8.6.2 Streptococci and enterococci 965

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8.6.2 Streptococci and enterococci 965 diphtheria vaccine is reduced in children aged 7 years and older so that reactogenicity is minimized. The recommended schedule for vaccination against diphtheria varies between countries. In the United Kingdom three primary doses of adsorbed diphtheria–tetanus–pertussis–haemophilus influenzae type b vaccine (DTP-Hib) are given at 2, 3, and 4 months; a first booster dose with DTP at age 3 to 5 years, and a second booster dose with DT at school leaving. The primary course does not need to be repeated if boosters are delayed. People living in low-endemic or nonendemic countries should receive booster doses of DT approximately every 10 years. It is now recom- mended by the World Health Organization that DT rather than T (tetanus toxoid alone) should be used when tetanus prophylaxis is needed following injury. Tetanus-diphtheria vaccine is recom- mended for all travellers who have not received the vaccine within the last 10 years. Where diphtheria is endemic the primary course alone should be sufficient to prevent an epidemic of diphtheria, as natural mech- anisms such as frequent skin infections caused by C. diphtheriae probably contribute to maintaining immunity. One or two DT or DTP booster doses may need to be added to the routine schedule in areas at increased risk of diphtheria. Adults in developing coun- tries do not require routine immunization. Aggressive action is needed in the event of a diphtheria outbreak. Groups at risk should be immunized, there should be prompt diag- nosis and management of cases, and identification of close con- tacts should be made so that the spread of infection can be halted. A single dose of DTP should be used for children under 3 years of age, and DT for children aged over 3 years and adults. Additional doses of vaccine will be needed in nonimmunized (Schick test posi- tive) people. Susceptibility to diphtheria may be assessed using the Schick test: 0.1 ml of toxin is injected into the skin of one forearm (test site) and the same quantity of a heat-inactivated toxin injected into the other forearm (control site). A positive reaction occurs in in- dividuals without toxin-neutralizing antibodies and consists of an area of redness appearing after 24–36 h at the test site only and persisting for 4–5 days. If no toxin-neutralizing antibodies are pre- sent, there will be either no reaction at either site (negative test) or a pseudoreaction at either site due to antibodies to substances other than diphtheria toxin in the test materials. This test is no longer commonly performed due to limited availability of the test materials. FURTHER READING Celik T, et al. (2006). Prognostic significance of

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Br J Biomed Sci, 62, 1–4. 8.6.2 Streptococci and enterococci Dennis L. Stevens and Sarah Hobdey ESSENTIALS The streptococci are a diverse group of Gram-positive pathogenic cocci that cause clinical disease in humans and domestic animals. They are traditionally classified on the basis of serological reac- tions, particularly Lancefield grouping based on cell-wall carbo- hydrates, and haemolytic activity on blood agar. Six groups can be defined by genetic analysis: pyogenic streptococci, milleri or anginosus group, mitis group, salivarius group, mutans group, and bovis group. Group A streptococci (S. pyogenes) Group A streptococci are carried, usually in the nose or throat, by 5–20% of children and 0.5% of adults. More than any other human pathogen, group A streptococci cause a wide variety of infections ranging from pharyngitis, erysipelas, cellulitis, and Acknowledgement: The author of the present chapter and the editors acknow- ledge the inclusion of much material from the chapter in previous editions by Professor S. K. Eykyn.

 necrotizing fasciitis to the postinfectious sequelae: rheumatic fever and poststreptococcal glomerulonephritis. These microbes con- tinue to evolve, as evidenced by over 150 different genetic types and the emergence of novel infections such as streptococcal toxic shock syndrome. Group A streptococci are easy to culture in the laboratory from appropriate samples; diagnosis can also be made by detection of the group A antigen or confirmed serologically. All strains remain sensi- tive to penicillin, which is the antibiotic of choice, with erythromycin usually given to those who are penicillin allergic, although epidemics of pharyngitis caused by erythromycin-resistant strains have been widely reported. Genetic differences and the presence of multiple virulence factors have frustrated efforts to develop effective vaccines. Group B streptococci (S. agalactiae) Group B streptococci are carried in the throat by 5–10% of adults, as well as in the urethra, vagina, perineum, and anorectum. They cause a variety of infections: (1) neonatal infection—including bacteraemia and meningitis; screening for vaginal carriage during the third tri- mester of pregnancy and intrapartum treatment with intravenous penicillin has reduced

the incidence of early-onset neonatal disease; (2) post-partum infection—puerperal infection usually manifests
as endometritis with fever and uterine tenderness, occurring within 24–48 h of delivery or abortion; also (3) skin and soft tissue infec- tions, urinary tract infections, and bacteraemias (especially in patients with diabetes mellitus, malignancy, HIV infection, and chronic renal or liver disease). Group B streptococci are readily isolated from any clinical spe- cimen in the laboratory, and detection of group B antigen in body fluids by latex particle agglutination enables rapid diagnosis. They are sensitive to penicillin (the antibiotic of choice), erythromycin, and cephalosporins. The polysaccharide capsule of group B strepto- coccus is a major virulence factor, with at least six different serotypes identified: experimental immunization using the polysaccharide pro- vides type specific protection, but no such vaccine has yet been de- veloped for human use. Other groups of streptococci Groups C and G—produce infections that are similar to those caused by group A streptococci but tend to be less virulent. They are im- portant causes of cellulitis, particularly recurrent cellulitis associated with saphenous vein donor site infections in patients with coronary artery bypass surgery. Streptococcus milleri or Streptococcus anginosus group—includes S. constellatus, S. intermedius, and S. anginosus. These are found in the normal flora of the upper respiratory tract, gastrointestinal tract, and genital tract; commonly isolated from a range of pyogenic infections (e.g. dental or other abscesses), sometimes in pure culture, but often with other organisms, particularly anaerobes. Streptococcus mitis, Streptococcus salivarius, and Streptococcus mutans groups of streptococci (oral/viridans streptococci)—these in- clude S. pneumoniae (see Chapter 8.6.3) and those oral streptococci that are the most common causes of infective endocarditis of oral or dental origin. They occasionally cause bacteraemia in neutropenic patients, particularly those who have received prophylaxis with fluoquinolones such as ciprofloxacin. Streptococcus bovis group—a gastrointestinal commensal; most pa- tients with S. bovis bacteraemia will have endocarditis in association with colonic pathology or cirrhosis of the liver. Streptococcus suis—an occupational cause of septicaemia, menin- gitis, septic arthritis, pneumonia, and endophthalmitis among those working with pigs and pork in Southeast Asia. Enterococci Part of the normal gut flora of humans and animals, these are an increasingly important cause of nosocomial infection and colon- ization, possibly the result of the large-scale use of antibiotics such as cephalosporins and quinolones to which they are inherently resistant. Enterococcus faecium and E. faecalis have also become vancomycin resistant, a characteristic dramatically increasing treat- ment failures, although they remain sensitive (at the time of writing) to linezolid, an oxazolidinone antimicrobial. Introduction The term streptococcus was first used by Billroth in 1874 to describe chain-forming cocci found in infected wounds. In 1879, Pasteur also found them in the blood of women with puerperal sepsis. In 1884, Rosenbach defined these streptococci as Streptococcus pyo- genes. This organism remains one of the most important human pathogens. The genus Streptococcus contains many other species of varying degrees of pathogenicity for humans and animals. S. faeca- lis and S. faecium were split from the genus Streptococcus in 1984 and became Enterococcus spp. and numerous other species have since been included in this genus. The nutritionally variant strepto- cocci S. adjacens and S. defectivus have also been assigned to a new genus Abiotrophia, to which the newly described species A. elegans has been added. Classification Traditionally, classification of streptococci has relied on serological reactions, particularly the Lancefield grouping based on cell-wall carbohydrates, and haemolytic activity on blood agar, which has led to rather unsatisfactory streptococcal taxonomy. Genetic analysis has now enabled the subdivision of the species of Streptococcus into six clusters or groups as follows: pyogenic streptococci, milleri or anginosus group, mitis group, salivarius

group, mutans group, and bovis group. Since the medically important members of the mitis, salivarius, and mutans groups are all oral streptococci and are of clinical relevance predominantly in endocarditis, they will be con- sidered together. Pyogenic streptococci The pyogenic streptococci include the major human pathogen S. pyogenes (Lancefield group A), group B streptococci (S. aga- lactiae), and groups C and G streptococci. These organisms are β-haemolytic on blood agar.

8.6.2 Streptococci and enterococci 967 S. pyogenes (b-haemolytic group A) The prevalence and severity of streptococcal pharyngitis has re- mained constant over the centuries of recorded history, although the incidence of complications such as peritonsillar abscess and mastoiditis have declined with the advent of antibiotics. Since the beginning of the 20th century, and long before the introduction of antibiotics, the prevalence and severity of scarlet fever and rheum- atic fever following infections with S. pyogenes declined until the 1980s. In the mid-1980s, highly virulent streptococci appeared causing very severe infections such as streptococcal toxic shock syn- drome and necrotizing fasciitis, often in otherwise healthy people. Such cases occurred not only in the United Kingdom but also in most of the developed world. S. pyogenes infection is usually com- munity-acquired but can be acquired in hospital where the most ser- ious infections are postoperative. Carriage Although S. pyogenes is an invasive organism, it survives on epi- thelial surfaces (asymptomatic carriage) usually in the nose and throat. Carriage can also be anal, vaginal, and on the scalp. Pharyngeal carriage rates are usually much higher in children (5– 20%) than in adults (0.5%) and also vary with season, year, and geographical location. They are higher in crowded living condi- tions. S. pyogenes can persist for months after acute pharyngitis, though in decreased numbers. Survival in the environment is poor and S. pyogenes can only survive on skin and inanimate objects for a limited period of time. Pathogenicity, virulence, and typing S. pyogenes is an extracellular pathogen and produces virulence factors that enable it to avoid host defences and spread in tissues. An important virulence factor is the M protein and streptococci rich in M protein resist phagocytosis by granulocytes. Immunity to S. pyogenes infection is associated with the development of op- sonic antibodies to antiphagocytic epitopes of M protein; the im- munity is usually type specific and lasts for many years. M protein was first described in the 1920s by Rebecca Lancefield; over 100 M types have now been differentiated. Lancefield also developed the supplementary T typing system which distinguishes 26 serotypes of a trypsin-resistant surface protein (T antigen), most of which can be expressed by several different M types. Certain M types also produce a serum opacity factor (OF+). These typing systems are still widely used in epidemiological studies to distinguish between strains of S. pyogenes. However, more modern methods utilize procedures to sequence the M protein gene. Recent studies have shown consider- able genetic diversity in S. pyogenes, and horizontal transfer and re- combination of virulent genes have played a major role. This finding is likely relevant to the emergence of new unusually virulent clones of the organism. In addition to M protein, lipoteichoic acid, important in the host– bacterial interaction, is expressed on the surface of the organism and is the adhesin that binds the organism to fibronectin on the surface of the oral epithelial cell membranes and initiates the colonization that precedes infection. S. pyogenes has a hyaluronate capsule which, like M protein, is also antiphagocytic, and is an additional virulence factor. The extent of encapsulation varies, and colonies with prom- inent capsules are very mucoid on blood agar. Strains of S. pyogenes that are both rich in M protein and heavily encapsulated are readily transmitted from person to person and have been associated with epidemics of acute rheumatic fever. S. pyogenes produces many extracellular substances, several of which are important in the pathogenesis of infection. The most familiar are streptolysin O, deoxyribonuclease (DNase) B, and hyaluronidase, as serum antibodies

to these provide retrospective confirmation of recent streptococcal infection. Other extracellular products include DNases A, C, and D, streptolysin S, proteinase, streptokinase, and the substances previously known as erythrogenic toxins. These toxins have now been designated streptococcal pyro- genic exotoxins (SPE)-A, -B, -C, and more recently several others. SPE-A and SPE-C are coded by a phage gene and readily transmitted to susceptible strains. These toxins, known as superantigens, have diverse effects on the host. In addition to the rash of scarlet fever, they cause fever and induce lethal shock in animals. They have pro- found effects on the immune system including increasing suscep- tibility to endotoxic shock, induction of cytokine production, and cause clonal proliferation of T lymphocytes. Recently, nicotine adenine dinucleotidase (NADase) has been found in 100% of strains of group A streptococci (GAS) associated with invasive GAS infections such as toxic shock syndrome and necrotizing fasciitis. There is evidence that the gene for NADase is found in all strains of GAS but only produced extracellularly in these invasive strains. In addition, production of NADase by M1 strains, the most common strain associated with invasive types of infections, began around 1985, just before the recognition of severe invasive GAS infections.
S. pyogenes can penetrate the upper respiratory tract mucosa or a break in the skin, causing local infection or may spread along tissue planes or lymphatics. The M protein is not toxic in itself but pro- tects the streptococcus from phagocytosis, and antibodies to the M protein are opsonic. In about two-thirds of patients with serious in- vasive disease, who might present with fever, shock, and renal im- pairment, the portal of entry is the skin and infection of soft tissue is apparent, but in others the site of infection might be deep in the fascia or muscle. Infections caused by S. pyogenes
S. pyogenes causes a variety of illnesses ranging from very common infections such as pharyngitis, impetigo, and cellulitis to less common, more severe infections such as puerperal sepsis, necro- tizing fasciitis, bacteraemia, and toxic shock. S. pyogenes is also as- sociated with the nonsuppurative sequelae of acute rheumatic fever and acute glomerulonephritis. Streptococcal pharyngitis Streptococcal pharyngitis or tonsillitis is one of the most common bacterial infections in children from 5 to 15 years, but all ages are susceptible. The incubation period, at least in outbreaks, is short (1– 3 days) and the onset of the infection is marked by the abrupt onset of sore throat and pain on swallowing with malaise, fever, and head- ache. The signs are redness and oedema of the pharynx, enlarged red tonsils (Fig. 8.6.2.1) with spots of white exudate, fever, and en- larged tender anterior cervical lymph glands. Nausea, vomiting, and abdominal pain are common in children, and in infants and pre- school children there may be few definite signs of pharyngitis but

 fever, nasal discharge, enlarged cervical lymph glands, and otitis media occur. Direct extension of streptococcal pharyngitis can give rise to acute sinusitis or otitis media, and other suppurative complications include peritonsillar abscess (quinsy), mastoiditis, retropharyngeal abscess, and suppurative cervical lymphadenitis. Scarlet fever Scarlet fever results from infection with a strain of S. pyogenes that pro- duces SPE (erythrogenic toxin). It is usually associated with strepto- coccal pharyngitis but can follow streptococcal infections at other sites including surgical site infections. Scarlet fever rarely follows streptococcal pyoderma. Most cases occur in school-age children and the rash must be distinguished from viral exanthems, Kawasaki's disease, and staphylococcal toxic shock syndrome. The rash, which generally appears on the second day of clinical illness, is usually a diffuse erythema, symmetrical, and blanches on pressure. It is seen most often on the neck, chest, folds of the axilla, and groin. Occlusion of sweat glands gives the skin a 'sandpaper' texture, a useful sign in dark-skinned patients. The face appears flushed with circumoral pallor. There are small red haemorrhagic spots on the palate, and the

tongue is initially covered with a white fur through which red papillae appear (‘strawberry tongue’); after the rash develops, the white fur peels off leaving a raw red papillate surface (‘raspberry tongue’). The rash persists for several days and later (up to 3 weeks) peeling (des- quamation) may occur, usually on the tips of the fingers, toes, or ears, and less often over the trunk and limbs. A similar rash may develop as a reaction to streptokinase thrombolytic therapy. Streptococcal perianal infection (cellulitis) This is a superficial well-demarcated rash spreading out from the anus in young children, usually boys, associated with itching, rectal pain on defaecation, and blood-stained stools. S. pyogenes is iso- lated from perianal cultures and usually also from pretreatment throat swabs. Streptococcal vulvovaginitis Vulvovaginitis in prepubertal girls is often caused by S. pyogenes and presents with serosanguinous discharge and erythema of the labia and vaginal orifice. As with perianal infections, S. pyogenes is usu- ally also found in the throat. In both streptococcal perianal infec- tion and vulvovaginitis, more than one child in the family may be affected and nasopharyngeal carriage is likely in both infected and uninfected children. Streptococcal skin and soft tissue infections Pyoderma/impetigo Almost any purulent lesion of the skin can yield S. pyogenes, sometimes with Staphylococcus aureus. Such le- sions include impetigo, infected cuts and lacerations, insect bites, scabies, intertrigo, and ecthyma. S. pyogenes often causes secondary infection in varicella, occasionally with resultant bacteraemia. The term pyoderma is used synonymously with impetigo for discrete purulent, apparently primary infections of the skin that are preva- lent in many parts of the world, especially in children. These lesions are initially papules, then vesicular with surrounding erythema, and finally pustules with crusting exudate; they may be localized to one part of the body or generalized. Outbreaks of impetigo can occur among adults subject to skin trauma, such as rugby football players (scrumpox), and streptococcal infection of cuts on the hands and forearms are an occupational hazard for workers in the meat trade. Epidemics of impetigo can occur in day care centres, prisons, and schools. Ecthyma is an ulcerated form of impetigo in which the ul- ceration extends into the dermis. In recent times, approximately 50% of cases of impetigo are caused by Staphylococcus aureus. Invasive streptococcal infections of skin and soft tissues Erysipelas This is an acute inflammation of the skin with lymph- atic involvement. The streptococci are localized in the dermis and hypodermis. It usually affects the face, particularly in elderly people, but may occur elsewhere. It may be bilateral (Fig. 8.6.2.2) and is sometimes recurrent. There is generally a history of sore throat, but the mode of spread to the skin is unknown. It is usually accom- panied by fever, rigors, and toxicity. The cutaneous lesion begins as Fig. 8.6.2.2 Bilateral facial erysipelas. Copyright S. J. Eykyn. Fig. 8.6.2.1 Streptococcal tonsillitis: suppurative complications. Copyright D. A. Warrell.

 a localized area of brilliant erythema and swelling and then spreads with rapidly advancing raised red margins that are well demarcated from adjacent normal tissue. Facial erysipelas begins over the bridge of the nose and spreads over the cheeks. Vesicles and bullae appear, which become crusted when they rupture. There is marked oedema and the eyes are often closed. When the infection resolves it is often followed by desquamation. Intense local allergic reactions to topical agents, such as cosmetics, may cause confusion. Cellulitis Cellulitis (Fig. 8.6.2.3) is commonly caused by strepto- cocci and Staphylococcus aureus. This is an acute spreading inflam- mation of the skin and subcutaneous tissues with local pain swelling and erythema. Fever, rigors, and malaise may precede by a few hours the appearance of the skin lesion and associated lymphangitis and tender lymphadenopathy. Streptococcal cellulitis differs from ery- sipelas in that the lesion is not raised and the demarcation between affected and unaffected skin is indistinct. It can result from infection of burns, mild trauma, or surgical wounds. When this involves

the leg, fungal infection of the feet is often present and predisposes to streptococcal invasion. After the first episode, there is a tendency for recurrence in the same area. Recurrences are more common in patients with chronic venous insufficiency, lymphatic obstruction, and at the saphenous vein donor site in patients following coronary bypass surgery. These latter infections are most commonly caused by group C or G streptococci. Intravenous drug users are also at risk of streptococcal cellulitis associated with skin and tissue infection and septic thrombophlebitis. (Type II) necrotizing fasciitis (streptococcal gangrene) This in- fection, described by Meleney in 1924, involves the deep subcuta- neous tissues and fascia (and occasionally muscle as well) with extensive necrosis and gangrene of the skin and underlying struc- tures. It is generally community-acquired, usually involving the arm or leg, but can also occur after surgery, which can sometimes be quite minor. Some people with this infection are diabetic, but the majority are previously healthy. Risk factors providing a portal of entry include surgery, trauma, childbirth, intravenous drug abuse, and chickenpox. Blunt trauma and muscle strain and the use of non- steroidal anti-inflammatory agents are also risk factors. The infection begins at the site of trivial or even inapparent trauma with redness, swelling, fever, and rapidly escalating focal pain followed by purple discoloration and the development of bullae, which are often haem- orrhagic. In patients who develop infection deeply in traumatized tissue such as muscle, fever, and severe pain may be the only initial signs and symptoms of infection. Bacteraemia is often present and within days skin necrosis occurs followed by extensive sloughing. The patient is profoundly ill and the disease has a high case fatality rate of 30–70%. Features of streptococcal toxic shock syndrome are associated in many cases. The United Kingdom media memorably dubbed S. pyogenes the ‘flesh-eater’ in reports of a cluster of cases of necrotizing fasciitis in 1994. Treatment involves early intravenous antibiotics. The organisms are sensitive to penicillin but, paradox- ically, the drug may not be effective in high concentrations (the ‘Eagle effect’). Clindamycin has advantages over penicillin, based on animal studies and one retrospective study in humans. The efficacy of clindamycin is likely due to its ability rapidly to inhibit toxin pro- duction by Gram-positive pathogens. Urgent surgical debridement of necrotic tissue and intensive care to support failing organs and systems (e.g. cardiovascular and renal) are extremely important. Benefits of immunoglobulin are suggestive but inconclusive. Streptococcal toxic shock syndrome This syndrome was described in 1989 in patients with severe S. pyo- genes infection and clinical features remarkably similar to those of the staphylococcal toxic shock syndrome described a decade earlier. Streptococcal toxic shock syndrome is defined as any acute S. pyogenes infection associated with the sudden onset of shock and multiorgan failure. Streptococcal toxic shock syndrome may be as- sociated with necrotizing fasciitis, myositis, pneumonia, peritonitis, or post-partum sepsis. It can occur at all ages and many of those affected are young and previously healthy. Most cases have been community-acquired, though it can be acquired in hospital. M1 has been the predominant serotype in many countries, though others, especially 3, 4, 6, 11, 12, and 28, have also been implicated. Most strains produce SPE-A. Interestingly there is an amino acid hom- ology of 50% and immunological cross-reactivity between SPE-A and staphylococcal enterotoxins B and C, which together with staphylococcal toxic shock syndrome toxin-1 are relevant in non- menstrual staphylococcal toxic shock syndrome. Diffuse scarlatina type rash is present in only 5–10% of cases (Fig. 8.6.2.4). Streptococcal bacteraemia In parallel with the increase in serious S. pyogenes infections, there has been an increase in bacteraemic infections, both community- and Fig. 8.6.2.3 Cellulitis. Copyright S. J. Eykyn. Fig. 8.6.2.4 Scarlatina-like rash of streptococcal toxic shock syndrome. Copyright D. A. Warrell.

section 8 Infectious diseases 970 hospital-acquired (usually postoperative) (Fig. 8.6.2.5). While many patients have an underlying disease, generally malignancy, im- munosuppression, or diabetes, others are previously healthy adults between 20 and 50 years old. The portal of entry is usually the skin. The mortality is higher in patients with underlying disease, those with necrotizing fasciitis, myositis, pneumonia, or post-partum sepsis, and the very young or old. Puerperal and neonatal infection Historically S. pyogenes has always been an important cause of puer- peral sepsis (‘childbed fever’). However, in the postantibiotic era, it was rarely encountered in obstetric practice until the 1980s when sporadic cases occurred, some with streptococcal toxic shock syn- drome, and some women have died. These infections follow abortion or delivery when streptococci (usually colonizing the patient herself) invade the endometrium, lymphatics, and bloodstream. They can be devastatingly severe and present with nonspecific signs such as restlessness and gastrointestinal upset that may not immediately sug- gest sepsis. Fever may be absent resulting in further diagnostic con- fusion. The streptococcal infection involves the uterus and adnexae and sometimes distant sites such as joints as well. It can also affect the baby, causing serious neonatal infection including meningitis. Instrumentation in the presence of asymptomatic vaginal or anorectal carriage of S. pyogenes can result in severe infection. Small epidemics of puerperal sepsis have been reported where a healthcare provider has been a carrier that caused infection. In some cases, S. pyogenes can cause infection in the third trimester, before delivery. In these cases, this bacterium causes a transient bacteraemia that seeds the placenta or amnion, sometimes in association with abruptio pla- centa. These are devastating infections for the mother and the child. Other infections S. pyogenes can cause pneumonia (usually associated with viral in- fection or pulmonary disease), osteomyelitis, septic arthritis, menin- gitis, pericarditis (Fig. 8.6.2.6), endophthalmitis, and endocarditis. Laboratory diagnosis of S. pyogenes infection S. pyogenes is easy to culture in the laboratory and usually grows on blood agar in 24 h in atmospheres containing 10% CO_2. Throat swabs must be taken before antibiotics are given or the chance of recovery is greatly reduced. Kits for the detection of the group A antigen directly from throat swabs are available and give few false-positive reactions; they are seldom used in the United Kingdom but are commonly used in the United States of America. Ideally, two swabs are obtained. One is used for the rapid test and, if negative, the other is cultured ap- propriately. Even trivial skin lesions, such as impetigo or surgical site infection, are worth swabbing (if necessary with a moistened swab). Swabs from the surface of cellulitis and erysipelas rarely yield strepto- cocci, although they may be recovered from specimens obtained by aspiration approximately 20% of the time, although this is seldom carried out. Blood cultures should be done in any patient who is ill, whether febrile or not. Serological confirmation of infection with S. pyogenes when the organism has not been isolated can be obtained by the detection of raised antibodies to its extracellular products. Most laboratories tend to use two or more tests. Interpretation requires knowledge of the level of titres in the community for those without a history of recent streptococcal infection. In the United Kingdom the upper limit of titres in teenagers and young adults without such a his- tory is antistreptolysin O (ASO) 200, antideoxyribonuclease B (ADB) 240, and antihyaluronidase (AHT) 128. Management and antibiotic treatment of S. pyogenes infection Remarkably, S. pyogenes remains exquisitely sensitive to penicillin and this is the antibiotic of choice for treatment, parenterally for se- vere infections and orally otherwise. Conventionally, 10 days’ treat- ment is recommended for pharyngeal infections to eradicate the organism and prevent acute rheumatic fever. In practice, compliance with this regimen is poor as once the symptoms abate there is a natural reluctance to continue the antibiotic. Treatment of patients allergic to penicillin is usually with erythromycin or the newer macrolides (azithromycin and clarithromycin), but some 3–5% of strains are Fig. 8.6.2.5

S. pyogenes bacteraemia 3 days after a skin graft. Copyright S. J. Eykyn. Fig. 8.6.2.6 Peeling of the skin of the soles of the feet in a patient with S. pyogenes pericarditis. Copyright S. J. Eykyn.

8.6.2 Streptococci and enterococci 971 erythromycin resistant in most of the Western world. Epidemics caused by erythromycin-resistant strains have been described in Japan, Finland, Sweden, and the United States of America. S. pyogenes is also sensitive to cephalosporins. Topical agents such as mupirocin and fusidic acid are useful in addition to systemic antibiotic treat- ment in impetigo and other skin lesions. Patients with streptococcal toxic shock syndrome require intensive care and many require ino- tropic support, ventilation, and haemodialysis. Urgent surgical inter- vention is needed for necrotizing fasciitis and myositis. Clindamycin (in addition to penicillin) has been recommended for patients with established invasive streptococcal infections, since this drug stops the metabolic activity of the streptococci and thus halts further produc- tion of toxin. This is especially relevant in type II necrotizing fasciitis/ myositis and streptococcal toxic shock syndrome. Recently there has been emergence of clindamycin resistance in strains causing invasive infections and scarlet fever, and linezolid or tedizolid are reasonable alternatives. Intravenous immunoglobulin has also been used in an attempt to neutralize the streptococcal toxins, but reports of its effects are inconclusive, largely because neutralizing antibodies, though pre- sent, are in low concentration and there are batch-to-batch variations from the same and different suppliers. Prevention of recurrent cellu- litis of the lower legs involves meticulous foot hygiene with treatment of tinea pedis (if present) and reduction in skin carriage using top- ical mupirocin. Oedematous limbs can benefit from elastic stockings. Antibiotic prophylaxis may be required in cases of frequent recur- rence refractory to these measures. Lastly, it should be remembered that S. pyogenes is readily transmitted from person to person and thus appropriate infection control precautions should be taken until swabs show that the organism has been eradicated. β-Haemolytic group B streptococci (S. agalactiae) The group B streptococcus has been known for over a century as a cause of bovine mastitis, and in the 1930s it was recognized as a vaginal commensal, an occasional cause of puerperal fever, and an uncommon cause of invasive disease in adults. Not until the 1960s was it realized that the group B streptococcus was an important neo- natal pathogen, and some 20 years later it had replaced Escherichia coli as the predominant neonatal pathogen. Group B streptococcus can also cause a broad range of infections in nonpregnant adults including skin and soft tissue infections, bacteraemia, urinary tract infections, bone and joint infections, endocarditis, and meningitis. Carriage Group B streptococci can be recovered from various sites in healthy adults, but vaginal carriage has been most extensively investigated. Swabs from the lower vagina are more often positive than cervical swabs and carriage rates of 3% to over 40% have been reported. Higher rates have been obtained with selective media and enrich- ment techniques. Carriage also increases with sexual activity and is highest in women attending genitourinary clinics. The urethra, va- gina, perineum, and anorectal region have all been suggested as the prime site of carriage. Approximately 5–10% of healthy adults carry group B streptococci in the throat, independent of urogenital and anorectal carriage. Pathogenicity, virulence, and typing The chief determinant of virulence appears to be the capsular polysaccharide, and most human strains carry one of six sialic acid-containing polysaccharides that surround the cell wall. In add- ition, a protein antigen (c, X, or R) may be carried. Certain combin- ations are common; serotypes III or III/R form one-quarter of all isolates from superficial sites on women, but three-quarters of all group B streptococci causing meningitis in infants. They are also the most common serotypes found in adult (nonpregnant) infections. The type polysaccharide, like the M protein of S. pyogenes, inhibits phagocytosis. Colonization of the mucous membranes of the

neo- nate results from vertical transmission of the organism from the mother either in utero by the ascending route or at delivery. The rate of vertical transmission in neonates born to mothers colonized with group B streptococci is about 50%, but the incidence of symptomatic infection in neonates born to colonized mothers is only about 1–2%. It is much higher in preterm infants. Nosocomial colonization of neonates can also occur. In most cases of adult infections (other than in pregnant women) the source of the infection is unknown. Infections caused by group B streptococci These are commonly neonatal or puerperal infections, but group B streptococci also cause infection in nonpregnant adults, particularly in those with diabetes. Neonatal infection The frequency of neonatal infection (bacteraemia, meningitis, or both) has been variously quoted as between 0.3 and 5.4 cases/1000 live births, but these figures have wide confidence limits. Two fairly distinct clinical patterns of disease predominate, but the spectrum is wide and includes impetigo neonatorum, septic arthritis, osteomye- litis, pneumonitis, peritonitis, pyelonephritis, facial cellulitis, con- junctivitis, and endophthalmitis. Early-onset disease Symptoms of group B streptococcus (GBS) disease develop within the first 6 days of life with a mean of 20 hours, although they can present at birth suggesting an intrauterine onset of infection. Early-onset disease usually presents with bacteraemia with no identifiable focus of infection, but can also be pneumonia or, infrequently, meningitis. The presenting signs include lethargy, poor feeding, jaundice, grunting respirations, pallor, and hypotension and they are common to all types of disease. Respiratory symptoms are nearly always present. The only reliable way of detecting meningitis is by lumbar puncture. Mortality rates are high in low birth weight babies. In addition to positive blood cultures, the infecting strain can be found in the mother’s vagina and cultured from ‘screening’ sites on the baby; these include ear, throat, and nasogastric aspirate. Late-onset disease Late-onset GBS disease usually presents be- tween 7 days and 3 months after birth, often in previously healthy babies born after a normal labour who are admitted unwell from home. The pathogenesis is less clear than in cases of early-onset dis- ease and only about one-half of these cases are associated with mu- cosal colonization during delivery. Most babies have meningitis and concomitant bacteraemia and present with nonspecific symptoms such as lethargy, poor feeding, irritability, and fever. Neurological sequelae are common among survivors. Late, late-onset disease This is also called very-late-onset or GBS beyond early infancy. It occurs in infants more than 3 months of age and is more common in babies born before 28 weeks’ gestation or in those with underlying immunodeficiency.

section 8 Infectious diseases 972 Puerperal infection Puerperal infection with group B streptococci usually oc- curs within 24–48 hours of delivery or abortion. The source of the organism is always the vagina and infection is more likely when there has been premature rupture of the membranes and chorioamnionitis. Most infections are endometritis with fever and uterine tenderness sometimes associated with retained products of conception, but group B streptococci can also cause wound infection after caesarean section. Bacteraemia is common. Other bacteria, both aerobes and anaerobes, are sometimes iso- lated from the genital tract and wounds in addition to the group B streptococcus. Very rarely the streptococcus may spread to other sites in puerperal women. Infection in nonpregnant adults The prominence given to group B streptococci as neonatal and puer- peral pathogens has tended to overshadow their importance in men and nonpregnant women in whom they cause significant morbidity and mortality. The incidence is 4 to 7 per 100 000 population, al- though rates as high as 26 per 100 000 have been reported in those aged over 65 years. In view of the reductions in GBS infection seen in pregnant women and infants, infection in nonpregnant adults now account for three-quarters of invasive disease. Most infections

are community-acquired, occur in middle-aged and elderly people, and are as common in men as women. Risk factors for invasive infection include diabetes mellitus, malignancy, alcoholism, chronic renal or liver disease, cardiovascular disease, collagen vascular diseases, and trauma. Skin and soft tissue infections are especially common in pa- tients with diabetes. Occasional urinary tract infections occur, in men as well as women. Bacteraemic infections serve to emphasize the virulence of group B streptococci, and they have increased in incidence, or perhaps have been increasingly recognized, since the early 1990s. Other clinical manifestations include endocarditis, ver- tebral osteomyelitis, septic arthritis, endophthalmitis, and menin- gitis. As with staphylococcal infections, some bacteraemic patients have more than one metastatic focus of infection, which can lead to diagnostic confusion. Laboratory diagnosis of group B streptococcal infection Group B streptococci are readily isolated from any clinical specimen and easily identified by Lancefield grouping. The group B antigen is not shared by any other streptococcus. Importantly the antigen can be reliably detected in fluids such as blood, urine, or cerebrospinal fluid by latex particle agglutination enabling a rapid diagnosis. It is routine practice to obtain third trimester vaginal cultures during the third trimester of infection. Treatment of group B streptococcal infection Group B streptococci are sensitive to penicillin and this is the anti- biotic of choice for treatment. They are rather less sensitive to peni- cillin than S. pyogenes with minimum inhibitory concentrations some fourfold to tenfold higher. For this reason, penicillin is some- times combined with gentamicin for meningitis and other serious infections, though this is not of proven benefit. Certainly, the max- imum recommended dose of parenteral penicillin should be given whether combined with gentamicin or not. Penicillin allergy is not likely to be an issue in neonates; adults with meningitis can be treated with chloramphenicol. Most group B streptococci are sensi- tive to erythromycin and they are sensitive to cephalosporins. Prevention of neonatal infection with group B streptococci Intrapartum antibiotic prophylaxis Risk factors for early-onset GBS disease include: delivery at less than 37 weeks' gestation; premature rupture of membranes; prolonger rupture of membranes (>18 h before delivery); chorioamionitis; GBS bacteriuria during pregnancy; temperature >38°C during la- bour); sustained intrapartum fetal tachycardia; previous infant with GBS disease. These factors have been used to develop guidelines for the prevention of early-onset GBS disease. The United States Centers for Disease Control recommends screening of pregnant women by culture at 35–37 weeks' gestation and intrapartum antibiotic prophy- laxis for women found to be colonized with GBS. This has resulted in a dramatic decline in the incidence of early-onset GBS disease from 1.8 to 0.28 cases per 1000 live births between 1990 and 2008. In contrast the United Kingdom Royal College of Gynaecologists advo- cates a risk factor-based approach, as there are no clinical trial data to support routine antibiotic prophylaxis and concerns related to antibiotic use. Recent analyses, however, suggest that culture-based screening may be more cost effective than the current risk factor- based strategy. Vaccination The capsular polysaccharide antigens (Ia, Ib, II, III, IV, V, VI, and VIII) and C surface proteins of GBS have long been recognized to generate protective antibody responses. Analysis of genome sequences from GBS strains has identified several antigens and pro- teins that could potentially be used as vaccine candidates and some of these are in clinical trials. β-Haemolytic groups C and G streptococci These streptococci are sometimes referred to as 'large colony-forming group C and G streptococci' to distinguish them from the small colony-forming strains of streptococci with the same Lancefield antigens that belong to the anginosus or milleri group (see next). Groups C and G streptococci are closely related genetically. They are most conveniently regarded as 'pyogenes-like', as the infections they cause are similar to those caused by S. pyogenes though these streptococci tend to be less virulent than S. pyogenes. Infections with these streptococci are less common than S. pyogenes infections. Although

poststreptococcal glomerulonephritis has been associated with pharyngitis caused by both groups C and G streptococci, acute rheumatic fever has not. Group C streptococci are less frequently encountered in human infections than group G and most group C infections are caused by Streptococcus dysgalactiae subsp. equisilmi- lis. Those caused by Streptococcus dysgalactiae subsp. zooepidemicus have an animal source. Animal infections include mastitis in cows and ‘strangles’ in horses. Risk factors for infection with group C and G streptococci include: advanced age; underlying medical condition (e.g. diabetes mellitus, cardiovascular disease, cirrhosis, alcoholism, bone and joint disease, skin conditions); immunocompromise (e.g. malignancy, immunosuppressive drugs, HIV infection); surgical procedures; animal exposure. Clinical manifestations include pha- ryngitis, cellulitis, septic arthritis, bacteraemia, endocarditis, and a wide range of other infections.

8.6.2 Streptococci and enterococci 973 Streptococci of the anginosus or milleri group This group of streptococci has been a source of considerable taxonomic confusion, partly as a result of a lack of international consensus on no- menclature but also because of a lack of reliable phenotypic differences between taxa within the group. Most clinicians are familiar with the organism they know as ‘Streptococcus milleri’. There are three species of milleri streptococci, S. anginosus, S. constellatus, and S. intermedius, but despite increasing awareness of the clinical significance of the milleri group little is known about the association between individual spe- cies and specific sites of isolation and diseases. These streptococci are found in large numbers in the normal flora of the upper respiratory tract, gastrointestinal tract, and genital tract, and are commonly iso- lated from a range of pyogenic infections, sometimes in pure culture but often with other organisms, particularly anaerobes. These infec- tions include dental abscesses, intra-abdominal abscesses (especially of the liver), subphrenic abscesses, lung abscesses and empyema, and brain abscesses. Such is the propensity of these organisms to cause deep-seated abscesses that isolation of a milleri streptococcus from a blood culture should prompt investigations to detect such a focus. Milleri streptococci are also commonly isolated from inflamed appen- dices and postappendicectomy wound infection. Unlike other viridans and nonhaemolytic streptococci, milleri streptococci seldom cause endocarditis. They form minute colonies on blood agar and are pref- erentially anaerobic on primary isolation. They may be α-, β-, or non haemolytic. Some have the Lancefield antigens A, C, G, or F. All group F streptococci are milleri group whereas not all milleri streptococci are group F. Another useful clue to their identity in the laboratory is the distinct caramel smell of many strains on blood agar, the result of the diacetyl metabolite. Most strains are very sensitive to penicillin. Streptococci of the mitis, salivarius, and
mutans groups (oral/viridans streptococci) This group of usually α-haemolytic (viridans) streptococci includes S. pneumoniae and those oral streptococci (S. mitis, S. oralis, S. san- guis, S. gordonii, and, rarely, S. salivarius) that are the most common cause of infective endocarditis of oral or dental origin. These strepto- cocci occasionally cause bacteraemia in neutropenic patients, who sometimes have detectable mouth lesions, and neonatal infection, as they are found as part of the normal vaginal flora. These infec- tions should be suspected in neutropenic patients who have received prophylaxis with fluoroquinolones such as ciprofloxacin. Streptococci of the bovis group Although this group comprises at least three species, S. bovis is the main species of medical importance. S. bovis is similar to the en- terococci in that it bears the Lancefield group D antigen and is a gastrointestinal commensal, but, unlike the enterococci, it is sen- sitive to penicillin. It can be misidentified in the laboratory either as an oral streptococcus or as an enterococcus. Most patients with S. bovis bacteraemia will have endocarditis and it is seldom isolated from other sites.

It is important to recognize S. bovis in a blood culture as the organism is associated with colonic pathology or liver cirrhosis, and patients should be specifically investigated for these. With the advent of more comprehensive identification methods, Streptococcus bovis biotype I—the organism commonly associated with infective endocarditis and colorectal cancer—has been renamed S. gallolyticus subspecies gallolyticus. Nutritionally variant organisms previously classified as streptococci, now Abiotrophia spp. These organisms, which occasionally cause endocarditis, require pyridoxal or thiol group supplementation for growth in the la- boratory and tend to form satellite colonies surrounding colonies of Staphylococcus aureus. Although most blood culture media will support their growth, successful subculture requires supplementa- tion or cross-streaking of the plates with Staphylococcus aureus to provide the necessary growth factors. The Abiotrophia include three species, S. adjacens, S. defectivus, and the recently described A. ele- gans. They are less susceptible to penicillin than other streptococci. Streptococcus suis This streptococcus, which can be misidentified in the laboratory as S. bovis or an enterococcus as it reacts with group D antiserum, is an important pathogen of young pigs causing meningitis, septicaemia, arthritis, pneumonia, and endocarditis and is also carried in the pharynx of healthy pigs. S. suis type II (also referred to as group R streptococci) is not only the most invasive type in pigs, it can cause serious infection—mainly septicaemia and meningitis, but also septic arthritis, pneumonia, and endophthalmitis—in humans, in whom it is an occupational disease of pig farmers, abattoir workers, and fac- tory workers handling pig meat (Fig. 8.6.2.7) (see Chapter 24.11.1). The streptococcus probably enters the bloodstream via skin abrasions that are common in the abovementioned occupations. S. suis type II meningitis results in deafness in about one-half of those affected. Enterococci Enterococci are Lancefield group D, Gram-positive cocci that can grow and survive in extreme cultural conditions, and are also more resistant to antibiotics than streptococci. They form part of the normal gut flora of humans and animals. Overall, the most common clinical isolates of enterococci are Enterococcus faecalis, but the more antibiotic-resistant species E. faecium is increasingly encountered in hospitals. Nosocomial isolates of enterococci dra- matically increased in the 1990s. Other species, including E. cas- seliflavus, E. durans, and E. avium, are occasionally isolated. In most cases it is unnecessary to determine the species of enterococci in a clinical laboratory but sometimes differentiation between E. faeca- lis and E. faecium is helpful (e.g. in epidemiological studies and in endocarditis because of their different antibiotic susceptibilities). Infections caused by enterococci Enterococci are an increasingly important cause of nosocomial infection and colonization, possibly as a result of the large-scale

 use of antibiotics such as cephalosporins and quinolones to which they are inherently resistant. They occasionally cause community- acquired urinary tract infections, but the most important community-acquired infection is endocarditis, which is increasing in incidence. This infection is almost always caused by E. faeca- lis. Any patient admitted from the community with E. faecalis in blood cultures should be assumed to have endocarditis until proved otherwise. Enterococci are predominantly hospital pathogens and cause urinary infection, particularly after instrumentation, intra- abdominal infections, wound infections (usually with other organ- isms), infections associated with intravascular devices and dialysis, and occasionally endocarditis. Antibiotic sensitivity and treatment Enterococci are not only intrinsically resistant to many antibiotics, but they also show a remarkable ability to acquire new mechanisms of resistance. This allows them to survive in environments in which large quantities of antibiotics are used and also has important therapeutic consequences, particularly for the treatment of endocarditis and other serious infections. Fortunately, many patients from whom entero- cocci are isolated do not require antibiotic treatment. Sensitive en- terococci cannot be killed by

ampicillin/amoxicillin alone, although combination with an aminoglycoside is bactericidal (synergy); but many strains now exhibit high-level gentamicin resistance and for them the combination is not bactericidal. E. faecium is almost always resistant to ampicillin/amoxicillin and E. faecalis is occasionally. The first published report of vancomycin-resistant enterococci was in 1988 from a London hospital outbreak, though such strains had been recognized a year before in Paris. Most strains of vancomycin- resistant enterococci in the London outbreak were E. faecium and overall most are E. faecium. There are four recognized phenotypes of vancomycin resistance; the first isolates of vancomycin-resistant enterococci were highly resistant to vancomycin and teicoplanin and exhibit what is known as the VanA resistance phenotype. Since then, levels of resistance to teicoplanin in this phenotype have been more varied. Most VanA enterococci are E. faecium, but this phenotype also occurs in E. faecalis and occasionally in other species. The VanB phenotype is associated with low-level vancomycin resistance and sensitivity to teicoplanin and is found in both E. faecalis and E. fae- cium. Both VanA and VanB are acquired traits. The VanC phenotype is an intrinsic property of E. casseliflavus and E. gallinarum and these species have low-level resistance to vancomycin but are sensitive to teicoplanin. A fourth phenotype, VanD, has been described in a single strain of E. faecium. Vancomycin-resistant E. faecium, though not vancomycin-resistant E. faecalis, is sensitive to quinupristin/ dalfopristin and all vancomycin-resistant enterococci are sensitive to the oxazolidinone linezolid. The antibiotic susceptibilities of the enterococci outlined here serve to emphasize that these bacteria are the most antibiotic-resistant Gram- positive bacteria now encountered in hospital practice. Fortunately, many, perhaps most, of the patients from whom they are isolated do not require antibiotic treatment at all, but for those who do, the ef- fective treatment of serious infection caused by enterococci and par- ticularly antibiotic-resistant strains requires microbiological expertise. FURTHER READING Bisno AL, Brito MO, Collins CM (2003). Molecular basis of group A streptococcal virulence. Lancet, 3, 191–200. Bisno AL, Stevens DL (2000). Streptococcus pyogenes (including strepto- coccal toxic shock syndrome and necrotizing fasciitis). In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases, pp. 2101–17. Churchill Livingstone, New York, NY. Colman G, et al. (1993). The serotypes of Streptococcus pyogenes pre- sent in Britain during 1980 to 1990 and their association with dis- ease. J Med Microbiol, 39, 165–78. Davies MR, et al. (2015). Emergence of scarlet fever Streptococcus pyogenes emm12 clones in Hong Kong is associated with toxin ac- quisition and multidrug resistance. Nat Genet, 47, 84–7. Edwards MS, Baker CJ (2000). Streptococcus agalactiae (group B streptococcus). In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases, pp. 2156–67. Churchill Livingstone, New York, NY. Jacobs JA (1997). The ‘streptococcus milleri’ group: Streptococcus ang- inosus, Streptococcus constellatus and Streptococcus intermedius. Rev Med Microbiol, 8, 73–80. Katz AR, Morens D (1992). Severe streptococcal infections in histor- ical perspective. Clin Infect Dis, 14, 298–307. (a) (b) Fig. 8.6.2.7 (a) S. suis septicaemia with meningitis in a Vietnamese pig farmer. (b) S. suis pyogenic arthritis in a Thai abattoir worker. (a) Copyright D. A. Warrell. (b) Courtesy of the late Professor Prida Phuapradit.

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