

# Treatment Challenges of Group A Beta-hemolytic Streptococcal Pharyngo-Tonsillitis

Itzhak Brook<sup>1</sup>

<sup>1</sup>Department of Pediatrics / Medicine, Georgetown University, Washington, District of Columbia, United States

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Address for correspondence Itzhak Brook, MD, Professor, Department of Pediatrics/Medicine, Georgetown University, 4431 Albemarle St. NW, Washington, District of Columbia 20057-0004, United States (e-mail: ib6@georgetown.edu).

## Abstract

**Introduction** Despite its in vitro efficacy, penicillin often fails to eradicate Group A  $\beta$ -hemolytic streptococci (GABHS) from patients with acute and relapsing pharyngo-tonsillitis (PT).

**Objective** This review of the literature details the causes of penicillin failure to eradicate GABHS PT and the therapeutic modalities to reduce and overcome antimicrobial failure.

**Data Synthesis** The causes of penicillin failure in eradicating GABHS PT include the presence of  $\beta$  lactamase producing bacteria (BLPB) that “protect” GABHS from any penicillin; the absence of bacteria that interfere with the growth of GABHS; co-aggregation between GABHS and *Moraxella catarrhalis*; and the poor penetration of penicillin into the tonsillar tissues and the tonsillo-pharyngeal cells, which allows intracellular GABHS and *Staphylococcus aureus* to survive. The inadequate intracellular penetration of penicillin can allow intracellular GABHS and *S. aureus* to persist. In the treatment of acute tonsillitis, the use of cephalosporin can overcome these interactions by eradicating aerobic BLPB (including *M. catarrhalis*), while preserving the potentially interfering organisms and eliminating GABHS.

**Conclusion** In treatment of recurrent and chronic PT, the administration of clindamycin, or amoxicillin-clavulanic acid, can eradicate both aerobic and anaerobic BLPB, as well as GABHS. The superior intracellular penetration of cephalosporin and clindamycin also enhances their efficacy against intracellular GABHS and *S. aureus*.

## Keywords

- ▶ tonsillitis
- ▶ penicillin
- ▶ cephalosporins
- ▶ clindamycin
- ▶ streptococcus pyogenes

## Introduction

The frequently reported inability of penicillin to eradicate of Group A  $\beta$ -hemolytic streptococci (GABHS) from patients with pharyngo-tonsillitis (PT) despite its excellent in vitro efficacy is of concern.<sup>1</sup> Although about half of the patients who harbor GABHS following therapy may be carriers, the rest may still show signs of infection and represent true clinical failure. Studies have shown that the recommended doses of either oral penicillin V or intramuscular (IM) penicillin failed to eradicate GABHS in acute-onset pharyngitis in 35% patients treated with oral penicillin V and 37% of those treated with IM penicillin.<sup>1</sup>

Penicillin failure in eradicating GABHS tonsillitis has several explanations (► **Table 1**). These include noncompliance with 10-day course of therapy, carrier state, reinfection from another person or object,<sup>2</sup> penicillin tolerance,<sup>3</sup> and the poor penetration of penicillin into the tonsillar tissues as well as into the tonsillar epithelial cells which allows intracellular GABHS to survive.<sup>4,5</sup> Some postulate that bacterial interactions between GABHS and members of the pharyngotonsillar bacterial flora can explain these failures. These include the protection of GABHS by the enzyme  $\beta$ -lactamase that is produced by  $\beta$ -lactamase-producing bacteria (BLPB), which colonize the pharynx and tonsils.<sup>6</sup> Other mechanisms are the coaggregation between *Moraxella catarrhalis* and GABHS,

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**Table 1** Causes for penicillin failure in the treatment of GABHS pharyngo-tonsillitis

|                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| • Bacterial Interactions                                                                                                                                              |
| – The presence of $\beta$ -lactamase-producing bacteria that “protect” GABHS from penicillin                                                                          |
| – Coaggregation between GABHS and <i>M. catarrhalis</i>                                                                                                               |
| – Absence of members of the oral bacterial flora capable of interfering with the growth of GABHS (through production of bacteriocins and/or competition on nutrients) |
| • Poor penetration of penicillin into the tonsillar cells and tonsillar surface fluid (allowing intracellular survival of GABHS)                                      |
| • Internalization of GABHS (survives within epithelial cells escaping eradication by penicillin)                                                                      |
| • Resistance (i.e., erythromycin) or tolerance (i.e., penicillin) to the antibiotic used                                                                              |
| • Inappropriate dose, duration of therapy, or choice of antibiotic                                                                                                    |
| • Poor compliance                                                                                                                                                     |
| • Reacquisition of GABHS from a contact or an object (i.e., toothbrush or dental braces)                                                                              |
| • Carrier state, not disease                                                                                                                                          |

which can enhance the colonization by GABHS,<sup>7</sup> and the absence of competitive and interfering normal flora bacteria which makes it easier for GABHS to colonize and invade the pharyngo-tonsillar area.<sup>8</sup> Repeated penicillin administration can induce many of these changes. It can result in a shift in the oral microflora with selection of  $\beta$ -lactamase-producing strains of *S. aureus*, *Haemophilus* spp., *Moraxella catarrhalis*, *Fusobacterium* spp., pigmented *Prevotella* and *Porphyromonas* spp., and *Bacteroides* spp.<sup>9</sup>

This review describes the causes and treatments of penicillin failure in the eradication of GABHS PT.

## Review of Literature and Discussion

### Materials and Methods

I conducted a literature search of the Cochrane Library, EMBASE, TRIP, and MEDLINE databases from their inception (1993 for the Cochrane Library, 1980 for EMBASE, 1997 for TRIP, and 1966 for MEDLINE) through June 25, 2015. The search terms used were: pharyngitis, sore throat, tonsillitis, pharyngotonsillitis, *Streptococcus pyogenes*, Group A  $\beta$ -hemolytic *Streptococcus pyogenes*, and streptococcal pharyngitis. Searches were limited to type of article or document (practice guideline or guideline) with no language restrictions or language limits.

I closely evaluated results of these searches, and excluded articles and documents that were not pertinent or were redundant. This review was focused on causes of penicillin failure and treatment of GABHS tonsillitis.

Clinical failure of antimicrobial therapy is defined as continuation of clinical symptoms and findings beyond five

days. Bacteriological failure of antimicrobial therapy is defined as detection of GABHS by culture or detection of bacterial antigen in the tonsils through rapid method of identification beyond five days.

### Causes of Penicillin failure in Eradicating GABHS PT

#### Intracellular Survival of GABHS due to the Inadequate Penetration of Penicillin into the Tonsils

In vitro and in vivo studies have demonstrated that GABHS strains can survive within the tonsillar epithelial cells and become “internalized.”<sup>4</sup> An internalization-associated gene, *prtF1/sfbl*, has been found more in patients with eradication failure of GABHS than in patients with successful eradication.<sup>5</sup> One study found intracellular GABHS and intracellular *Staphylococcus aureus* in 3 (10%) and 13 (45%) of 29 recurrently infected tonsils, respectively.<sup>10</sup> Since penicillin penetrate mammalian cells poorly, intracellular survival of GABHS possibly enables the pathogens to survive despite treatment with this antibiotic.<sup>11</sup>

The intracellular niche may therefore shield GABHS strains from penicillin that does not reach high intracellular concentration. This hypothesis is supported by studies that illustrate the ability of GABHS strains to survive for 4–7 days within cultured epithelial cells.<sup>12</sup> Thus, internalization and intracellular survival of GABHS represent a novel explanation for its ability to survive penicillin therapy.

Using an epithelial cell culture model, Marouni et al<sup>12</sup> compared the survival of GABHS strains recovered from patients who failed penicillin therapy to those isolated from individuals who responded to penicillin. Strains recovered from patients who were “eradication failure” showed significantly increased intracellular survival, compared with the “eradication success” strains. These results illustrated how the intracellular reservoir of GABHS may play a role in the etiology of eradication failure using penicillin.

Kaplan et al<sup>1</sup> examined the viability of intracellular GABHS in a human laryngeal epithelial cell line (HEP-2epithelial cell) after exposure to several antibiotics (penicillin V, erythromycin, azithromycin, cephalothin, and clindamycin) that are frequently used for GABHS PT therapy. They employed three techniques to evaluate the antibiotic killing of ingested GABHS: 1) electron microscopy examination of ultrathin sections of internalized GABHS; 2) qualitative determination of intra-epithelial cell antibiotic; and 3) special stain evaluation of intracellular GABHS viability within antibiotic-treated epithelial cells. GABHS survived intracellularly despite exposure of the organism-infected epithelial cells to penicillin. In contrast, cephalothin and clindamycin were more effective than penicillin in killing ingested GABHS. However, the macrolides (erythromycin and azithromycin), known to accumulate to high levels within cells, were more effective than cephalothin and clindamycin in killing ingested GABHS. Even though the study was not done in tonsillar cells, these findings suggest that GABHS carrier state may result from its intra-cellular survival, and penicillin's failure to kill the internalized bacteria.

Penicillin's failure to eradicate GABHS from pharyngo-tonsillar tissue may be the result of its inability to eradicate intracellular GABHS as well as its failure in maintaining sufficient concentration within the tonsillar fluid.

The inflammatory stage of GABHS PT can determine the concentration of penicillin in tonsillar surface fluid. Stjernquist-Desatnik et al<sup>11</sup> investigated the concentration of penicillin in serum, as well as its penetration to tonsillar surface fluid and saliva. Despite the high serum penicillin concentrations (mean, 2.04 µg/mL), they detected no penetration to tonsillar surface fluid or to saliva in the nine healthy subjects that were studied. Of the nine patients with acute GABHS PT, eight manifested high concentrations of penicillin in tonsillar surface fluid (mean, 0.34 µg/mL) on the first day of treatment, but only two individuals had penicillin detected in their saliva. On the tenth day of treatment, penicillin was present in the tonsillar surface fluid of only one patient and was not present in the saliva of any patient. Orrling et al<sup>13</sup> demonstrated that cephalosporin (loracarbef) and clindamycin maintained higher concentration in tonsillar surface fluid for a longer duration than penicillin.

A delicate microbial balance occurs in the oropharynx, which includes the pharyngo-tonsillar area, between potential pathogens (e.g., GABHS, *Haemophilus* spp, *Moraxella* spp, and *Streptococcus pneumoniae*) and the normal oropharyngeal bacterial flora.<sup>14</sup>

### Bacterial Interference

Prevention of upper respiratory tract bacterial infections is partially due to bacterial interference.<sup>14</sup> The normal oropharyngeal flora employs several mechanisms that interfere with colonization and subsequent infection by potential pathogens. These include competition for nutrients and the production of antibiotic-like substances that are called "bacteriocins," which kill other bacteria.<sup>14,15</sup> The oropharyngeal flora of over 85% of otitis media-, sinusitis-, or tonsillitis-prone children contains organisms that are capable of interfering with the in vitro growth of potential bacterial pathogens. In contrast, only 25% to 30% of children who suffer from recurrent upper respiratory tract bacterial infections harbor such interfering bacteria.<sup>14,15</sup>

Only a third of individuals who suffer from recurrent GABHS PT are colonized by organisms capable of interfering with GABHS.<sup>14</sup> In contrast, 85% of individuals who are GABHS PT-free harbor those protective organisms. The predominant aerobic protective organisms are gamma- and α-hemolytic streptococci (AHS), and the main anaerobic bacteria are *Peptostreptococcus* spp. and *Prevotella* spp. These bacteria play a homeostatic role by colonizing the pharyngo-tonsillar area in large enough numbers to prevent colonization and subsequent infection by GABHS.

A series of studies performed in Göteborg, Sweden, attempted to prevent relapsing GABHS PT through the use of therapeutic colonization of the nasopharynx with interfering AHS.<sup>16–18</sup> These studies illustrated the efficacy of this approach in reducing the bacteriological and clinical recurrence rate of GABHS PT in the AHS-treated children as compared with placebo treated ones. However, the therapeutic use of AHS as a probiotic agent is not yet accepted as a treatment modality and is at present only experimental.

Even though therapeutic reconstitution of the interfering flora may be helpful, preservation of the normal interfering flora is even more desirable. Since administration of antimicrobials can affect the composition of the nasopharyngeal flora, including the reduction of interfering bacteria, judicious use of antimicrobials is essential in the preservation of the normal interfering flora.<sup>19</sup> Oropharyngeal flora microorganisms with interfering capabilities are generally susceptible to amoxicillin, and include aerobic- and anaerobic-streptococci, as well as penicillin-susceptible *Prevotella* spp. Amoxicillin-clavulanate is also effective against potentially interfering β-lactamase-producing Gram-negative bacilli (i.e., *Prevotella* spp.). In contrast, these microorganisms are relatively resistant to the extended spectrum and second- and third-generation cephalosporins.<sup>20</sup> Treatment with antibiotics effective against interfering organisms can lead to their elimination from the flora.

Brook and Gober<sup>19</sup> compared the effects of amoxicillin-clavulanate and cefdinir on the nasopharyngeal flora in children with acute otitis media. While both antimicrobials are effective against potential pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*), they have selective activity against members of the normal nasopharyngeal flora. Upon conclusion of amoxicillin-clavulanate treatment, the oral flora was more depleted of aerobic and anaerobic organisms with interfering capability than was observed after cefdinir therapy. The differences between the two treatment groups persisted for at least two months and correlated with more rapid reacquisition of potential bacterial pathogens that occurred in those treated with amoxicillin-clavulanate.

The above study<sup>19</sup> illustrates a potential beneficial effect of utilizing a narrow-spectrum antimicrobial that selectively spares interfering organisms while eliminating pathogenic organisms. The advantage of such treatment is the prevention of reacquisition of pathogenic bacteria in the oropharynx. In contrast, administration of a broad-spectrum antimicrobial is associated with prolonged absence of interfering organisms, and a rapid recolonization of the oropharynx with potential pathogens.

### Beta-Lactamase-Producing Bacteria

Treatment with penicillin has resulted in a shift in the oral microbial flora over time by selecting for β-lactamase-producing strains of *Haemophilus* spp, *Staphylococcus aureus* (including methicillin resistant *S. aureus* or MRSA), *M. catarrhalis*, and anaerobic Gram-negative bacilli (e.g., pigmented *Prevotella*, *Porphyromonas*) and *Fusobacterium* spp.<sup>9</sup> These organisms are typically recovered from those who were recently treated with β-lactam antibiotics.<sup>6,9</sup>

The inactivation of penicillin by BLPB, protects GABHS and allows it to survive.<sup>6</sup> Therapy with β-lactam antibiotics can select for BLPB that in the oropharyngeal flora,<sup>9</sup> and is especially common following repeated courses of β-lactam antibiotics administered therapeutically or prophylactically.<sup>21</sup> Antibiotic-treated individuals can also be a source for spread BLPB to other individuals.<sup>22</sup>

An association has been found in GABHS PT therapy between the failure of patients to respond to penicillin and the pre-existence of BLPB in the oropharynx.<sup>23</sup> Over three fourths of tonsils removed as a result of recurrent tonsillitis harbor BLPB

**Table 2** Prevalence of beta-lactamase-producing bacteria in excised tonsils

| Investigators (country, year)                | No. of Patients | % $\beta$ lactamase producing bacteria |
|----------------------------------------------|-----------------|----------------------------------------|
| Brook et al <sup>24</sup> (USA, 1981)        | 50              | 74                                     |
| Reilly et al <sup>25</sup> (UK, 1981)        | 41              | 78                                     |
| Tuner and Nord <sup>26</sup> (Sweden, 1982)  | 167             | 73                                     |
| Chagollan et al <sup>27</sup> (Mexico, 1984) | 10              | 80                                     |
| Kielmovitch et al <sup>28</sup> (USA, 1989)  | 25              | 100                                    |
| Brook et al <sup>29</sup> (USA, 1995)        | 50              | 94                                     |

(► **Table 2**).<sup>24–29</sup> Free  $\beta$ -lactamase enzyme was detected in the core of most of the excised tonsils that harbored BLBP.<sup>30</sup> Antibiotics that are effective against GABHS and are also resistant to the enzyme  $\beta$ -lactamase achieve higher success rates in eradication of acute and recurrent GABHS PT. These antibiotics included cephalosporins, clindamycin, lincomycin, macrolides, and amoxicillin-clavulanate.<sup>31–36</sup>

A correlation was noted between the rate of recovery of BLBP in healthy children and the rate of amoxicillin failure to eradicate GABHS. Brook and Gober obtained pharyngo-tonsillar cultures from 228 children with GABHS PT, treated with amoxicillin for 10 days, and 663 healthy children.<sup>37</sup> Amoxicillin failed to eradicate GABHS from 48 of the 228 (21%) children. Amoxicillin failure rate varied from month to month; it was generally higher between October and May (22–32%); and low between June and September (8% to 12%). They recovered BLBP from 226 of 663 (34%) healthy children. The rate of recovery of BLBP in healthy children also varied; it was also generally high between October and May (40–52%) and lowest between June and September (10–12%). Prior to their treatment, the researchers recovered BLBP from 26 of the 48 (54%) children who eventually failed amoxicillin therapy, and from 28 of the 180 (16%) who did not fail ( $p < 0.001$ ). A high failure rate of penicillin in eradication of GABHS in PT can therefore serve as sensitive indicator for a high prevalence rate of BLBP in the community.

A study of 44 children who had undergone elective tonsillectomy reported the isolation of MRSA in the cores of in 7 (16%) of the surgically excised tonsils.<sup>38</sup> Since most of the MRSA (5 of 7) were also  $\beta$ -lactamase producers, their presence could potentially interfere with the eradication of GABHS by penicillin. MRSA that is also able to produce  $\beta$ -lactamase can survive treatment with  $\beta$ -lactam antibiotics and continue to “shield” GABHS from penicillin through the production of the enzyme  $\beta$ -lactamase. Most of the *S. aureus* isolated from the tonsillar cores of the patients in the study (19 of 26 or 73%) were, however,  $\beta$ -lactamase producers and not MRSA. These organisms are susceptible to  $\beta$ -lactamase-resistant penicillin as well as most cephalosporins.

### Coexistence of Both Bacterial Interference and $\beta$ -Lactamase-Producing Bacteria

Studies have found coexistence of BLBP presence with the absence of interfering organisms in children who failed penicillin therapy of acute GABHS PT<sup>15</sup> or became carriers of GABHS.<sup>39</sup>

Brook and Gober<sup>15</sup> determined the association among bacterial interference and  $\beta$ -lactamase production and penicillin failure in treating streptococcal PT. They evaluated 52 children who had GABHS PT and were treated for 10 days with penicillin. Based on eradication of GABHS, 38 of the patients were in the classification bacteriologic “cure”; and 14 were in the classification bacteriologic “failure” after therapy.

In the cured group, before therapy the authors recovered AHS inhibiting their own GABHS in the cultures of 14 children (37%), and detected BLBP in the cultures of two children (5%). After therapy, they recovered inhibiting AHS in 31 cultures (82%), and detected BLBP in five cultures (13%). In contrast, in the failure group, before therapy AHS were isolated in one culture (7%) and BLBP were recovered from nine cultures (64%). After therapy, AHS were recovered in four cultures (29%), and BLBP was recovered in 13 cultures (93%). These data show that the absence of interfering AHS and the presence of BLBP is associated with penicillin failure in the treatment of GABHS PT.

Brook and Gober<sup>39</sup> compared the frequency of recovery of aerobic and anaerobic organisms with interfering capability against GABHS and BLBP from the tonsils of GABHS carriers and non-carriers. The authors evaluated the presence of aerobic and anaerobic bacteria capable of such interference in vitro in cultures obtained from the tonsils of 20 healthy children who were non-GABHS carriers and 20 who were GABHS carriers. They also assessed 20 children who were asymptomatic after completing a course of penicillin for acute GABHS PT and were non-GABHS carriers and 20 who were GABHS carriers. In healthy children, 32 interfering isolates were recovered from 16 non-GABHS carriers (1.6 per child) and 13 were isolated from 7 GABHS carriers (0.65 per child) ( $p < 0.001$ ).

In children who had suffered acute GABHS PT, they recovered 26 interfering organisms from 15 non-GABHS carriers and isolated 8 from 5 GABHS carriers.<sup>39</sup> Among the healthy children, they recovered 13 BLBP from 5 non-GABHS carriers and isolated 13 from 6 GABHS carriers. In children who had suffered acute GABHS PT, they recovered 14 BLBP from 5 (25%) non-GABHS carriers and isolated 32 from 17 (85%) GABHS carriers ( $p < 0.05$ ). This study demonstrated that there was a higher rate of recovery of aerobic and anaerobic organisms capable of interfering with GABHS in non-GABHS carriers than in GABHS carriers. This was observed in all GABHS non-carriers and included healthy children, as well as those recently treated for



symptomatic GABHS PT with penicillin that failed to eradicate GABHS. A higher rate of recovery of BLPB was observed only in GABHS carriers who were treated with penicillin for GABHS PT.

The presence of bacterial biofilm in tonsillitis may also play a role in bacterial interactions that take place in the tonsils. The milieu of a biofilm can trap microorganisms in close proximity to each other, thus enabling bacterial interactions.<sup>40</sup>

### Coaggregation between *M. Catarrhalis* and GABHS

Several studies suggest that tonsillar colonization by GABHS and other aerobic and anaerobic bacteria can contribute to the inflammatory process and the ultimate failure of penicillin treatment.<sup>41</sup> The existence of mutual symbiotic enhancement between GABHS and other aerobic and anaerobic bacteria was illustrated in vitro and in an animal model.<sup>42</sup> Such a synergistic relationship may also occur in patients with PT. An example of such synergy is the ability of *M. catarrhalis* to increase GABHS adherence to human epithelial cells through species-specific coaggregation.<sup>7</sup>

Brook and Gober<sup>43</sup> investigated whether the isolation of *M. catarrhalis*, *H. influenzae*, *S. aureus*, and *S. pneumoniae* is associated with the recovery of GABHS. Among 548 children with acute PT, GABHS was isolated from 112 (20.4%) children. Of the 114 *H. influenzae* isolates, 32 isolates were associated with GABHS and 82 isolates were recovered without GABHS ( $p < 0.05$ ). Of the 69 *M. catarrhalis* isolates, 25 isolates were associated with GABHS and 44 isolates were recovered without GABHS ( $p < 0.05$ ). In contrast, there was no association between the isolation of GABHS and *S. aureus* or *S. pneumoniae*. One hundred four isolates of GABHS were recovered from 548 healthy children. Of the 69 *M. catarrhalis* isolates, 24 isolates were associated with GABHS (23% of all patients with GABHS) and 80 isolates were recovered without GABHS (10%) ( $p < 0.05$ ). There was no association between the isolation of GABHS and the presence of *H. influenzae*, *S. aureus*, or *S. pneumoniae* among healthy children. This study illustrates an association between the isolation of GABHS and *H. influenzae* and *M. catarrhalis* from patients with PT, and between GABHS and *M. catarrhalis* from healthy children.

The increased recovery of *H. influenzae* (in PT only) and *M. catarrhalis* in association with GABHS may be due to a synergy between these organisms.<sup>7,43</sup> The ability of *H. influenzae* and *M. catarrhalis* to produce the enzyme  $\beta$ -lactamase, which can inactivate the penicillin in the tonsillar tissues,<sup>7</sup> may protect these organisms, as well as GABHS from eradication, and contribute to the failure of penicillin treatment.

An indirect support for the clinical importance of the synergistic relationship between GABHS and *H. influenzae* and *M. catarrhalis* is the better clinical efficacy in eradicating GABHS, as compared with penicillin, of antimicrobials active against these organisms. These antimicrobials include the second, extended-spectrum, and third-generation cephalosporins<sup>44,45</sup> as well as amoxicillin-clavulanate.<sup>33,34</sup> The superior efficacy of these antimicrobials compared with penicillin may be due to their activity against GABHS as well as  $\beta$ -lactamase producing *H. influenzae* and *M. catarrhalis*.

### Susceptibility of GABHS to Penicillin

Antimicrobial resistance of GABHS to penicillin has rarely been an issue in the management of PT. A clinical isolate of GABHS was never found to be resistant to penicillin. Despite the extensive use of penicillin in the past half century, no resistance has emerged in the treatment of GABHS infections.<sup>46,47</sup>

Sporadic reports correlated in vitro penicillin tolerance (i.e., significantly decreased bactericidal effect of penicillin) with GABHS eradication failure. However, conflicting findings have been reported by various investigators<sup>3,48</sup> and there is no common consensus about the role of tolerance in penicillin failure.

## Treatment of acute and recurrent GABHS PT

### Acute Pharyngo-Tonsillitis

Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. Despite its relatively high clinical and bacteriological failure rate to other antimicrobials, penicillin is still used for the treatment of acute GABHS PT,<sup>49,50</sup> mostly because of its long track record and low cost. Many antibiotics are available for the treatment of PT caused by GABHS. Most oral antimicrobials should be administered for 10 days to achieve the best eradication rates of GABHS; however, there have been reports of newer agents achieving comparable rates of bacteriologic and clinical cure of GABHS PT when administered for less than five days. These include azithromycin,<sup>51</sup> Clarithromycin,<sup>52</sup> cefuroxime,<sup>53</sup> cefixime,<sup>54</sup> ceftibuten,<sup>55</sup> cefdinir,<sup>56</sup> and cefpodoxime.<sup>57</sup>

The recommended treatment for GABHS infection is penicillin administered for 10 days.<sup>49,50</sup> Oral penicillin-VK is used more often than intramuscular benzathine penicillin-G. However, IM penicillin can be given as initial therapy in those who cannot tolerate oral medication or to ensure compliance. An alternative medication is amoxicillin, which is as active against GABHS, but its absorption is more reliable, blood levels are higher, plasma half-life is longer, and protein binding is lower, giving it theoretical advantages. Furthermore, oral amoxicillin has better compliance (better taste). In comparative clinical trials, once-daily amoxicillin (50 mg/kg, to a maximum of 1000 mg) for 10 days has been shown to be effective for GABHS pharyngitis.<sup>58</sup> Amoxicillin should not be used, however, in patients suspected of infectious mononucleosis, where it can produce a skin rash.

Treatment of GABHS PT with a single daily dose of penicillin has been unsuccessful.<sup>59</sup> Once-daily azithromycin<sup>60</sup> and once-daily regimens of several cephalosporins (e.g., cefadroxil,<sup>61</sup> cefixime,<sup>62</sup> ceftibuten,<sup>63</sup> cefpodoxime,<sup>64</sup> cefprozil,<sup>65</sup> and cefdinir<sup>66</sup>), were effective in eradicating GABHS PT. However, only azithromycin, cefadroxil, cefixime, and cefdinir are FDA-approved as once-daily therapies for GABHS PT in children.

There are, however, individuals for whom more effective antimicrobials should be considered. Individual medical, economic, and social issues should be taken into consideration before selecting an antimicrobial for the treatment of

**Table 3** Antibacterial activity of penicillin compared with cephalosporins in the management of acute GABHS tonsillitis

| Antimicrobial Activity                   | Penicillin | Cephalosporins |
|------------------------------------------|------------|----------------|
| Aerobic betalactamase-producing bacteria | No         | Yes            |
| Interfering organisms                    | Yes        | No             |
| GABHS                                    | Yes        | Yes            |

GABHS PT. The existence of a high probability for the presence of BLPB in the pharyngo-tonsillar area, the absence of interfering organisms, the recent failure of penicillin therapy, or a history of relapsing GABHS PT should be considered.

Macrolides are an alternative to penicillin. However, the increased use of macrolides has been associated with increased GABHS resistance to these agents - up to 60% in Italy, Finland, Japan, Spain, and Turkey.<sup>67</sup> Of particular concern is the recent increase of such resistance in the United States,<sup>68,69</sup> reaching 48% in specific populations.<sup>68</sup> Therefore, it is advisable to avoid the routine administration of macrolides for GABHS PT and to save these antimicrobials for patients who are Type I penicillin-allergic.

When treating acute GABHS PT, amoxicillin-clavulanate was not superior to penicillin.<sup>70</sup> Furthermore, the use of this agent at the earlier stages of the infection can reduce the number of the aerobic- and anaerobic-interfering organisms, which may be counterproductive.<sup>71</sup>

The high failure rates in the treatment of GABHS PT by penicillin and amoxicillin may be due to their inability to eradicate BLPB (bacteria) and their ability to eradicate the beneficial interfering bacteria. In contrast to cephalosporins, especially those that are  $\beta$ -lactamase stable, are effective in the treatment of individuals who are likely to fail penicillin therapy as well as those with recurring infection. The efficacy of cephalosporins is explained by their ability to eradicate aerobic BLPB, preserve aerobic and anaerobic interfering organisms, and eliminate GABHS (**► Tables 3 and 4**).

When making a choice to select broader spectrum antimicrobial, it is important to consider the potential of selection of resistant organisms.

Several antimicrobials are not recommended for treatment of GABHS PT. Tetracyclines should not be used as resistance in GABHS patients is common.<sup>72</sup> Sulfonamides and trimethoprim-sulfamethoxazole resistance is also prevalent and these agents often fail to eradicate GABHS from patients with acute PT.<sup>3</sup> Older fluoroquinolones (e.g., ciprofloxacin) have limited antibacterial activity against GABHS and are not recommended for the treatment of GABHS PT.<sup>49</sup> The newer fluoroquinolones (e.g.,

levofloxacin and moxifloxacin) are effective in vitro against GABHS; however, they are expensive and possess a broad spectrum of activity. They are therefore not recommended for routine treatment of GABHS PT.<sup>49</sup>

Penicillin allergic patients can be treated with cephalosporins, macrolides, or clindamycin. It is important to note that some penicillin-allergic individuals (up to 10%) are also allergic to cephalosporins, which should not be used in patients with immediate (anaphylactic-type) hypersensitivity to penicillin.<sup>73</sup> Clindamycin resistance among GABHS isolates in the United States is ~1%, and this is a reasonable agent for treating penicillin-allergic patients.<sup>69</sup>

Because of the general increase in rates of bacterial resistance to antimicrobials, antibiotic therapy should be administered only for proven episodes of GABHS PT.<sup>49,50</sup>

The length of therapy of acute tonsillitis with medication other than penicillin has not been determined by large comparative controlled studies. However, certain new agents have been administered in shorter courses of 5 or more days. Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms. However, spontaneous disappearance of fever and other symptoms generally occurs within 3 to 4 days, even without antimicrobials. Furthermore, acute rheumatic fever can be prevented even when therapy is postponed up to 9 days.

Prevention of recurrent tonsillitis due to GABHS by prophylactic administration of daily oral or monthly benzathine penicillin should be attempted in patients who suffered from rheumatic fever. American Heart Committee guidelines on the prevention of rheumatic fever<sup>74</sup> should be followed, and if any family members are carrying GABHS, the disease should be eradicated and the carrier state monitored.

### Recurrent Pharyngo-Tonsillitis

Penicillin failure in treatment of recurrent and chronic tonsillitis is even higher than the failure of therapy of acute infection. Several clinical studies demonstrated the superiority of lincomycin, clindamycin, and amoxicillin-clavulanic acid over penicillin in the treatment of recurrent

**Table 4** Antibacterial activity of cephalosporins against aerobic Beta-Lactamase-Producing Bacteria (BLPB)

| BLPB                  | First generation (cephalothin) | Second generation (cefuroxime) | Extended spectrum (cefdinir, cefpodoxime) | Third generation (cefixime, ceftibuten) |
|-----------------------|--------------------------------|--------------------------------|-------------------------------------------|-----------------------------------------|
| <i>S. aureus</i>      | Yes                            | Yes                            | Yes                                       | No                                      |
| <i>H. influenzae</i>  | No                             | Yes                            | Yes                                       | Yes                                     |
| <i>M. catarrhalis</i> | No                             | Yes                            | Yes                                       | Yes                                     |

**Table 5** Studies of therapy of acute and recurrent group A streptococcal pharyngitis

|                                     |                 | Failure rate        |                                                                                                          |                 |
|-------------------------------------|-----------------|---------------------|----------------------------------------------------------------------------------------------------------|-----------------|
|                                     | No. of Patients | Penicillin          | Other drugs                                                                                              |                 |
| ACUTE                               |                 |                     |                                                                                                          |                 |
| Breese et al <sup>75,76</sup>       | 262             | 29%                 | Lincomycin                                                                                               | 13%             |
| Randolph & DeHaan <sup>77</sup>     | 525             | 14%                 | Lincomycin                                                                                               | 8%              |
| Howie & Ploussard <sup>57</sup>     | 156             | 40%                 | Lincomycin                                                                                               | 13%             |
| Randolph et al <sup>78</sup>        | 128             | 21%                 | Clindamycin                                                                                              | 7%              |
| Stillerman et al <sup>80</sup>      | 103             | 18%                 | Clindamycin                                                                                              | 10%             |
| Chaudhary et al <sup>81</sup>       | 99              | 28%                 | Penicillin & rifampin                                                                                    | 0%              |
| Massell (prophylaxis) <sup>82</sup> | 202             | 25%                 | Clindamycin                                                                                              | 12%             |
| Casey et al <sup>85</sup>           | 4278            | Pen 16%<br>Amox 14% | Cephalosporin (1 <sup>st</sup> )<br>Cephalosporin (2 <sup>nd</sup> )<br>Cephalosporin (3 <sup>rd</sup> ) | 14%<br>9%<br>7% |
| RECURRENT                           |                 |                     |                                                                                                          |                 |
| Brook and Hirokawa <sup>32</sup>    | 30              | 87%                 | Erythromycin                                                                                             | 60%             |
|                                     |                 |                     | Clindamycin                                                                                              | 7%              |
| Tanz et al (carriers) <sup>83</sup> | 48              | 45%                 | Clindamycin                                                                                              | 8%              |
| Brook <sup>33</sup>                 | 40              | 30%                 | Amoxicillin & clavulanate                                                                                | 0%              |
| Smith et al <sup>84</sup>           | 74              | 83%                 | Dicloxacillin                                                                                            | 50%             |
| Orrling et al <sup>85</sup>         | 48              | 64%                 | Clindamycin                                                                                              | 0%              |
| * with rifampin                     |                 |                     |                                                                                                          |                 |

Abbreviations: Amox, amoxicillin; Pen, penicillin.

PT.<sup>32–34,57,75–85</sup> Only one of these studies showed reduction in the need for tonsillectomies following treatment with clindamycin (►Table 5).<sup>32</sup> These antimicrobial agents are effective against aerobic, as well as anaerobic BLPB and GABHS, in eradicating recurrent tonsillar infection. However, no studies have shown them to be superior to penicillin in treatment of acute tonsillitis.

A study<sup>86</sup> of 774 patients with acute recurrent GABHS PT that compared oral clindamycin 300mg BID and oral amoxicillin-clavulanate 1 g BID achieved comparable rates of bacteriologic eradication at 12 days and 3 months and comparable clinical cure rates at three months. Patients who received clindamycin had significantly greater clinical cure rates at 12 days (92.6% versus 85.2%).

Other drugs that may also be effective in the therapy of recurrent or chronic tonsillitis are penicillin plus rifampin and a macrolide (e.g., erythromycin) plus metronidazole (►Table 6). Referral of a patient for tonsillectomy should be considered only after these medical therapeutic modalities have failed.

Amoxicillin-clavulanate and clindamycin, which are also active against the anaerobic component (including the anaerobic BLPB) of the oropharyngeal flora, are appropriate for the treatment of patients with chronic tonsillitis and in those with recurrent PT who had failed treatment and are considered for elective tonsillectomy. Clindamycin has also been found to be effective in eradicating the GABHS carrier state.<sup>87</sup> This may be due to its ability to eradicate the BLPB present<sup>39</sup> in these children as well as penetrate into the tonsillar cells.<sup>1</sup>

**Table 6** Oral antimicrobials in treatment of GABHS tonsillitis

| Acute                       | Recurrent/Chronic                    | Carrier State            |
|-----------------------------|--------------------------------------|--------------------------|
| Penicillin (amoxicillin)    | Clindamycin, amoxicillin-clavulanate | Clindamycin              |
| Cephalosporins <sup>b</sup> | Metronidazole plus macrolide         | Penicillin plus rifampin |
| Clindamycin                 | Penicillin plus rifampin             | –                        |
| Amoxicillin-clavulanate     | –                                    | –                        |
| Macrolides <sup>a</sup>     | –                                    | –                        |

<sup>a</sup>GABHS may be resistant.

<sup>b</sup>All generations.

### The Carrier State

Antimicrobial therapy is not indicated for most individuals who are chronic streptococcal carriers. However, some circumstances justify the eradication of the organism. These include: (1) during an outbreak of acute rheumatic fever, acute post-streptococcal glomerulonephritis, or invasive GABHS infection in the community; (2) during an outbreak of GABHS PT in a closed community; (3) in those with a personal or family history of acute rheumatic fever; (4) in families with excessive anxiety about GABHS infections; or (5) when GABHS carriage is considered as an indication for tonsillectomy.

Several antimicrobials have been found to be more effective than penicillin or amoxicillin in eliminating chronic streptococcal carriage. These include clindamycin<sup>87</sup> and the combination of penicillin (IM or PO) and rifampin.<sup>83</sup>

### Final Comment

There have been 13 national guidelines published regarding GABHS PT management since 1999.<sup>49,50,74,88–97</sup> These include six from European countries (France, United Kingdom, Finland, Holland, Scotland, and Belgium), six from the United States, and one from Canada. Recommendations differ substantially with regard to the use of a rapid antigen diagnostic test or throat culture and the indications for antibiotic treatment. The North American, Finnish, and French guidelines recommend performing one timely microbiologic investigation in suspected cases, and prescribing antibiotics in confirmed cases to prevent suppurative complications and acute rheumatic fever. According to the remaining European guidelines, however, acute sore throat is considered a benign, self-limiting disease. Microbiologic tests are not routinely recommended by these latter guidelines, and antibiotic treatment is reserved for well-selected cases. Without microbiological testing, bacteriological failure of therapy cannot be detected.

Penicillin remains the antibiotic of choice recommended by all national guidelines,<sup>49,50,74,88–97</sup> although other antibiotics are more effective in the bacteriological eradication and clinical cure of acute and recurrent GABHS PT.<sup>33–36</sup> Macrolides and cephalosporins are more effective clinically and bacteriologically than penicillin in acute GABHS PT,<sup>44,45</sup> while lincomycin, clindamycin, and amoxicillin-clavulanate are more effective in relapsing GABHS PT.<sup>32–34,57,75–85</sup>

The goal of the treatment of PT in individuals who failed penicillin therapy is also to eradicate the BLPB that protect GABHS from penicillin, while preserving whatever “protective” interfering organisms (i.e., AHS) that may be present in the pharyngo-tonsillar area.

Cephalosporins have been successful in eradicating GABHS better, and in some instances even faster than penicillin.<sup>44,45</sup> Thirty-five randomized studies showed that all classes of cephalosporins have a higher success rate in eradicating GABHS than penicillin (a third of the failure rate of penicillin,<sup>44,45</sup> and 12 studies illustrated equal or better success rate in 5 to 7 days of therapy, compared with 10 days of penicillin.<sup>73</sup> The frequency of

symptomatic relapses of GABHS PT following all generations of cephalosporins was significantly lower compared with penicillin<sup>98</sup> (►Table 5). The explanation for the superiority of cephalosporins over penicillin is that even though they are as efficacious in vitro as penicillin in eradicating GABHS, penicillin also eliminates the aerobic- and anaerobic-interfering bacteria. Penicillin use may therefore deprive the patient of the potential beneficial effects of interfering organisms, which can decrease colonization with GABHS. In contrast, cephalosporins are less inhibitory of aerobic- and anaerobic-interfering organisms; thus, they are more likely to survive the antimicrobial therapy.<sup>42</sup> The higher the generation of the cephalosporins, the less effective they are against both aerobic- and anaerobic-interfering organisms (►Tables 5 and 6).

Cephalosporins lesser efficacy against interfering bacteria accounts for their potential advantage. The administration of a cephalosporin has therefore a selective effect: eradicating GABHS while preserving both aerobic- and anaerobic-interfering organisms (►Tables 3 and 4). The sparing effects of the cephalosporins persisted for at least two months after their administration.<sup>20</sup>

Cephalosporins are generally resistant to  $\beta$ -lactamase and are not hydrolyzed by extracellular  $\beta$ -lactamases produced by BLPB. However, cephalosporins antibacterial efficacy against BLPB is generation-dependent (►Table 3). First generation cephalosporins (e.g., cephalexin, cefadroxil) are effective only against *S. aureus*; second generation (cefuroxime acetyl) and extended-spectrum third generation (cefdinir and cefpodoxime axetil) cephalosporins are effective against *S. aureus*, *Haemophilus* spp., and *Moraxella* spp.; and third generation (e.g., cefixime, ceftibuten) cephalosporins are only effective against *Haemophilus* spp. and *Moraxella* spp.<sup>99</sup>

The selective activity of cephalosporins has been demonstrated in an animal model study of mixed infection,<sup>21</sup> as well as in patients treated with an extended-spectrum cephalosporin prior to elective tonsillectomy.<sup>100</sup> Brook and Foote<sup>100</sup> compared two treatment modes of recurrent GABHS tonsillitis: one with penicillin and the other with an extended-spectrum cephalosporin (cefdinir). Both antimicrobials were given for 10 days prior to elective tonsillectomy to children who suffered from recurrent GABHS tonsillitis and were scheduled for surgery. Of the two, cefdinir was more effective in eradicating GABHS, reducing the number of BLPB, and preserving AHS capable of inhibiting GABHS. These results illustrate the ability of an oral extended-spectrum cephalosporin, in comparison to penicillin, to eradicate GABHS as well as BLPB, while preserving the interfering AHS.

The data presented suggest that consideration should be given to utilization of antimicrobials other than penicillin for the treatment of GABHS PT, especially in clinical settings where penicillin failure had occurred or is high. Further studies are warranted to demonstrate if this approach would reduce the need for tonsillectomies.

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