Streptococcus pyogenes: Recent Research Provides New Insights into an Important Pathogen

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After nearly nine decades of intensive laboratory research and even with the availability of effective antimicrobial therapies, group A streptococcal infections remain serious health threats worldwide. *Streptococcus pyogenes*, the group A streptococcus (GAS), is a well-known important pathogen of children. In fact, the common pharyngeal infections caused by this organism have been referred to as “occupational diseases of childhood”. If painful symptoms were the only manifestations of these infections, treatment could be largely ignored. However, the knowledge that a small percentage of these patients have the potential to develop severe, even life-threatening, infections or their sequelae demands rigorous attention to accurate diagnosis and appropriate, efficacious treatment.

Although there are many antibiotic treatment options available for patients presenting with acute streptococcal pharyngitis, penicillin remains the recommended drug of choice by many policy groups and organizations. Penicillin is inexpensive, and it is readily available in most parts of the world. Group A streptococci remain highly susceptible to penicillin. In fact, the MIC of penicillin for GAS has remained unchanged over nearly 9 decades, and, to date, no penicillin-resistant GAS strain has ever been confirmed. Yet despite these seemingly ideal characteristics, unexpectedly high penicillin treatment failure rates have been reported. For example, in one study of pediatric patients presenting with acute streptococcal pharyngitis, 35% of those treated with oral penicillin and 37% of those treated with benzathine penicillin G were still carrying the same GAS strain after completion of therapy.

What possible factors should be considered when attempting to determine the cause of penicillin GAS treatment failure? One factor is compliance. If a patient discontinues treatment before GAS eradication is complete or misses doses and does not achieve sufficiently high antibiotic serum levels, the treatment will likely fail. However, in the report mentioned above, the failure rate for penicillin administered intramuscularly was comparable to the failure rate for penicillin given orally. Thus, compliance is clearly not the only factor causing penicillin failure.

Another factor is the possibility that an apparent treatment failure is, in fact, a treatment success (complete eradication of the original infecting strain) followed by rapid reinfection with a new GAS strain. GAS strains can be quickly transmitted from one individual to another, especially when people are in close contact such as in school settings or even the family environment. We refer to this rapid movement of GAS back and forth between individuals as “ping-ponging” to use an analogy from the popular table tennis game. We often observe this phenomenon in children and families with histories of multiple and frequent occurrences of GAS pharyngitis. To determine whether an apparent treatment failure could in fact simply represent reinfection with a new GAS strain requires laboratory “typing” of the strains involved. In the report described above, each of the patients who failed treatment was confirmed by serotyping to be carry-
ing the same GAS strain before and after treatment. Therefore, reinfection does not explain the high failure rates observed in that study.

Many other possible explanations for GAS penicillin treatment failure have been proposed, but the one we consider most feasible is associated with what is termed the streptococcal carrier. An individual with a true GAS infection is defined by having not only GAS in the upper respiratory tract but also evidence that the host recognizes the streptococcus by producing an antibody response, usually measured by an increase in either antistreptolysin O (ASO) or anti-deoxyribonuclease B (ADB) titer\(^7\). One characteristic of a streptococcal carrier, therefore, is carriage of GAS without stimulating a response to streptococcal antigens. The streptococcal carrier state is very poorly understood, but the difficulty in eradicating streptococci from carriers with penicillin is well known\(^8\). There are no reliable estimates of prevalence rates of true streptococcal carriers in different populations. However, it has been observed that in the United States in some schools at certain times of the year, as many as 30% of children may be asymptomatic carriers of GAS. If an outbreak of viral illness with symptoms of sore throat were superimposed on this population of carriers, it is easy to see that many of these children would likely be incorrectly diagnosed with acute GAS pharyngitis. If penicillin treatment were prescribed for these apparent GAS infections, GAS eradication failure rates would likely be high. It must be noted that many involved in the study of GAS and GAS infections believe that the carrier state is a relatively benign condition posing little risk to the patient or to contacts of the patient, and that in most instances it is difficult to justify the cost required to eradicate GAS from carriers\(^9\).

It is further believed by many in the field that the primary explanation for the high penicillin failure rates reported from some studies is due to contamination of the study population with streptococcal carriers. They argue convincingly that penicillin re-mains a highly effective treatment for those individuals with true, acute streptococcal pharyngitis, with success rates comparable to those obtained with more expensive, newer generation antibiotics\(^5,15\).

Recent studies are beginning to shed light on the mechanism by which carriers are able to harbor GAS for extended periods of time and by which the streptococci are able evade killing by penicillin. Some GAS carry proteins on their surface that enhances their ability to not only adhere to pharyngeal cells but also to become internalized in these cells. Presence of the gene for one of these proteins, protein F1, has been associated with strains persisting in asymptomatic carriers\(^10\). Further, it has been hypothesized and later demonstrated that GAS strains in such an intracellular milieu are protected from bactericidal effects of penicillin due to the poor ability of this antibiotic to gain high intracellular concentrations\(^11-14\).

Identification of the carrier state requires reliable tests to measure antibody to streptococcal antigens. Antibody tests, especially antistreptolysin O (ASO) and anti-deoxyribonuclease B (ADB), are also crucial in the diagnosis of the post-streptococcal sequelae acute rheumatic fever (ARF) and acute glomerulonephritis (AGN). Because the initial manifestations of these illnesses occur some days after the triggering infection, throat cultures are often negative at the time of presentation. Diagnosis is aided by demonstration of an antibody response\(^17\). To effectively interpret these antibody test results, however, it is important to understand the nature of the immune response. First, although an understanding of upper limits of normal for titers to these antibodies in a specific population is useful when interpreting a single serum result, knowing the change in titer between two (or more) appropriately timed serum samples is much more informative. A true streptococcal carrier may harbor the same streptococcal strain for many months while maintaining persistently high antibody titers. In such a situation, a single point culture
together with a corresponding single point antibody titer might lead to the erroneous conclusion that the patient had a true, acute GAS pharyngeal infection. ASO and ADB titers are generally believed to reach their peak 3–4 weeks after the onset of the acute infection.\(^5\)\(^6\)

False negative ASO tests do occur; it has been reported that approximately 15–30% of patients with acute rheumatic fever will not have an elevated ASO titer.\(^2\)\(^6\) Also, ASO response is often poor following skin infections making this test less reliable for the diagnosis of AGN.\(^5\)\(^6\) Further, the ASO test can give false positive results; both group C and group G streptococci produce streptolysin O, and infection with these streptococci can result in a significant rise in ASO titer. The ADB test, in contrast, is specific for GAS. Often when the ASO test is negative, the ADB test will show a response. Thus, the most reliable antibody results will be obtained when both ASO and ADB are tested.\(^2\)\(^6\)

Recent applications of molecular and genetic technology has advanced our knowledge of the group A streptococcus and renewed interest in the dream of prevention of streptococcal infections through development of a practical vaccine. The number of GAS antigens identified through use of these techniques and proposed as possible vaccine targets is large and increasing as each month’s new journal articles are published. However, several specific vaccine strategies appear to show particular promise.

The earliest antigen proposed as a potential vaccine target is a GAS cell surface protein designated M-protein. This antigen has long been known to be an important GAS virulence factor responsible for protecting the bacterium from opsonization and phagocytosis. Host antibodies to this protein, developed in response to GAS infection, neutralize this protective effect and allow phagocytosis and killing of the streptococcus. However, one difficulty in developing a vaccine targeting M-protein is that there are more than 150 M-protein types of GAS, and the antibodies necessary for neutralization are type specific. This has been partially addressed by the construction of vaccines carrying multiple M-type determinants. One of these, carrying portions of 26 different M-proteins, is currently in clinical trials.\(^6\) The M-types used to construct this vaccine were chosen to represent those commonly associated with invasive infections in the USA at a specific point in time. Therefore, given the dynamic epidemiology of streptococcal strains in a population, an important question, in addition to the vaccine’s efficacy, is whether it can be quickly and cost effectively re-engineered to protect against different M-protein types found in different geographic regions or at future points in time.

An alternative to the M-type specific vaccine strategy is to target a region of the M-protein that is highly conserved among different M-types. Such an approach, if successful, would provide protection against a wide range of streptococcal serotypes. Preliminary studies have shown production of mucosal antibodies in response to immunization, and these antibodies appear to prevent colonization of mucosal surfaces by GAS thus preventing infection. Additional work is being done in this area.

Another antigen being targeted for vaccine development is an enzyme called streptococcal C5a peptidase. This enzyme degrades complement factor C5a thus blocking the signal that attracts PMNs to the site of infection. Preliminary studies have demonstrated that mice immunized with an inactive form of the enzyme cleared GAS from their oral and nasal mucosa more quickly than did control mice.\(^4\) This is a promising strategy that has the potential to confer protection against a broad range of GAS serotypes.

The many decades of extensive clinical and research laboratory streptococcal research is increasingly revealing the extreme complexity of the group A streptococcus. But, as the complexity is revealed, we are also beginning to see more clearly potential solutions to the problems that have likely existed
since man first encountered the streptococcus. No one can predict if or when the group A streptococcus will finally be conquered, but the dramatic increase in the amount of knowledge being gained offers hope for new strategies in the ongoing battle with this still formidable pathogen.

**References**


