Clinical Review

Penicillin Failure and Copathogenicity in Streptococcal Pharyngotonsillitis

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Recurrent group A β-hemolytic streptococcus (GABHS) pharyngotonsillitis related to penicillin failure presents a serious clinical problem. Failure to eradicate streptococci from patients can occasionally lead to rheumatic fever and rarely to glomerulonephritis.

β-lactamase–producing strains of aerobic and anaerobic bacteria in inflamed tonsils have been associated with increased failure rates of penicillins in the eradication of these infections. These organisms include *Staphylococcus aureus, Haemophilus influenzae* and *H parainfluenzae, Moraxella catarrhalis, Fusobacterium* sp, and pigmented *Prevotella* and *Porphyromonas* spp.

The indirect pathogenicity of these organisms is apparent in their ability not only to survive penicillin therapy but also to protect penicillin-susceptible pathogens from that drug. These organisms have demonstrated the ability to protect GABHS in vitro and in vivo from penicillin. Numerous reports have described the successful therapy of recurrent GABHS tonsillitis with antimicrobials directed at both GABHS and the β-lactamase–producing organisms.

Key words. Penicillin resistance; *Streptococcus pyogenes*; tonsillitis; pharyngitis; beta-lactamases; bacteria, anaerobic.
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Recurrent, persistent, or chronic group A β-hemolytic streptococcus (GABHS) pharyngotonsillitis presents a serious clinical problem. In contrast to acute tonsillitis, *recurrent infection* occurs a short time after a recent episode and may be caused by either the original GABHS isolate or a new strain. *Persistent tonsillitis* signifies the continuation of the acute process despite therapy and is caused by the original streptococcal strain. *Chronic infection* is the presence of inflammation for more than 14 days. Failure to eradicate streptococci from patients can occasionally lead to rheumatic fever and rarely to glomerulonephritis. Therefore, the frequently reported inability of penicillin to eradicate GABHS is of great concern. Tonsillectomy is often performed on patients who suffer from recurrent tonsillitis in an effort to curb the infection.

Although the incidence of rheumatic fever has declined in Western Europe and the United States, it still poses a major problem in many countries. A resurgence occurred in the past decade even in the United States. The recent recovery of mucoid isolates of GABHS with increased virulence from patients with rheumatic fever raises the possibility of a causal relation to the resurgence.[1]

Tonsillitis is a complex infection that can involve streptococci as well as other bacteria and viruses. Although streptococci may be the most virulent organism, causing septic and nonseptic complications, targeting therapy at it alone may prove inadequate.

This article summarizes the data that demonstrate a copathogenic role of aerobic and anaerobic organisms other than GABHS in tonsillitis. These organisms colonize the oropharynx, and may participate in the infectious process directly or indirectly by "shielding" GABHS from penicillin through the production of β-lactamase.

Penicillin Failure Rates

Bacteriologic failure rates of 25% or more in penicillin-treated patients with acute tonsillitis and even higher

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rates in retreatment have been documented.[2] Although about one half of the patients who harbor GABHS following therapy may be carriers, the others may still show signs of infection and represent true clinical failure. With the emergence of increased treatment failures, it has been necessary to consider alternative therapies for patients who cannot tolerate or who do not respond to penicillin.

Various theories have been offered to explain penicillin failure in the eradication of GABHS tonsillitis. These include noncompliance with a full 10-day course of therapy, the presence of a carrier state, reinfection, bacterial interference, and penicillin tolerance. One theory is that repeated penicillin administration results in a shift in the oral microflora with selection of β-lactamase–producing strains of aerobic and anaerobic bacteria. These include *Haemophilus* sp, *Staphylococcus aureus, Moraxella catarrhalis, Bacteroides* sp, *Fusobacterium* sp, and pigmented *Prevotella* and *Porphyromonas* spp.[3–5]

Role of Anaerobes in Tonsillitis

The role of anaerobic bacteria in acute tonsillitis is supported by several observations: anaerobic bacteria outnumber their aerobic counterparts at a ratio of 10:1 to 100:1 in the tonsillar tissues.[5] Anaerobes are predominant in tonsillar or retropharyngeal abscesses[6] and cause Vincent's angina.[7] Encapsulated pigmented *Prevotella* and *Porphyromonas* were isolated in greater numbers in acutely inflamed tonsils than in normal tonsils[8] and were recovered from the cores of recurrently inflamed non-GABHS tonsils.[9] Patients with non-GABHS tonsillitis respond to antibiotics directed against anaerobes[10]; and elevated serum levels of antibodies to *Prevotella intermedia* have been found in patients with recurrent non-GABHS tonsillitis.[11]

Several studies in which imidazoles (ie, metronidazole) were administered to patients with infectious mononucleosis provide indirect support for the role of anaerobes in tonsillitis.[12–14] Imidazoles alleviated the clinical symptoms of tonsillar hypertrophy and shortened the duration of fever. Metronidazole, which has no antimicrobial activity against aerobic bacteria, is effective only against anaerobes. A possible mechanism of its action could be suppression of the oral anaerobic bacterial flora that might contribute to the inflammation induced by the Epstein-Barr virus.[12] We have recently found more anaerobic bacteria on the surface of tonsils of patients with acute infectious mononucleosis than on repeat tonsillar cultures 2 months later.[15]

Table 1. Recovery of β-Lactamase–Producing Organisms (BLPO) from the Cores of Excised Tonsils of Patients with Recurrent Tonsillitis

Literature Cited	No. of Patients	% of Patients with BLPO in Tonsils
Brook et al[23]	50	74
Reilly et al[24]	41	78
Tunér and Nord[4]	167	73
Chagollan et al[25]	10	80
Kielmovitch et al[26]	25	100

Copathogenicity of β-Lactamase–Producing Organisms in Recurrent Tonsillitis

It is possible that β-lactamase–producing organisms (BLPO) can protect GABHS from penicillin by inactivating the antibiotic. When present in a localized soft tissue infection, BLPOs can degrade penicillin in the area of the infection, thereby protecting not only themselves but also penicillin-susceptible pathogens. Thus, penicillin therapy directed against a susceptible pathogen might be rendered ineffective. In vitro and in vivo studies have demonstrated this phenomenon. An increase in resistance of GABHS to penicillin was observed when GABHS was inoculated with *S aureus*,[16] *Haemophilus* sp,[17] and *Bacteroides* sp.[18]

Several studies using animals have demonstrated the activity of the enzyme β-lactamase in polymicrobial infections. *Bacteroides* sp protected a penicillin-sensitive *Fusobacterium* sp[19] and GABHS from penicillin therapy in mice.[20] Clindamycin or the combination of penicillin and clavulanic acid (a β-lactamase inhibitor), which are active against both GABHS and *Bacteroides*, were effective in eradicating the infection.[20]

Recovery of BLPO in Penicillin Failures

Clinical evidence supporting the ability of a BLPO to protect GABHS was first suggested in the 1960s.[16,21] These studies limited their search for recovery of BLPO on the surface of the tonsils, and the only organism looked for was *S aureus*. They demonstrated a significantly higher carrier rate of penicillin-resistant *S aureus* in patients with penicillin treatment failure than in patients with treatment success. In contrast, Quie et al[22] found no correlation between the presence of *S aureus* before therapy or at follow-up in treatment failures or success.

Studies conducted in the early 1980s searched for organisms in the core of the tonsils (Table 1) and sug-

Table 2. Failure Rates in the Treatment of Recurrent Group A β-Hemolytic Streptococcus Tonsillitis

Literature Cited	Failure Rate	
	Penicillin, No. (%)	Amoxicillin/Clavulanic Acid, No. (%)
Kaplan and Johnson[35]	17 (71)	2 (10)
Brook[36]	6 (29)	0 (0)
Klietman et al[37]	16 (21)	1 (1)

gested that β-lactamase–producing *M catarrhalis* and gram-negative anaerobic bacteria[4,23–26] may also have a role in penicillin failure. Scheifele and Fussel[17] correlated the recovery of β-lactamase–producing *Haemophilus parainfluenzae* on the surface of tonsils with penicillin failure.

An association between the presence of BLPO even prior to therapy and the outcome of 10 days of oral penicillin therapy was also demonstrated.[27] Of 98 children with acute GABHS tonsillitis, 36 failed to respond to therapy. Before therapy, BLPO were detected in 16 (26%) of those who were eventually cured and in 25 (69%) of the children in whom therapy failed. BLPO can emerge rapidly in the oropharynx following penicillin therapy.[28] Aerobic and anaerobic BLPO were isolated in 3 of 21 (14%) children prior to penicillin therapy, and in 10 of 21 (48%) following a 7-day course of penicillin. Similar organisms were also isolated from household contacts of children repeatedly treated with penicillin, suggesting their possible transfer within a family.[28] The organisms persisted in the oral flora of more than a quarter of similarly treated children up to 3 months later.[29]

Therapeutic Trials with Antimicrobials

Several clinical studies demonstrated the efficacy of lincomycin and clindamycin, antimicrobial agents that are effective against aerobic and anaerobic BLPO and GABHS in the eradication of *recurrent* tonsillar infection.[30–34] Data also indicate the usefulness of a combination of amoxicillin and clavulanic acid[35–37] (Table 2). Other drugs that may be effective in the therapy of recurrent or chronic tonsillitis are combinations of penicillin and rifampin,[38] and a macrolide (ie, erythromycin) and metronidazole (yet to be tested).

In contrast to the clear-cut data regarding therapy of recurrent or chronic tonsillitis, two other recent studies[39,40] failed to show any advantage of amoxicillin/clavulanate over penicillin in the treatment of *acute* GABHS tonsillitis. Both studies were carried out during a period when the penicillin failure rate was low (less than 8%). However, one study notes a correlation between treatment failure and β-lactamase production.[40] These two studies suggest that penicillin is still a viable first-line treatment for acute tonsillitis, particularly when its clinical failure rate is low and it proves effective in a given community. The low cost of penicillin makes it accessible to patients at all socioeconomic levels. Further studies are warranted to investigate the efficacy of alternative therapies where penicillin failure is higher.

Monitoring the clinical success rate of penicillin therapy in a community or individual primary care practice is therefore of great practical value. Monitoring consists of obtaining cultures from patients who are symptomatic after completion of an adequate course of penicillin therapy.

Management of Acute GABHS Tonsillitis

The recommended optimal treatment for GABHS tonsillopharyngitis is a 10-day course of penicillin. Amoxicillin, an alternative medication, is equally active against GABHS except that blood levels are higher, plasma half-life is longer, and protein binding is lower, giving the medication potential advantages. Oral amoxicillin also has better compliance (better taste) and fewer failures in the prophylaxis of endocarditis.[41]

Alternative agents for the treatment of acute GABHS tonsillitis include macrolides (if GABHS resistance to them is low) or a first- or second-generation cephalosporin. The length of therapy with medication other than penicillin has not been determined by controlled studies. Until such studies are completed, it is safe to use the same length (10 days) of therapy as with penicillin.

Amoxicillin should not be used in patients suspected of having infectious mononucleosis, as it can produce a skin rash. Infectious mononucleosis can sometimes present a clinical picture resembling streptococcal tonsillitis. In some cases, however, infectious mononucleosis pharyngitis may be generally more exudative and streptococcal pharyngitis generally follicular. Infectious mononucleosis also is a more generalized illness with lymphadenitis, splenomegaly, and lymphocytosis with atypical white blood cells.

With the availability of rapid tests for GABHS, proof of infection caused by this organism can generally be obtained within 10 to 30 minutes at the physician's office. Since a false-negative result may occur in less than 5% of the patients, it is recommended by some that a bacterial culture be performed when the rapid streptococcal test is negative. Antimicrobials are generally not needed when the rapid test is negative.

In most cases, there is no need to routinely obtain cultures following completion of penicillin therapy in asymptomatic individuals. Recovery of GABHS from asymptomatic patients usually signifies a carrier state and may cause undue anxiety. Cultures should be obtained from symptomatic individuals to verify whether symptoms are related to persistent or recurrent GABHS infection.

Conclusions

Tonsils can be colonized with various β-lactamase–producing aerobic and anaerobic organisms. Although the cause of penicillin failure may be multifactorial, the presence of these organisms in the tonsillar tissue of patients with GABHS tonsillitis may account for penicillin treatment failure. Penicillin therapy can be effective in treating acute tonsillitis, especially in children who do not develop penicillin-resistant flora, and therefore should be administered to patients presenting with acute tonsillitis. In instances of poor compliance, intramuscular administration of penicillin may be advisable. Retreatment of persistent or recurrent tonsillitis with penicillin is generally associated with a failure rate of over 50%.[2,35]

Data now available suggest that therapy of persistent, recurrent, or chronic tonsillitis should be directed toward eradication of β-lactamase–producing protective organisms as well as GABHS pathogens. Recurrent infection resulting from exposure to infected close contacts can be aborted by treating other infected family members simultaneously. Patient referral for tonsillectomy should be considered only after all other medical measures have failed.

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