Diagnosis and Treatment of Pharyngitis in Children

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Pharyngitis is an inflammation of the mucous membranes and underlying structures of the throat. Acute pharyngitis is one of the most common illnesses for which children visit primary care physicians; pediatricians in the United States make the diagnosis of acute pharyngitis, acute tonsillitis, or streptococcal sore throat more than 7 million times annually [1]. Many viral and bacterial agents are capable of producing pharyngitis, either as a separate entity or as part of a more generalized illness (Table 1). Most cases of acute pharyngitis in children are caused by viruses and are benign and self-limited. Group A beta-hemolytic streptococcus (GAS) is the most important of the bacterial causes of acute pharyngitis. Strategies for the diagnosis and treatment of pharyngitis are directed at distinguishing children with viral pharyngitis, who would not benefit from antimicrobial therapy, from children with group A beta-hemolytic streptococcal pharyngitis, for whom antimicrobial therapy would be beneficial. Making this distinction is crucial in attempting to minimize the unnecessary use of antimicrobial agents in children.

Etiology

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses, such as influenza virus, parainfluenza virus, rhinovirus,

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Table 1
Etiology of acute pharyngitis

Etiologic agent	Associated disorders or clinical findings
Bacterial	
Streptococci	
Group A	Scarlet fever
Groups C and G	
Mixed anaerobes	Vincent's angina
Neisseria gonorrhoeae	
Corynebacterium diphtheriae	Diphtheria
Arcanobacterium haemolyticum	Scarlatiniform rash
Yersinia enterocolitica	Enterocolitis
Yersinia pestis	Plague
Francisella tularensis	Tularemia (oropharyngeal form)
Viral	
Rhinovirus	Common cold
Coronavirus	Common cold
Adenovirus	Pharyngoconjunctival fever; acute respiratory disease
Herpes simplex virus types 1 and 2	Gingivostomatitis
Parainfluenza virus	Common cold; croup
Coxsackievirus A	Herpangina; hand-foot-and-mouth disease
Epstein-Barr virus	Infectious mononucleosis
Cytomegalovirus	Cytomegalovirus mononucleosis
HIV	Primary HIV infection
Influenza A and B viruses	Influenza
Mycoplasmal: *Mycoplasma pneumoniae*	Acute respiratory disease; pneumonia
Chlamydial	
Chlamydia psittaci	Acute respiratory disease; pneumonia
Chlamydia pneumoniae	Pneumonia

Modified from Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guideline for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113–25.

coronavirus, adenovirus, and respiratory syncytial virus, are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include coxsackievirus, echovirus, and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (eg, splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents, including cytomegalovirus, rubella virus, and measles virus, may be associated with acute pharyngitis.

GAS is the most common bacterial cause of acute pharyngitis, accounting for 15% to 30% of cases of acute pharyngitis in children. Other bacteria also can cause acute pharyngitis, however, including groups C and G beta-hemolytic streptococci and *Corynebacterium diphtheriae*. *Arcanobacterium haemolyticum* is a rare cause of acute pharyngitis, particularly in teenagers, and *Neisseria gonorrhoeae* occasionally can cause acute pharyngitis in sexually active adolescents. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* and mixed infections with anaerobic bacteria (eg, Vincent's angina) are rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have

been implicated as causes of acute pharyngitis, particularly in adults. Although other bacteria, such as *Staphylococcus aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae,* are cultured frequently from the throats of children with acute pharyngitis, their etiologic role in this disease has not been established.

Epidemiology

Most cases of pharyngitis occur during the colder months of the year, when respiratory viruses (eg, rhinovirus, coronavirus, influenza virus, and adenovirus) are prevalent. Spread among family members in the home is a prominent feature of the epidemiology of most of these agents, with children being the major reservoir of infection. Group A beta-hemolytic streptococcal pharyngitis is primarily a disease of children age 5 to 15. In temperate climates, it usually occurs in the winter and early spring.

The incidence of gonococcal pharyngitis is highest among older adolescents and young adults. The usual route of infection is orogenital sexual contact with an infected sexual partner. Sexual abuse must be strongly considered if *N. gonorrhoeae* is isolated from the pharynx of a prepubertal child. Widespread immunization with diphtheria toxoid has made diphtheria a rare disease in the United States, with fewer than five cases reported annually in recent years.

Groups C and G beta-hemolytic streptococci can cause acute pharyngitis with clinical features similar to those of group A beta-hemolytic streptococcal pharyngitis. Group C streptococcus is a relatively common cause of acute pharyngitis among college students and adults evaluated in emergency departments [2,3]. Group C streptococcus also can cause epidemic food-borne pharyngitis; family and school outbreaks of group C streptococcal pharyngitis related to ingestion of contaminated food products, such as unpasteurized cow's milk, have been described [4]. Although there have been several well-documented food-borne outbreaks of group G streptococcal pharyngitis, the etiologic role of group G streptococcus in acute, endemic pharyngitis is unclear. A community-wide, respiratory outbreak of group G streptococcal pharyngitis in a pediatric population was described in which group G streptococcus was isolated from 56 of 222 (25%) consecutive children with acute pharyngitis seen in a private pediatric office [5]. Results of DNA fingerprinting of the group G streptococcus isolates suggested that 75% of them were the same strain.

The role of groups C and G streptococci in acute pharyngitis may be underestimated for several reasons. Anaerobic incubation increases the yield of these organisms, but many laboratories do not use anaerobic incubation routinely for throat cultures. In addition, because many groups C and G streptococci are bacitracin resistant, and laboratories may report only bacitracin-sensitive streptococci (consistent with GAS), many groups C and G streptococci would be missed. Finally, many clinicians no longer perform throat cultures, but instead rely solely on rapid antigen detection tests (RADTs), and groups C and G streptococci would not be identified by a RADT for GAS [6].

Clinical manifestations

Acute group A beta-hemolytic streptococcal pharyngitis has certain clinical characteristics and epidemiologic patterns (Table 2). Patients with group A beta-hemolytic streptococcal pharyngitis commonly present with sore throat (generally of sudden onset), severe pain on swallowing, and fever. Headache, nausea, vomiting, and abdominal pain also may be present. On examination, patients typically have tonsillopharyngeal erythema with or without exudates and tender, enlarged anterior cervical lymph nodes. Other findings include a beefy, red, swollen uvula; petechiae on the palate; excoriated nares (especially in infants); and a scarlitiniform rash. None of these findings is specific for group A beta-hemolytic streptococcal pharyngitis. Many patients with streptococcal pharyngitis exhibit signs and symptoms that are milder than a "classic" case of this illness. Some of these patients have bona fide group A beta-hemolytic streptococcal pharyngitis, whereas others are merely colonized with GAS and have pharyngitis resulting from an intercurrent viral illness.

Scarlet fever is an upper respiratory tract infection associated with a characteristic rash, which is caused by an infection with pyrogenic exotoxin (erythrogenic toxin)–producing GAS in individuals who do not have antitoxin antibodies. Scarlet fever is encountered less commonly and is less virulent than in the past, but the incidence is cyclical, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of trans-

Table 2
Clinical and epidemiologic findings and diagnosis of group A streptococcal pharyngitis

Features suggesting group A streptococcus as etiologic agent
Sudden onset
Sore throat
Fever
Scarlet fever rash
Headache
Nausea, vomiting, and abdominal pain
Inflammation of pharynx and tonsils
Patchy discrete exudates
Tender, enlarged anterior cervical nodes
Patient age 5–15 y
Presentation in winter or early spring
History of exposure
Features suggesting viral etiology
Conjunctivitis
Coryza
Cough
Diarrhea
Characteristic exanthems
Characteristic enanthems

Modified from Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guideline for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113–25.

mission, age distribution, and other epidemiologic features are otherwise similar to the features for group A beta-hemolytic streptococcal pharyngitis.

The rash of scarlet fever appears within 24 to 48 hours after the onset of symptoms, although it may appear with the first signs of illness. The rash often begins around the neck and spreads over the trunk and extremities. It is a diffuse, finely papular, erythematous eruption producing a bright red discoloration of the skin, which blanches on pressure. Involvement is often more intense along the creases of the elbows, axillae, and groin. The involved skin has a goose-pimple appearance and feels rough. The face is usually spared, although the cheeks may be erythematous with pallor around the mouth. After 3 to 4 days, the rash begins to fade and is followed by desquamation, first on the face, progressing downward, and often resembling that seen after a mild sunburn. Occasionally, sheetlike desquamation may occur around the free margins of the fingernails, palms, and soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with group A beta-hemolytic streptococcal pharyngitis. In addition, the tongue usually is coated, and the papillae are swollen. After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance.

The absence of fever or the presence of clinical features such as conjunctivitis, cough, hoarseness, coryza, anterior stomatitis, discrete ulcerative lesions, viral exanthem, and diarrhea suggests a viral etiology rather than GAS. Acute pharyngitis caused by adenovirus typically is associated with fever, erythema of the pharynx, enlarged tonsils with exudate, and enlarged cervical lymph nodes. Adenoviral pharyngitis may be associated with conjunctivitis, and, when it is, it is referred to as pharyngoconjunctival fever. The pharyngitis of pharyngoconjunctival fever can persist for 7 days, the conjunctivitis can persist for 14 days, and both resolve spontaneously. Outbreaks of pharyngoconjunctival fever have been associated with transmission in swimming pools; widespread epidemics and sporadic cases also occur.

Enteroviruses (coxsackievirus, echovirus, and newer enteroviruses) can cause acute pharyngitis, especially during the summer and early fall. The pharynx may be erythematous, but tonsillar exudate and cervical adenopathy are unusual. Fever may be prominent. Resolution usually occurs within a few days. Herpangina is a specific syndrome caused by coxsackievirus A or B or echoviruses and is characterized by fever and painful, discrete, gray-white papulovesicular lesions on an erythematous base in the posterior oropharynx. These lesions become ulcerative and usually resolve within 7 days. Hand-foot-mouth disease is a specific syndrome caused by coxsackievirus A16. It is characterized by painful vesicles and ulcers throughout the oropharynx associated with vesicles on the palms, soles, and sometimes on the trunk or extremities. These lesions usually resolve within 7 days.

Primary oral herpes simplex virus infections usually occur in young children and typically produce acute gingivostomatitis associated with ulcerating vesicular lesions throughout the anterior mouth, including the lips, but sparing the posterior pharynx. The gingivostomatitis can last 2 weeks and often is associated

with high fever. The pain may be intense, and the oral intake of fluids may be impaired, leading to dehydration. Herpes simplex virus also can produce a mild pharyngitis in adolescents and adults that may or may not be associated with typical ulcerating vesicular lesions.

Acute pharyngitis is a common finding in adolescents and young adults with infectious mononucleosis caused by Epstein-Barr virus. The pharyngitis of infectious mononucleosis can be severe with clinical findings virtually identical to those of group A beta-hemolytic streptococcal pharyngitis. Generalized lymphadenopathy and hepatosplenomegaly also may be present, however. Fever and pharyngitis typically last 1 to 3 weeks; the lymphadenopathy and hepatosplenomegaly resolve over 3 to 6 weeks. Laboratory findings include the presence of atypical lymphocytosis, heterphil antibody, and specific antibodies to Epstein-Barr virus antigens.

The acute pharyngitis caused by *A. haemolyticum* may closely resemble group A beta-hemolytic streptococcal pharyngitis, including the presence of a scarlitiniform rash in many patients. In rare cases, *A. haemolyticum* can produce a membranous pharyngitis that can be confused with diphtheria.

Pharyngeal diphtheria is characterized by a grayish brown pseudomembrane that may be limited to one or both tonsils or may extend widely to involve the nares, uvula, soft palate, pharynx, larynx, and tracheobronchial tree. Involvement of the tracheobronchial tree may lead to life-threatening respiratory obstruction. Soft tissue edema and prominent cervical and submental lymphadenopathy may create a bull-neck appearance.

Diagnosis

The decision to perform a microbiologic test on a patient presenting with acute pharyngitis should be based on the clinical and epidemiologic characteristics of the illness (see Table 2). A history of close contact with a well-documented case of group A beta-hemolytic streptococcal pharyngitis or a high prevalence of group A beta-hemolytic streptococcal infections in the community also may be helpful. Testing usually does not need to be performed on patients with acute pharyngitis whose clinical and epidemiologic features do not suggest GAS as the etiology. Selective use of diagnostic studies for GAS not only increases the proportion of positive test results, but also the percentage of patients with positive tests who are truly infected rather than merely GAS carriers.

Efforts have been made to incorporate clinical and epidemiologic features of acute pharyngitis into scoring systems that attempt to predict the probability that a particular illness is caused by GAS [7–9]. These clinical scoring systems are helpful in identifying patients at such low risk of infection with GAS that a throat culture or RADT is usually unnecessary. The signs and symptoms of group A beta-hemolytic streptococcal and non–group A beta-hemolytic streptococcal pharyngitis overlap too broadly, however, and the clinical diagnosis of group A beta-hemolytic streptococcal pharyngitis cannot be made with accuracy even by

the most experienced physicians. Guidelines from the Infectious Diseases Society of America (IDSA) [10], American Academy of Pediatrics [11], and American Heart Association [12] indicate that microbiologic confirmation (with a throat culture or RADT) is required for the diagnosis of group A beta-hemolytic streptococcal pharyngitis.

New practice guidelines from the Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians (AAFP), and American College of Physicians–American Society of Internal Medicine (ACP-ASIM) recommend the use of a clinical algorithm without microbiologic confirmation as an acceptable approach to the diagnosis of group A beta-hemolytic streptococcal pharyngitis in adults only [12,13]. Although the goal of this algorithm-based strategy was to reduce the inappropriate use of antibiotics in adults with pharyngitis, there was concern that their use would result in the administration of antimicrobial treatment to an unacceptably large number of adults with non–group A beta-hemolytic streptococcal pharyngitis [14].

The authors of the CDC/AAFP/ACP-ASIM guidelines suggested that prospective studies should be conducted to compare this particular strategy with other strategies in terms of relevant patient outcomes and cost. McIsaac et al [15] performed a retrospective analysis to assess the impact of six different guidelines (including the IDSA and CDC/AAFP/ACIP-ASIM guidelines) on identification and treatment of group A beta-hemolytic streptococcal pharyngitis in children and adults. Guidelines that recommend selective use of RADTs or throat cultures and treatment based only on positive test results significantly reduced the inappropriate use of antibiotics in adults. In contrast, the empirical strategy proposed in the CDC/AAFP/ACIP-ASIM guidelines resulted in the administration of unnecessary antibiotics to an unacceptably large number of adults. Before abandoning the concept of treatment only after laboratory confirmation of GAS in adults with pharyngitis (IDSA guideline), additional prospective studies need to be performed to compare empirical and laboratory-based strategies in terms of relevant patient outcomes and cost.

Throat cultures

Culture of a specimen obtained by throat swab on a sheep blood agar plate is the standard laboratory procedure for the microbiologic confirmation of the clinical diagnosis of acute group A beta-hemolytic streptococcal pharyngitis [16]. If performed correctly, a single throat swab has a sensitivity of 90% to 95% in detecting the presence of GAS in the pharynx [17].

Several variables may affect the accuracy of the throat culture results. One of the most important is the manner in which the swab is obtained [18,19]. Throat swab specimens should be obtained from the surface of both tonsils (or tonsillar fossae) and the posterior pharyngeal wall. Other areas of the pharynx and mouth are not acceptable sites and should not be touched during the culturing procedure. Even with an appropriately collected specimen, false-negative results may be obtained if the patient has received antibiotics before the throat swab is taken.

Anaerobic incubation and the use of selective culture media have been reported to increase the sensitivity of throat cultures [20,21]. The data regarding the impact of the atmosphere of incubation and the culture media conflict, however, and, in the absence of definite benefit, the increased cost and effort associated with anaerobic incubation and selective culture media are difficult to justify, particularly for physicians processing throat cultures in their own offices [22–24].

Duration of incubation is another variable that can affect the yield of throat cultures. When plated, cultures should be incubated at 35°C to 37°C for 18 to 24 hours before reading. An additional overnight incubation at room temperature would identify a considerable number of positive throat cultures, however, that would not otherwise have been identified. Armengol et al [25] found that more than 40% of the positive confirmatory throat cultures obtained on patients with pharyngitis and negative RADTs were negative after 24 hours of incubation, but positive after 48 hours. Although initial therapeutic decisions may be made on the basis of an overnight culture, it is advisable to examine plates that are negative at 24 hours again at 48 hours.

The clinical significance of the number of colonies of GAS present on the throat culture plate is controversial. Patients with bona fide acute group A beta-hemolytic streptococcal pharyngitis are likely to have more colonies of GAS on their culture plates than patients who are GAS carriers. There is too much overlap in the colony count, however, between patients acutely infected with GAS and GAS carriers to permit differentiation on the basis of degree of positivity [24].

Probably the most widely used test for differentiation of GAS from other beta-hemolytic streptococci in physicians' offices is the bacitracin disk test. This test provides a presumptive identification based on the observation that greater than 95% of GAS show a zone of inhibition around a disk containing 0.04 units of bacitracin, whereas 83% to 97% of non-GAS are not inhibited by bacitracin [24].

An alternative and highly specific method for the differentiation of GAS from other beta-hemolytic streptococci is the detection of the group-specific cell wall carbohydrate antigen directly on isolated bacterial colonies. Commercial kits employing group-specific antisera are available for this purpose. Such tests are appropriate for use by clinical microbiology laboratories, but most physicians performing throat cultures would find it difficult to justify the additional expense for the minimal improvement in accuracy that serogrouping of beta-hemolytic streptococci would provide over the bacitracin disk test [24].

Rapid antigen detection tests

The major disadvantage of culturing a specimen obtained by throat swab on blood agar plates is the delay in obtaining culture results. RADTs have been developed for the identification of GAS directly from throat swabs. Although RADTs are more expensive than blood agar plate cultures, the advantage they offer over the traditional procedure is the speed with which they can provide

results. Rapid identification and treatment of patients with group A beta-hemolytic streptococcal pharyngitis can reduce the risk of the spread of GAS, allow the patient to return to school or work sooner, and speed clinical improvement [17,26]. In addition, in certain environments (eg, emergency departments), the use of RADTs has been shown to increase significantly the number of patients appropriately treated for group A beta-hemolytic streptococcal pharyngitis compared with the use of throat cultures [27].

Most currently available RADTs have specificities of 95% or greater compared with blood agar plate cultures [28]. False-positive test results are unusual, and therapeutic decisions can be made with confidence on the basis of a positive RADT result. The sensitivity of most RADTs is 80% to 90% [28]. Although it has been suggested that many false-negative RADT results occur in patients who are GAS carriers, it has been shown that a large proportion of patients with false-negative RADT results are truly infected with GAS [29].

The first RADTs used latex agglutination methodology, were relatively insensitive, and had unclear end points [28]. Subsequent tests based on enzyme immunoassay techniques had a more sharply defined end point and increased sensitivity. More recently, RADTs using optical immunoassay and chemiluminescent DNA probes have been developed [28]. These tests may be more sensitive than other RADTs and perhaps even as sensitive as blood agar plate cultures [28]. Because of conflicting and limited data about the optical immunoassay [28] and other commercially available RADTs, however, advisory groups recommend that physicians electing to use any RADT in children and adolescents without culture backup of negative results should do so only after showing in their own practice that the RADT is as sensitive as throat culture [10,11].

Currently, two of the most important issues regarding the use of RADTs for the diagnosis of group A beta-hemolytic streptococcal pharyngitis are the relative sensitivities of the different tests and whether any RADTs are sensitive enough to mitigate against the need to perform throat cultures in patients with negative test results. Most studies that have evaluated the sensitivities of RADTs have compared the performance of a single type of RADT with a standard culture. Because of considerable variability in study designs and culture techniques, it is difficult to compare the sensitivity of a RADT as determined in one study with the sensitivity of another RADT as determined in a different study [28]. The relative sensitivities of different RADTs can be determined only by direct comparisons. There have been to date only four direct comparisons of different RADTs reported in the English literature (one of which was a letter to the editor) [30–33]. The relative sensitivities of different RADTs have not been established.

Few studies have investigated the performance of the RADTs currently being used in clinical practice [25,31–35]. Armengol et al [25] attempted to validate the sensitivity of the specific RADT being used in their practice before abandoning confirmatory throat cultures for negative RADT results [10,11]. In this study performed over three winter seasons and using the on-site physician office laboratory

at the pediatric group practice, they found that the RADT had a sensitivity of approximately 85% compared with a single blood agar plate culture. The investigators concluded that the sensitivity of this particular RADT was too low for them to consider abandoning the confirmatory throat culture in their practice. In contrast, Mayes and Pichichero [36] reviewed the experience with RADTs in a different pediatric group practice between January 1996 and June 1999. During this period, 11,427 RADTs were performed, and 8385 (73.4%) were negative. A confirmatory blood agar plate culture was performed for 8234 (98.2%) of these 8385 negative tests. Of these, 200 (2.4%) were determined to have been negative RADT results with a positive throat culture. A cost analysis showed that elimination of confirmatory throat cultures for negative RADT results could produce substantial saving to a practice and to patients. The investigators concluded that culture confirmation of negative RADT results may not be necessary in all circumstances [36].

Neither the blood agar plate culture nor the RADT can differentiate accurately individuals with bona fide group A beta-hemolytic streptococcal pharyngitis from asymptomatic GAS carriers with intercurrent viral pharyngitis. They do facilitate, however, the withholding of antibiotics from most patients with sore throats, whose cultures or RADTs are negative, and this is extremely important. There are an estimated 6.7 million visits to primary care providers by adults who complain of sore throat each year in the United States, and antibiotics are prescribed at 73% of these visits [14]. Although more recent trends suggest a decline in the use of antibiotics in children and adolescents with pharyngitis, in 1999–2000, 68.6% of children and adolescents who were seen by their primary care provider for pharyngitis received a prescription for antibiotics [37].

Antistreptococcal antibody titers reflect past and not present immunologic events and are of no value in the diagnosis of acute group A beta-hemolytic streptococcal pharyngitis. They are valuable for confirmation of prior group A beta-hemolytic streptococcal infections in patients suspected of having acute rheumatic fever or poststreptococcal acute glomerulonephritis. Antistreptococcal antibody titers also are helpful in prospective epidemiologic studies in trying to differentiate patients with acute group A beta-hemolytic streptococcal infections from patients who are GAS carriers.

Repeat diagnostic testing

Most asymptomatic patients who have confirmed positive throat cultures after completing a course of appropriate antimicrobial therapy are GAS carriers [38]. Follow-up throat cultures (or RADTs) are not routinely indicated for asymptomatic patients who have completed a course of antibiotic therapy for GAS. There are specific situations, however, when follow-up throat cultures (or RADTs) on asymptomatic individuals should be performed. Patients with a history of rheumatic fever should have routine follow-up testing. Such testing also should be considered in patients who develop acute pharyngitis during outbreaks of either acute rheumatic fever or poststreptococcal acute glomeru-

lonephritis and during outbreaks of group A beta-hemolytic streptococcal pharyngitis in closed or semiclosed communities [38].

Treatment

Antimicrobial therapy is indicated for individuals with symptomatic pharyngitis after the presence of GAS in the throat has been confirmed by either throat culture or RADT. In situations in which the clinical and epidemiologic evidence results in a high index of suspicion, antimicrobial therapy can be initiated while awaiting laboratory confirmation, provided that such therapy is discontinued if the diagnosis of group A beta-hemolytic streptococcal pharyngitis is not confirmed by a laboratory test. Early initiation of antimicrobial therapy for group A beta-hemolytic streptococcal pharyngitis results in a shortening of the clinical course of the illness [26]. Group A beta-hemolytic streptococcal pharyngitis is usually a self-limited disease, however, and most signs and symptoms resolve spontaneously within 3 or 4 days of onset even without antimicrobial therapy [39]. In addition, the initiation of antimicrobial therapy can be delayed for 9 days after the onset of symptoms and still prevent the occurrence of acute rheumatic fever [40]. There can be flexibility in initiating antimicrobial therapy during the evaluation of an individual patient with presumed group A beta-hemolytic streptococcal pharyngitis.

Numerous antimicrobial agents have been shown to be effective in the treatment of group A beta-hemolytic streptococcal pharyngitis, including penicillin and its congeners (eg, ampicillin and amoxicillin) and numerous cephalosporins, macrolides, and clindamycin. When selecting an antimicrobial for the treatment of group A beta-hemolytic streptococcal pharyngitis, it is important to consider efficacy, safety, antimicrobial spectrum (narrow versus broad), dosing schedules, compliance, and cost. Based on such considerations, several advisory bodies recommend penicillin as the treatment of choice for this infection [9–11]. Although the problem of increasing antimicrobial resistance among bacteria is one of the most important current infectious disease issues, GAS has never developed resistance to any of the penicillins or cephalosporins or shown any increase in penicillin minimal inhibitory concentrations over at least 5 decades [41]. Amoxicillin often is used in place of oral penicillin V in young children; the efficacy appears equal. This choice is related primarily to acceptance of the taste of amoxicillin suspension. Orally administered erythromycin is indicated for patients allergic to penicillin. Other macrolides, such as clarithromycin or azithromycin, also are effective. First-generation cephalosporins also are acceptable in penicillin-allergic patients who do not manifest immediate-type hypersensitivity to β-lactam antibiotics.

Casey and Pichichero [42] presented a meta-analysis of 35 clinical trials performed between 1970 and 1999 in which a cephalosporin was compared with penicillin for the treatment of group A beta-hemolytic streptococcal pharyngitis.

Based on this analysis, they concluded that cephalosporins should be added "as a treatment of choice for [group A beta-hemolytic streptococcal] tonsillo-pharyngitis...." This report has several major flaws, however, that make it impossible to accept the validity of this conclusion [43].

Although the use of cephalosporins for group A beta-hemolytic streptococcal pharyngitis could reduce the number of patients (most merely chronic carriers) who continue to harbor the organism in their throats after completing therapy, the economic and ecologic costs involved would make this a Pyrrhic victory for those who advocate the use a cephalosporin as the drug of choice for streptococcal pharyngitis. Penicillin has stood, the test of time satisfactorily for 5 decades, and there are compelling reasons (eg, its narrow antimicrobial spectrum, inexpensive cost, and impressive safety profile) to continue to recommend it as the drug of choice.

Most oral antibiotics must be administered for 10 days to achieve maximal pharyngeal eradication rates of GAS. It has been reported that several antimicrobial agents, including clarithromycin, cefuroxime, cefixime, ceftibuten, cefdinir, cefpodoxime, and azithromycin, are effective in eradication of GAS from the pharynx when administered for 5 or fewer days [10,44]. Many of the studies of short-course therapy have serious methodologic flaws, however, that raise questions about the validity of their conclusions. In addition, the spectra of these antibiotics are much broader than that of penicillin, and even when they are administered for short courses, they are more expensive [44]. Additional studies are needed before these short-course regimens can be recommended [10,11].

Attempts to treat group A beta-hemolytic streptococcal pharyngitis with a single daily dose of penicillin have been unsuccessful [45]. In recent years, investigators have shown that several antimicrobial agents, including azithromycin, cefadroxil, cefixime, ceftibuten, cefpodoxime, cefprozil, and cefdinir, are effective in eradicating pharyngeal streptococci when given as a single daily dose [10,44]. These agents are expensive, however, and have broad spectra of activity compared with penicillin. Preliminary investigations have shown that once-daily amoxicillin therapy is effective in the treatment of group A beta-hemolytic streptococcal pharyngitis [46,47]. If confirmed by additional investigations, once-daily amoxicillin therapy, because of its low cost and relatively narrow spectrum, could become an alternative regimen for the treatment of group A beta-hemolytic streptococcal pharyngitis.

Antimicrobial therapy for group A beta-hemolytic streptococcal pharyngitis may be given orally or parenterally. Table 3 gives recommendations for several antimicrobials proved to be effective for the treatment of group A beta-hemolytic streptococcal pharyngitis [10]. Intramuscular benzathine penicillin G is preferred in patients who are unlikely to complete a full 10-day course of oral therapy.

Antimicrobial resistance has not been a significant issue in the treatment of group A beta-hemolytic streptococcal pharyngitis in the United States [48]. There has never been a clinical isolate of GAS documented to be resistant to penicillin anywhere in the world. Although there have been geographic areas with relatively high levels of resistance to macrolide antibiotics [49,50], the rate

Table 3
Antimicrobial therapy for group A streptococcal pharyngitis

Route of administration, antimicrobial agent	Dosage	Duration
Oral		
Penicillin*	Children: 250 mg bid or tid	10 d
	Adolescents and adults: 250 mg tid or qid	10 d
	Adolescents and adults: 500 mg bid	10 d
Intramuscular		
Benzathine penicillin G	1.2×10^6 U (for patients $\geq$27 kg)	1 dose
	6×10^5 U (for patients <27 kg)	1 dose
Mixtures of benzathine and procaine penicillin G	Varies with formulation[†]	1 dose
Oral, for patients allergic to penicillin		
Erythromycin	Varies with formulation	10 d
First-generation cephalosporins[‡]	Varies with agent	10 d

* Amoxicillin is often used in place of oral penicillin V in young children because of the acceptance of the taste of the suspension, not because of any microbiologic advantage.

[†] Dose should be determined on basis of benzathine component.

[‡] These agents should not be used to treat patients with immediate-type hypersensitivity to β-lactam antibiotics.

Modified from Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guideline for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35:113–25.

of macrolide resistance among isolates of GAS in the United States generally has remained low at less than 5%. In an investigation of antibiotic resistance patterns of 245 pharyngeal isolates and 56 invasive isolates of GAS obtained between 1994 and 1997 from 24 states and the District of Columbia, only 8 (2.6%) of the 301 isolates were determined to be macrolide resistant [41]. Higher resistance rates occasionally have been reported, however. Nine percent of pharyngeal and 32% of invasive GAS strains collected in San Francisco during 1994–1995 were reported to be macrolide resistant [51]. Martin et al [52], during a longitudinal investigation of group A beta-hemolytic streptococcal disease in a single elementary school in Pittsburgh, Pennsylvania, found that 48% of the isolates of GAS collected between October 2000 and May 2001 were resistant to erythromycin. None were resistant to clindamycin. Molecular typing indicated that this outbreak was due to a single strain of GAS. In addition, of 100 randomly selected isolates of GAS obtained from the community between April and June 2001, 38 (38%) were resistant to erythromycin [52].

Tanz et al [53] reported the results of a prospective, multicenter, community-based surveillance of pharyngeal isolates of GAS recovered from children 3 to 18 years old during three successive respiratory seasons between 2000 and 2003. During this 3-year period, the macrolide resistance rate among pharyngeal GAS in the United States was less than 5%, and it was stable. Clindamycin resistance was found in 1.04% of isolates over the 3-year study period and did not vary by study year. There was no evidence of wide dissemination of spe-

cific macrolide-resistance clones, increasing clindamycin resistance, or increasing erythromycin minimal inhibitory concentrations over the 3-year study period. There was, however, considerable geographic variability in macrolide resistance rates in each study year and year-to-year variability at individual study sites [53].

Although these results are reassuring, clinicians need to be aware of local resistance rates. In the future, if there are significant increases in rates of macrolide resistance among GAS strains, it may be necessary to reconsider recommendations for treatment of group A beta-hemolytic streptococcal pharyngitis in penicillin-allergic patients.

The primary reason to identify either group C or group G streptococcus as the cause of acute pharyngitis is to initiate antimicrobial therapy that may mitigate the clinical course of the infection. There is currently no convincing evidence, however, from controlled studies of clinical response to antimicrobial therapy in patients with acute pharyngitis and either group C or group G streptococcus isolated from their pharynx. If one elects to treat either group C or group G streptococcal pharyngitis, the treatment should be similar to that for group A beta-hemolytic streptococcal pharyngitis with penicillin as the antimicrobial agent of choice [6].

Complications

Group A beta-hemolytic streptococcal pharyngitis can be associated with suppurative and nonsuppurative complications. Suppurative complications result from the spread of GAS to adjacent structures and include peritonsillar abscess, retropharyngeal abscess, cervical lymphadenitis, sinusitis, otitis media, and mastoiditis. Before antimicrobial agents were available, suppurative complications of group A beta-hemolytic streptococcal pharyngitis were common; however, antimicrobial therapy has reduced greatly the frequency of such complications.

Acute rheumatic fever, acute poststreptococcal glomerulonephritis, and poststreptococcal reactive arthritis are recognized nonsuppurative sequelae of group A beta-hemolytic streptococcal pharyngitis. Acute rheumatic fever occurs after an episode of group A beta-hemolytic streptococcal pharyngitis (usually after a 2- to 4-week latent period) and not after group A beta-hemolytic streptococcal infections of the skin. Appropriate antimicrobial therapy begun within 9 days of the onset of pharyngitis can prevent this complication. In contrast to acute rheumatic fever, acute poststreptococcal glomerulonephritis can occur after a group A beta-hemolytic streptococcal infection of either the pharynx or skin and does not seem to be prevented by antimicrobial therapy of the antecedent group A beta-hemolytic streptococcal infection. The latent period for glomerulonephritis is about 3 weeks after a skin infection and 10 days after an upper respiratory tract infection. Poststreptococcal reactive arthritis is similar to other postinfectious arthritides. The relationship of this entity to acute rheumatic fever is still unclear.

Acute glomerulonephritis has been reported as an extremely unusual complication of group C streptococcal pharyngitis, but a causal relationship between group G streptococcal pharyngitis and acute glomerulonephritis has not been established. Acute rheumatic fever has not been described as a complication of either group C or group G streptococcal pharyngitis [6].

Treatment failures, chronic, carriage and recurrences

Antimicrobial treatment failures with group A beta-hemolytic streptococcal pharyngitis traditionally have been classified as either clinical or bacteriologic failures. The significance of clinical treatment failures (usually defined as persistent or recurrent signs or symptoms suggesting group A beta-hemolytic streptococcal pharyngitis) is difficult to determine, however, because group A beta-hemolytic streptococcal pharyngitis is a self-limited illness even without antimicrobial therapy [39]. In addition, without the repeat isolation of the infecting strain of GAS (ie, true bacteriologic treatment failure), it is particularly difficult to determine the clinical significance of persistent or recurrent signs or symptoms suggesting group A beta-hemolytic streptococcal pharyngitis.

Bacteriologic treatment failures can be classified as either *true* or *apparent* failures. *True* bacteriologic failure refers to the inability to eradicate the specific strain of GAS causing an acute episode of pharyngitis with a complete course of appropriate antimicrobial therapy. *Apparent* bacteriologic treatment failure reflects a variety of circumstances.

Most *apparent* bacteriologic treatment failures are patients who are GAS carriers (ie, patients with GAS in the upper respiratory tract, but without illness or immunologic response). GAS carriers are unlikely to spread GAS to their close contacts and are at low, if any risk, for developing suppurative or nonsuppurative complications [54]. During the winter and spring in temperate climates, 20% of asymptomatic school-age children are GAS carriers [54]. *Apparent* bacteriologic failure also can occur when newly acquired GAS isolates are mistaken for the original infecting strain of GAS, when the infecting strain of GAS is eradicated but then rapidly reacquired, or when compliance with antimicrobial therapy is poor.

Although the specific reasons for true bacteriologic treatment failures have not been determined, several explanations have been proposed. It has been suggested that GAS may have become more resistant to penicillin; however, there is no evidence to support this hypothesis [48], and no penicillin-resistant strains of GAS have been identified. It also has been suggested that some strains of GAS have developed penicillin tolerance (ie, a discordance between the concentration of penicillin required to inhibit and to kill the organisms); however, the role of penicillin tolerance in true bacteriologic treatment failures has never been established [55,56]. It also has been suggested that other species of bacteria present in the normal pharyngeal flora contribute to true bacteriologic failures

either by enhancing the colonization and growth of GAS in the upper respiratory tract or by producing β-lactamases that inactivate penicillin. The precise role, if any, of these other organisms has not been determined yet, however [48].

Routine throat cultures (or RADTs) for asymptomatic individuals after completion of antibiotic therapy for group A beta-hemolytic streptococcal pharyngitis are generally not indicated. The interpretation of a positive throat culture (RADT) after a course of treatment may be difficult even if the patient remains symptomatic because it is not possible to distinguish persistent carriage from persistent or recurrent infection. Under these circumstances, many clinicians elect to administer a second course of antimicrobials.

When the physician suspects "ping pong" spread to be associated with multiple repeated episodes of group A beta-hemolytic streptococcal infections in a family, simultaneous cultures of all family contacts and treatment of persons whose cultures are positive may be helpful. There is no credible evidence that family pets are reservoirs for GAS, and they do not contribute to familial spread.

A patient with repeated episodes of acute pharyngitis associated with a positive throat culture (or RADT) is a common and difficult problem for the practicing physician. The fundamental question that must be addressed is whether this patient is experiencing repeated episodes of bona fide group A beta-hemolytic streptococcal pharyngitis or is a GAS carrier experiencing repeated episodes of viral pharyngitis. The latter situation is considerably more common than the former. Such a patient is likely to be a GAS carrier if (1) the clinical and epidemiologic findings suggest a viral etiology, (2) there is little clinical response to appropriate antimicrobial therapy, (3) throat cultures (or RADTs) are also positive between episodes of pharyngitis, and (4) there is no serologic response to GAS extracellular antigen (eg, antistreptolysin O, anti-DNase B).

In contrast, a patient with repeated episodes of acute pharyngitis associated with positive throat cultures (or RADTs) for GAS is likely to be experiencing repeated episodes of bona fide group A beta-hemolytic streptococcal pharyngitis if (1) the clinical and epidermiologic findings suggest group A beta-hemolytic streptococcal pharyngitis as the etiology, (2) there is a demonstrable clinical response to appropriate antimicrobial therapy, (3) throat cultures (or RADTs) are negative between episodes of pharyngitis, and (4) there is a serologic response to GAS extracellular antigens. When it has been determined that the patient is experiencing repeated episodes of bona fide group A beta-hemolytic streptococcal pharyngitis, some have suggested prophylactic oral penicillin V. The efficacy of this regimen has never been proved, however, and antimicrobial prophylaxis is not recommended except to prevent recurrences of rheumatic fever in patients who have experienced a previous episode of rheumatic fever. Tonsillectomy may be considered in a rare patient whose symptomatic episodes do not diminish in frequency over time and in whom no alternative explanation for the recurrent group A beta-hemolytic streptococcal pharyngitis is evident. Tonsillectomy has been shown to be beneficial for a relatively small group of these patients, however, and any benefit can be expected to be relatively short-lived [57–59].

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