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Supplement to

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Considerations in the Use of Antibiotics for Streptococcal Pharyngitis

Key Points and Recommendations

- The diagnosis of group A beta-hemolytic streptococci (GABHS) requires a microbiologic test for all age-groups. (SOR: A)
- The primary goal of therapy is eradication of GABHS from the pharynx. (SOR: A)
- Treatment failure of GABHS is defined as the persistence of GABHS on throat culture (bacteriologic failure) and/or a persistent positive throat culture with recurrent clinical signs or symptoms of pharyngitis (clinical failure). (SOR: C)
- GABHS has not developed resistance to penicillin or shown any significant increase in penicillin minimal inhibitory concentrations over at least 5 decades. (SOR: A)
- Although penicillin resistance in GABHS has not been demonstrated, there have been frequent reports of increased bacteriologic and clinical failure rates associated with traditional penicillin therapy for streptococcal pharyngitis. (SOR: B)
- Pooled data from multicenter studies and a meta-analysis of 35 qualified studies revealed superior bacteriologic and clinical cure rates of streptococcal pharyngitis with a cephalosporin compared with penicillin. (SOR: A)

While penicillin has been the traditional treatment for pharyngitis caused by group A beta-hemolytic streptococci (GABHS), a wide variety of antibiotics, dosages, routes, and lengths of therapy have been investigated. Though many of these trials have been small, a recently published pooled analysis and another meta-analysis of clinical trials suggest that a reexamination of the role of penicillin may be warranted.

Background

Pharyngotonsillitis is the primary diagnosis for more than 10 million office visits to primary care physicians in the United States annually.^{1,2} Acute pharyngitis represents approximately 1% of all office visits³ and 6% of all visits to pediatricians and family practitioners.^{2,4} There is a resurgence of severe group A streptococcal infection (the main cause of bacterial pharyngitis) and its sequelae.⁵ One Swedish study estimated that lost productivity accounts for 75% of the total cost of a tonsillitis episode.⁶

Stephen Brunton, MD

Cabarrus Family Medicine Residency
Concord, NC

Michael Pichichero, MD

Professor of Microbiology and Immunology
Rochester School of Medicine and Dentistry
Rochester, NY



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TABLE 1

Complications of group A beta-hemolytic streptococcal pharyngitis

Suppurative complications	Nonsuppurative complications
Bacteremia	Glomerulonephritis
Cervical lymphadenitis	Acute rheumatic fever
Endocarditis	Reactive arthritis
Mastoiditis	Sydenham's chorea
Meningitis	Other autoimmune movement disorders
Otitis media	Autoimmune dystonia secondary to striatal necrosis
Peritonsillar abscess	Pediatric autoimmune neuropsychiatric disorders
Pneumonia	
Retropharyngeal abscess	
Sinusitis	

Etiology

In adults, 30% to 65% of pharyngitis cases are idiopathic, 30% to 60% have a viral cause, and 5% to 10% are caused by bacteria.⁷ The most common bacterial pathogen is Lancefield group A beta-hemolytic *Streptococcus pyogenes*, which accounts for 15% to 36% of pediatric cases and 5% to 10% of adult pharyngitis.^{2,8,9} Thus, streptococcal pharyngitis is primarily a disease of children. The other beta-hemolytic streptococci—groups C and G—are possibly innocent bystanders during viral infection and do not increase the risk of postinfectious complications like GABHS.¹⁰

Diagnosis With Microbiologic Tests

Group A beta-hemolytic streptococcal pharyngitis is naturally self-limited; most signs and symptoms resolve spontaneously within 3 to 4 days with or without antibiotic therapy.⁸ Nevertheless, proper diagnosis by use of a rapid test or throat culture is important, primarily because it helps to reduce unnecessary antibiotic use by identifying those for whom antibiotic therapy would be justified.^{9,11} With the exception of group A streptococcal pharyngitis and relatively rare bacterial pharyngitides (*Corynebacterium diphtheriae* and *Neisseria gonorrhoeae*), there are no compelling data to justify antibiotic therapy in patients with evidence of other bacterial pharyngitis, including other beta-hemolytic species, such as groups C and G streptococci.^{8,9} Only patients with GABHS pharyngitis are at risk of serious suppurative and nonsuppurative poststreptococcal sequelae (TABLE 1).^{7,12-15}

Testing for GABHS can be associated with more discretionary prescribing, potentially reducing unnecessary antibiotic therapy and the possible associated adverse

effects.² A recent large analysis of US physicians showed that GABHS testing was performed for 53% of children who had sore throat. There was no association between GABHS testing and antibiotic prescribing, except for children with a diagnosis code for pharyngitis, tonsillitis, or streptococcal sore throat. For these children, there was a significant reduction in antibiotic prescribing between those who had had a GABHS test (57%) and those who did not (73%).² The decision to perform a microbiologic test for streptococcal pharyngitis is based on clinical and epidemiologic factors, as well as consideration of GABHS prevalence in the community and history of contact with a person with well-documented GABHS pharyngitis.

Diagnostic tools

While the history of fever, presence of tonsillar exudates, swollen and tender lymph nodes, and lack of cough are positive predictors of GABHS infection,⁷ clinical diagnosis without throat cultures is unreliable even for seasoned clinicians using sophisticated scoring systems.¹⁰

Throat cultures are the gold standard for the diagnosis of streptococcal pharyngitis. When performed properly, the sensitivity and specificity of throat cultures for GABHS average 90% and 99%, respectively.⁷ The American Academy of Pediatrics, the US Centers for Disease Control and Prevention, and the Infectious Diseases Society of America recommend a GABHS test prior to treating children with suspected streptococcal pharyngitis.² A throat culture also is recommended for adult patients to confirm the clinical diagnosis.¹⁶ When this is inappropriate or impractical, such as with patients who have extensive contact with others, work full-time jobs, or may be difficult to reach, the rapid antigen detection test (RADT) is recommended initially.

The RADT has a sensitivity of 80% to 95% and a specificity of 70% to 95% (compared with blood agar plate culture), with results available in 5 to 10 minutes.^{7,9,17} The cost of the RADT is offset by the financial savings it ultimately provides by helping to select true positives, thus avoiding unnecessary use of antibiotics.¹⁷ Once the high sensitivity of RADTs has been confirmed in a given practice, a positive RADT can be relied upon to start antibiotic therapy in the initial office visit, thereby accelerating clinical and bacteriologic recovery. For adults, a positive RADT should be followed by a throat culture.¹⁶ Throat cultures are recommended in cases of negative RADTs for pediatric patients with suspected GABHS pharyngitis.

Beginning antibiotic therapy

Antibiotic therapy can be prescribed for children after a negative RADT if there are clinical and epidemiologic

reasons to highly suspect GABHS pharyngitis. As in adults, such antibiotic therapy should be discontinued if throat cultures are subsequently negative. A negative RADT may be used to exclude the diagnosis in adults since the prevalence of streptococcal pharyngitis and risk of rheumatic fever or carditis are low in this age-group.⁹

Results of either RADTs or throat cultures must be compared with the patient's clinical presentation, since neither can distinguish between acute GABHS pharyngitis and acute viral infection with coexisting GABHS carrier state.

Selective follow-up testing

A follow-up RADT or a throat culture performed after antibiotic therapy in asymptomatic patients is not routinely recommended; positive results in asymptomatic patients indicate presumed group A streptococcal carriers. Follow-up testing is recommended for symptomatic patients; patients with a history of acute rheumatic fever (ARF) or poststreptococcal glomerulonephritis; patients at risk for a recurrence of GABHS; patients with previous treatment failure or recurrence of GABHS; children in daycare; school-aged children; immunocompromised patients; and patients experiencing a "ping-pong" spread of GABHS within a group, such as a large family.⁹

Goals of Therapy

Antibiotic therapy is indicated for symptomatic patients with a positive microbiologic test result for GABHS.⁸ The primary goal of therapy is eradication of GABHS from the pharynx to provide primary prevention against suppurative and nonsuppurative complications of GABHS pharyngitis. Other goals include abating clinical signs and symptoms, reducing bacterial transmission to close contacts, and minimizing adverse effects of therapy.⁷ Early initiation of antimicrobial therapy for GABHS pharyngitis helps shorten the clinical course. Early and prompt eradication of GABHS also minimizes the overall impact and cost of disease.⁸

Eradicating pathogenic GABHS may minimize or eliminate the risk of ARF; a persistent bacterial burden may intensify an adverse autoimmune response. Although there is little evidence that group A streptococci directly affect the tissues of patients with ARF, there is epidemiologic and immunologic evidence of an indirect effect.⁵ Historically, ARF or reactive arthritis follows outbreaks of GABHS; adequate antibiotic treatment of GABHS pharyngitis reduces the risk of ARF; and antibiotic prophylaxis prevents ARF recurrence.¹² Poor eradication of GABHS can lead to disease failure or recurrence, as well as infection of close contacts, additional costs, diminished quality of life, and reduced productivity.¹

Possible Explanations for Treatment Failure

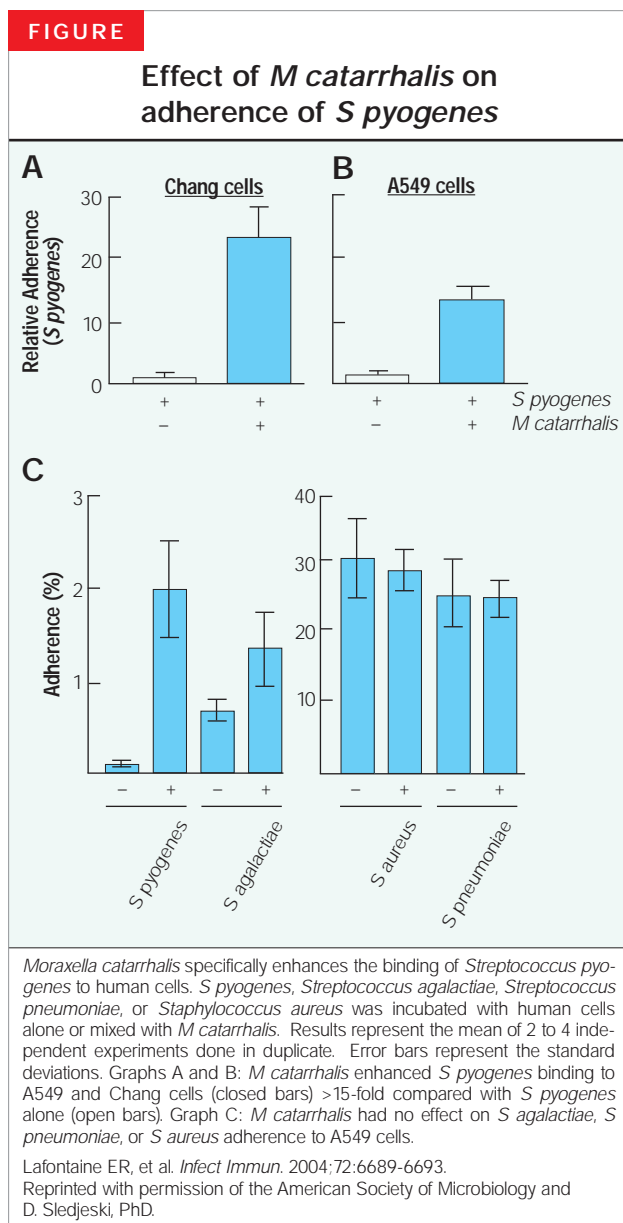
Treatment failure can be defined as the persistence of GABHS on throat culture (bacteriologic failure) and/or a persistent positive throat culture with recurrent clinical signs or symptoms of pharyngitis (clinical failure).¹⁸ Bacteriologic failure has generally been observed in 10% to 30% of patients treated with penicillin; patients in about half of these cases are carriers, and the remainder are true treatment failures.^{7,10,19-22} Clinical treatment failures can appear to be nonresponders (no clinical improvement within 72 hours after initiation of treatment) or to have recurrent GABHS infection (relapse of symptoms associated with positive throat culture 5 to 20 days after completion of therapy). Some possible causes for treatment failure include bacterial coaggregation or copathogenicity; GABHS reinfection; antibiotic nonadherence or subtherapeutic drug levels; penicillin tolerance; or blunting of an effective immune response.

Bacterial copathogenicity

Normal colonization of the pharynx by beta-lactamase-producing bacteria (BLPB), such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, or anaerobes is seen in some patients.²² The BLPB are resistant to penicillin and amoxicillin. Moreover, such bacteria can inactivate penicillin and its congeners—including amoxicillin—in vivo. Consequently, the use of these drugs fosters an environment for preexisting BLPB to dominate; there is a clear association between penicillin treatment failure or recurrent infection and the preexistence of BLPB copathogens in patients with recurrent GABHS pharyngotonsillitis.²²⁻²⁴ Some drugs that resist beta-lactamase degradation, such as amoxicillin-clavulanate and some cephalosporins, are more effective at eradicating GABHS than is penicillin.^{20,25}

Protective effect of coaggregation

Carriage rates for *S pyogenes* and *M catarrhalis* among asymptomatic persons can be relatively high; each is capable of upper respiratory tract infection. Lafontaine et al have shown that *M catarrhalis* unilaterally and significantly increases *S pyogenes* adherence to epithelial cells in vitro (FIGURE).²⁶ The effect was observed not with *S aureus* or *Streptococcus pneumoniae* but only with group B streptococci, indicating a unique effect that is not shared by other gram-positive human pathogens. These data suggest that preexisting colonization by *M catarrhalis* could increase colonization by *S pyogenes* and, therefore, promote disease. Because more than 90% of *M catarrhalis* are also resistant to beta-lactamase degradation, it is also possible that coaggregation protects *S pyogenes* against beta-lactam antibiotics,



similar to the resistance *M catarrhalis* confers upon *S pneumoniae* against beta-lactam antibiotics in continuous-biofilm studies.²⁶

Another possible explanation for treatment failure includes the antibiotic eradication of normal pharyngeal flora, such as alpha-hemolytic streptococci (AHS), which normally inhabit the tonsillopharynx but are not pathogenic there. These microbes serve as natural host defenses by preventing the establishment of GABHS colonization.^{10,21} Penicillin and amoxicillin eradicate AHS much more effectively than do macrolides or cephalosporins.

Nonadherence to treatment

Complexity of drug administration is indirectly related to adherence, such that the percentage of patients failing to take 25% to 50% of a prescription rises from 7% with once-daily regimens, to 30% with twice-daily regimens, 60% for 3-times-daily regimens, and 70% for 4-times-daily regimens.²⁵ Adherence also may be affected by palatability, especially in children. One recent investigation involving 86 adult evaluators compared 11 antibiotics to amoxicillin with respect to appearance, smell, texture, taste, and aftertaste.²⁷ Significant differences were observed (TABLE 2). The 3 most palatable antibiotic suspensions were loracarbef, cefdinir, and cefixime, which were comparable to amoxicillin.

Subtherapeutic drug levels

Subtherapeutic drug levels in the nasopharynx, usually secondary to inadequate dosage, can result in treatment failure. Also, tissue levels of penicillin are quite reduced in the absence of inflammation. This may be important since most patients now typically seek medical care early in the course of infection, while inflammation may be minimal.

GABHS carrier state

The GABHS carrier state is not a cause for treatment failure; rather, it may represent a false-positive treatment failure in practice and in some studies. It is unlikely that penicillin will eradicate GABHS in persons with a GABHS carrier state; this requires the addition of rifampin or the use of clindamycin alone. In general, the GABHS carrier state may be defined as those patients with GABHS-positive throat culture results that show neither signs nor symptoms of pharyngitis nor a demonstrable rise in streptococcal antibodies. However, increases in antibody titers are attenuated after early antibiotic therapy.²⁵ Microbiologic tests cannot distinguish between carriers with acute viral pharyngitis and persons who are true positives. This makes measurement of treatment failure/success more complex.

TABLE 2

Overall taste* of antibiotic suspensions

1. Loracarbef	7. Clarithromycin
2. Cefdinir	8. Trimethoprim
3. Cefixime	9. Amoxicillin-clavulanate
4. Azithromycin	10. Cefpodoxime
5. Ciprofloxacin	11. Cefuroxime
6. Trimethoprim-sulfamethoxazole	

*Most to least palatable
Steele RW, et al. *Pediatr Infect Dis J*. 2001;20:1-5.

Antibiotic Therapy for Streptococcal Pharyngitis

Once a decision has been made to treat based on microbiologic test results, an antibiotic should be chosen in a dose and for a duration that is likely to eradicate the infecting microorganism from the pharynx, commensurate with the primary goal of therapy.⁹ Thus, it is important to know the underlying prevalence of resistance to relevant antibiotics. Physicians should consider the age or body size of the patient; drug safety; antibiotic spectrum; the patient's history of drug allergies; and cost of drug therapy (TABLE 3),²⁸ as well as total cost of therapy, and probability of adherence (including palatability).^{7-9,27} If there is a high suspicion of streptococcal pharyngitis at the initial visit, it is reasonable to start antibiotic therapy pending throat culture results. Antibiotic therapy should be discontinued if the diagnosis cannot be confirmed.^{8,9}

Options for antibiotic therapy include penicillin and its congeners, such as ampicillin, amoxicillin, and semi-synthetic penicillins, as well as numerous cephalosporins and macrolides and clindamycin.

Penicillins

Barring type I hypersensitivity reactions to penicillin or amoxicillin, or predictable nonadherence with 3-times-daily dosing, penicillin V for 10 days is recommended for GABHS pharyngitis in all authoritative treatment guidelines.^{8,10,11,19,29} Advantages of penicillin include a narrow spectrum of activity and low cost. Prevention of ARF has also been demonstrated, but only with parenteral penicillin. Although GABHS has not developed resistance to penicillin or shown any significant increase in penicillin minimal inhibitory concentrations over at least 5 decades,^{8,30,31} bacterial failure rates ranging from 10% to 30% and clinical failure rates of 5% to 15% have been reported.^{7,32} Benzathine penicillin G is an effective alternative when adherence with even 2- or 3-times-daily dosing with orally administered penicillin is questionable. Once-daily, orally administered penicillin, however, is ineffective.⁹

In pediatric practices especially, amoxicillin is prescribed more frequently than penicillin because of the poor taste of the penicillin suspension, and partly because of familiarity with the use of amoxicillin for the treatment of upper respiratory infections. Gopichand et al tested the efficacy of amoxicillin 3-times daily versus conventional penicillin V therapy for the treatment of documented GABHS infection and showed that amoxicillin achieved significantly greater bacteriologic and clinical treatment rates as well as a reduced carrier state.³² The number of doses missed appeared similar between the groups. Similar results favorable to amoxicillin compared with penicillin have been observed by Curtin-Wirt et al,

TABLE 3

Antibiotic therapy

Drug	Regimen	Cost range per regimen* [†]
Children		
Penicillin V	25-50 mg/kg/d x 10 d	+
Cefdinir	14 mg/kg/d x 10 d	++
Cefpodoxime	10 mg/kg/d x 10 d	+++
Cefprozil	15 mg/kg/d x 10 d	++
Cefuroxime axetil	10 mg/kg/d x 10 d	++
Erythromycin estolate	20 mg/kg/d x 10 d	+
Azithromycin	12 mg/kg/d x 5 d	++
Clarithromycin	15 mg/kg/d x 10 d	+
Clindamycin	20-30 mg/kg/d x 10 d	++
Adults		
Penicillin V	500 mg bid x 10 d	+
Cefdinir	600 mg qd x 10 d	+++
Cefditoren	200 mg bid x 10 d	-
Cefpodoxime	100 mg bid x 4 d	++
Cefprozil	500 mg qd x 10 d	+++
Cefuroxime axetil	250 mg bid x 4 d	++
Erythromycin base	500 mg qid x 10 d	+
Azithromycin	500 mg qd x 3 d	++
Clarithromycin	250 mg bid x 10 d	+++

*15 kg child

[†]Source: DrugStore.com as of 4/14/2006

+ = \$1-39; ++ = \$40-79; +++ = ≥ \$80

Gilbert DN, et al, eds. *The Sanford Guide to Antimicrobial Therapy 2006*. Sperryville, Va: Antimicrobial Therapy, Inc; 2006.

especially in children 12 years of age or less, regardless of dosage.³³ Reasons for the difference in efficacy between penicillin and amoxicillin were not obvious to the investigators, causing both to speculate that the doses of penicillin used, although consistent with guidelines at the time of the studies, were too low.

Cephalosporins

Due to increased acquisition cost and a broader spectrum of activity, cephalosporins have been traditionally reserved for patients with relapse or recurrence of streptococcal pharyngitis.^{7,10} They also have been traditionally accepted as alternatives for patients allergic to penicillin, sometimes with the caveat that patients with type I hypersensitivity to penicillin should never be given a cephalosporin because of potential cross-reactivity.²⁹ However, recent data reveal that cross-allergy to penicillin

does not occur for selected second- and third-generation cephalosporins.³⁴

Significantly lower treatment failure rates have been observed with the use of cephalosporins compared with penicillin. A meta-analysis of 19 studies involving 1169 patients treated with penicillin and 1290 treated with a cephalosporin revealed a significant difference in the overall bacteriologic failure rates (16% and 8%, respectively; $P < .001$).³⁵ A meta-analysis of only 12 of these studies revealed clinical failure rates of 11% and 5%, respectively ($P < .001$).¹⁰ Inclusion criteria for the studies included symptomatic patients with acute pharyngitis, comparison of cephalosporins to penicillin in the same population, pretreatment GABHS-positive throat cultures, 10 days' duration of therapy, strict adherence monitoring, and posttreatment throat cultures to document bacteriologic success.

Using the Cochrane Collaborative methodology, a more robust meta-analysis of 35 studies from 1966 through 2000, encompassing 7125 children, with stratification of study quality, was published in 2004.¹⁹ The calculated odds ratios (OR) for bacterial (OR = 3.02) and clinical (OR = 2.34) cure rates were significantly in favor of cephalosporins versus penicillin ($P < .001$). The trends favoring cephalosporin therapy were consistent over each of 3 decades analyzed and achieved statistical significance when trials were grouped by detailed adherence monitoring, presence of serotyping or genotyping, trials that eliminated carriers from analysis, or trials with a test of cure 3 to 14 days posttherapy (TABLE 4). Cefadroxil, cefdinir, cefixime, cefpodoxime, cefprozil, ceftibuten, cefuroxime, and cephalexin, individually, as well as the first-, second-, and third-generation cephalosporins as groups, were statistically superior with respect to bacterial and clinical eradication of GABHS compared with penicillin (TABLE 5). The conclusions withstood secondary analysis for statistical heterogeneity, publication bias, and exclusion of GABHS carriers.

This meta-analysis has been criticized for including some low-quality studies, using ORs inappropriately, contaminating data by including streptococcal carriers, and injudiciously recommending more expensive and broader-spectrum therapy. The meta-analysis and criticism of it illustrate the controversy over recommending cephalosporins despite increased reports of penicillin/amoxicillin treatment failure.

A shortened course of antibiotic therapy may enhance medication adherence. Pooled data from randomized, controlled, investigator-blinded, multicenter clinical trials in which either children or adults received cefdinir once or twice daily for 5 or 10 days or penicillin 4 times daily for 10 days revealed significantly higher bacteriologic (92% vs 77%) and clinical (94% vs 83%) cure rates for cefdinir compared with penicillin.¹

Cefdinir, along with azithromycin and cefpodoxime, is approved by the US Food and Drug Administration (FDA) for 5-day treatment of GABHS pharyngotonsillitis and eradication of GABHS. Nearly all cephalosporins can be administered less frequently than penicillin or amoxicillin, with data suggesting that shorter courses of therapy may increase adherence.²⁰ However, a 5-day treatment course of penicillin or amoxicillin is inadequate.

Most cephalosporins are not degraded by BLPB. Cephalosporins are less active than penicillin or amoxicillin against AHS and anaerobes, which can keep overgrowth of BLPB in check. Paradoxically, the relative inactivity of cephalosporins against AHS is a benefit.^{22,23}

Macrolides

Ten days of erythromycin is recommended as a first alternative for patients with streptococcal pharyngitis and penicillin allergy since it has a low probability of serious side effects, a relatively narrow spectrum of activity, and relatively low cost.¹⁰ Worldwide, there are areas of GABHS resistance to erythromycin associated with treatment failure, but resistance in the United States has generally remained less than 5%.^{8,29,31,36} Yet, considerable geographic variability exists. During 1994 and 1995, York et al found *S pyogenes* resistance rates up to an unusually high 39% in San Francisco, with significantly higher rates isolated from patients with invasive disease (32%) compared with pharyngitis (9%).³⁷ All erythromycin-resistant strains were susceptible to penicillin. In an outbreak of group A streptococcus observed in Pittsburgh beginning in January 2001, 48% of isolates were erythromycin-resistant.³⁸

Once-daily azithromycin for 5 days has been shown to be as effective as 10 days of penicillin for the treatment of GABHS pharyngitis. The use of azithromycin is associated with fewer gastrointestinal side effects compared with erythromycin use. Azithromycin is approved by the FDA as a second-line alternative for patients 16 years of age or older,^{7,8,29} while clarithromycin is approved for pharyngitis due to *S pyogenes* in children and adults.³⁹ A 5-day course of clarithromycin extended-release, 500 mg once daily, yielded bacteriologic eradication rates comparable to those of oral penicillin, 500 mg 3 times daily, for 10 days (89% vs 90%, respectively).⁴⁰ Concerns regarding the role of azithromycin also exist. At least one expert is dubious of the study methods in many of the short course studies and raises questions about the validity of their conclusions.⁸ Azithromycin is more expensive and has a broader antibiotic spectrum of activity than penicillin. Finally, because of the geographic variability observed in erythromycin resistance, it is advisable to be aware of local resistance rates before choosing a macrolide.¹⁶

TABLE 4

Cure rates of cephalosporins vs penicillin in GABHS tonsillopharyngitis

	Cephalosporin n/N	Penicillin n/N	OR		Weight %	OR (95% CI Random)
			Favors Penicillin 1	Favors Cephalosporins		
Bacterial Cure Rates						
Years 1970-1979	324/356	267/320			12.4	2.06 (1.27, 3.34)
Years 1980-1989	815/879	685/831			22.2	2.84 (1.97, 4.09)
Years 1990-1999	2538/2734	1592/2005			65.4	3.25 (2.49, 4.23)
Total	3677/3969	2544/3156			100.0	3.02 (2.49, 3.67)
Clinical Cure Rates						
Years 1970-1979	212/234	187/230			12	2.19 (1.25, 3.85)
Years 1980-1989	814/867	706/823			23.2	2.36 (1.65, 3.37)
Years 1990-1999	2352/2509	1541/1785			64.8	2.30 (1.62, 3.26)
Total	3378/3610	2434/2838			100.0	2.34 (1.84, 2.97)

CI, confidence interval; OR, odds ratio

Summarized results by decade from a meta-analysis of 35 studies (1966-2000). Reproduced with permission from Casey JR, Pichichero ME. *Pediatrics*. 2004;113:866-882. Copyright © 2004 by the American Academy of Pediatrics.

TABLE 5

Cure rates of individual cephalosporins vs penicillin in GABHS tonsillopharyngitis

	Cephalosporin n/N	Penicillin n/N	OR		Weight %	OR (95% CI Random)
			Favors Penicillin 1	Favors Cephalosporins		
Bacterial Cure Rates						
Cephalexin	476/525	435/531			16.4	2.17 (1.49, 3.14)
Cefadroxil	910/973	823/975			22.9	2.70 (1.93, 3.77)
Cefaclor	105/113	96/114			4.1	2.36 (0.96, 5.81)
Cefuroxime	469/510	226/306			13.2	3.31 (1.47, 7.45)
Cefprozil	235/248	185/220			6.1	3.63 (1.83, 7.18)
Loracarbef	214/239	161/218			8.8	2.59 (0.74, 9.12)
Cefpodoxime	368/396	213/268			9.5	3.29 (2.01, 5.40)
Ceftibuten	268/294	106/132			5.9	2.53 (1.40, 4.55)
Cefixime	45/48	36/47			1.8	4.58 (1.19, 17.68)
Cefdinir	429/455	159/227			7.1	7.06 (4.34, 11.49)
Total	3677/3969	2544/3156			100	3.02 (2.49, 3.67)
Clinical Cure Rates						
Cephalexin	353/482	414/477			16.3	2.42 (1.51, 3.88)
Cefadroxil	724/774	672/780			21.1	2.32 (1.60, 3.37)
Cefaclor	98/113	95/114			7.3	1.27 (0.44, 3.64)
Cefuroxime	473/510	242/306			13.5	2.96 (1.88, 4.64)
Cefprozil	232/248	184/220			9.1	2.88 (1.54, 5.38)
Loracarbef	205/239	190/218			9.9	0.73 (0.21, 2.61)
Cefpodoxime	370/396	238/268			9.8	1.95 (1.11, 3.44)
Ceftibuten	285/294	117/132			4.8	4.06 (1.73, 9.54)
Cefixime	47/48	39/47			1.2	9.64 (1.16, 80.47)
Cefdinir	441/455	196/227			6.3	4.98 (2.59, 9.57)
Total	3378/3610	2434/2838			100	2.34 (1.84, 2.97)

CI, confidence interval; OR, odds ratio

Summarized results by therapy from a meta-analysis of 35 studies (1966-2000). Reproduced with permission from Casey JT, Pichichero ME. *Pediatrics*. 2004;113:866-882. Copyright © 2004 by the American Academy of Pediatrics.

Summary

Microbiologic testing is recommended to diagnose GABHS pharyngitis and is required to maximize the selection of patients at highest risk of complications from true infection. The primary goal of therapy is eradication of GABHS. Penicillin has been the first-line treatment of choice for nonallergic patients; yet, there may be reason to reexamine the role of penicillin since there are now considerable data from clinical trials, pooled multicenter studies, and meta-analyses demonstrating frequent bacteriologic and clinical failure. While the contribution of pathogen resistance remains unclear, evolving evidence suggests that these failures also may be related to bacterial coaggregation or copathogenicity; GABHS reinfection; antibiotic nonadherence or subtherapeutic drug levels; penicillin tolerance; or blunting of an effective immune response. At the same time, some clinical evidence suggests that treatment failure with some cephalosporins may occur less frequently than with penicillin. Although cephalosporins are generally more expensive than oral penicillin, the benefits of cephalosporins include activity against BLPB and evolving data that support less frequent dosing than penicillin. Consequently, a reassessment of the role of cephalosporins in the treatment of pharyngitis may be appropriate.

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