With the advent of antimicrobials during World War II, and a natural decline that began before then, dread diseases began to assume a less important role, especially in industrialised countries. By the 1970s, acute rheumatic fever and acute glomerulonephritis were rarely seen, even though acute streptococcal infections continued to occur with their usual frequency and severity. In the 1980s, attention was once again focused on infections caused by group A streptococcus and its sequelae. The most common infections caused by group A streptococcus are pharyngitis and pyoderma, which occur in children particularly.

Introduction

More than a century after its discovery by Louis Pasteur in 1879, the entire genome of an M1 strain of group A streptococcus was sequenced in 2001, and later, a further eight strains were sequenced. Group A streptococcus is a Gram-positive organism. On blood agar, group A streptococcus displays characteristic beta-haemolysis, due to the haemolysin streptolysin S. It is differentiated from other streptococci by Lancefield grouping, based on serological specificity of cell wall group-specific carbohydrates. With genetic sequencing, to date, more than 40 virulence-associated genes have been revealed. The cell surface M protein is the main antigenic determinant of group A streptococcus. It aids in adherence, and most importantly, enables the bacterium group A streptococcus to evade phagocytosis, the major defense of the human host. The cell surface M protein is the main antigenic determinant of group A streptococcus. It aids in adherence, and most importantly, enables the bacterium group A streptococcus to evade phagocytosis, the major defense of the human host. Lipoteichoic acid, fibronectin binding proteins, and the hyaluronic acid capsule aid in adherence to epithelial cells. M protein, capsule, streptokinase, DNases, hyaluronidase and SpeB, all contribute to the tissue invasive capacity of group A streptococcus. CSa peptidase limits recruitment of phagocytes. Streptococcal inhibitor of complement helps evade complement-mediated killing. Streptococcal pyrogenic exotoxins are responsible for the clinical features of streptococcal toxic shock syndrome (STSS) and scarlet fever, by acting as superantigens, which stimulate 20% of the T-cell population by binding directly to the T-cell receptor, rather than having to be presented in the major histocompatability complex (MHC) II binding groove.

Rheumatic fever is the result of an interaction between a group A streptococcus strain with certain undefined features that confers an ability to cause acute rheumatic fever in a host with inherited susceptibility. This interaction leads to an autoimmune response directed against cardiac, synovial, subcutaneous, epidermal, and neuronal tissues. Traditional teaching states that acute rheumatic fever follows group A streptococcus pharyngitis, but not pyoderma, although this has recently been questioned. An autoimmune response to group A streptococcus infection is also responsible for acute poststreptococcal glumerulonephritis (APSGN), probably due to deposition of a streptococcal antigen directly in the glomerulus.

Pharyngitis

The group A streptococcus is the main bacterial cause of pharyngitis, and is responsible for 15-30% of cases of acute pharyngitis in children. The features suggestive of group A streptococcus include an age of five to 12 years, fever, tender and enlarged anterior cervical lymph nodes, and tonsillopharyngeal erythema and exudates. The onset of symptoms in patients with streptococcal pharyngitis is often abrupt. In addition to throat pain, symptoms may include fever, chills, malaise, a headache, and, particularly in young children, abdominal pain, nausea, and vomiting. Occasionally, streptococcal pharyngitis is accompanied by scarlet fever, which manifests as a finely popular erythematous rash that spares the face, may be accentuated in skin folds, and may desquamate during convalescence. A cough, coryza, and conjunctivitis, are not typical symptoms of streptococcal pharyngitis. If present, they suggest an alternative cause, such as a viral infection. Throat pain may be severe, and it is often worse on one side.
However, severe unilateral pain, or an inability to swallow, should raise concerns about a local suppurative complication, such as peritonsillar or retropharyngeal abscess, particularly if these symptoms arise, or progress, several days into illness. Among children < 3 years of age, exudative pharyngitis, due to streptococcal infection, is rare. In this age group, streptococcal infection may manifest as coryza, excoriated nares, and generalised adenopathy. In most persons, fever resolves within three to five days, and throat pain resolves within one week, even without specific treatment.11,12

**Diagnosis of streptococcal throat infections**

Streptococcal throat infections are properly diagnosed by paying careful attention to the epidemiological and clinical aspects of acute upper respiratory infections, and identification of group A streptococci or streptococcal antigens in specimens from infected throats. Recent advances in the rapid identification of streptococcal antigens (the "rapid test") are changing the approach to the management of streptococcal throat infections. The gold standard for the laboratory diagnosis of streptococcal pharyngitis is a properly processed and interpreted throat culture on sheep blood agar. Rapid streptococcal tests are highly specific, but not as sensitive.13 Most false-negative rapid streptococcal tests appear to be caused by small numbers of streptococci in the pharynx. Other reasons for false-negative tests are still unclear.

The physician may wish to tailor the use of a rapid streptococcal test vs. the use of a conventional throat culture as follows. If a patient has an upper respiratory illness suggestive of streptococcal pharyngitis, and in the opinion of the physician could benefit from immediate antimicrobial therapy, a rapid streptococcal test would appear to be the prudent group course of action to take. If positive, it is certain that there are group A streptococci in the pharynx. However, if negative, a throat culture should be carried out. A positive rapid streptococcal test allows the physician to complete a diagnostic work-up during the initial visit. If the rapid streptococcal test is negative, there is then the added expense of a second test, namely the throat culture. The clinician should be aware of the sensitivity of a single throat culture. A positive throat culture or a positive rapid streptococcal test can, and should, be interpreted in the context of the epidemiological and clinical picture presented by the patient.14 Recently, the value of a single throat culture and the rapid streptococcal test has been questioned.15 Inoculation of a throat swab onto sheep blood agar, with a sensitivity of 90-95%, remains the gold standard for diagnosis.16

**Treatment of streptococcal pharyngitis**

Penicillin, the time-honoured therapy, is still the drug of choice for the treatment of streptococcal pharyngitis. It is effective in preventing rheumatic fever. Penicillin-resistant streptococci have not been described. Penicillin is inexpensive, and it is relatively non-toxic and safe. Bass17 points at that the optimal treatment of streptococcal pharyngitis varies with clinical circumstances, and outlines the appropriate use of injectable benzathine penicillin, oral penicillin V, penicillinase-resistant penicillins, erythromycin, cephalosporins, and clindamycin. Antibiotics other than penicillin play a more prominent role in the management of penicillin treatment failure. The appearance of erythromycin-resistant group A streptococci in Finland is disturbing. The primary care clinician needs to be aware of this, and be prepared to react appropriately if current studies show that resistant strains are problematic in this country.

The following new formulations of amoxicillin plus clavulanic acid have been registered:19
- **For children**: 90 mg/kg amoxicillin plus 6.4 mg/kg clavulanic acid, divided into two doses per day.
- **For adults**: Sustained-release tablets of 1 g amoxicillin plus 62.5 mg clavulanic acid, two tablets twice daily.

Both these formulations alleviate the need to use standard doses of amoxicillin plus clavulanic acid and additional amoxicillin to achieve concentrations recommended in previous guidelines.

Gatifloxacin, has been discontinued and is no longer available.

Gemifloxacin (320 mg daily) has been registered as a five-day course for acute bacterial sinusitis.

Ciprofloxacin with dexamethasone, as an otic suspension, has been registered for the local treatment of acute otitis media with tympanostomy tubes (AOMT).

**Antibiotic pharmacokinetic/pharmacodynamic parameters**

Concerning the duration of treatment for acute bacterial sinusitis (ABS), recent studies have shown that bacteriological eradication occurs within 72 hours with moxifloxacin (400 mg once daily), or with high-dose, short-course levofloxacin (750 mg daily for five days).20,21 This higher dose of levofloxacin improves the pharmacokinetic (PK)/pharmacodynamic (PD) profile of the agent. In a comparative trial of this dose vs. levofloxacin 500 mg once daily for 10 days, clinical and microbiological efficacy of the high-dose, short-course treatment was found to be similar.22 These studies might eventually impact on recommendations for the duration of treatment of ABS.

Based upon PK/PD findings and a clinical trial of otitis media, cefprozil (15 mg/kg twice daily) should not be used empirically in this setting, as it is only effective against penicillin-susceptible pneumococci.23,24

**Rheumatic fever**

Coinciding with the apparent resurgence of invasive group A streptococcus disease in the developed world, acute rheumatic fever has also reappeared in middle-class areas.25
Acute rheumatic fever is a major problem in developing countries, and in populations living in poverty in industrialised countries. It begins approximately three weeks after a group A streptococcus infection. It is often asymptomatic. The clinical features of acute rheumatic fever are outlined in the Jones criteria, which were last updated in 1992. In experienced hands, echocardiography can help to identify and characterise rheumatic valvarul disease, including subclinical value lesions.

### Acute poststreptococcal glumerulonephritis

APSGN, unlike acute rheumatic fever, tends to occur in outbreaks associated with virulent skin strains of group A streptococci. The symptoms and signs of APSGN appear one to three weeks after group A streptococcus pharyngitis. Whereas acute rheumatic fever rarely occurs in children younger than four years, APSGN may occur in younger children, sometimes in the first two years of life. The most common presentation of APSGN is dark urine and facial oedema. Hypertension occurs in about 70% of cases, primarily as a result of water and salt retention, although in some cases a nephrotic syndrome may occur.

With the activation of the alternative pathway of the complement system, C3 levels are almost always diminished early in the disease. This is an important diagnostic test in APSGN. Other causes of nephritis include systemic lupus erythematosus, which can present with similar features, and low serum complement levels. In APSGN, the depression of C3 is transient, and should return to normal after six to eight weeks. Therefore, the C3 level should be rechecked at six to eight weeks. If it remains depressed, other diagnoses, including systemic lupus erythematosus, must be considered.

There is no evidence that primary prophylaxis, i.e. treatment of a person already infected with a nephritogenic strain to prevent the development of APSGN, is effective. However, on a public health level, mass benzathine penicillin administration during an outbreak may prevent further cases, particularly by targeting treatment of children with skin sores, and household contacts of those affected. Epidemic APSGN in children has a very favourable outcome, with a 10-year renal survival rate of 92%, and minimal risk of hypertension.

### Pyoderma

Pyoderma refers to a localised purulent infection of the skin. It is an umbrella term for non-bullous impetigo, bullous impetigo, and folliculitis. Nonbullous impetigo is the most common form of pyoderma, and is usually due to group A streptococcus, whereas bullous impetigo and folliculitis are usually due to *Staphylococcus aureus*. The aetiology of pyoderma differs between developing and industrialised nations. Pyoderma is endemic in children in many developing countries, with prevalence rates averaging 7%.

Clinically, group A streptococcus non-bullous impetigo is usually indistinguishable from non-bullous impetigo caused by *S. aureus*. The infection commonly presents as a small pimple, which evolves to a purulent lesion covered by a honey-coloured crust. Lesions are most commonly found on the arms or legs and at the sites of minor trauma, which are invariably needed for the organism to establish an infection. The organism is highly transmissible, so affected children may develop lesions elsewhere on their bodies, and multiple cases within the same household or classroom are quite common.

In industrialised countries where superficial bacterial skin disease is less common, where the causative organism is often *S. aureus*, and where the local complications and poststreptococcal sequelae are less common, most mild cases will respond to topical treatment with mupirocin. Moderate cases can be treated successfully with oral antistaphylococcal antibiotics, such as flucloxacillin or cephalaxin. A recent Cochrane review of 57 trials suggests that topical mupirocin or fusidic acid is at least as effective as oral antistaphylococcal antibiotics. In addition, the possible, but as yet unproven, link between group A streptococcus skin disease and acute rheumatic fever increases the importance of adequate treatment. Currently, intramuscular benzathine penicillin G is the treatment of choice for streptococcal impetigo, although oral antibiotics, such as flucloxacillin or cephalaxin, are good alternatives when adherence can be assured. The effectiveness of benzathine penicillin G may be reduced if *S. aureus* emerges as a major cause of impetigo in developing countries and indigenous populations. It is important to ensure that underlying scabies is appropriately treated, and that family members and other close contacts are also examined, and treated for pyoderma and scabies. In populations with high rates of scabies-related pyoderma, community treatment with scabicides alone has been shown to reduce rates of pyoderma.

### Streptococcal toxic shock syndrome

Streptococcal toxic shock syndrome (STSS) occurs when the infecting strain of group A streptococcus produces superantigens. Most patients have fever, and 50% have hypotension at presentation. The other 50% will develop hypotension within four hours. The typical “sunburn”-type rash in STSS is widespread, erythematous, macular, and blanching. Characteristically, there is subsequent desquamation two weeks after the initial illness. Scarlet fever shares these clinical features of erythematous rash, although desquamation and scarlet fever and STSS are at extreme ends of the spectrum of streptococcal toxin-mediated diseases. Although STSS was first described in the mid-1980s, it almost certainly existed before this time, and it is likely that the early descriptions of severe, or septic, scarlet fever, were in fact cases of STSS. Toxic shock syndrome (TSS) has been described in association with numerous foci of infection, but soft tissue infection, usually necrotising fasciitis, is the most common focus (approximately 60% of STSS cases). The group A streptococcus has been isolated in blood cultures in approximately 60-80% of STSS cases.
cases. In contrast, in staphylococcal toxic syndrome, S. aureus has been cultured from blood in only 3% of patients. Aggressive supportive care is the most important aspect of management of severe group A streptococcus disease, particularly in STSS. Patients often require massive fluid resuscitation, due to the capillary leak syndrome. Wide surgical debridement of non-viable tissue in necrotising fasciitis has been shown to improve outcome. Penicillin is the antibiotic of choice for all group A streptococcus infections, including severe invasive disease. In the early stages of severe invasive disease, particularly in impending or established STSS or necrotising fasciitis, clindamycin should be added to penicillin. Clindamycin has the theoretical benefit of circumventing the Eagle effect, reducing group A streptococcus toxin production, and potentiating phagocytosis. It also has superior tissue penetration, and a longer postantibiotic effect. However, clindamycin should not be used alone because of the possibility of resistance. It only needs to be used for the first few days of management, until the patient is stabilised.

**Poststreptococcal reactive arthritis**

Poststreptococcal reactive arthritis differs from acute rheumatic fever by the early development of arthritis after pharyngitis, and more protracted arthritis or arthralgia with a less dramatic response to aspirin. Other factors that differentiate poststreptococcal reactive arthritis from acute rheumatic fever are the age of onset, the nonmigratory character, the high incidence of occurrence of erythema nodosum and erythema multiforme, as well as evidence of poststreptococcal reactive transient hepatitis and axial arthritis. Arthritis being the hallmark of this disease, “poststreptococcal reactive arthritis” is probably the proper nomenclature. It affects the age group of five to 15 years mainly, and is associated with elevated antistreptolysin O (ASO) and antideoxyribonuclease B (anti-DNAse B) titres. Involvement of cardiac tissue is seen in approximately five 5% of cases in follow-up, which is termed “silent carditis”. Proposed diagnostic criteria in poststreptococcal reactive arthritis include the presence of characteristic arthritis with evidence of antecedent group A streptococcal infection, without fulfilling the criteria of modified Jones for diagnosis of acute rheumatic fever. Nonsteroidal anti-inflammatory drugs (NSAIDs), as a group of analgesics, are the principal drugs used for the treatment of acute rheumatic fever, without any special advantage over aspirin. Antimicrobials are to be given after initial diagnosis, to eradicate streptococcal infection.

All patients with poststreptococcal reactive arthritis should receive penicillin prophylaxis. The American Heart Association suggests prophylaxis for one year, to be discontinued after that if carditis does not appear by then. But some centres in the West prefer to continue penicillin prophylaxis up to the age of 21 years, or for a minimum of five years, whichever is earlier. The proper duration of treatment and appropriate guidelines for patient selection have not been conclusive until now. Clarity will only be possible if a collaborative effort is made to accurately define this illness, including analysis of its aetiopathogenesis and natural history. Even then, each physician should evaluate the potential risks and benefits of penicillin prophylaxis, in view of the risk of rheumatic fever in the individual.

**Streptococcal disease in Africa**

Group A streptococcus causes a broad spectrum of disease, from severe invasive infections and the poststreptococcal complications of acute rheumatic fever and APSGN, to mild superficial infections of the throat or skin. There are many areas in which the data are deficient, particularly from less developed countries. Worldwide, data relating to the prevalence of rheumatic heart disease are the most comprehensive of all group A streptococcus diseases.

The number of studies conducted, and the diversity of populations studied, is sufficient to engender confidence about the regional prevalence estimates for sub-Saharan Africa and South and Central Asia. Although not many studies are reported from Latin America, the Middle East and North Africa, prevalence estimates from these regions are in accordance with the anecdotal impressions of clinicians and public health physicians in those regions. Similarly, although only one study from an established market economy was found, the prevalence of 0.3 per 1 000 corresponds with earlier data from developed countries.

A Nigerian study reported that approximately 6% of APSGN cases in children progressed to acute renal failure, and that approximately 2% died of this complication. Only one population-based study was found, of invasive group A streptococcus infections carried out in Kenya. Over a four-year period (1998-2002), 48 cases of Group A streptococcus sepsis in 16 570 admitted children aged < 15 years were reported. The incidence of group A streptococcus bacteraemia in neonates was 0.55 per 1 000 live births, and in children aged < 1 year, 2 years and 5 years, it was 96, 63 and 29 per 100 000, respectively. Group A streptococcus was the third most common cause of neonatal bacteraemia, and the most common cause of bacteraemia in infants aged 7-59 days, and the fifth most common cause of community-acquired bacteraemia in children aged < 1 year and < 5 years. The overall incidence of group A streptococcus bacteraemia in children aged < 15 years was 13 per 100 000, with a 25% case fatality rate. The high incidence of invasive group A streptococcus disease in young infants in Kenya reinforces the findings of the recent WHO Young Infants Study, which found that group A streptococcus is one of the three leading causes of bacteraemia in children aged < 90 days, and accounts for 29% of all positive isolates in four less developed countries (Papua New Guinea, Ethiopia, Gambia and the Philippines). Group A streptococcus sepsis in neonates is usually due to colonisation or infection acquired in the birth canal.

Although children have the highest prevalences of pyoderma and scabies, these diseases have also been found to be...
common in adults. Studies suggest scabies prevalence ranges from approximately 1-10% in African and Asian countries, to 50-80% in the Pacific region. A prospective study of 678 people in Egypt (1967-1969) documented an incidence of serologically proven group A streptococcal pharyngitis of 0.42 per person year in children aged 2-4 years, 0.31 in children aged 6-12 years, and 0.10 in adults aged > 25 years. Group A streptococcus is the most common bacterial cause. It is estimated to account for 15-30% of cases in children, and 5-10% of cases in adults.

Notwithstanding the limitations of the data, estimates suggest that group A streptococcus causes a substantial burden of disease and death on a global scale, mainly in children and young adults, and in less developed countries (although they also remain relatively important diseases in more developed countries). Data of better quality from a number of key regional sites in less developed countries would allow a more detailed analysis of regional differences, and perhaps reveal markers that might enable local authorities to determine if they should be investing resources into efforts to control group A streptococcus diseases. Such data may also improve our understanding of the individual diseases and how to prevent them.

Conclusion

The disease-producing potential of group A streptococci was called to our attention. Close examination of the status of management and treatment is required. Patients should be chosen carefully, using appropriate epidemiologic and clinical data, to obtain a rapid streptococcal test and a throat culture. The management of treatment failures should be tailored to the individual patient. Treatment failure caused by non-compliance should be handled by offering injectable benzathine penicillin. Complying patients should probably be treated with an antibiotic that is beta-lactamase-resistant.

References