Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis

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EXECUTIVE SUMMARY

The objective of this practice guideline is to provide recommendations for the accurate diagnosis and optimal treatment of group A streptococcal pharyngitis in children and adults.

The desired outcomes are prevention of acute rheumatic fever, prevention of suppurative complications, improvement of clinical symptoms and signs, reduction in transmission of group A β-hemolytic streptococci to close contacts of patients, and minimization of potential adverse effects of inappropriate antimicrobial therapy.

This statement is an update of the practice guideline published in 1997 [1] and takes into account relevant research published since that time. A major substantive change is the acceptance of negative results of rapid antigen detection testing (RADT) for exclusion of acute streptococcal pharyngitis, without the previously mandated confirmation with a negative culture result, provided certain criteria are met, as detailed below.

Diagnosis. Acute pharyngitis is one of the most frequent illnesses for which pediatricians, internists, and other primary care physicians are consulted. Although the group A streptococcus is the most common bacterial cause of acute pharyngitis, only a small percentage of patients with this condition are infected by group A streptococci. Moreover, group A streptococcal pharyngitis is the only *commonly occurring* form of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, for a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether the pharyngitis is attributable to group A streptococci.

The signs and symptoms of group A streptococcal and other (most frequently viral) pharyngitides overlap broadly. Therefore, unless the physician is able with confidence to exclude the diagnosis of streptococcal pharyngitis on epidemiological and clinical grounds, a laboratory test should be done to determine whether group A streptococci are present in the pharynx. The test may be either culture of a throat swab specimen or an RADT, which detects the presence of group A streptococcal carbohydrate on a throat swab. A positive result of throat culture or RADT for a patient with signs and symptoms of acute pharyngitis is considered, for clinical purposes, to establish the diagnosis of "strep throat." However, because some RADTs appear to be considerably less sensitive than is culture of a throat swab specimen, a negative RADT result for a child or adolescent should be confirmed by performance of a throat culture, unless the physician has ascertained in his or her practice that the RADT being used is comparable in sensitivity to a throat culture. Because of the epidemiological features of acute pharyngitis in adults (e.g., low incidence of streptococcal infection and extremely low risk of rheumatic fever), diagnosis of this infection in adults on the basis of the results of an RADT, without confirmation of negative RADT results

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by negative results of culture, is an acceptable alternative to diagnosis on the basis of throat culture results (figure 1). The generally high specificity of RADTs should minimize overprescription of antimicrobials for treatment of adults.

Therapy. Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. A number of antibiotics have been shown to be effective in treating group A streptococcal pharyngitis. These include penicillin and its congeners (such as ampicillin, amoxicillin, and the semisynthetic penicillins), as well as numerous cephalosporins and macrolides and clindamycin. Penicillin, however, remains the agent of choice because of its proven efficacy, safety, narrow spectrum, and its low cost. Amoxicillin is often used in place of oral penicillin V to treat young children; the efficacy appears to be equal. This choice is primarily related to acceptance of the taste of the suspension. Preliminary investigations have demonstrated that once-daily amoxicillin therapy is effective in the treatment of group A β-hemolytic streptococcal pharyngitis [2, 3]. If these results are confirmed by additional investigations, once-daily amoxicillin therapy, because of its low cost and relatively narrow spectrum, could become an alternative regimen to treat group A β-hemolytic streptococcal pharyngitis.

Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10-day course of oral therapy. Erythromycin is a suitable alternative for patients allergic to penicillin. First-generation cephalosporins are also acceptable for patients who do not exhibit immediate-type hypersensitivity to β-lactam antibiotics.

Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci, but certain newer agents have been reported to achieve comparable rates of bacteriologic and clinical cure of streptococcal pharyngitis when administered for $\leqslant$5 days. However, no definitive results from comprehensive studies are available to allow final evaluation of these proposed shorter courses of oral antibiotic therapy [4], which, therefore, cannot be recommended at this time. Moreover, these antibiotics have a much broader spectrum than does penicillin, and most, even when administered for short courses, are more expensive.

Except under special circumstances, neither repeat bacteriologic testing (culture or RADT) of patients who are asymptomatic after a course of antimicrobial therapy nor routine testing of asymptomatic household contacts of a patient with group A streptococcal pharyngitis is recommended.

A small percentage of patients will have a recurrence of acute pharyngitis associated with results of throat culture or RADT that are positive for group A streptococci within a short time after completion of a course of antimicrobial therapy. Such episodes may be treated with an antimicrobial agent appropriate for treatment of the initial illness. If the previous treatment was with an oral agent and compliance is in question, a second course of intramuscular benzathine penicillin G therapy should be considered. When multiple episodes occur over the course

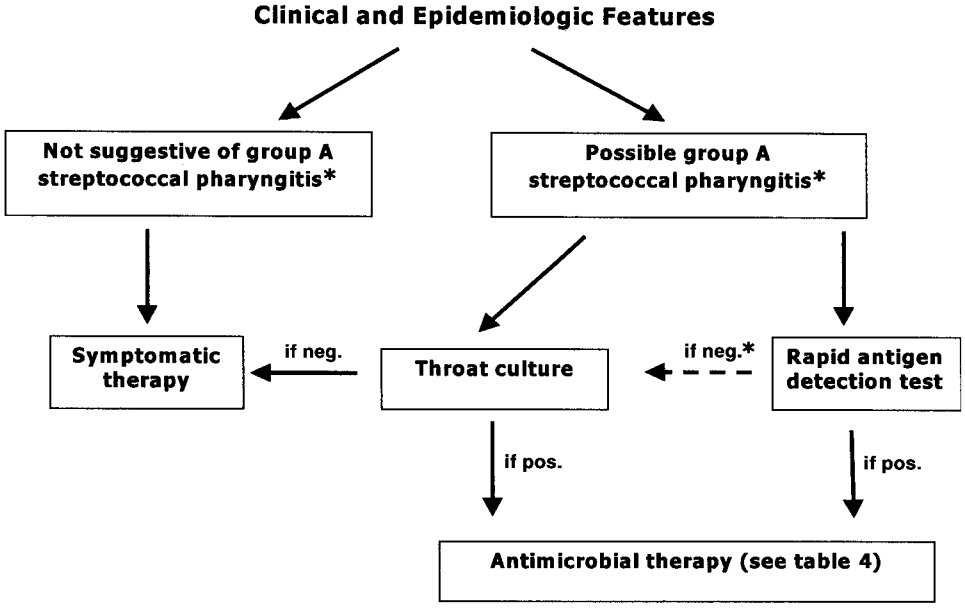

Figure 1. Diagnosis and management of acute pharyngitis. The algorithm applies to uncomplicated cases of acute pharyngitis. Additional diagnostic and therapeutic measures may be necessary for patients with suppurative complications (e.g., peritonsillar abscess or cervical lymphadenitis) or infection with uncommon pharyngeal bacterial pathogens (e.g., *Corynebacterium diphtheriae, Neisseria gonorrhoeae*) is suspected. *See the discussion in Diagnosis of Group A Streptococcal Pharyngitis. Neg., negative result; pos., positive result.

Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for rating recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.

INTRODUCTION

Definition. Group A streptococcal pharyngitis (pharyngotonsillitis) is an acute infection of the oropharynx and/or nasopharynx that is caused by *Streptococcus pyogenes.*

Objectives. The objective of this practice guideline is to provide recommendations for the accurate diagnosis and optimal treatment of group A streptococcal pharyngitis in children and in adults.

Options. The physician caring for a patient with acute pharyngitis must formulate a differential diagnosis and determine which, if any, confirmatory tests should be performed. Should clinical and laboratory evaluation result in a diagnosis of group A β-hemolytic streptococcal pharyngitis, penicillin remains the drug of choice for treatment. For the patient allergic to penicillin, several alternative antimicrobial agents are available.

Outcomes. The desired outcomes are as follows: prevention of acute rheumatic fever; prevention of suppurative complications (e.g., peritonsillar abscess, cervical lymphadenitis, and mastoiditis); improvement in clinical symptoms and signs; rapid decrease in infectivity, to reduce transmission of group A β-hemolytic streptococci to family members, classmates, and other close contacts of the patient, and to allow the rapid resumption of usual activities; and minimization of potential adverse effects of inappropriate antimicrobial therapy.

Evidence. A large number of clinical trials of diagnostic and treatment strategies for group A streptococcal pharyngitis were reviewed. The reports were examined for indicators of quality. Studies of treatment, for example, were evaluated for randomization, blinding, use of streptococcal typing to differentiate treatment failures from new infections, duration and timing of follow-up examinations, and statistical power [5, 6]. For particular recommendations and statements, the strength of the supporting evidence and quality of the data are rated by use of an Infectious Diseases Society of America–United States Public Health Service grading system [6] (table 1). A rating of A–E indicates the strength of a recommendation, and the Roman numerals I–III indicate the quality of the supporting evidence. These ratings are presented in parentheses after specific recommendations.

Valuation of options. In evaluating diagnostic options, a high value was placed on selecting the diagnostic test with the greatest accuracy in differentiating acute pharyngitis due to group A β-hemolytic streptococci from that due to other agents. For evaluation of treatment, particularly high values were assigned to proven clinical and bacteriologic efficacy, safety, spectrum of antimicrobial activity, and relative cost.

Benefits and costs. Group A β-hemolytic streptococcus is the most common bacterial cause of acute pharyngitis [7]. Accurate diagnosis followed by appropriate antimicrobial therapy is important for the reasons stated above (see the section "Outcomes").

Although acute pharyngitis is one of the most frequent illnesses for which pediatricians and other primary care physicians are consulted, only a relatively small percentage of patients with this condition are infected by group A streptococci. Moreover, the signs and symptoms of group A streptococcal and nonstreptococcal pharyngitis overlap so broadly that accurate diagnosis on clinical grounds alone is usually impossible [8].

With the exception of very rare infections by certain other pharyngeal bacterial pathogens (e.g., *Corynebacterium diphtheriae* and *Neisseria gonorrhoeae;* see table 2), antimicrobial therapy is of no proven benefit as treatment for acute pharyngitis due to bacteria other than group A streptococci. Therefore, it is extremely important that physicians exclude the diagnosis of group A streptococcal pharyngitis to prevent inappropriate administration of antimicrobials to large numbers of patients with pharyngitis. Not only does such therapy unnecessarily expose patients to the expense and hazards of antimicrobial therapy, it contributes to the emergence of antibiotic-resistant bacteria, which is being reported with increasing frequency in the United States and elsewhere.

If the clinical suspicion of group A streptococcal pharyngitis is supported by identification of the organism in specimens from the pharynx, the clinician should select the most appropriate antimicrobial therapy, choosing from a number of antimicrobial agents known to be effective against group A streptococci. Because the cost to the patient may vary as much as 20-fold, depending on the drug chosen, our recommendations are based on specificity, safety, and cost.

DIAGNOSIS OF GROUP A STREPTOCOCCAL PHARYNGITIS

Differential Diagnosis

Nonbacterial infectious agents. Viruses are the most common cause of acute pharyngitis (table 2) [7]. Respiratory viruses, such as adenovirus, influenza virus, parainfluenza virus, rhinovirus, and respiratory syncytial virus, frequently cause acute pharyngitis. Other viral agents of acute pharyngitis include coxsackievirus, echoviruses, and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by the other clinical features of infectious mononucleosis (e.g., generalized lymphadenopathy and splenomegaly). Systemic infections with cytomegalovirus, rubella virus, measles virus, and a number of other viral agents may be associated with acute pharyngitis. Other pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* are uncommon causes of acute pharyngitis.

Bacteria. Group A β-hemolytic streptococci are the most common cause of bacterial pharyngitis, but other bacteria can also cause acute pharyngitis (table 2). These include groups C

Table 2. Microbial etiology of acute pharyngitis.

Type of pharyngitis, pathogen	Associated disorder(s) or symptom(s)
Bacterial	
Streptococci	
Group A	Tonsillitis and scarlet fever
Groups C and G	Tonsillitis and scarlatiniform rash
Mixed anaerobes	Vincent's angina
Neisseria gonorrhoeae	Tonsillitis
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 and acute respiratory disease
Herpes simplex virus types 1 and 2	Gingivostomatitis
Parainfluenza virus	Cold and croup
Coxsackievirus A	Herpangina and 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*	Pneumonia and bronchitis
Chlamydial	
Chlamydia psittaci	Acute respiratory disease and pneumonia
Chlamydia pneumoniae	Pneumonia

NOTE. Modified from [9].

and G β-hemolytic streptococci and *C. diphtheriae* [10–13]. *Arcanobacterium haemolyticum* is a rare cause of acute pharyngitis that may be associated with a rash similar to that seen in cases of scarlet fever, particularly in teenagers [14, 15]. *N. gonorrhoeae* can occasionally cause acute pharyngitis in sexually active persons, and infections with other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* and mixed infections with anaerobic bacteria (e.g., Vincent's angina) are rare causes of acute pharyngitis.

As is evident from this list of potential etiologic agents, group A β-hemolytic streptococcal pharyngitis is the only commonly occurring form of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, for a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether the pharyngitis is attributable to group A β-hemolytic streptococci.

Clinical Diagnosis

Acute group A β-hemolytic streptococcal pharyngitis has certain characteristic epidemiological and clinical features [8, 16, 17] (table 3). The disorder is primarily a disease of children 5–15 years of age, and, in temperate climates, it usually occurs in the winter and early spring. Patients with group A β-hemolytic streptococcal pharyngitis commonly present with sore throat (generally of sudden onset), severe pain on swallowing, and fever. Headache, nausea, vomiting, and abdominal pain may also be present, especially in children [8]. On examination, patients have tonsillopharyngeal erythema, with or without exudates, and tender, enlarged anterior cervical lymph nodes (lymphadenitis). Other findings may include a beefy, red, swollen uvula; petechiae on the palate; excoriated nares (especially in infants); and a scarlatiniform rash. However, none of these findings is specific for group A β-hemolytic streptococcal pharyngitis. Conversely, 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 strongly suggest a viral rather than a streptococcal etiology.

Table 3. Clinical and epidemiological findings and diagnosis of pharyngitis due to group A β-hemolytic streptococci (GABS).

Features suggestive of GABS as etiologic agent
Sudden onset
Sore throat
Fever
Headache
Nausea, vomiting, and abdominal pain
Inflammation of pharynx and tonsils
Patchy discrete exudate
Tender, enlarged anterior cervical nodes
Patient aged 5–15 years
Presentation in winter or early spring
History of exposure
Features suggestive of viral etiology
Conjunctivitis
Coryza
Cough
Diarrhea

NOTE. Clinical and epidemiological findings, either individually or collectively, cannot definitively predict the presence of group A β-hemolytic streptococcal pharyngitis. They can, however, identify persons for whom the probability of group A β-hemolytic streptococcal pharyngitis is high (and for whom throat culture or rapid antigen detection testing is indicated) or low (thus, neither is required).

Microbiological Tests

Who should be tested for group A β-hemolytic streptococcal pharyngitis? When deciding whether to perform a microbiological test for a patient presenting with acute pharyngitis, the clinical and epidemiological findings mentioned above should be considered first. A history of close contact with a well-documented case of streptococcal pharyngitis is helpful, as is an awareness of a high prevalence of group A β-hemolytic streptococcal infections in the community. Testing usually need not be done for patients with acute pharyngitis that has clinical and epidemiological features not suggestive of a group A streptococcal etiology. Selective use of diagnostic studies for group A β-hemolytic streptococci will increase not only the proportion of positive test results but also the percentage of cases in which patients have positive test results and are truly infected, rather than merely *Streptococcus* carriers (A-II).

Efforts have been made to incorporate the clinical and epidemiological features of acute pharyngitis into scoring systems that attempt to predict the probability that a particular illness is caused by group A β-hemolytic streptococci [18–21]. These clinical scoring systems are helpful in identifying patients who are at such low risk of streptococcal infection that performance of a throat culture or an RADT is usually unnecessary. However, the signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly for diagnosis to be made with the requisite diagnostic precision on clinical grounds alone. The clinical diagnosis of group A β-hemolytic streptococcal pharyngitis cannot be made with certainty even by the most experienced physicians, and bacteriologic confirmation is required (A-II).

Special considerations in the diagnosis of acute pharyngitis in adults. Group A streptococci cause 15%–30% of cases of acute pharyngitis in pediatric patients but only 5%–10% of such illnesses in adults [22–24]. However, the risk of acute pharyngitis due to group A streptococci is higher for parents of school-aged children and adults whose occupation brings them into close association with children. The risk of a first attack of acute rheumatic fever is extremely low in adults, even

if they should have an undiagnosed and untreated episode of streptococcal pharyngitis.

Because of these epidemiological distinctions, the use of a clinical algorithm without microbiological confirmation has recently been recommended as an acceptable alternative basis for diagnosis of infection in adults [25, 26]. In emergency department practice, this 4-factor algorithm predicted a positive result of group A streptococcal throat culture with an accuracy of 32%–56%, depending on the number of required clinical features present [20]. Use of this diagnostic strategy would result in treatment of an unacceptably large number of adults with nonstreptococcal pharyngitis; that is an undesirable result in this age group, which has a low prevalence of streptococcal pharyngitis and very low risk of rheumatic fever or rheumatic carditis. However, because of the aforementioned features of acute pharyngitis in adults, exclusion of the diagnosis on the basis of negative RADT results, without confirmation by negative culture results, is an acceptable alternative to diagnosis on the basis of throat culture results. The generally high specificity of RADT should minimize overprescription of antimicrobials for treatment of adults. This latter point is of particular importance in view of national data indicating that antibiotics—frequently, the more expensive, broader-spectrum antibiotics—are prescribed for approximately three-quarters of adults who consult community primary care physicians because of a sore throat [27].

Throat culture. Culture of a throat swab on a sheep-blood agar plate remains the standard for the documentation of the presence of group A streptococci in the upper respiratory tract and for the confirmation of the clinical diagnosis of acute streptococcal pharyngitis [28] (A-II). If done correctly, culture of a single throat swab on a blood agar plate has a sensitivity of 90%–95% for the detection of the presence of group A β-hemolytic streptococci in the pharynx [29] (A-II).

Several variables affect the accuracy of throat culture results. For example, the manner in which the swab is obtained has an important impact on the yield of streptococci from the culture [30, 31]. Throat swab specimens should be obtained from the surface of both tonsils (or tonsillar fossae) and the posterior pharyngeal wall. Other areas of the oral pharynx and mouth are not acceptable sites, and these sites should not be touched with the swab before or after the appropriate areas have been sampled. Health care providers who compromise in trying to obtain a throat swab from an uncooperative child may obtain a specimen that is neither adequate nor representative. In addition, false-negative results may be obtained if the patient has received antibiotics shortly before or at the time the throat swab is obtained.

It has also been reported that the use of anaerobic incubation and selective culture media may increase the proportion of positive culture results [32, 33]. However, data are conflicting with regard to the impact of the atmosphere of incubation and the culture media, and, in the absence of a definite benefit, the increased cost and effort associated with use of anaerobic incubation and selective culture media are difficult to justify, particularly for physicians who process throat cultures in their own offices [32, 34, 35] (A-II).

Another variable that can affect the yield of the throat culture is the duration of incubation. Once the swab is plated, a culture should be incubated at 35°C–37°C for 18–24 h before reading. An additional incubation overnight at room temperature, however, will identify a considerable number of positive throat culture results that would not otherwise have been identified. Thus, although initial therapeutic decisions may be made on the basis of an overnight culture, it is advisable to examine plates that yield negative results at 24 h again at 48 h [36] (A-II).

The clinical significance of the number of group A β-hemolytic streptococcal colonies present on the throat culture plate is problematic. Although patients with true acute group A streptococcal pharyngitis are likely to have more-strongly positive cultures than are patients who are *Streptococcus* carriers, there is so much overlap in the degree of positivity of throat culture results that the differentiation cannot be made accurately on this basis alone [35] (A-II).

Probably the most widely used test for differentiation of group A streptococci from other β-hemolytic streptococci in physicians' offices is the bacitracin disk test. This test provides a presumptive identification on the basis of observation that >95% of group A streptococci demonstrate a zone of inhibition around a disk containing 0.04 U of bacitracin, whereas 83%–97% of non–group A streptococci do not demonstrate this [37, 38].

An alternative and highly specific method of identifying streptococcal serogroups is by detection of the group-specific cell wall carbohydrate antigen directly in isolated bacterial colonies. Commercial kits containing 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 provided by serogroup identification with an antigen detection test [35].

RADT. A disadvantage of culturing a throat swab on blood agar plates is the delay (overnight or longer) in obtaining the result. RADTs have been developed for the identification of group A β-hemolytic streptococci directly from throat swabs. Although these rapid tests are more expensive than blood agar culture, they provide results faster. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk of the spread of group A β-hemolytic streptococci, allowing the patient to return to school or work sooner, and

can reduce the acute morbidity associated with the illness [29, 39, 40] (A-II). The use of RADTs for certain populations (e.g., patients in emergency departments) has been shown to significantly increase the number of patients who are appropriately treated for streptococcal pharyngitis, compared with use of traditional throat cultures [41].

The great majority of the RADTs that are currently available have an excellent specificity of ⩾95%, compared with blood agar plate culture [29] (A-II). This means that false-positive test results are unusual, and, therefore, therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 80%–90%, or even lower, compared with blood agar plate culture (A-II). It has been suggested that most of the false-negative RADT results occur for patients who are merely *Streptococcus* carriers and are not truly infected. However, early studies of first-generation RADTs demonstrated that a large proportion of patients with false-negative RADT results were truly infected with group A β-hemolytic streptococci and were not merely carriers [42].

The first RADTs used latex agglutination methods, were relatively insensitive, and had unclear end points. Newer tests based on EIA techniques offer increased sensitivity and a more sharply defined end point [43]. More recently, RADTs that use optical immunoassay and chemiluminescent DNA probes have become available. These tests may be more sensitive than other RADTs and perhaps even as sensitive as standard throat culture on sheep-blood agar plates [44–46]. However, in view of conflicting data about the optical immunoassay RADT [47] and other commercially available RADTs, as well as the paucity of studies directly comparing the various tests, physicians who use any RADT for diagnosis in children and adolescents and who do not use culture to confirm negative results should do so only after confirming in their own practice that the RADT has a sensitivity similar to that of throat culture [48]. Moreover, the practitioner should be aware that, for some of these tests, the Clinical Laboratory Improvement Act of 1988 does not waive the need for certification; use of those that are not waived requires proper certification of the physician's laboratory.

Neither conventional throat culture nor RADTs accurately differentiate acutely infected persons from asymptomatic *Streptococcus* carriers with intercurrent viral pharyngitis. Nevertheless, they allow physicians to withhold antibiotics from the great majority of patients with sore throats for whom results of culture or RADT are negative. This is of extreme importance, because, nationally, 70% of patients with sore throats who are seen in primary care settings receive prescriptions for antimicrobials [49].

Antistreptococcal antibody titers reflect past and not present immunologic events and are of no value in the diagnosis of acute pharyngitis. They are valuable for confirmation of previous streptococcal infections in patients suspected of having acute rheumatic fever or poststreptococcal acute glomerulonephritis. They also are helpful, in prospective epidemiological studies, for distinguishing patients with acute infection from patients who are carriers.

Recommendations

The diagnosis of acute group A streptococcal pharyngitis should be suspected on clinical and epidemiological grounds and then supported by performance of a laboratory test. A positive result of either throat culture or RADT provides adequate confirmation of the presence of group A β-hemolytic streptococci in the pharynx. However, for children and adolescents, a negative RADT result should be confirmed with a throat culture result, unless the physician has ascertained in his or her own practice that the RADT used is comparable to a throat culture. Because of the epidemiological features of acute pharyngitis in adults (e.g., low incidence of streptococcal infection and extremely low risk of rheumatic fever), diagnosis of this infection in adults on the basis of the results of an RADT, without confirmation of negative RADT results by negative results of culture, is an acceptable alternative to diagnosis on the basis of throat culture results. The generally high specificity of RADTs should minimize overprescription of antimicrobials for treatment of adults (A-II).

With regard to repetition of diagnostic tests, the majority of asymptomatic patients who have group A β-hemolytic streptococci remaining in their upper respiratory tracts after completing a course of antimicrobial therapy are *Streptococcus* carriers [50, 51]. Therefore, follow-up culture of throat swabs is not routinely indicated for asymptomatic patients who have received a complete course of therapy for group A streptococcal pharyngitis (A-II). There are, however, special situations in which asymptomatic persons should have follow-up cultures of throat swabs performed. They should be performed routinely for patients with a history of rheumatic fever and should also be considered for patients who develop acute pharyngitis during outbreaks of either acute rheumatic fever or poststreptococcal acute glomerulonephritis, as well as during outbreaks of group A streptococcal pharyngitis in closed or partially closed communities [48, 51]. Follow-up throat cultures may also be indicated when "ping-pong" spread of group A streptococci has been occurring within a family (B-III). With rare exceptions, follow-up throat cultures are not indicated for asymptomatic patients who have received a complete course of therapy for group A streptococcal pharyngitis.

MANAGEMENT OF GROUP A STREPTOCOCCAL PHARYNGITIS

Antimicrobial therapy is indicated for persons with symptomatic pharyngitis if the presence of the organism in the throat

Table 4. Recommendations for antimicrobial therapy for group A streptococcal pharyngitis.

Route of administration, antimicrobial agent	Dosage	Duration[a]	Rating
Oral			
Penicillin V[b]	Children: 250 mg b.i.d. or t.i.d.	10 days	A-II
	Adolescents and adults: 250 mg t.i.d. or q.i.d.	10 days	A-II
	Adolescents and adults: 500 mg b.i.d.	10 days	C-III
Intramuscular			
Benzathine penicillin G	1.2×10^6 U	1 dose	A-II[c]
	6.0×10^5 U	1 dose[d]	A-II
Mixtures of benzathine and procaine penicillin G	Varies with formulation[e]	1 dose	B-II
Oral, for patients allergic to penicillin			
Erythromycin	Varies with formulation[f]	10 days	A-II
First-generation cephalosporins[g]	Varies with agent	10 days	A-II

[a] Although shorter courses of azithromycin and some cephalosporins have been reported to be effective for treating group A streptococcal upper respiratory tract infections, evidence is not sufficient to recommend these shorter courses for routine therapy at this time.
[b] Amoxicillin is often used in place of oral penicillin V for young children; efficacy appears to be equal. The choice is primarily related to acceptance of the taste of the suspension.
[c] See the discussion of benzathine penicillin G therapy in Management of Group A Streptococcal Pharyngitis.
[d] For patients who weigh <27 kg.
[e] Dose should be determined on basis of the benzathine component. For example, mixtures of 9×10^5 U of benzathine penicillin G and 3×10^5 U of procaine penicillin G contain less benzathine penicillin G than is recommended for treatment of adolescents or adults.
[f] Available as stearate, ethyl succinate, estolate, or base. Cholestatic hepatitis may rarely occur in patients, primarily adults, receiving erythromycin estolate; the incidence is greater among pregnant women, who should not receive this formulation.
[g] These agents should not be used to treat patients with immediate-type hypersensitivity to β-lactam antibiotics.

is confirmed by culture or RADT (figure 1). If there is clinical or epidemiological evidence that results in a high index of suspicion, antimicrobial therapy can be initiated while the physician is waiting for laboratory confirmation, provided that the therapy is discontinued if the diagnosis of streptococcal pharyngitis is not confirmed by results of a laboratory test. Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms [39, 40, 52] (A-I). However, 2 facts should be remembered. First, group A streptococcal pharyngitis is usually a self-limited disease; fever and constitutional symptoms disappear spontaneously within 3–4 days of onset, even without antimicrobial therapy [53]. This makes objective judgment of clinical improvement associated with therapy even more difficult. Second, therapy can be safely postponed for up to 9 days after the onset of symptoms and still prevent the occurrence of the major nonsuppurative sequela, acute rheumatic fever [54] (A-I).

These facts allow the clinician flexibility in initiating antimicrobial therapy during the evaluation of an individual patient with presumed group A streptococcal pharyngitis. Since the first therapeutic studies were published, nearly 50 years ago [55, 56], numerous antimicrobial agents have been examined in clinical trials and have been shown to be capable of eradication of group A streptococci from the upper respiratory tract. However, the only currently recommended antimicrobial therapy that has been examined in controlled studies and has been shown to prevent initial attacks of rheumatic fever is intramuscular repository-penicillin therapy [55, 56] (A-I). These studies were done with procaine penicillin G in oil containing aluminum monostearate [55, 56], a preparation that has since been supplanted by benzathine penicillin G. (For this reason, no regimens listed in table 4 are rated A-I.) Although they are not definitive, there are data indicating that benzathine penicillin G is effective in primary prevention of rheumatic fever (i.e., prevention of an initial attack of rheumatic fever after group A streptococcal pharyngitis) [57, 58]. Benzathine penicillin G has also been shown to decrease the occurrence of cases of rheumatic fever during streptococcal epidemics in military recruit camps [59]. Moreover, benzathine penicillin G has been proven effective in prevention of rheumatic fever in patients who have had a previous episode of the disease (i.e., as secondary prophylaxis) [60] (A-I). Other antimicrobials can effectively eradicate group A streptococci from the upper respiratory tract, and it is assumed that such eradication is a surrogate for effectiveness in primary prevention of rheumatic fever.

Antimicrobial resistance has not been a significant issue in the treatment of group A streptococcal pharyngitis in the United States. No clinical isolate of group A *Streptococcus* anywhere in the world has been documented to be resistant to penicillin. Although relatively high levels of resistance to macrolide and azalide antibiotics have been reported from several countries [61, 62], <5% of group A streptococci isolates in the United States have been shown to be resistant to erythromycin [63]. Although there have been recent isolated reports of macrolide resistance in the United States [64, 65], there is no

evidence that this is widespread at the present time. However, given the increasing use of macrolides and azalides for upper and lower respiratory-tract infections, physicians should be cognizant of local patterns of antimicrobial resistance. Sulfonamides (including trimethoprim-sulfamethoxazole) and tetracyclines are not recommended for treatment of group A streptococcal pharyngitis because of the higher rates of antimicrobial resistance to these agents among group A streptococci and the frequent failure of these agents to eradicate even susceptible organisms from the pharynx.

Antimicrobial Therapy

When selecting an antimicrobial for treatment of group A streptococcal pharyngitis, important issues to consider include efficacy, safety, antimicrobial spectrum (narrow vs. broad), dosing schedule, associated compliance with therapy (i.e., adherence), and cost. These factors influence the cost-effectiveness of antimicrobial therapy.

A number of antibiotics have been shown to be effective in treating group A streptococcal pharyngitis. These include penicillin and its congeners (such as ampicillin and amoxicillin), as well as numerous cephalosporins and macrolides and clindamycin. Penicillin, however, remains the treatment of choice because of its proven efficacy and safety, and its narrow spectrum and low cost [48, 66, 67]. Amoxicillin is often used in place of penicillin V as oral therapy for young children; the efficacy appears to be equal. This choice is primarily related to acceptance of the taste of the suspension. Erythromycin is a suitable alternative for patients allergic to penicillin. First-generation cephalosporins are also acceptable for patients allergic to penicillin who do not manifest immediate-type hypersensitivity to β-lactam antibiotics. For the rare patient infected with an erythromycin-resistant strain of group A *Streptococcus* who is unable to tolerate β-lactam antibiotics, clindamycin is an appropriate alternative.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci. It has been reported that clarithromycin [68], cefuroxime [69], cefixime [70], ceftibuten [71], cefdinir [72], cefpodoxime [73], and azithromycin [74] are effective in eradicating group A streptococci from the pharynx when administered for $\leqslant$5 days, although only the latter 3 are approved for a 5-day course of therapy by the US Food and Drug Administration (FDA) at this writing. However, many studies of short-course therapy lack strict entry criteria, include no assessment of compliance with therapy, and do not include serotypic differentiation between infections for which treatment failed and newly acquired infections. In addition, the spectra of these antibiotics are much broader than is the spectrum of penicillin, and, even when the antibiotics are administered for short courses, they are more expensive [4]. Therefore, use of these shorter courses of oral antimicrobial therapy cannot be endorsed at this time [4, 75].

Attempts to treat pharyngitis due to group A β-hemolytic streptococci with a single daily dose of penicillin have been unsuccessful [76]. In recent years, investigators have demonstrated that once-daily azithromycin [77] and once-daily regimens of several cephalosporins (e.g., cefadroxil [78], cefixime [79, 80], ceftibuten [81], cefpodoxime [73], cefprozil [82], and cefdinir [83]), are effective in eradicating pharyngeal streptococci. Currently, only azithromycin, cefadroxil, cefixime, and cefdinir are FDA approved as once-daily therapy for streptococcal pharyngitis in children.

Preliminary investigations have demonstrated that once-daily amoxicillin therapy is effective treatment for group A β-hemolytic streptococcal pharyngitis [2, 3]. If its effectiveness is 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 β-hemolytic streptococcal pharyngitis.

Antimicrobials for group A streptococcal upper respiratory tract infections may be given either orally or parenterally. Table 4 lists recommended regimens for several antimicrobials proven to be effective for the treatment of uncomplicated group A streptococcal pharyngitis and gives ratings for the quality of the supporting evidence and the data on which the recommendations are based. Intramuscular benzathine penicillin G therapy is preferred for those patients unlikely to complete a full 10-day course of oral therapy.

Recommendations. Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent at a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. On the basis of its narrow spectrum of antimicrobial activity, the infrequency with which it produces adverse reactions, and its modest cost, penicillin is the drug of choice for treatment of patients who are not allergic to it.

Management of Close Contacts and Pharyngeal Carriers

On average, ~25% of asymptomatic persons in the household of each index patient harbor group A streptococci in their upper respiratory tracts [84]. Usually, however, it is not necessary to test these asymptomatic contacts for group A streptococcal colonization or to treat them, if they have positive test results. In those rare situations in which posttreatment testing of an asymptomatic index patient is indicated (see the section "Recommendations" in Diagnosis of Group A Streptococcal Pharyngitis), it is recommended that culture be performed for asymptomatic family contacts and treatment be administered to those with positive culture results.

Close contacts of patients with invasive group A streptococcal infections, such as necrotizing fasciitis or toxic shock syndrome,

may be at increased risk of developing colonization or infection with the invasive strains. Management of such contacts goes beyond the scope of this guideline and has been addressed in detail elsewhere [85].

Recommendations. Except in specific situations in which there is increased risk of frequent infections or of nonsuppurative streptococcal sequelae, routine culture of throat swab specimens obtained from or treatment of asymptomatic household contacts of patients with group A streptococcal pharyngitis is not recommended (B-III).

Management of Patients with Recurrent Episodes of Acute Pharyngitis and Positive Results of Culture or RADT for Group A β-Hemolytic Streptococci

Routine performance of throat culture (or RADT) for asymptomatic persons after they have completed a course of antibiotic therapy is not necessary except in special circumstances (see the section "Recommendations" in Diagnosis of Group A Streptococcal Pharyngitis). Because routine retesting is no longer advised, only those patients who have signs and symptoms of acute pharyngitis that return in the few weeks after completion of therapy are likely to seek reassessment. Should such symptomatic patients again have culture or RADT results positive for group A streptococci, there are several possible explanations: persistence of carriage in the face of intercurrent viral infection [50]; noncompliance with the prescribed antimicrobial regimen [86]; or a new infection with group A streptococci acquired from family, the classroom, or community contacts. A second episode of pharyngitis caused by the original infecting strain of group A *Streptococcus* (i.e., treatment failure) cannot be ruled out, but this occurs rarely [87].

Streptococcus carriers do not ordinarily require further antimicrobial therapy. Carriers have group A β-hemolytic streptococci present in their pharynxes but have no evidence of immunologic responses to the organism [88]. During the winter and spring in temperate climates, as many as 20% of asymptomatic school-aged children may be *Streptococcus* carriers. They may be colonized by group A β-hemolytic streptococci for several months and, during that period, may experience episodes of intercurrent viral pharyngitis. Testing may reveal that these patients have group A β-hemolytic streptococci in their pharynxes, and they appear to have acute streptococcal pharyngitis. *Streptococcus* carriers are unlikely to spread the organism to their close contacts and are at very low risk, if any, for developing suppurative complications or nonsuppurative complications (e.g., acute rheumatic fever) [88]. Moreover, it is much more difficult to eradicate group A streptococci from the upper respiratory tracts of carriers than from patients with acute infections [50]. This has been shown to be true for penicillin therapy and may also be true for some other antimicrobials. In fact, clinical and epidemiological evidence suggests that, in many of the published studies showing that penicillin has relatively high failure rates for eradicating group A streptococci from the upper respiratory tract, the patient population was likely "contaminated" with carriers [89, 90].

In practice, it is difficult to differentiate a carrier with an intercurrent viral infection from a patient with acute streptococcal pharyngitis. Helpful clues include patient age, season of the year, local epidemiology (e.g., the local prevalence of influenza and/or enteroviral illnesses), and the precise nature of the presenting signs and symptoms (see Clinical Diagnosis).

In many instances, however, the clinician may not be able to distinguish persistent carriage from acute infection and will elect to administer another course of antimicrobials. For single episodes of pharyngitis that are associated with laboratory confirmation of group A streptococci and that occur shortly after completion of a course of appropriate antimicrobial therapy, treatment with any of the agents listed in table 4 is appropriate. Because patient compliance with oral antimicrobial therapy often is an issue, a regimen of intramuscular benzathine penicillin G should be considered. For these single second episodes, it is not necessary to obtain additional throat swab specimens for culture after the second course of therapy unless the patient remains or becomes symptomatic or unless special circumstances are present (see the section "Recommendations" in Diagnosis of Group A Streptococcal Pharyngitis).

An even more challenging clinical circumstance is the person (usually a school-aged child or adolescent) who, within a period of months to years, experiences multiple episodes of acute pharyngitis for which culture or RADT results are positive for group A streptococci. It is likely that most of these patients are carriers experiencing nonstreptococcal infections. For a patient with frequent distinct episodes, information regarding the clinical response to antibiotic therapy and the presence or absence of group A streptococci in cultures of throat swabs obtained during asymptomatic intervals is helpful in distinguishing persistent carriage from recurrent episodes of acute pharyngitis. Serotyping or genotyping of streptococcal isolates recovered from specimens obtained during distinct episodes from an individual patient may also assist in arriving at this determination, but such studies are available only from specialized research laboratories.

If a physician suspects that "ping-pong" spread of infections is the explanation for multiple recurrent episodes of group A streptococcal infections in a family, it may be helpful to obtain specimens simultaneously from all family contacts and treat those for whom culture results are positive (B-III). There is no credible evidence that family pets are reservoirs for group A streptococci or that they contribute to familial spread.

Continuous antimicrobial prophylaxis is not recommended except to prevent the recurrence of rheumatic fever in patients who have experienced a previous episode of rheumatic fever.

Table 5. Recommendations for treatment of symptomatic persons with multiple, recurrent, episodes of pharyngitis proven by culture or rapid antigen detection testing.

Route of administration, antimicrobial agent	Dosage	Duration	Rating
Oral			
Clindamycin	Children: 20–30 mg/kg/day in 3 equally divided doses	10 days	B-II
	Adults: 600 mg/day in 2–4 equally divided doses[a]	10 days	B-III
Amoxicillin–clavulanic acid	Children: 40 mg/kg/day in 3 equally divided doses[b,c]	10 days	B-II
	Adults: 500 mg b.i.d[a,c]	10 days	B-III
Parenteral with or without oral			
Benzathine penicillin G	For im dosages, see table 4[d]	1 dose	B-II
Benzathine penicillin G with rifampin	Rifampin: 20 mg/kg/day orally in 2 equally divided doses	4 days	

NOTE. Macrolides (e.g., erythromycin) and cephalosporins are not included in the table, because there are insufficient data to support their efficacy in this specific circumstance.

[a] Adult doses are extrapolated from data for children. Use of this drug for this indication has not been studied in adults.

[b] Maximum dose, 750 mg of amoxicillin per day.

[c] Refers to amoxicillin component. Note that two 250-mg tablets of amoxicillin–clavulanic acid are not equivalent to one 500-mg tablet, because both the 250-mg and the 500-mg tablets contain 125 mg of clavulanic acid.

[d] Treatment with benzathine penicillin G is useful for patients in whom compliance with previous courses of oral antimicrobials is in question. Addition of rifampin to benzathine penicillin G may be beneficial for eradication of streptococci from the pharynx [95]. It has also been reported that addition of rifampin (20 mg/kg/day, once daily) during the final 4 days of a 10-day course of oral penicillin V may achieve high rates of eradication [96]. The maximum daily dose of rifampin is 600 mg; rifampin is relatively contraindicated for pregnant women.

Surgical removal of the tonsils may be considered for the rare patient whose symptomatic episodes do not diminish in frequency over time and for whom no alternative explanation for the recurrent pharyngitis is evident. Tonsillectomy may decrease the number of recurrences of symptomatic pharyngitis in some patients, but only for a limited time [91] (A-I).

There have been no definitive controlled studies of treatment of multiple repeated symptomatic episodes of culture-positive acute pharyngitis in the same person. However, the regimens listed in table 4 have been reported to result in low rates of bacteriologic failure [92–94].

Recommendations. A small percentage of patients will have a second episode of acute pharyngitis with results of throat culture (or RADT) positive for group A streptococci within a short time after completion of a course of antimicrobial therapy. A single such episode may be retreated with the regimens listed in table 4. When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral infections in a carrier from true group A streptococcal infections. Certain antimicrobial agents have been shown to yield high rates of pharyngeal eradication of streptococci under these particular circumstances (A-II). Suggested regimens that use these agents are listed in table 5.

Indicators of the Quality of Care

Indicators of the quality of care of patients with acute pharyngitis include the following: (1) for patients suspected of having group A streptococcal pharyngitis, performance of throat cultures or RADT; (2) for patients with acute pharyngitis and positive tests for group A streptococci, prescription of one of the antimicrobial regimens recommended in table 4; (3) for patients with negative microbiological test results for group A streptococci, withholding or discontinuation of antimicrobial therapy; (4) for asymptomatic patients who have received an adequate course of antimicrobial therapy, omission of routine performance of follow-up cultures or RADT; (5) for asymptomatic family contacts of patients with group A streptococcal pharyngitis, avoidance of routine throat cultures or RADT; and (6) avoidance of prescription of continuous long-term antimicrobial prophylaxis to prevent recurrent episodes of acute pharyngitis (except for patients with a history of rheumatic fever).

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