis

Virulence factors

Str. agalactiae produces several virulence factors, including haemolysins, capsule polysaccharide, C5a peptidase (only human pathogenic strains), hyaluronidase (not all strains), and various surface proteins that bind human IgA and serve as adhesins.

Nine different types of the capsular polysaccharide have been identified (Ia, Ib, and II–VIII). The serotype most frequently associated with neonatal infections is type III, whereas infections in adults are more evenly distributed over the different serotypes.

Among the haemolysins produced by *Str. agalactiae*, one, known as the CAMP factor (so-called because it was originally described by Christie, Atkins and Munch-Petersen), plays an important role in the recognition of this species in the laboratory. The CAMP factor lyses sheep or bovine red blood cells pre-treated

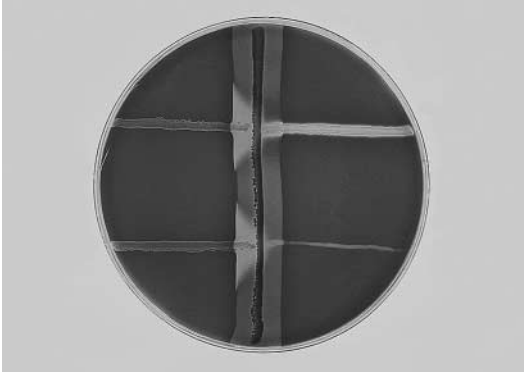


Fig. 16.4 Blood agar culture of strains of *Str. pyogenes* (group A) (upper right), *Str. equisimilis* (group C) (lower right), and *Str. agalactiae* (group B) (upper and lower left) surrounding a vertical streak of *Staph. aureus*. The two *Str. agalactiae* strains show a positive CAMP reaction.

with the β -toxin of *Staph. aureus* (Fig. 16.4). Purified CAMP factor protein is lethal to rabbits when injected intravenously.

Clinical features

Infection in the neonate

Two different entities are recognized:

- *early-onset disease*, most cases of which present at or within 12 h of birth
- *late-onset disease*, presenting more than 7 days and up to 3 months after birth.

Early-onset disease. This results from ascending spread of *Str. agalactiae* from the vagina into the amniotic fluid, which is then aspirated by the infant, and results in septicaemia in the infant or the mother or both. Infants borne by mothers carrying *Str. agalactiae* may also become colonized during passage through the vagina, but early-onset disease is an uncommon outcome (about 1% of cases).

Depending on the site of initial contamination, neonates may be ill at birth or develop acute and fulminating illness a few hours, or a day or two, later. The clinical symptoms include lethargy, cyanosis and apnoea; when septicaemia progresses, shock ensues and death will occur if treatment is not quickly instituted. Meningitis and pulmonary infection may be associated.

Due to improved recognition and prompt treatment of babies with symptoms, the fatality rate has been reduced to less than 10%. However, considerable morbidity persists among some survivors, especially those with meningitis.

Risk factors for neonatal colonization and infection are:

- premature rupture of membranes
- prolonged labour
- premature delivery
- low birth weight
- intrapartum fever.

The immune status of the mother, and hence the level of maternal IgG antibodies in the infant, appears to be more important than the degree of colonization of the mother's genital tract by *Str. agalactiae*.

It is possible that *Str. agalactiae* may itself cause premature rupture of membranes as a result of secretion of proteases and activation of local inflammation.

Late-onset disease. Purulent meningitis is the most common manifestation, but septic arthritis, osteomyelitis, conjunctivitis, sinusitis, otitis media, endocarditis and peritonitis also occur. The incidence of invasive infection is higher among preterm infants than among those born at term.

The pathogenesis is distinct from that of early-onset disease. There is usually no history of obstetric complications and the disease is unrelated to vaginal colonization in the mother. Many cases are acquired in hospital. Ward staff can be carriers of *Str. agalactiae*, and contamination of the baby may occur during nursing procedures, with subsequent baby-to-baby spread. Mastitis in the mother has also been described as a source of infection.

Infections in the adult

Ascending spread of *Str. agalactiae* leading to amniotic infection may result in abortion, chorioamnionitis, postpartum sepsis (endometritis) and other infections (e.g. pneumonia) in the postpartum period in young, previously healthy women.

Str. agalactiae is also a frequent cause of infection in certain risk groups of non-pregnant adults. Disease may manifest as sepsis, pneumonia, soft tissue infections such as cellulitis and arthritis, and urinary tract infections complicated by bacteraemia. The risk factors in these patients are diabetes mellitus, liver cirrhosis, renal failure, stroke and cancer. Older age, independent of underlying medical conditions, increases the risk of invasive *Str. agalactiae* infection.

OTHER PYOGENIC STREPTOCOCCI

Group C and G streptococci

Several species of streptococci that carry the Lancefield group C or group G antigens occasionally cause infections similar to those of *Str. pyogenes*. Most of these

species have their primary habitat in horses, cattle and pigs, but some strains have become adapted to the human host and then produce some of the virulence factors primarily associated with *Str. pyogenes*. They can cause epidemic sore throat, especially in communities such as schools, nurseries and institutions often associated with consumption of unpasteurized milk. Group C streptococci have been associated with acute glomerulonephritis but not with rheumatic fever. The most important of the group C streptococci in human medicine is *Str. equisimilis*.

Group R streptococci

Str. suis serotype 2 (group R streptococci) cause septicaemia and meningitis in pigs. They belong to a phylogenetic lineage separate from the other pyogenic streptococci. They occasionally infect people in contact with contaminated pork or infected pigs, and may cause septicaemia, meningitis and respiratory tract infections. Abattoir workers, butchers and, to a lesser extent, housewives are at risk.

STREPTOCOCCUS PNEUMONIAE

Str. pneumoniae, commonly called the pneumococcus, is a member of the oropharyngeal flora of 5–70% of the population, with the highest isolation rate in children during the winter months. In contrast to other streptococci, *Str. pneumoniae* generally occurs as characteristic diplococci (Fig. 16.1). Although genetically closely related to the commensal *Str. mitis* and *Str. oralis*, *Str. pneumoniae* is an important pathogen, which is largely ascribed to its capsular polysaccharide. It primarily causes disease of the middle ear, paranasal sinuses, mastoids and the lung parenchyma but may spread to other sites, such as the joints, peritoneum, endocardium and biliary tract and, in particular, the meninges.

Str. pneumoniae is genetically very flexible because of frequent recombination between individual strains. Gene transfer is by transformation and may result in expression of a different capsular serotype. Experimental transfer of capsule genes in pneumococci was the basis of the original demonstration that DNA contains the genetic information in cells.

Pathogenesis

Virulence factors

Capsule. The capsular polysaccharide is a crucial virulence factor. The capsule is antiphagocytic, inhibit-

ing complement deposition and phagocytosis where type-specific opsonic antibody is absent. A total of 90 different capsular serotypes have been identified.

The serotypes are designated by numbers, and those that are structurally related are grouped together (1, 2, 3, 4, 5, 6A, 6B etc.). The different serotypes differ in virulence. Thus, about 90% of cases of bacteraemic pneumococcal pneumonia and meningitis are caused by some 23 serotypes.

IgA1 protease. Like the two other principal causes of bacterial meningitis (*Neisseria meningitidis* and *Haemophilus influenzae*), pneumococci produce an extracellular protease that specifically cleaves human IgA1 in the hinge region. This protease enables these pathogens to evade the protective functions of the principal immunoglobulin isotype of the upper respiratory tract.

Pneumolysin. Pneumococci produce an intracellular membrane-damaging toxin known as pneumolysin, which is released by autolysis. Pneumolysin inhibits:

- neutrophil chemotaxis
- phagocytosis and the respiratory burst
- lymphocyte proliferation and immunoglobulin synthesis.

In experimental models it induces the features of lobar pneumonia and contributes to the mortality of this disease. Pneumolysin is immunogenic and it might be suitable for a new pneumococcal vaccine.

Autolysin. When activated, the pneumococcal autolysin breaks the peptide cross-linking of the cell wall peptidoglycan, leading to lysis of the bacteria. Autolysis enables the release of pneumolysin and, in addition, large amounts of cell wall fragments. The massive inflammatory response to these peptidoglycan fragments is an important component of the pathogenesis of pneumococcal pneumonia and meningitis.

Clinical features

Predisposing factors

Most *Str. pneumoniae* infections are associated with various predisposing conditions. Although occasional clusterings of pneumococcal infections are recognized, person-to-person spread is uncommon.

Pneumonia results from aspiration of pneumococci contained in upper airway secretions into the lower respiratory tract; for example, when the normal mechanisms of mucous entrapment and expulsion by an intact glottic reflex and mucociliary escalator are impaired. This situation may arise in:

- disturbed consciousness in association with general anaesthesia, convulsions, alcoholism, epilepsy or head trauma

- respiratory viral infections, such as influenza
- chronic bronchitis and other forms of chronic bronchial sepsis.

Other predisposing disease states in which pneumococcal pneumonia may be the terminal event include:

- valvular and ischaemic heart disease
- chronic renal failure
- diabetes mellitus
- bronchogenic and metastatic malignancy
- advancing age.

Immune deficiencies that predispose to pneumococcal infection include:

- hypogammaglobulinaemia
- asplenia or hyposplenism
- malignancies such as multiple myeloma.

In these conditions there is either a relative or absolute deficiency of opsonic antibody activity or an inability to induce a sufficient type-specific antibody response. *Tufts*in, a naturally occurring tetrapeptide secreted by the spleen, also plays a role in combating pneumococcal sepsis; particularly at risk are those deficient in splenic activity:

- congenital asplenia
- traumatic removal
- functional impairment, e.g. homozygous sickle cell disease.

Human immunodeficiency virus (HIV) infection carries an increased risk of bacterial infections, including those caused by the pneumococcus, particularly in children.

Acute infections of the middle ear and paranasal sinuses occur in otherwise healthy children, but are usually preceded by a viral infection of the upper respiratory tract leading to local inflammation and swelling and obstruction of the flow from these sites.

Pneumonia

Str. pneumoniae is the most frequent cause of pneumonia. The estimated annual incidence is 1–3 per 1000 of the population, with a 5% case fatality rate. Pneumococcal pneumonia follows aspiration with subsequent migration through the bronchial mucosa to involve the peribronchial lymphatics. The inflammatory reaction is primarily focused within the alveolus of a single lobule or lobe, although multilobar disease can also occur. Contiguous spread commonly results in inflammatory involvement of the pleura; this may progress to empyema.

Pericarditis is another uncommon but well recognized complication. Occasionally, lung necrosis and intrapul-

monary abscess formation occur with the more virulent pneumococcal serotypes. Bacteraemia may complicate pneumococcal pneumonia in up to 15% of patients. This can result in metastatic involvement of the meninges, joints and, rarely, the endocardium.

Mortality from pneumococcal pneumonia in those admitted to hospital in the UK is approximately 15%. It is increased by age, underlying disease, bloodstream involvement, metastatic infection and certain types of pneumococci with large capsules (e.g. serotype 3).

Otitis media and sinusitis

Middle ear infections (otitis media) affect approximately half of all children between the ages of 6 months and 3 years; approximately one-third of cases are caused by *Str. pneumoniae*. Disease occurs after acquisition of a new strain to which there is no pre-existing immunity. The prevalence is highest among children attending primary school, where there is a constant exchange of pneumococcal strains.

Meningitis

Str. pneumoniae is among the leading causes of bacterial meningitis. It is assumed that invasion arises from the pharynx to the meninges via the bloodstream since bacteraemia usually co-exists. Meningitis may occasionally complicate pneumococcal infection at other sites, such as the lung.

The incidence of pneumococcal meningitis is bimodal and affects children less than 3 years of age and adults of 45 years and above. The fatality rates are 20 and 30%, respectively, which are considerably higher than those associated with other types of bacterial meningitis.

COMMENSAL STREPTOCOCCI

Viridans streptococci

The viridans streptococci, and in particular the species of the mitis and salivarius groups, are dominant members of the resident flora of the oral cavity and pharynx in all age groups. They play an important role by inhibiting the colonization of many pathogens, including pyogenic streptococci. This is achieved by two different mechanisms:

- production of bacteriocins (p. 34)
- production of hydrogen peroxide (also responsible for α -haemolysis).

Most strains secrete bacteriocins. Experimental implantation of strains of *S. salivarius* with strong bacteriocin activity prevents colonization with *Str. pyogenes* in man.



Mitis group. *Str. mitis*, *Str. oralis*, *Str. sanguis* and *S. gordonii* colonize tooth surfaces as well as mucosal membranes. Because of their presence in the bacterial deposits (dental plaque) on tooth surfaces, these species may enter the bloodstream during dental procedures such as tooth extraction or vigorous tooth cleaning, particularly if the gingival tissue is inflamed.

In healthy individuals, such bacteria of low virulence are cleared from the circulation within 1 h. However, in patients with various predisposing conditions (Table 16.2), in particular heart valve damage due to post-streptococcal rheumatic fever, the circulating streptococci may settle in a niche protected from phagocytic cells. Local growth on the surface of heart valves eventually causes scarring and functional deficiency. As the disease progresses over several months, it is referred to as *subacute bacterial endocarditis*. It is usually accompanied by intermittent fever. Disruption of bacteria from the cardiac vegetations may cause embolic abscesses in various organs, including the brain. Until endocarditis due to skin staphylococci became more prevalent as a result of intravenous drug abuse, viridans streptococci were the most frequent causes of infective endocarditis.

Str. mitis and *Str. oralis* are increasingly recognized as causes of often fatal septicaemias in immunocompromised patients.

Mutans group. *S. mutans* and *S. sobrinus* exclusively colonize tooth enamel and do not occur until tooth eruption. Their proportions in dental plaque are closely related to sugar consumption, and they are a major cause of dental caries because of their ability to produce large amounts of lactic acid even at pH values below pH 5.0. Like most other plaque streptococci they may cause subacute bacterial endocarditis.

Anginosus group. *S. anginosus*, *S. intermedius* and several other ill-defined taxa are regular members of the commensal bacteria on tooth surfaces, in particular in the gingival crevices. They are often isolated from abscesses and other opportunistic purulent infections.

Bovis group. *Str. bovis* is found in various animal species, including the human gut. It occasionally causes

bacteraemia and subacute endocarditis, and is then often associated with colon carcinoma, which jeopardizes the barrier function of the intestinal wall.

Abiotrophia species

These bacteria were formerly referred to as ‘nutritionally variant streptococci’. They grow as satellite colonies around other micro-organisms and in complex media only when supplemented with cysteine. They were previously thought to be mutants of other streptococci, but are genetically quite distinct from members of the genus *Streptococcus*. The three current species are all normal inhabitants of the oral cavity and occasionally cause infective endocarditis.

Enterococcus species

As indicated by the name, members of the genus *Enterococcus* have their natural habitat in the human intestines. The species most commonly associated with human disease are *E. faecalis* and *E. faecium*. The diseases with which they are associated are:

- urinary tract infection
- infective endocarditis
- biliary tract infections
- suppurative abdominal lesions
- peritonitis.

E. faecalis and *E. faecium* are important causes of wound and urinary tract infection in hospital and may cause sporadic outbreaks. Bacteraemia carries a poor prognosis as it often occurs in patients with major underlying pathology and in those who are immunocompromised.

LABORATORY DIAGNOSIS

Collection of specimens

The diagnosis of streptococcal infections is established by demonstrating the presence of the pathogen in throat or skin swabs, pus, blood cultures, cerebrospinal fluid (CSF), expectorates or urine according to the site of infection.

Particular problems are associated with the collection of expectorates for detection of *Str. pneumoniae*. Although it is the commonest cause of community-acquired pneumonia, sputum culture is positive in only about 20% of cases for several reasons:

- There may be difficulty in obtaining an expectorated specimen; postural drainage or inhaled aerosolized saline can encourage its production. Sputum may also

Table 16.2 Factors predisposing to infective endocarditis

Cardiac factors	Non-cardiac factors
Rheumatic heart disease	Dental manipulations ^a
Atherosclerotic heart disease	Endoscopy
Congenital heart disease	Intravenous drug abuse
Cardiac surgery	Intravenous cannulae and shunts
Prosthetic heart valves	Sepsis
Previous endocarditis	

^a Procedures in which bleeding occurs.

be obtained by bronchoscopy in patients who are ventilated.

- Previous antibiotic treatment substantially reduces the chance of isolating the pneumococcus from the sputum.

The adequacy of the sputum sample should be confirmed by microscopy, which should show a predominance of pus cells rather than squamous epithelial cells from the mouth. The specimen is then homogenized with an agent such as *N*-acetylcysteine which permits semi-quantitative culture.

In pneumococcal meningitis the CSF is often macroscopically cloudy. The cell count is usually markedly increased and shows a predominance of polymorphonuclear leucocytes. Typical Gram-positive diplococci can commonly be demonstrated, sometimes in enormous numbers, by Gram stain examination of a CSF deposit. The appearance is often typical, and a presumptive diagnosis can be made to allow appropriate therapy to be started before the identity of the organism is confirmed by culture.

Blood cultures are of value in patients with invasive streptococcal infections. This is also the case in patients with suspected pneumococcal pneumonia, particularly when this is severe, since up to 15% of patients will be bacteraemic.

Other body sites that may merit investigation according to the clinical presentation include joint and peritoneal fluids. Tympanocentesis provides the possibility of establishing the microbial cause of otitis media, but since most of these infections settle spontaneously, or with the assistance of a few days' antibiotic treatment, tympanocentesis is not usually necessary.

Cultivation and identification

Unlike staphylococci, streptococci lack the enzyme catalase, which releases oxygen from hydrogen peroxide. Catalase-negative Gram-positive cocci are therefore likely to be streptococci. The appearance of cocci in obvious chains (Fig. 16.1) is another useful criterion, but the length of the chains varies with the species and the conditions of growth. Optimal chain formation is seen in broth cultures. There may be marked variation in size and shape, particularly in older cultures or in direct smears from purulent exudates.

The primary cultivation medium for streptococci is blood agar, supplemented, whenever enterococci are suspected, with an agar medium (e.g. MacConkey's medium) selective for enterobacteria. Streptococci of aetiological significance will usually predominate in the culture even when the sample is taken from a site with a resident microflora.

The pyogenic streptococci are detected initially by their β -haemolytic activity. The colonies are small (1 mm in diameter) and, in contrast to those of staphylococci, lack pigment. Colonies of pneumococci are α -haemolytic, smooth and may vary in size according to the amount of capsular polysaccharide produced; those of serotypes 3 and 37 are usually larger than the rest and have a watery or mucoid appearance. During prolonged incubation, autolysis of bacteria within the flat pneumococcal colonies results in a typical subsidence of the centre ('draughtsman colonies').

Species identification of pyogenic streptococci is largely based on serological detection of group antigens by immune precipitation or co-agglutination techniques. An additional test that is helpful in the presumptive identification of *Str. pyogenes* is the bacitracin sensitivity test. In contrast to most other streptococci, *Str. pyogenes* is uniformly sensitive and large inhibition zones are formed round bacitracin discs on blood agar. Likewise, *Str. agalactiae* can be presumptively identified by the CAMP reaction (Fig. 16.4).

Pneumococci are distinguished from other α -haemolytic streptococci by their characteristic sensitivity to optochin (ethylhydrocupreine). Growth of pneumococci is inhibited around an optochin disc applied to an inoculated blood agar plate. With few exceptions other α -haemolytic streptococci are not inhibited. In doubtful cases the identity of pneumococci is confirmed by demonstrating bile solubility, autolysis or reactivity to a poly-specific antiserum ('omni-serum') against capsular polysaccharides.

Other streptococci are identified by biochemical characteristics, such as the ability to ferment various carbohydrates and hydrolyse amino acids. However, some of the viridans streptococci are notoriously difficult to identify.

Enterococci are unique among the streptococci in their ability to grow on bile-containing media.

Antigen detection

Numerous commercial kits are available for the detection of *Str. pyogenes* directly in throat swabs without cultivation. These diagnostic kits use specific antibodies to detect the group A antigen in the material on the swab. They allow private practitioners to test if a throat infection is caused by *Str. pyogenes*, but the sensitivity and specificity of individual tests vary.

Antibody detection

Detection of antibodies against antigens of *Str. pyogenes* is an important means of establishing the diagnosis of post-streptococcal rheumatic fever and

glomerulonephritis. In many cases the initiating infection in the throat or on the skin is no longer present.

Immune responses vary depending on whether the original focus is the throat or skin. Antibodies against streptolysin O (the ASO test) are used to document antecedent streptococcal infection in the throat of patients with clinical signs of rheumatic fever. A significant increase in antibody titre appears 3–4 weeks after the initial exposure to the micro-organism. Detection of increased levels of serum antibodies to streptococcal hyaluronidase and DNAase B is also of diagnostic importance.

ASO estimation is unreliable in pyoderma-associated acute glomerulonephritis. An elevated ASO titre is not observed in these patients, perhaps because lipids present in the skin inactivate the streptolysin O. Detection of antibodies against streptococcal DNAase B is recommended as a diagnostic tool in these patients.

Typing of streptococci

Strains of *Str. pyogenes* can be subdivided into serological types. The most comprehensive typing scheme is based on structural differences in the highly variable surface M protein. Over 80 different M types may be distinguished with type-specific antisera. Some reference laboratories perform M typing by detecting sequence differences in the gene (*emm*) encoding the M protein. An alternative typing scheme is based on the surface protein known as the T antigen.

Apart from serving epidemiological purposes, particular M types are associated with particular types of infections. Thus, certain M types are more commonly associated with skin infections than mucosal infections. Recent increases in the rate and severity of invasive *Str. pyogenes* infections (toxic shock syndrome and necrotizing fasciitis) have been primarily associated with serotypes M-1 and M-3. Rheumatic fever is often, but not exclusively, associated with serotypes M-5 and M-6. Recent outbreaks in the USA were due to M-18.

Pneumococci are typed on the basis of the differences in capsular polysaccharides, of which 90 have been described. The addition of India ink to a suspension of pneumococci will show the presence of the capsule as a clear halo around the organisms. Mixing a suspension of pneumococci with type-specific antisera increases the visibility of the capsule in the microscope, and is the basis of the *quellung reaction* or *capsular swelling test*. Serotyping of pneumococci is mainly carried out in reference laboratories.

TREATMENT

Streptococci are naturally susceptible to penicillin and to a wide range of other antibiotics. However, acquired resistance to other agents has become an increasing problem. Although streptococci are intrinsically resistant to aminoglycosides, these agents interact synergically with penicillins and the combination is often used in the treatment of streptococcal and enterococcal endocarditis.

Penicillin resistance has never been detected in *Str. pyogenes*. As a result, benzylpenicillin (penicillin G) or oral phenoxymethylpenicillin (penicillin V) are the drugs of choice for treatment of infections with *Str. pyogenes*. Antibiotic sensitivity tests are currently unnecessary if that species is identified as the infecting organism. In cases of hypersensitivity to penicillin, erythromycin is usually the second choice, but resistance occurs and is common in some countries.

Treatment for 3–5 days will limit the effect of severe attacks of streptococcal infection and prevent suppurative complications such as otitis media, but the streptococci will be eliminated from the infected area only if treatment is continued for 10 days. Treatment of uncomplicated throat infections with *Str. pyogenes* is not warranted in areas in which post-streptococcal sequelae are rare.

Surgery is essential to remove damaged tissue in case of necrotizing fasciitis, as antibiotic penetration of the infected area is poor. Clindamycin is preferred to penicillin because it inhibits protein synthesis, including production of exotoxin.

Most strains of *S. agalactiae* are susceptible to penicillins, macrolides and glycopeptides.

Resistance to penicillin in pneumococci and viridans streptococci, caused by mutations in the target penicillin-binding proteins, is widespread. These mutations have accumulated in strains of *Str. mitis* and *Str. oralis* and the altered genes have subsequently been transferred by genetic transformation to *Str. pneumoniae*.

Most pneumococcal infections with strains exhibiting intermediate-level resistance to penicillin (minimum inhibitory concentration 0.1–1 mg/l) respond to high dose therapy; an exception is meningitis, because of problems of penetration into the CSF. High-level penicillin resistance (minimum inhibitory concentration above 2 mg/l) was first recognized in 1977 in South Africa, where it was responsible for an epidemic of pneumococcal meningitis unresponsive to penicillin. The incidence of penicillin resistance is quite variable geographically and reflects the local level of usage of antibiotics.

Penicillin resistance in pneumococci and other viridans streptococci is often linked to resistance to several other

antibiotics. Resistance to erythromycin, tetracycline and chloramphenicol is not uncommon, and even tolerance to vancomycin has been reported.

The dose of penicillin necessary to treat susceptible pneumococcal infection is largely determined by pharmacological factors at the site of infection. For example, pneumococcal pneumonia will respond to doses of penicillin as low as 0.3 g (0.5 mega-units) twice daily, whereas pneumococcal meningitis requires much higher doses. In patients unable to tolerate penicillin, erythromycin is the most widely used alternative agent for respiratory pneumococcal infections.

Unlike other streptococci, enterococci are intrinsically resistant to cephalosporins. Sensitivity to penicillins and other antibiotics varies widely, and clinical isolates must be tested for their susceptibility. Vancomycin resistance has been observed in enterococci and is a problem in high-dependency areas of some hospitals.

PREVENTION AND CONTROL

Hygienic measures

Skin infections with *Str. pyogenes* are usually associated with poor hygiene, and can to a large extent be prevented by standard hygienic measures. Late-onset neonatal infections with *Str. agalactiae* may also be prevented or significantly reduced by standard aseptic nursing procedures.

Likewise, hygiene is the most important preventive measure in relation to dental caries, which can be largely prevented by regular tooth-brushing with a fluoride-containing dentifrice.

Chemoprophylaxis

Prophylactic use of antibiotics is relevant in some streptococcal infections. As the primary attack of rheumatic fever usually occurs during childhood, long-term penicillin prophylaxis until adulthood is recommended to reduce the risk of further attacks and further heart injury. This is not the case in patients with acute glomerulonephritis because of the lack of recurrences.

Two different approaches are used to prevent early-onset neonatal *Str. agalactiae* infections:

- A risk-based strategy in which women of unknown colonization status receive intrapartum antibiotic prophylaxis in case of: threatened delivery <37 weeks' gestation; premature rupture of the membranes; intrapartum fever; or previous delivery of a child developing neonatal infection.
- A screening-based approach in which all pregnant women at 35–37 weeks' gestation are screened for

S. agalactiae colonization in vaginal and rectal specimens. All identified carriers are offered intrapartum chemoprophylaxis.

Intravenous or intramuscular penicillin is the agent of choice because its antimicrobial spectrum, narrower than that of ampicillin, reduces the likelihood of resistance developing in other bacteria. A cephalosporin is an appropriate alternative for patients with penicillin allergy as increasing proportions of *Str. agalactiae* are resistant to erythromycin and clindamycin.

Patients at risk of developing infective endocarditis (Table 16.2) should be given prophylactic antibiotics in association with dental procedures that lead to bleeding. The current international recommendations are amoxicillin 1 h before dental treatment or, in case of penicillin allergy, clindamycin. If the patient has been on long-term penicillin prophylaxis the oral streptococci are likely to have reduced susceptibility to penicillins, and clindamycin or vancomycin are recommended as the alternative. It is imperative that patients at risk maintain healthy periodontal conditions and that the amount of dental plaque is kept to a minimum.

Vaccines

Pyogenic streptococci

Attempts to develop a vaccine against *Str. pyogenes* infections have been hampered by two problems:

- the considerable antigenic diversity of the M protein and other vaccine candidate antigens
- the potential immunological cross-reactivity of many of the antigens with host tissue components.

Several strategies are currently being tested, including oral vaccination.

A vaccine against neonatal *Str. agalactiae* infection based on protein-conjugated type III capsular polysaccharide is being tested for use primarily in women of reproductive age. However, additional serotypes are increasingly prevalent.

Pneumococci

Before the widespread availability of effective antimicrobial drugs the treatment of pneumococcal infections was based on the use of type-specific antiserum. This reduced mortality in bacteraemic pneumococcal pneumonia but not to the same extent that penicillin was subsequently shown to achieve. However, it indicated that type-specific antibody had a role in the control of pneumococcal disease and led to a variety of prototype vaccines. The vaccine that has been in use for many years contains



a mixture of 23 polysaccharide serotypes chosen according to the prevalence of serotypes responsible for bacter-aemic pneumococcal infection. It offers protection against 90% of isolates.

Like other vaccines based on pure polysaccharides, the immunogenicity of the multivalent vaccine is inadequate in those below 2 years of age and in those immunosuppressed as a result of malignancy, steroid therapy or other chronic disease. To overcome this problem, new pneumococcal vaccines containing capsular polysaccharide coupled to a carrier protein are becoming available. These vaccines increase the immunogenicity of the polysaccharide by rendering the response dependent on T lymphocyte help. The current conjugate vaccine only includes seven of the capsular polysaccharides, but vaccines with more comprehensive coverage are anticipated. Some countries contemplate inclusion of the new vaccine in the childhood vaccination programme.

The recommended indications for vaccine use in the UK are shown in Table 16.3. In some countries, including the USA, where the vaccine has been used most widely, it is also recommended for those over 65 years of age, with or without previous ill health, although

there have been difficulties in establishing scientifically the efficacy in this group.

Immunization is particularly recommended for those with congenital or surgical asplenia and those with hereditary haemoglobinopathies such as sickle cell disease, since in these patients pneumococcal infection can be fulminant. Vaccine efficacy is not complete and many clinicians also prescribe oral phenoxymethylpenicillin as long-term chemoprophylaxis in this high-risk group.

Table 16.3 Recommended indications for the use of pneumococcal vaccine in the UK (for use in children over 2 years and adults)
Asplenia or severe dysfunction of the spleen Homozygous sickle cell disease and coeliac disease Chronic renal disease or nephrotic syndrome Immunodeficiency or immunosuppression caused by disease or treatment, including HIV infection at all stages Chronic heart disease Chronic lung disease Chronic liver disease, including cirrhosis Diabetes mellitus

RECOMMENDED READING

Cunningham M W 2000 Pathogenesis of group A streptococcal infections. *Clinical Microbiology Reviews* 13:470–511

Douglas C W I, Heath J, Hampton K K, Preston F E 1993 Identity of viridans streptococci isolated from cases of infective endocarditis. *Journal of Medical Microbiology* 39: 179–182

Fraser J, Arcus V, Kong P, Baker E, Proft T 2000 Superantigens – powerful modifiers of the immune system. *Molecular Medicine Today* 6:125–132

Johnson A P, Speller D C E, George R C et al. 1996 Prevalence of antibiotic resistance and serotypes in pneumococci in England and Wales: results of observational surveys in 1990 and 1995. *British Medical Journal* 312: 1454–1456

Kilian M 1998 *Streptococcus and Lactobacillus*. In Balows A and Duerden BI (eds) *Topley and Wilson's Microbiology and Microbial Infections*, 9th edition, Volume 2. Arnold, London, pp. 633–667

Marsh P D, Martin M W 1999 *Oral Microbiology*, 3rd edn. Wright, Oxford

Schrag S J, Zywicki S, Farley M M et al. 2000 Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *New England Journal of Medicine* 342:15–20

Schuchat A 1999 Group B streptococcus. *Lancet* 353:51–56

Stevens D L, Kaplan E L (ed) 2000 *Streptococcal Infections. Clinical Aspects, Microbiology, and Molecular Pathogenesis*. Oxford University Press, Oxford

Tomasz A 2000 *Streptococcus pneumoniae. Molecular Biology and Mechanisms of Disease*. Mary Ann Liebert, Inc., Larchmont, NY

Internet site

Centers for Disease Control and Prevention:
www.cdc.gov/ncidod/dbmd/diseaseinfo/