Group A streptococci revisited

In the first half of this century group A streptococci were one of the most important of all bacterial pathogens, causing large outbreaks of scarlet fever with a high mortality, puerperal fever and neonatal sepsis, rheumatic fever and glomerulonephritis as well as suppurrative conditions such as empyema, osteomyelitis, and septic arthritis. Time and penicillin have assuaged our fear and replaced it with complacency.

Recently, however, there have been increasing reports to the Public Health Laboratory Service of severe and sometimes fatal episodes of sepsis caused by group A streptococci. What sets this organism apart from other pathogenic bacteria is its potential to cause delayed, non-suppurative complications, namely rheumatic fever and glomerulonephritis. The decline of rheumatic fever in developed countries was never satisfactorily explained and recent reports from widely separated locations in the United States suggest the disease may be resurgent. The old lessons of epidemiology and treatment are having to be re-emphasised for a new generation of physicians.

The organism

*Streptococcus pyogenes* (Lancefield group A) is a Gram positive coccus. The cell wall is composed mainly of carbohydrate, the antigenic properties of which determine the (Lancefield) group specificity. The cell wall is surrounded by a layer of hyaluronic acid which gives colonies a mucoid appearance. The recent outbreaks of rheumatic fever in the United States have coincided with the appearance of more mucoid strains. Hair like fimbriae containing lipoteichoic acid project from the cell wall and are responsible for adherence to epithelial cells. Over 60 different strains can be differentiated on the basis of serologically distinct M proteins, associated with the fimbriae. Certain M proteins confer resistance to phagocytosis and increase virulence. Associations are recognised between certain M proteins and diseases such as pharyngitis and impetigo.

Group A streptococci manufacture and release a variety of biologically active substances. Two haemolysins are produced, streptolysins O and S, which can damage cell membranes and subcellular membranous organelles and thus are toxic to polymorphonuclear leucocytes, lysosomes, and platelets as well as red blood cells. Streptolysin O is antigenic and antistreptolysin O (ASO) antibodies are a useful marker of recent infection. An erythrogenic toxin is produced by some strains and is responsible for the rash of scarlet fever. Other extranuclear products are enzymes which may facilitate the formation of pus and the spread of infection through tissue planes. These include enzymes that degrade deoxyribonucleic acid (DNAases, A, B, C, and D) and streptokinase that promotes the breakdown of clot. Antibody against DNAase B has also been used in the serodiagnosis of streptococcal infection.

**Streptococcal sore throat**

The most common clinical expression of group A streptococcal infection in developed countries is pharyngitis and tonsillitis. The need to diagnose and eradicate the streptococcus in order to prevent suppurrative complications (otitis media, sinusitis, peritonsillar, and cervical abscess), later non-suppurative complications, and spread within the community has dictated hard learnt rules of treatment and stimulated a search for rapid diagnostic kits for the 'strep throat'. Streptococcal tonsillitis occurs predominantly in school age children and has a rate of recurrence of one infection every three to five years during childhood. Older age groups are, however, susceptible, particularly in situations of overcrowding such as military camps, prisons, and remand centres. After an incubation period of one to four days there is an abrupt onset of illness with sore throat, malaise, fever, and headache. It is often accompanied by nausea, vomiting, and abdominal pain. The tonsils and pharynx are inflamed. A greyish white exudate on the tonsils is common but not invariable. Tender lymph nodes are palpable at the angle of the mandible. A range of severity exists, however, and illness can be deceptively mild. The natural history is for symptoms to subside within three to five days unless suppurrative complications intervene. The average latent period for the development of acute glomerulonephritis is 10 days and for rheumatic fever 18 days.
from pharyngitis neutralising type-specific antibody does not develop for six to eight weeks, but then confers resistance to subsequent infection by that serotype. Exudative pharyngitis below the age of 3 is hardly ever due to group A streptococci, although infected infants can develop an illness characterised by low grade fever, lymphadenopathy, and rhinorhoea.

Close contact favours the spread of streptococcal pharyngitis by large droplets or by physical transmission of respiratory secretions. Children are most infectious during the acute phase of the illness. Most secondary spread occurs within the first 14 days after acquisition. Up to 20% of children carry group A streptococci in the throat and are without symptoms or subsequent evidence of an immunological response (carrier state). The role of carriers in the spread of infection is controversial: they appear less likely to transmit the organism than acutely infected patients and are at significantly reduced risk of developing rheumatic fever.

The diagnosis of streptococcal sore throat on clinical grounds alone is unreliable. Throat culture is the 'gold standard' of diagnosis against which newly developed rapid diagnostic tests have to be judged. Approximately one third of those complaining of sore throat will have a throat culture positive for streptococcus. Some of these will be carriers with another intercurrent infection responsible for their symptoms. Does accurate diagnosis matter? Why not treat all children with sore throat with penicillin regardless of a throat culture? It is debatable that penicillin makes much difference to the acute illness. A recent double blind controlled trial of penicillin and regular anti-inflammatory treatment compared with placebo and regular anti-inflammatory treatment showed no significant improvement in malaise, fever, adenitis, or pharyngitis in the penicillin group. Penicillin, however, does reduce the acute complication rate and eliminates pharyngeal streptococci thus reducing the risk of rheumatic fever and preventing transmission. Elimination of pharyngeal streptococci depends on prolonged rather than high dose penicillin treatment. With reduction in rheumatic fever rates the use of unpleasant intramuscular injections of long acting benzathine penicillin went out of vogue. The alternative, oral penicillin V, must be continued for a full 10 days. Even the most compliant child or parent finds it difficult to complete a full course especially when symptoms have abated. A throat culture should be taken so that culture negative patients could stop penicillin after 48 hours while a positive culture would allow reinforcement that the course of penicillin should be completed. Rheumatic fever may be preceded by a mild illness or even asymptomatic infection. An accurate diagnosis of streptococcal pharyngitis is important when cases of rheumatic fever are rare, but vital if rheumatic fever is epidemic. Treatment of a streptococcal sore throat as late as 10 days after onset will prevent rheumatic fever.

Rapid diagnostic tests

The development of rapid diagnostic tests for group A streptococci was greeted with enthusiasm as a way of knowing within an hour of taking a throat swab which patients to treat. This has been tempered by doubts as to their accuracy. They rely on the extraction of the group specific carbohydrate from the cell wall and its recognition by agglutination. False positive results are not a problem. Facklam, in a recent review of the literature, found specificities of ≥95% in 75% of kits tested. False negatives are of more concern. Facklam found 44% of kits had sensitivities of ≤85%, some as low as 60%, and less than 40% had sensitivities ≥90%. The false negatives often correlate with throat cultures showing only scanty growth of bacteria. This would be bearable if the false negatives represent carriers where a small amount of antigen is present, but Gerber et al suggest otherwise. They found that a third of individuals with false negative rapid antigen detection tests had a subsequent rise of streptococcal antibody titres suggesting infection. Summarising a decade since the introduction of rapid streptococcal diagnostic kits into commercial use, Kaplan suggests that a positive result indicates with relative certainty that streptococcal antigen is present but when negative a confirmatory throat culture is prudent.

Other clinical manifestations

Impetigo caused by group A streptococcus is common in tropical and subtropical countries. The bacteria initially colonise unbroken skin and cause lesions an average of 10 days later possibly via surface abrasions or insect bites. Impetigo may be followed by acute glomerulonephritis but not, interestingly, rheumatic fever. Bacteraemia with group A streptococci is usually associated with a focus of infection, most often the skin or respiratory tract, with varicella, or in immunocompromised patients. Infections can be severe with significant mortality. Streptococcal pneumonia may follow preceding viral infections such as measles and influenza but can also be primary and occur in outbreaks. A third of cases are associated with empyema. Metastatic foci may follow bacteraemia,
including osteomyelitis, septic arthritis, and meningitis.20

**Rheumatic fever**

In Britain the number of cases of rheumatic fever has fallen in parallel with other western countries. The incidence fell from five cases per 100 000 population in 1963 by at least 10 fold by 1985 (ND Noah, S Hall, Communicable Diseases Surveillance Centre, personal communication). These figures are based on the Hospital Inpatient Enquiry, a 10% sampling of hospital discharges and deaths. When a disease becomes uncommon these figures may not be a true reflection of incidence. To overcome this, the British Paediatric Surveillance Unit (BPSU) performed a ‘one-off’ retrospective enquiry for 1987 the data from which are still being analysed. It is hoped to put acute rheumatic fever on the BPSU monthly reporting system this year. The explanation for falling rates of rheumatic fever was never clear. Improved living conditions with lessening of malnutrition and of overcrowding do not explain the change over the last 20 years when decline of rheumatic fever has been the greatest. It is of interest that the recent American outbreaks have affected white, middle income, suburban families. While the assiduous use of throat culture and penicillin in populations at risk probably reduces rates of rheumatic fever23 overall rates were falling before the introduction of antibiotics and continued to fall recently when patterns of antibiotic use did not change. A change of streptococcal virulence has been suggested. Certainly scarlet fever in England and Wales has shown a considerable decrease in both incidence and severity in this century24 but there is nothing to suggest that streptococcal sore throat is a declining disease. The search for ‘rheumatogenic’ strains of streptococci has been unsuccessful. Even though only 25% of rheumatic fever patients will have streptococci isolated from the pharynx at the time of presentation a careful study of those strains found in patients and their sibling contacts from the recent outbreaks in the United States showed that several different serotypes were responsible even within a specific geographic location.3 Host factors, such as rheumatic fever sufferers possessing a particular B cell alloantigen,25 do not adequately explain rapid changes in incidence of disease.

**Conclusion**

Group A streptococci remain important and serious pathogens. Vigorous detection and treatment of the streptococcal sore throat is to be encouraged. The recognition and accurate reporting of rheumatic fever and the characterisation of group A streptococci isolated from these patients should be emphasised so that, if a return of rheumatic fever is upon us, it can be understood better than its previous decline.

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**References**


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