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Management of Group A β-Hemolytic Streptococcal Pharyngotonsillitis in Children

Acute pharyngotonsillitis is one of the most common infections encountered by pediatricians and family physicians. According to the US Vital Health Statistics report, acute pharyngotonsillitis is responsible for more than 6 million office visits each year by children younger than 15 years of age and an additional 1.8 million visits by adolescents and young adults aged 15 to 24 years.[1] Most children with acute pharyngotonsillitis have symptoms that can be attributed to infection with a respiratory virus, such as adenovirus, influenza virus, parainfluenza virus, rhinovirus, and respiratory syncytial virus.[2,3] However, in approximately 30% to 40% of cases, acute pharyngotonsillitis is of bacterial etiology.[4] Group A β-hemolytic streptococci (GABHS) are responsible for most bacterial cases of acute pharyngotonsillitis, although other pathogens, such as *Neisseria gonorrhoeae*, *Arcanobacterium haemolyticum*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, may be the causative agents in sporadic cases.[5] Pharyngotonsillitis caused by these latter pathogens can sometimes be distinguished from that caused by GABHS by considering the patient's medical history in concert with the clinical presentation. In some cases, acute pharyngotonsillitis may have an

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STATEMENT OF NEEDS

Sore throat is an extremely frequent complaint in children and accounts for millions of pediatrician office visits every year. The diagnosis of pharyngotonsillitis should be supported by a rapid antigen detection test or a throat swab culture (standard), since the clinical presentation does not predict the causative agent. Due to the fact that the majority of pharyngotonsillitis cases have a viral etiology, only an accurate diagnosis of group A β-hemolytic streptococcus (GABHS) or other bacterial infection should warrant antimicrobial therapy. Although the recommended first-line therapies, penicillin and amoxicillin, are efficacious against GABHS pharyngotonsillitis, cure rates and bacterial eradication observed for cephalosporins are higher. Selecting an antimicrobial agent that can effectively eradicate the infection is critical, and should be based on a number of factors, including clinical efficacy, patient tolerance, frequency of dosing, duration of therapy, and palatability.

EDUCATIONAL OBJECTIVES

- Apply appropriate antibiotic therapy for the treatment of acute pharyngotonsillitis, according to current recommendations of the Infectious Diseases Society of America (IDSA) and the American Academy of Pediatrics (AAP)
- In order to improve outcomes for your patients, evaluate the incidence of treatment failure with penicillin V in acute GABHS pharyngotonsillitis and choose appropriate treatment options
- Given the high incidence of recurrence after penicillin treatment, determine potential reasons for treatment failure in order to reduce recurrences and improve outcomes
- Evaluate cross-reactivity between penicillins and cephalosporins in patients with a history of penicillin allergy, in order to determine appropriate medication management
- Compare the efficacy of penicillins and cephalosporins in GABHS pharyngotonsillitis according to current recommendations of the IDSA
- Evaluate options for improving compliance of antibiotic therapy in GABHS pharyngotonsillitis, particularly in your pediatric population

METHOD OF INSTRUCTION

Read the supplement in its entirety. After reviewing the supplement, complete the evaluation and posttest online at www.ScepterCME.com/pharyngotonsillitis to receive your certificate of completion immediately.

You may also complete the accompanying evaluation and posttest, and return them via US mail as directed in the accompanying evaluation. The test will be graded and a certificate will be mailed to you within 4 to 6 weeks of receipt of the evaluation and posttest. You may also choose to receive your certificate by e-mail.

A minimum score of 70% is required for certification. If you do not pass the test, you will be contacted by Scepter™ for a retake.

TARGET AUDIENCE

This supplement is intended for family physicians, clinical pediatricians, primary care physicians, and other health care professionals interested in the care of children with pharyngotonsillitis.

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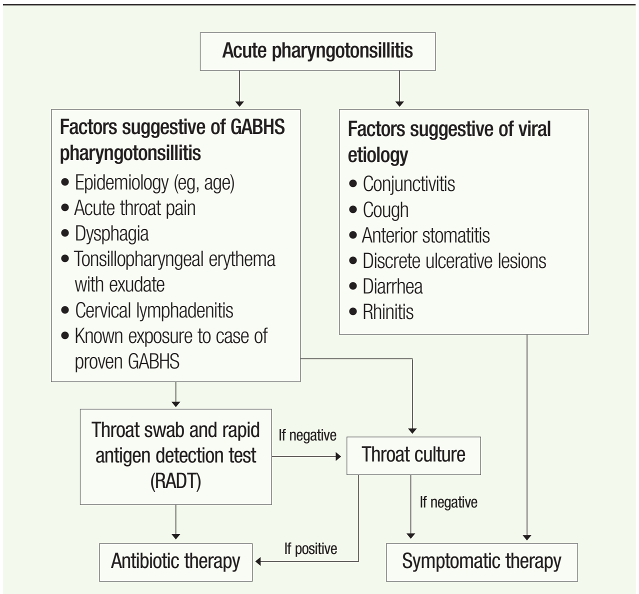
FIGURE 1
Algorithm for diagnosing GABHS pharyngotonsillitis



Algorithm for the diagnosis of GABHS pharyngotonsillitis. Modified from IDSA Practice Guidelines.[3,6]

idiopathic etiology. An accurate diagnosis of GABHS infection is important because it is the only common form of acute pharyngotonsillitis for which antibiotic therapy is definitely indicated.[3] Antibiotic therapy can shorten the clinical course of GABHS pharyngotonsillitis, reduce the rate of transmission, and prevent suppurative and nonsuppurative complications, such as peritonsillar abscess and acute rheumatic fever.[2] Although the threat of rheumatic fever is much lower for children in the United States than in developing nations, preventing rheumatic fever and the spread of disease is the primary goal of antibiotic therapy in GABHS pharyngotonsillitis treatment and a cornerstone of practice guidelines.

Diagnosis of GABHS Pharyngotonsillitis

The presence of GABHS pharyngotonsillitis may be suspected on the basis of clinical findings, and the diagnosis should be confirmed by laboratory testing (**FIGURE 1**).[3,6] GABHS infections usually occur in children aged 5 to 15 years during the winter and early spring in temperate climates. Symptoms frequently include acute throat pain, severe pain on swallowing, and fever, but headache, nausea, vomiting, and abdominal pain may also be present, especially in younger children. Clinical examination shows tonsillopharyngeal erythema, sometimes with exudate, and tender, enlarged anterior cervical lymph nodes (lymphadenitis). Other findings may also be present, including a scarlatiniform rash and palatal petechiae. Unfortunately, these signs and symptoms are not specific for GABHS pharyngotonsillitis and consequently are not sufficient for making an accurate diagnosis. On the other hand, a viral rather than a bacterial etiology is strongly suggested by the absence of fever or by the presence of certain clinical features, such as conjunctivitis, cough, hoarseness, coryza, anterior stomatitis, discrete ulcerative lesions, viral exanthem, and diarrhea.

When GABHS pharyngotonsillitis is suspected, a laboratory test—either throat culture or rapid antigen detection test (RADT)—should be conducted to document the presence of GABHS in the pharynx and confirm the diagnosis.[3,6] The culture of a throat swab on a sheep blood agar plate remains the gold standard and, when properly performed, has a sensitivity of 90% to 95% for detecting GABHS in the pharynx. Because culture results are not available for at least 1 day, RADTs were developed to permit the more timely identification of GABHS on a throat swab. The RADTs detect a carbohydrate antigen unique to GABHS by enzyme, optical immunoassay techniques, or the presence of unique gene sequences by chemiluminescent DNA probes. Compared to throat culture, most available RADTs have a specificity of ≥95%, making false-positive results unlikely.[3] Therapeutic decisions, therefore, can be made reliably from a positive RADT result. Rapid identification of GABHS permits earlier antibiotic therapy, thus reducing the risk of transmission and allowing children to return sooner to school.[2] However, the sensitivity of RADTs is in the range of 80% to 90%, which raises the possibility of false-negative results. Therefore, the Infectious Diseases Society of America (IDSA) recommends that negative RADT results in children and adolescents be confirmed with a throat culture, unless the physician has documented in his or her practice that the RADT that is being used provides results comparable to those provided by throat culture.[3]

Accurately diagnosing GABHS pharyngotonsillitis and treating with appropriate antibiotic therapy provides positive benefits, including prevention of complications such as acute rheumatic fever and tonsillar abscess, shortened clinical course, and decreased contagiousness. Conversely, improper diagnosis may result in negative consequences, including unnecessary antibiotic prescriptions that confer increased health care costs and contribute to the development of bacterial resistance, as well as adding the risk of adverse side effects, including allergic reactions from the antibiotic itself.[7]

Goals of GABHS Pharyngotonsillitis Therapy

Primary goals of therapy for acute GABHS pharyngotonsillitis include preventing acute rheumatic fever and suppurative complications (eg, peritonsillar abscess). Other goals of antimicrobial therapy include improving clinical symptoms, reducing transmission, and achieving bacteriologic eradication.[3] Following an appropriate diagnosis, patients with GABHS pharyngotonsillitis should be treated with an antibiotic in an adequate dosage for sufficient duration to eradicate the infecting organism from the pharynx.

According to IDSA clinical practice guidelines, antibiotic therapy is indicated for patients with acute pharyngotonsillitis if the presence of GABHS has been confirmed by RADT or throat culture.[3] In order to be considered for first-line treatment of GABHS pharyngotonsillitis, the US Food and Drug Administration (FDA) requires that an antibiotic achieve an eradication rate of at least 85% in a statistically adequate and well-controlled multicenter trial, in which bacteriologic eradication correlates with clinical cure.[8]

In selecting antibiotic therapy, it is important to consider the efficacy, safety, antimicrobial spectrum, dosing schedule, likely compliance with therapy, and cost. Several classes of antibiotics have been evaluated in clinical studies of the treatment of GABHS pharyngotonsillitis, including the penicillins, cephalosporins, macrolides, ketolides, and clindamycin.[3] Both the American Academy of Pediatrics (AAP) and IDSA guidelines list penicillin as the agent of choice for first-line treatment of GABHS pharyngotonsillitis due to its proven efficacy, safety, narrow spectrum, and low cost.[3,9] For young children, amoxicillin may be preferred to penicillin, since the suspension is more palatable. For patients unlikely to complete the full 10-day course of oral antibiotic therapy, an intramuscular injection of benzathine penicillin G is preferred. According to the recent IDSA guidelines, erythromycin is identified as a suitable alternative for patients allergic to penicillin; first-generation cephalosporins are also recommended, providing the patient does not have immediate-type hypersensitivity to β-lactam antibiotics.[3] Cephalosporins and macrolides have demonstrated greater bacteriologic eradication and clinical resolution of infection compared with penicillins.[10-13]

The 2006-2007 *Nelson's Pocket Book of Pediatric Antimicrobial Therapy* recommends cephalosporins as first-line treatment, representing what may be a justified challenge to AAP and IDSA guidelines that recommend penicillin as the preferred first-line therapy, with other antibiotics reserved for recurrences or treatment failures.[14]

As outlined and discussed in the first case (**CASE 1**), accurate diagnosis and appropriate treatment of

CASE 1

An 8-year-old patient presents in January with a 1-day history of sore throat, severe pain on swallowing, fever, and headache. The child is otherwise healthy and has been taking ibuprofen to control the symptoms. Physical examination reveals tonsillopharyngeal erythema with exudate, and tender, enlarged anterior cervical lymph nodes along with a scarlatiniform rash. A RADT result was negative for Group A streptococcus infection. A second throat swab was obtained and sent for culture. The patient's mother was given a prescription for amoxicillin and asked to refrain from filling the prescription until the culture results were available. The following day, the culture result was found to be positive and the patient's mother was called and instructed to fill the prescription. Eleven days later, the mother called and stated that the child had completed the entire course of amoxicillin. Although symptoms were markedly improved, the child's "neck glands" were still quite swollen and tender to touch and, at night, the child continued to experience a low-grade fever of 100°F. Further, the patient's 6-year-old sister had just begun to complain of sore throat and was being kept out of school. The children were seen in the office and RADT results were positive for GABHS in both children. Each child was treated with cefdinir 7 mg/kg twice daily for a total of 5 days. At the follow-up visit 1 week later, both children were asymptomatic, had normal physical examinations, and follow-up throat culture results were negative. A macrolide antibiotic would have been a poor choice in this case because of the increasing resistance of GABHS to macrolides in the United States. ∎

GABHS pharyngotonsillitis become essential to treatment success as the incidence of treatment failure with first-line penicillins increases.

Case 1 demonstrates the utility of following a negative RADT result with culture, a practice recommended by IDSA guidelines. As will be discussed in more detail, penicillin and amoxicillin kill both GABHS and α-hemolytic streptococci (AHS), while cefdinir only attacks GABHS. There is evidence that the presence of AHS prevents GABHS from attaching to the mucous membrane of the pharynx and thereby provides a protective barrier. Considering the higher eradication rates of GABHS with cephalosporins compared with those of penicillin/amoxicillin and the ability of cephalosporins to spare protective organisms, choosing a third-generation cephalosporin after amoxicillin failure was an appropriate and effective treatment decision.

The AAP and IDSA state that penicillin is the agent of choice for first-line treatment of GABHS pharyngotonsillitis.

Clinical cure with penicillin/amoxicillin should not be equated with eradication of pharyngeal GABHS—a common but potentially detrimental assumption sometimes made by clinicians. Lack of bacteriologic eradication can lead to lost school days for the child, lost workdays for parents, and transmission of infection to siblings and playmates, as well as increased treatment failure and recurrence. Indeed, treatment failure rates with penicillin have increased since the early 1970s, when the bacteriologic failure rate after 10 days of penicillin therapy was approximately 2% to 10%.[5] Several recent studies suggest that treatment failure after penicillin therapy may now approach 25% to 35% in the United States. Two multicenter, randomized, single-blind studies conducted in 1994 and 1995 reported that 35% of children aged 2 to 12 years treated with oral penicillin V and 37% treated with intramuscular benzathine penicillin G had a positive throat culture result for a concordant serotype of GABHS when tested either 10 to 14 days or 1 month after starting treatment (**FIGURE 2**).[15] All of these children were microbiological failures only; however, approximately half were also clinically symptomatic, and therefore not in a carrier state.

Notably, the rates of recurrence after penicillin or amoxicillin therapy—both within 30 days and 60 days—increased substantially during the early 1980s. A retrospective chart review of 1721 cases of acute GABHS pharyngotonsillitis treated with penicillin or amoxicillin from 1975 to 1996 showed that GABHS pharyngotonsillitis recurred within 30 days in 20.5% (n = 352) and within 60 days in 30.2% (n = 519) of children.[16] Moreover, the percentage of acute GABHS pharyngotonsillitis cases treated with penicillin or amoxicillin declined from 91% (1975 to 1979) to 67% (1995 to 1996) in this retrospective study. Many of the remaining cases were treated with cephalosporins and the 30-day recurrence rate was significantly lower after oral cephalosporin therapy (8.6%) than after penicillin (21.8%; $P<0.0001$) or amoxicillin (16.8%; $P<0.04$) treatment.

Despite the rising incidence of penicillin resistance, there has not been an overwhelming increase in the incidence of acute rheumatic fever. While the incidence and severity of acute rheumatic fever in the United States has declined significantly over the past 5 decades, reports beginning in the mid 1980s have cited a resurgence of this complication in several areas of the country.[17-19] Although the current incidence of acute rheumatic fever is still significantly lower than during the pre-antibiotic era, it still warrants consideration by physicians treating pediatric patients presenting with pharyngotonsillitis.

Economic Costs of GABHS Pharyngotonsillitis

Testing for and treating GABHS pharyngotonsillitis among children comprises a variety of economic costs. Most financial costs incurred during an episode of GABHS pharyngotonsillitis can be attributed to parental time lost from work.[20,21] One study estimated that parents' lost work productivity accounted for approximately 75% of the total cost of one such episode, whereas the cost of antibiotic therapy contributed only 3%.[20] Because the costs of lost work time routinely outweigh the medical costs associated with GABHS pharyngotonsillitis, even a minimal change in the duration of the illness can have a major impact on overall costs.[21]

Causes for Penicillin Failure in GABHS Pharyngotonsillitis

Both clinical failure and bacteriologic failure still occur despite 100% susceptibility of GABHS to penicillin in vitro. Bacterial interactions among the organisms that inhabit the nasopharynx may contribute to treatment failure with penicillin.

Copathogenicity: One cause of penicillin failure

The pharynx may be co-colonized by bacterial pathogens that can inactivate penicillins and make them ineffective against GABHS. Copathogenicity in acute GABHS pharyngotonsillitis may occur when β-lactamase-producing strains of *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis*, or *Staphylococcus aureus* colonize the inflamed pharynx.[5,22] Although these organisms are generally not pathogenic in the pharynx, they can produce the enzyme β-lactamase, which inactivates penicillins that are not β-lactamase-stable.[4]

A clear association has been established in the therapy of GABHS pharyngotonsillitis between the failure of patients to respond to penicillin and the preexistence of β-lactamase-producing bacteria (BLPB) in their pharyngotonsillar flora.[22] More than 75% of tonsils were removed because of recurrent tonsillitis harboring BLPB.[23-29] Free β-lactamase was detected in the core of most of those tonsils.[30] Antibiotics that are effective against GABHS and are also resistant to β-lactamase, such as cefuroxime axetil, cefdinir, or cefpodoxime, attain higher success eradication rates in relapsing GABHS pharyngotonsillitis.[23]

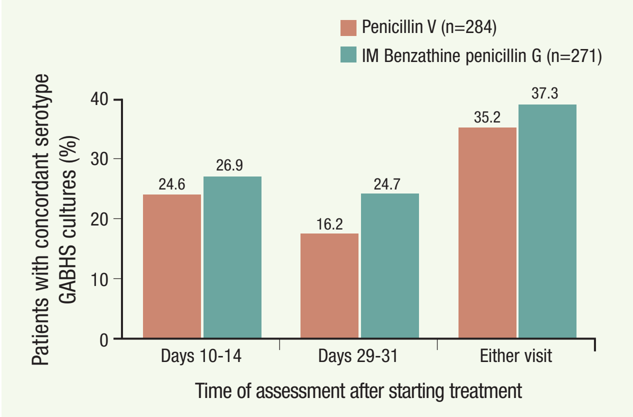
The co-localization of these organisms with GABHS was shown in a recent study of 548 children with acute pharyngotonsillitis, 20% of whom had GABHS isolated before treatment.[31] GABHS was isolated with a copathogen in 62% of the cases, most commonly *H influenzae* and *M catarrhalis* (29% and 22% of children, respectively) (**FIGURE 3**). Notably, all of the *M catarrhalis* isolates and about one third of the *H influenzae* isolates produced β-lactamases.[31] The impact of β-lactamase production in cases of penicillin failure is suggested by a recent study of 20 children with recurrent pharyngotonsillitis after penicillin V therapy.[32] β-lactamase-producing pathogens were recovered in 85% of these cases. Thus, copathogenicity may be one reason for penicillin failure.

Increased adherence of GABHS by coaggregation

The coaggregation of GABHS and *M catarrhalis* may contribute to penicillin failure in another way. Both organisms have appreciable carriage rates in the nasopharynx and depend on adherence to epithelial surfaces to express their pathogenicity. When tested on isolated human epithelial cells, the presence of *M catarrhalis* substantially increased the adherence of GABHS, but not of other bacterial species.[33] On microscopic evaluation, the organisms were co-localized on the same epithelial cell surface. The increased adherence of GABHS correlated with the ability of the 2 potential pathogens to coaggregate, an attribute which was not seen with other bacterial species and appeared to be mediated via proteins, known as adhesins, found on the *M catarrhalis*

FIGURE 2

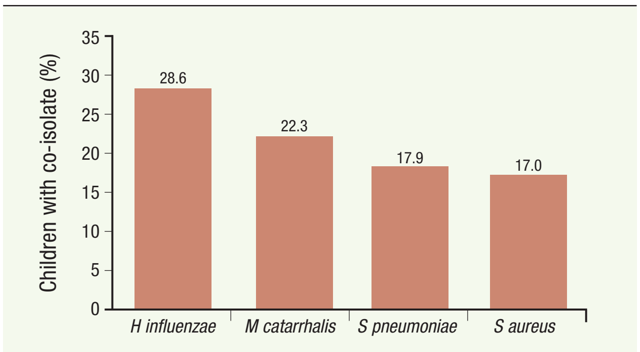
Treatment failure in children with acute GABHS pharyngotonsillitis



Percentage of children with acute GABHS pharyngotonsillitis who had failed treatment with either penicillin V or intramuscular benzathine penicillin G in 2 multicenter, randomized, single-blind studies conducted in 1994 and 1995. Throat cultures were evaluated at visits on days 10-14 and 29-31 after the start of penicillin treatment.[15]

FIGURE 3

Acute GABHS pharyngotonsillitis and other pathogens



N=548

Percentage of children with acute GABHS pharyngotonsillitis who also had other bacterial pathogens isolated on throat culture. All isolates of *M catarrhalis* and *S aureus* and 35% of *H influenzae* were β-lactamase-producing strains.[31]

surface. It has been suggested that coaggregation may contribute to the pathogenicity of GABHS in the pharynx. Moreover, because most *M catarrhalis* strains produce β-lactamases, GABHS found in the coaggregates may be more resistant to penicillin, and consequently, treatment failure with penicillin may be more likely.

Brook and Gober evaluated the recovery of *M catarrhalis* and *H influenzae* in association with GABHS in children with acute pharyngotonsillitis.[31] GABHS was recovered from 112 of 548 (20.4%) children with acute pharyngotonsillitis. Of the 114 isolates of *H influenzae* recovered, 32 were isolated in association with GABHS and 82 were recovered without GABHS (29% vs 19%, respectively; $P<0.05$). Similarly, 25 of the 69 isolates of *M catarrhalis* were recovered in association with GABHS and 44 were isolated without GABHS (22% vs 10%, respectively; $P<0.05$). This study demonstrates an association between the recovery of GABHS and *H influenzae* and *M catarrhalis* from pharyngotonsillar cultures of patients with acute pharyngotonsillitis.

Penicillin failure may be caused by the eradication of normal protective flora.

Eradication of Protective Organisms

Penicillin failure may also be caused by the eradication of normally protective flora, particularly AHS. AHS protect the pharynx from GABHS colonization by producing antibiotic-like substances called bacteriocins that inhibit GABHS growth as well as other growth-inhibitory substances.[34] AHS may also suppress GABHS growth by utilizing the nutrients in the nasopharyngeal environment essential for GABHS colonization. Penicillin is known to potently suppress AHS, which may then impair its protective properties. Patients who have recolonization with AHS after a course of antibiotic therapy have been shown to be less likely to develop recurrent GABHS pharyngitis than those without recolonization.[5,35] In a recent study of 40 children with recurrent tonsillitis, AHS was recovered significantly less often following treatment with penicillin V than with cefdinir (30% vs 75%; $P = 0.01$).[32] Moreover, AHS with GABHS-inhibiting activity were isolated less frequently after treatment with penicillin ($P = 0.014$). The minimal eradication of protective organisms may support the use of cefdinir in clinical practice.

Poor Compliance

Poor compliance with the full 10-day course of oral penicillin therapy is an important cause of penicillin failure in GABHS pharyngotonsillitis. Several factors contribute to poor compliance. First, patients may stop taking the prescribed antibiotic once they start to feel better. In GABHS pharyngotonsillitis, significant clinical improvement may be seen within the first 2 to 3 days of penicillin therapy—before bacterial eradication has occurred.[5] Second, poor compliance in young children may be related to the lack of palatability of an antibiotic suspension. Clearly, the full dosage may not be given when a child rejects an unpalatable suspension. In such situations, it may be particularly tempting for parents to shorten the treatment course once symptoms start to resolve. In young children, therefore, amoxicillin is often used instead of penicillin because the suspension is somewhat more palatable.[3] Third, side effects may prompt patients to discontinue antibiotic therapy. Finally, poor compliance may be related to the inconvenience of the dosing regimen.[4] Medications that must be taken 3 or 4 times each day show lower compliance rates than those that can be taken once or twice per day. Missing doses or, particularly in twice-daily dosing regimens, not receiving the full dosage can be expected to reduce the effectiveness of antibiotic therapy. Penicillin V has a short half-life and administering it only twice daily may lead to a greater rate of failures. Amoxicillin once or twice daily may lead to better compliance while maintaining efficacy, and this approach warrants further study to explore microbiological outcomes.[36,37]

Managing Recurrent GABHS Pharyngotonsillitis

Recurrent GABHS pharyngotonsillitis following penicillin therapy is relatively common, but the incidence of recurrent disease may be lower with other types of antibiotics. As previously described, recurrent GABHS pharyngotonsillitis developed within 30 days of therapy completion in 21.8% of cases treated with penicillin, 16.8% of cases treated with amoxicillin, 14% of cases treated with macrolides, and 8.6% of cases treated with cephalosporins.[16] For patients with recurrent GABHS pharyngotonsillitis, it is important to determine the possible cause of recurrence, which may include an intercurrent viral illness in a persistent GABHS carrier;

noncompliance with the originally prescribed antibiotic regimen; acquisition of a new GABHS infection through a family member, classmate, or community contact; or recurrence of the original infecting strain due to treatment failure.[3] In clinical practice, it may be difficult to distinguish a GABHS carrier with an intercurrent viral infection from a patient with acute GABHS pharyngotonsillitis. Helpful clues may be provided by the clinical signs and symptoms, as well as by certain epidemiologic considerations, such as patient age, season of the year, and local prevalence of respiratory viral illnesses. Random culture or end-of-therapy culture once the patient is asymptomatic may also be helpful, especially when eradication is documented prior to a clinical, culture-positive recurrence.

TABLE 1

Antibacterial activity of cephalosporins

β-lactamase-producing bacteria	Cephalosporins			
	First-generation (cephalothin)	Second-generation (cefuroxime)	Extended-spectrum (cefdinir, cefpodoxime)	Third-generation (cefixime, ceftibuten)
S aureus	Yes	Yes	Yes	No
H influenzae	No	Yes	Yes	Yes
M catarrhalis	No	Yes	Yes	Yes

Antibacterial activity of cephalosporins against aerobic and anaerobic β-lactamase-producing bacteria.

CASE 2

An 8-year-old male presents with a history of recurrent GABHS pharyngotonsillitis. He had been treated with oral penicillin for 10 days and improved initially, but had a recurrence of symptoms 4 days after the end of therapy. His 4-year-old sibling was treated with amoxicillin 2 weeks earlier for an ear infection. Tonsillar culture on the 8-year-old was positive for GABHS. This patient's failure to respond to penicillin is most likely due to the inability of the antibiotic to eradicate the organism. Even though his symptoms initially subsided, the organisms that were not completely eradicated by therapy re-emerged to renew the infection. The most likely explanation for this failure is the presence of β-lactamase-producing organisms in the child's nasopharynx that were acquired from his sibling who was recently treated with a β-lactam antibiotic. These could "shield" GABHS from the penicillin. The child was re-treated for 10 days with an oral extended-spectrum third-generation cephalosporin and had complete bacteriologic and clinical cure. ▪

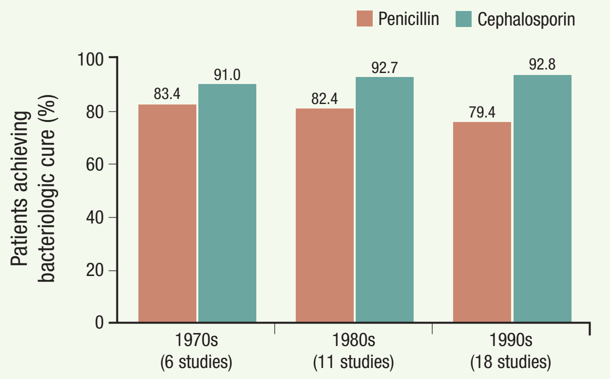
The IDSA considers any of the first-line treatment options to be suitable for single episodes of recurrent GABHS pharyngotonsillitis.[3] If patient compliance with an initial oral penicillin regimen was poor, then consideration may be given to the use of intramuscular benzathine penicillin G. IDSA guidelines recommend second- or third-generation cephalosporins for use in patients who fail first-line therapy with penicillin or amoxicillin. Additionally, it may be useful to substitute a β-lactamase-stable antibiotic, such as a second-generation (eg, cefuroxime axetil) or extended-spectrum third-generation (eg, cefdinir, cefpodoxime) cephalosporin, if copathogenicity is suspected in treatment failure.[32]

An advantage of the cephalosporins is that they are generally resistant to the enzyme β-lactamase. However, their efficacy against BLPB is generation-dependent (**TABLE 1**). First-generation cephalosporins (eg, cephalexin, cefadroxil) are effective only against *S aureus*; second-generation (cefuroxime axetil and cefprozil) and extended-spectrum third-generation (cefdinir and cefpodoxime) cephalosporins are effective against *S aureus*, *H influenzae*, and *M catarrhalis*; and third-generation (eg, cefixime, ceftibuten) cephalosporins are only effective against *H influenzae* and *M catarrhalis*. However, as a group, the cephalosporins are capable of overcoming BLPB (including *M catarrhalis* which allows for microbial coaggregation) when they are present, preserving the interfering organisms, and eradicating GABHS. Managing a patient with recurrent pharyngotonsillitis presents challenges and opportunities for optimal therapy (**CASE 2**).

Patients Allergic to Penicillin

Up to 10% of patients may be allergic to penicillin.[38] Allergic reactions to penicillin may be classified by their timing. Immediate-type reactions occur within the first hour after administration and are mediated by immunoglobulin E (IgE). These reactions may progress to anaphylaxis, with symptoms of wheezing, laryngeal edema, hypotension, and dysphagia. Accelerated allergic reactions that occur within 1 to 72 hours may also be IgE-mediated and may reflect the previous

FIGURE 4
Comparative cure rates of GABHS pharyngotonsillitis



Bacterial cure rates with penicillin and cephalosporins in acute GABHS pharyngotonsillitis. These results are from a meta-analysis of 35 randomized, controlled trials conducted in the 1970s, 1980s, and 1990s, which compared penicillin therapy with cephalosporin therapy.[41]

sensitization of the patient to penicillin. Penicillin-induced anaphylaxis has been reported at a rate of 1 in 5000 to 10,000 courses of therapy.[39] However, the most common reaction to penicillin is an idiopathic maculopapular rash, which emerges during treatment and does not appear related to IgE. Skin testing may be helpful in identifying which patients are likely to have a penicillin allergy. Skin testing is typically conducted with a mixture of penicillin derivatives that encompass both its major and minor determinants. In approximately 80% to 95% of patients who report a history of penicillin allergy, skin test results will be negative.[39,40] This finding indicates that the previous reaction to penicillin was not IgE-mediated or that IgE antibodies are no longer present. When skin test results are positive, they are predictive of allergic reactions in about 60% of cases.[38]

Skin reactions with cephalosporins occur less frequently than with penicillins—in about 1% to 3% of patients. Most reactions are not mediated by IgE.[40] Severe reactions and anaphylaxis are also rare with cephalosporins. Because penicillins and cephalosporins are both β-lactam antibiotics, the issue of cross-reactivity between the 2 antibiotic classes has been raised. However, penicillins and cephalosporins differ sufficiently in structure and develop distinct degradation products, consequently immunologic cross-reactivity is actually low.[38] Some early reports suggested that the rate of cross-allergenicity between penicillins and cephalosporins was 7% to 18%.[40] Subsequent review of more than 15,000 patients treated with cephaloridine, cephalexin, cephalothin, cefazolin, or cefamandole found that skin reactions occurred in 8.1% of patients with a history of penicillin allergy, as compared with 1.9% of patients without such history.[38,40] However, the early first-generation cephalosporins included in this analysis were produced by the *Cephalosporium* mold and actually contained trace amounts of penicillin. Accordingly, the cross-reactivity data in these reports is likely overestimated. It now appears that the cross-reactivity between penicillin and most second- and third-generation cephalosporins is very low and may actually be lower than the cross-reactivity between penicillin and other classes of antibiotics.[38]

Optimizing Antibiotic Efficacy in GABHS Pharyngotonsillitis

The efficacy of penicillin and amoxicillin in GABHS pharyngotonsillitis has waned over the past 3 decades, even though the incidence of acute rheumatic fever has not increased with the continued use of penicillin. In a meta-analysis of 35 randomized, controlled trials comparing penicillins, primarily penicillin V, with cephalosporins, the bacterial cure rate with penicillins declined from 83.4% for trials conducted in the 1970s to 79.4% for those conducted in the 1990s (**FIGURE 4**).[41] Over the same period, the bacterial cure rate remained essentially unchanged with cephalosporins, with rates ranging from 91% in the 1970s to 92.8% in the 1990s. Overall, the likelihood for bacterial cure of GABHS was 3 times higher when a cephalosporin was administered than when penicillin V was given (summary odds ratio of 35 trials analyzed = 3.02; 95% CI: 2.49 to 3.67; $P<0.00001$).[41] The cephalosporins showed a trend for increasing superiority over penicillin over the 3 decades ($P = 0.09$); 8 of the cephalosporins evaluated in the meta-analysis (cephalexin, cefadroxil, cefuroxime, cefpodoxime, cefprozil, cefixime, ceftibuten, and cefdinir) showed higher bacterial cure rates compared with penicillin.[41]

The explanation for the ability of cephalosporins to perform so well is that they are as effective as penicillin in eradicating GABHS. However, penicillin, which is also effective against both aerobic- and anaerobic-interfering organisms, has the potential of ridding the pharyngotonsillar area of these beneficial organisms and depriving the patient of their potential beneficial effects.

Cephalosporins, however, are less effective against both aerobic- and anaerobic-interfering organisms; therefore, these organisms are more likely to be preserved following cephalosporin therapy.[42] The higher their generation, the less effective are the cephalosporins against both aerobic- and anaerobic-interfering organisms. In a paradoxical way, the lesser efficacy of cephalosporins against interfering organisms is their potential advantage. Consequently, the administration of a cephalosporin has a selective effect: preserving both the patient's aerobic- and anaerobic-interfering organisms while eradicating their GABHS (**TABLE 2**). The extended-spectrum third-generation cephalosporins, as well as cefuroxime, possess unique antibacterial features that make their use optimal for eradication of GABHS and β-lactamase producing bacteria while preserving the interfering organisms (**TABLE 1**).

The clinical and bacteriologic efficacy of several extended-spectrum third-generation cephalosporins as compared with penicillin have been evaluated in the treatment of GABHS pharyngotonsillitis. A pooled analysis of 4 multicenter, randomized, controlled trials explored the efficacy of cefdinir compared with penicillin in the treatment of GABHS pharyngotonsillitis.[43] In total, these studies enrolled 2751 patients, of whom 569 patients received cefdinir once daily for 10 days, 568 patients received cefdinir twice daily for 10 days, 518 patients received cefdinir twice daily for 5 days, and the remaining 1096 patients received penicillin 4 times per day for 10 days. Overall, cefdinir produced a significantly higher microbiologic eradication rate than penicillin (92% vs 77%; $P<0.001$), which is consistent with the aforementioned meta-analysis. The eradication rates with the 10-day and 5-day regimens of cefdinir were 93% and 89%, respectively. Both therapies were well tolerated, with diarrhea, nausea, and headache reported as the most common adverse events (AEs) in both treatment groups.[43] Similarly, in another investigator-blinded study of pediatric patients aged 1 to 12 years, cefdinir administered at a dose of 7 mg/kg twice daily for 5 days produced higher eradication rates measured 4 to 10 days after completion of treatment than penicillin V 10 mg/kg 4 times daily for 10 days (89.7% vs 71.8%; $P<0.001$).[44] In this study, the incidence of AEs was similar between treatment groups (12.5% in the cefdinir group vs 13.6% in the penicillin V group; $P = 0.69$). Most AEs were considered mild to moderate, and diarrhea was the most common AE reported by patients receiving cefdinir, while vomiting ranked highest among the penicillin group.[44]

TABLE 2

Comparative antibacterial activity

Antimicrobial activity	Penicillins	Cephalosporins
Aerobic β-lactamase-producing bacteria	No	Yes
Interfering organisms	Yes	No
GABHS	Yes	Yes

Antibacterial activity of penicillin compared with cephalosporins in the management of acute GABHS pharyngotonsillitis.

High rates of GABHS eradication have also been seen with other cephalosporins.[45] Cefpodoxime administered twice daily for 5 days or cefpodoxime once a day for 10 days produced higher GABHS eradication rates than penicillin V given 3 times per day for 10 days in a multicenter, randomized, investigator-blinded study of 377 children aged 2 to 17 years.[46] At the end of therapy, the eradication rates for the 5- and 10-day regimens of cefpodoxime were 90% and 95%, respectively, compared with 78% for penicillin ($P = 0.02$ and $P = 0.003$, respectively). When assessed 32 to 38 days after treatment, bacteriologic failure was seen in 17% of children treated with cefpodoxime for 10 days and 19% of children treated with cefpodoxime for 5 days, compared with 35% of the penicillin V-treated children ($P \leq 0.005$). Treatment-related AEs were infrequent and similar in all 3 treatment groups, with gastrointestinal side effects being the most commonly reported.[46]

Similar trends have also been observed for macrolides. Erythromycin is recommended as an alternative for patients allergic to penicillin, and its benefits include a relatively narrow activity spectrum, low cost, and low risk of serious AEs.[4] Azithromycin represents another viable alternative for second-line treatment of pharyngotonsillitis. In a multicenter, randomized study that involved 484 children aged 2 to 12 years, GABHS eradication rates observed at the end of therapy were highest in children receiving azithromycin administered at 20 mg/kg once daily for 3 days (94.2%), compared with children given penicillin V for 10 days (84.2%) or a lower (10 mg/kg/d) dosage of azithromycin for 3 days (57.8%).[47] Significantly fewer treatment-related AEs were reported in the penicillin V group (3%) compared with azithromycin 10 mg (18.3%) and 20 mg (23%) groups.[47] Most AEs were mild-to-moderate

TABLE 3

Indications for the use of a cephalosporin to treat GABHS pharyngotonsillitis

Presence of β-lactamase-producing bacteria
Absence of "interfering flora" (recent antibiotic treatment)
Recurrent GABHS pharyngotonsillitis
Past failures to eradicate GABHS
High failures of penicillins in the community
Comorbidities
When failure is a medical, economic, or social hardship
Penicillin allergy (non-type 1)

gastrointestinal events.[41] Comparable results have been reported in studies with clarithromycin, which is approved for treating pharyngitis due to *Streptococcus pyogenes*.[48]

Even though the macrolides are an alternative therapeutic choice, the increased use of macrolides for the treatment of respiratory tract and various other infections has been associated with increased GABHS resistance to these agents. Resistance of GABHS to macrolides reached up to 60% in Finland, Italy, Japan, and Turkey.[49] Of particular concern is the recent significant increase of such resistance in the United States that reached 48% in specific populations.[50,51] It is therefore advisable to avoid the routine use of macrolides for GABHS pharyngotonsillitis and save these agents for patients who manifest a type I penicillin allergy.

Optimizing Compliance With Treatment Regimen

Treatment compliance may be improved by using short-course antibiotic therapy instead of the conventional 10-day regimen and by providing more palatable antibiotic preparations for pediatric patients. Currently, 3 antibiotics are approved for use in short-course therapy of GABHS pharyngotonsillitis in children: cefdinir 7 mg/kg twice daily, cefpodoxime 5 mg/kg twice daily, and azithromycin 12 mg/kg once daily, each for 5 days. These agents, when administered in short-course therapy, provide superior GABHS eradication rates compared with penicillin V given 3 or 4 times per day for 10 days.[44,46,47]

The palatability of antibiotic suspensions has been evaluated by both children and health care providers in many studies. In one study, 86 physicians and health care personnel randomly sampled 12 antibiotic suspensions, including the 3 antibiotics available for short-course treatment of GABHS pharyngotonsillitis.[52] Their ranking of these 3 antibiotics in order of overall palatability from highest to lowest was as follows: cefdinir, azithromycin, cefpodoxime. A preference for cefdinir was also seen in a pooled analysis of 7 randomized, single-blind, crossover studies, which compared the taste and smell acceptability of the cefdinir oral suspension with oral suspensions of amoxicillin, amoxicillin/clavulanate potassium, azithromycin, and cefprozil.[53] In these studies, 965 children aged 4 to 8 years used a visual smile-face scale to compare the taste and smell of 2 different antibiotic suspensions. Ratings were then converted to numeric scores ranging from 5 (really good) to 1 (really bad). Overall, the taste of the cefdinir suspension was rated as "really good" or "good" significantly more often than the other antibiotic suspensions (82.7% vs 73.8%, respectively; $P<0.001$). Cefpodoxime was not included in the pooled analysis, but it has generally scored low in taste tests, particularly because of its poor aftertaste.[54,55]

Summary

Once GABHS pharyngotonsillitis has been appropriately diagnosed, prevention of rheumatic fever is the goal of antibiotic treatment. Bacterial eradication is also seen as an important goal. While penicillin remains the first-line therapy for GABHS pharyngotonsillitis, treatment failure with penicillin has become more common, with 30-day recurrence rates now approaching 35%. Among the important factors contributing to the increasing rate of penicillin failure are polymicrobial interactions of the pharyngotonsillar flora, such as copathogenicity with β-lactamase-producing pathogens, coaggregation with *M catarrhalis*, and suppression of the protective actions of AHS against GABHS infection.

The choice of antimicrobial for the treatment of GABHS pharyngotonsillitis should be individualized. Cephalosporins should be considered in patients if the risk of penicillin failure is high, or if there are compelling medical, economic, or social reasons to utilize more effective agents as first-line therapy (**TABLE 3**). Cephalosporins have been shown to offer higher GABHS eradication rates than penicillins in numerous clinical studies of children, as well as of adolescents and

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adults. Cephalosporins inhibit microbial pathogenicity and coaggregation, and are superior to penicillin in preserving protective pharyngotonsillar flora. Because of these properties, the use of cephalosporins may help reduce treatment failures and GABHS recurrence. Factors that impact treatment compliance, such as dosing frequency and palatability, also need to be considered in order to achieve optimal success with antibiotic therapy. The availability of highly palatable antibiotics that can be administered in short-course therapy promises to improve the treatment of GABHS pharyngotonsillitis. ■

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Management of Group A β-Hemolytic Streptococcal Pharyngotonsillitis in Children

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POSTTEST

1. How often does acute pharyngotonsillitis have a bacterial etiology?
   a. 75% of the time
   b. 50% of the time
   c. 30% of the time
   d. 15% of the time

2. Which of the following signs or symptoms may be suggestive that acute pharyngotonsillitis does not involve GABHS?
   a. Tonsillopharyngeal erythema
   b. Acute throat pain
   c. Dysphagia
   d. Absence of fever

3. Which of the following methods is more sensitive for detecting GABHS in throat swabs?
   a. Throat culture
   b. RADT
   c. Both tests have equal sensitivity

4. What is the primary goal of antibiotic therapy in acute GABHS pharyngotonsillitis?
   a. Resolution of clinical signs and symptoms
   b. Bacteriologic eradication of GABHS
   c. Prevention of complications
   d. Reduction of duration of illness

5. Which of the following antibiotics is currently recommended for first-line therapy of acute GABHS pharyngotonsillitis in IDSA Practice Guidelines?
   a. Penicillin (either penicillin V or intramuscular benzathine penicillin G)
   b. Third-generation cephalosporins, such as cefdinir or cefpodoxime
   c. Macrolides, preferably erythromycin
   d. All of the above are considered acceptable options

6. In the retrospective chart review of children with acute GABHS pharyngotonsillitis, which of the following antibiotics was associated with the lowest 30-day recurrence rate?
   a. Penicillin
   b. Amoxicillin
   c. Cephalosporins
   d. Macrolides

7. How is copathogenicity believed to promote penicillin failure in GABHS pharyngotonsillitis?
   a. Other bacterial pathogens enhance the ability of GABHS to adhere to and then infect epithelial cells in the pharynx.
   b. Other bacterial pathogens act in concert with GABHS to augment symptoms.
   c. Other bacterial pathogens cause pharyngotonsillitis after penicillin has eradicated GABHS.
   d. Other bacterial pathogens produce enzymes that inactivate penicillin.

8. Why was cross-reactivity between penicillins and cephalosporins initially overestimated?
   a. Early first-generation cephalosporins were produced by the *Cephalosporium* mold and contained trace amounts of penicillin.
   b. Early studies were mostly conducted in patients with a history of penicillin allergy rather than in those with current evidence of penicillin allergy.
   c. Early studies considered the structural similarities between penicillins and cephalosporins and hence identified overlapping immunogenic determinants.
   d. Early studies did not distinguish between true allergic reactions and non–IgE-mediated skin reactions.

9. What is the significance of the meta-analysis of clinical studies comparing penicillins and cephalosporins?
   a. Penicillins and cephalosporins are both effective in treating acute GABHS pharyngotonsillitis.
   b. Patients treated with cephalosporins were about 3 times more likely than those given penicillins to have clinical resolution of symptoms by the end of treatment.
   c. Patients treated with cephalosporins were about 3 times more likely than those given penicillins to achieve eradication of GABHS.
   d. The efficacy of cephalosporins has improved significantly over the last 3 decades, whereas the efficacy of penicillins has declined.

10. Of the following antibiotics, which produce(s) higher eradication rates with short-course therapy (5 days) compared with a conventional 10-day course of penicillin V?
    a. Cefdinir
    b. Cefpodoxime
    c. Azithromycin
    d. All of the above

CME ACTIVITY EVALUATION/CERTIFICATE FULFILLMENT

Management of Group A β-Hemolytic Streptococcal Pharyngotonsillitis in Children

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Release Date: December 2006 **Expiration Date:** December 31, 2007

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RATING SCALE: (Circle one)
1 = Strongly Disagree 2 = Disagree 3 = Agree 4 = Strongly Agree

1. Were the following educational objectives met?

A. Apply appropriate antibiotic therapy for the treatment of acute pharyngotonsillitis, according to current recommendations of the Infectious Diseases Society of America (IDSA) and the American Academy of Pediatrics (AAP)	1	2	3	4
B. In order to improve outcomes for your patients, evaluate the incidence of treatment failure with penicillin V in acute GABHS pharyngotonsillitis and choose appropriate treatment options	1	2	3	4
C. Given the high incidence of recurrence after penicillin treatment, determine potential reasons for treatment failure in order to reduce recurrences and improve outcomes	1	2	3	4
D. Evaluate cross-reactivity between penicillins and cephalosporins in patients with a history of penicillin allergy, in order to determine appropriate medication management	1	2	3	4
E. Compare the efficacy of penicillins and cephalosporins in GABHS pharyngotonsillitis according to current recommendations of the IDSA	1	2	3	4
F. Evaluate options for improving compliance of antibiotic therapy in GABHS pharyngotonsillitis, particularly in your pediatric population	1	2	3	4

2. How would you rate this activity based on the statements below?

A. The activity content was useful and relevant to my practice.	1	2	3	4
B. The activity provided information I will apply to my practice.	1	2	3	4

3. CME activities must be "free of commercial bias for or against any product." In this regard, how would you rate this activity?

❒ Unsatisfactory ❒ Satisfactory ❒ Excellent ❒ Superior

If unsatisfactory, please explain:

4. As a result of what you've learned in this activity, will you change your practice behaviors?
Please explain:

5. Do you have any suggestions for improving the activity?

6. Overall, how would you rate the "Management of Group A β-Hemolytic Streptococcal Pharyngotonsillitis in Children" CME supplement?

❒ Excellent ❒ Good ❒ Adequate ❒ Inadequate

Additional Comments:__________

I certify that the actual time spent to complete this continuing medical education activity was _______ hour. (Maximum of 1.0 hour)

Signature: ____________________ Date: __________