AHA Scientific Statement

Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis

A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research

*Endorsed by the American Academy of Pediatrics**

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Abstract—Primary prevention of acute rheumatic fever is accomplished by proper identification and adequate antibiotic treatment of group A β-hemolytic streptococcal (GAS) tonsillopharyngitis. Diagnosis of GAS pharyngitis is best accomplished by combining clinical judgment with diagnostic test results, the criterion standard of which is the throat culture. Penicillin (either oral penicillin V or injectable benzathine penicillin) is the treatment of choice, because it is cost-effective, has a narrow spectrum of activity, and has long-standing proven efficacy, and GAS resistant to penicillin have not been documented. For penicillin-allergic individuals, acceptable alternatives include a narrow-spectrum oral cephalosporin, oral clindamycin, or various oral macrolides or azalides. The individual who has had an attack of rheumatic fever is at very high risk of developing recurrences after subsequent GAS pharyngitis and needs continuous antimicrobial prophylaxis to prevent such recurrences (secondary prevention). The recommended duration of prophylaxis depends on the number of previous attacks, the time elapsed since the last attack, the risk of exposure to GAS infections, the age of the patient, and the presence or absence of cardiac involvement. Penicillin is again the agent of choice for secondary prophylaxis, but sulfadiazine or a macrolide or azalide are acceptable alternatives in penicillin-allergic individuals. This report updates the 1995 statement by the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee. It includes new recommendations for the diagnosis and treatment of GAS pharyngitis, as well as for the secondary prevention of rheumatic fever, and classifies the strength of the recommendations and level of evidence supporting them. (***Circulation*. 2009;119:1541-1551.**)

Key Words: AHA Scientific Statements ■ pediatrics ■ infectious diseases ■ prevention ■ rheumatic heart disease ■ rheumatic fever ■ streptococcal pharyngitis

This scientific statement is an update of a 1995 statement on prevention of rheumatic fever by this committee.[1] Prevention of both initial and recurrent attacks of rheumatic fever depends on control of group A β-hemolytic streptococcal (GAS) tonsillopharyngitis (strep throat). Prevention of first attacks (primary prevention) is accomplished by proper identification and adequate antibiotic treatment of streptococcal infections. The individual who has had an attack of

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on November 25, 2008. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. LS-1968). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com

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rheumatic fever is at high risk of developing recurrences after subsequent GAS pharyngitis and needs continuous antimicrobial prophylaxis for years to prevent such recurrences (secondary prevention).[2–6]

In developing areas of the world, acute rheumatic fever and rheumatic heart disease are estimated to affect nearly 20 million people and are the leading causes of cardiovascular death during the first 5 decades of life.[7] In contrast, the incidence of acute rheumatic fever has decreased dramatically in most developed countries.[8] In certain areas of the United States, a few localized outbreaks in civilian and military populations were reported in the 1980s.[8,9] This reappearance of acute rheumatic fever serves as a reminder of the importance of continued attention to prevention of rheumatic fever in this and other developed countries; however, currently, the overall incidence of acute rheumatic fever remains very low in most areas of the United States.[10,11] The recommendations in the present statement are primarily based on this assumption. Physicians practicing in areas outside the United States with a higher incidence of acute rheumatic fever or in areas of the United States experiencing an outbreak of acute rheumatic fever need to take this into consideration.

The writing group was charged with the task of performing an assessment of the evidence and assigning a classification of recommendations and a level of evidence (LOE) to each recommendation. The American College of Cardiology/American Heart Association (AHA) classification system was used as follows:

Classification of Recommendations:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts, cases studies, or standard of care.

Prevention of Initial Attacks (Primary Prevention)

GAS infections of the pharynx are the precipitating cause of rheumatic fever. During epidemics over a half century ago, as many as 3% of untreated acute streptococcal sore throats were followed by rheumatic fever; in endemic infections, the incidence of rheumatic fever is substantially less.[12] Appropriate antibiotic treatment of streptococcal pharyngitis prevents acute rheumatic fever in most cases.[13] Unfortunately, at least one third of episodes of acute rheumatic fever result from inapparent streptococcal infections.[14] In addition, some symptomatic patients do not seek medical care. In these instances, rheumatic fever is not preventable.

Diagnosis of Streptococcal Infections

Prevention of initial episodes of acute rheumatic fever requires accurate recognition and proper antibiotic treatment of GAS pharyngitis. Streptococcal skin infections (impetigo or pyoderma) have not been proven to lead to acute rheumatic fever and are not discussed here. Acute pharyngitis is caused considerably more often by viruses than by bacteria. Viruses that commonly cause pharyngitis include influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, respiratory syncytial virus, Epstein-Barr virus, enteroviruses, and herpesviruses. Other causes of acute pharyngitis include groups C and G streptococci, *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Arcanobacterium hemolyticum*, and human immunodeficiency virus (HIV).

GAS pharyngitis is primarily a disease of children 5 to 15 years of age, and in temperate climates, it usually occurs in the winter and early spring. GAS is an uncommon cause of pharyngitis in preschool children, but outbreaks in child care settings have been reported.[15,16] However, rheumatic fever is rare in children younger than 3 years of age in the United States. Initial attacks of rheumatic fever are also rare in adults, but recurrences are well documented.

Clinical findings suggestive of GAS as the cause of an episode of acute pharyngitis (Table 1) include sore throat (generally of sudden onset), pain on swallowing, fever of varying degree (usually from 101°F to 104°F), and headache; abdominal pain, nausea, and vomiting may also occur, especially in children. Additional clinical findings include tonsillopharyngeal erythema with or without exudates, anterior cervical lymphadenitis, soft palate petechiae, beefy red swollen uvula, and a scarlatiniform rash. None of these clinical manifestations individually is specific enough to diagnose GAS pharyngitis, and these clinical signs and symptoms can occur with other upper respiratory tract infections. These clinical findings are noted primarily in children older than 3 years of age and in adults. Clinical findings in younger children can be different and less specific. For example, infants with GAS upper respiratory tract infections may present with excoriated nares or purulent nasal discharge. A history of close contact with a well-documented case of GAS pharyngitis may be helpful in making the diagnosis, as is an awareness of a high prevalence of GAS infections in the community. Clinical findings highly suggestive of a viral cause of an episode of acute pharyngitis include coryza, hoarseness, cough, diarrhea, conjunctivitis, and a characteristic viral enanthem and/or exanthem (Table 1).

Accurate differentiation of GAS pharyngitis from pharyngitis caused by other pathogens based on history and clinical findings is often difficult even for experienced clinicians. Therefore, some form of microbiological confirmation, with either a throat culture or a rapid antigen detection test (RADT), is required for the diagnosis of GAS pharyngitis

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Table 1. Clinical and Epidemiological Findings and Diagnosis of GAS Pharyngitis

Features suggestive of GAS as causative agent
Sudden-onset sore throat
Pain on swallowing
Fever
Scarlet fever rash
Headache
Nausea, vomiting, and abdominal pain
Tonsillopharyngeal erythema
Tonsillopharyngeal exudates
Soft palate petechiae ("doughnut" lesions)
Beefy, red, swollen uvula
Tender, enlarged anterior cervical nodes
Patient 5 to 15 years of age
Presentation in winter or early spring (in temperate climates)
History of exposure
Features suggestive of viral origin
Conjunctivitis
Coryza
Hoarseness
Cough
Diarrhea
Characteristic exanthems
Characteristic enanthems

(Class I, LOE B).[17] Neither the blood agar plate culture nor the RADT can accurately differentiate individuals with bona fide GAS pharyngitis from GAS carriers (defined as individuals with positive throat cultures for GAS without an immunologic response to GAS) with intercurrent viral pharyngitis. However, they do facilitate the withholding of antibiotics from the great majority of patients with sore throats, whose cultures or RADTs are negative, and this is extremely important. Pharyngeal carriage of GAS is a common finding, particularly in school-age children. In the winter and early spring, as many as 15% of school-age children may be asymptomatic GAS carriers.[18]

When deciding whether to perform a microbiological test for a patient with acute pharyngitis, the clinical and epidemiological findings in Table 1 need to be considered **(Class I, LOE B)**. If these findings are suggestive of GAS pharyngitis, then a throat culture or RADT should be performed to confirm the diagnosis. It is easier to exclude the diagnosis of GAS pharyngitis accurately than it is to establish the diagnosis accurately. Therefore, for patients with acute pharyngitis and clinical and epidemiological findings suggestive of a viral origin, the pretest probability of GAS is low, and testing usually does not need to be performed **(Class IIb, LOE B)**. Selective use of diagnostic testing for GAS will increase not only the proportion of positive test results but also the proportion of cases in which patients with a positive test are truly infected and not merely GAS carriers with viral pharyngitis. Although testing asymptomatic household contacts of children with GAS pharyngitis for GAS is not routinely recommended, throat swab specimens should be obtained from all household contacts of a child who has acute rheumatic fever, and if the test results are positive, that contact should be treated.

Adults with acute pharyngitis have a much lower incidence of GAS infections than children do. In addition, the risk of an initial attack of acute rheumatic fever is extremely low in adults, even those with an undiagnosed and untreated episode of GAS pharyngitis. Therefore, the use of a clinical algorithm without microbiological confirmation has been recommended recently by some authors as an acceptable strategy for diagnosing GAS pharyngitis in adults but not children.[19] However, use of this approach could result in the receipt of inappropriate antimicrobial therapy by an unacceptably large number of adults with nonstreptococcal pharyngitis and is not recommended **(Class III, LOE B)**.[17,20,21]

Throat Culture

Throat culture is the conventional method for establishing the diagnosis of GAS pharyngitis and is the criterion standard. In an untreated patient with GAS pharyngitis, a properly obtained (by vigorous swabbing of both tonsils and posterior pharynx) throat culture is almost always positive; however, a positive throat culture may reflect chronic colonization by GAS, and the acute illness may be caused by another agent. Quantitation of GAS from the throat swab culture cannot be used to differentiate carriage from infection, because sparse growth may be associated with true infection. A negative throat culture permits the physician to withhold antibiotic therapy from the large majority of patients with sore throats.

Antigen Detection Tests

Many GAS antigen detection tests are available commercially. These tests vary in method. Most of these tests have a high degree of specificity, but their sensitivity in clinical practice can be unacceptably low. Therefore, treatment is indicated for the patient with acute pharyngitis who has a positive RADT **(Class I, LOE B)**. As with the throat culture, a positive RADT may reflect chronic colonization by GAS, and the acute illness may be caused by another agent. With most RADTs, a negative test does not exclude the presence of GAS, and a throat culture should be performed **(Class I, LOE B)**.[17,22] Newer tests have been developed that may be more sensitive than other RADTs and perhaps even as sensitive as blood agar plate cultures.[23,24] However, the definitive studies to determine whether some RADTs are significantly more sensitive than others and whether any of the RADTs are sensitive enough to be used routinely in children without throat culture confirmation of negative test results have not been performed. Some experts believe that physicians who use an RADT without culture backup in children and adolescents should compare the results of that specific RADT with those of blood agar plate cultures to confirm adequate sensitivity in their practice **(Class IIa, LOE C)**.

Because of the epidemiological features of acute pharyngitis in adults (eg, low incidence of GAS infections and extremely low risk of acute rheumatic fever), diagnosis of GAS pharyngitis in most adults on the basis of an RADT alone, without confirmation of negative RADT results by a negative throat

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Table 2. Primary Prevention of Rheumatic Fever (Treatment of Streptococcal Tonsillopharyngitis)*

Agent	Dose	Mode	Duration	Rating
Penicillins				
Penicillin V (phenoxymethyl penicillin)	Children: 250 mg 2 to 3 times daily for ≤27 kg (60 lb); children >27 kg (60 lb), adolescents, and adults: 500 mg 2 to 3 times daily	Oral	10 days	IB
	or			
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days	IB
	or			
Benzathine penicillin G	600 000 U for patients ≤27 kg (60 lb); 1 200 000 U for patients >27 kg (60 lb)	Intramuscular	Once	IB
For individuals allergic to penicillin				
Narrow-spectrum cephalosporin† (cephalexin, cefadroxil)	Variable	Oral	10 days	IB
	or			
Clindamycin	20 mg/kg per day divided in 3 doses (maximum 1.8 g/d)	Oral	10 days	IIaB
	or			
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days	IIaB
	or			
Clarithromycin	15 mg/kg per day divided BID (maximum 250 mg BID)	Oral	10 days	IIaB

Rating indicates classification of recommendation and LOE (eg, IB indicates class I, LOE B); BID, twice per day.

*For other acceptable alternatives, see text. The following are not acceptable: sulfonamides, trimethoprim, tetracyclines, and fluoroquinolones.

†To be avoided in those with immediate (type I) hypersensitivity to a penicillin.

culture, is reasonable and an acceptable alternative to diagnosis on the basis of throat culture results **(Class IIa, LOE C)**.[19]

Streptococcal Antibody Tests

Antistreptococcal antibody titers reflect past and not present immunologic events and therefore cannot be used to determine whether an individual with pharyngitis and GAS in the pharynx is truly infected or merely a streptococcal carrier. When present, elevated or rising antistreptococcal antibody titers provide reliable confirmation of a recent GAS infection and are of value in identifying a preceding GAS infection in a patient suspected of having rheumatic fever. The most commonly used and commercially available antibody assays are antistreptolysin O and antideoxyribonuclease B. These tests are valuable in patients who have possible nonsuppurative complications of GAS infections (acute rheumatic fever or acute glomerulonephritis). The antistreptolysin O test is usually obtained first, and if it is not elevated, an antideoxyribonuclease B test may be performed. Antistreptolysin O titers begin to rise approximately 1 week and peak 3 to 6 weeks after the infection. Antideoxyribonuclease B titers begin to rise 1 to 2 weeks and peak 6 to 8 weeks after the infection. Elevated titers for both tests may persist for several months after even uncomplicated GAS infections.

It is not uncommon for laboratory personnel and physicians to misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are higher among school-age children than among adults.[25] Both the traditional antistreptolysin O and antideoxyribonuclease B tests are neutralization assays. Newer tests use latex agglutination or nephelometric assays. Unfortunately, these newer tests have not been well standardized against the traditional neutralization assays.[26] Physicians need to be aware of these potential problems when interpreting the results of streptococcal serological testing performed on their patients.

A commercially available slide agglutination test for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, Conn). This test is less well standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection **(Class III, LOE B)**.[27,28]

Recommended Treatment Schedules

Prevention of rheumatic fever requires adequate therapy for GAS pharyngitis. In selecting a regimen for the treatment of GAS pharyngitis, physicians should consider various factors, including bacteriologic and clinical efficacy, ease of adherence to the recommended regimen (frequency of daily administration, duration of therapy, and palatability), cost, spectrum of activity of the selected agent, and potential side effects. No regimen eradicates GAS from the pharynx in 100% of treated patients, even though 100% of GAS demonstrate in vitro susceptibility to all β-lactam agents (penicillins and cephalosporins).

Intramuscular benzathine penicillin G and oral penicillin V are the recommended antimicrobial drugs for the treatment of GAS, except in individuals with histories of penicillin allergy (**Class I, LOE B**; Table 2). The only currently recommended antimicrobial therapy that has been investigated in controlled studies and demonstrated to prevent initial attacks of acute rheumatic fever is intramuscular repository-penicillin therapy.[29,30] These studies were performed with procaine penicillin G in oil containing aluminum monostearate, a preparation that subsequently has been replaced by benzathine penicillin G. For this reason, none of the regimens listed

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in Table 2 have been given class I, LOE A ratings. Penicillin has a narrow spectrum of activity, long-standing proven efficacy, and is an inexpensive regimen. GAS resistant to penicillin have never been documented. Penicillin may be administered intramuscularly or orally depending on the physician's assessment of the patient's likely adherence to an oral regimen and the risks of rheumatic fever in a particular population. Even when started as long as 9 days after the onset of acute illness, penicillin effectively prevents primary attacks of rheumatic fever.[31] Therefore, a 24- to 48-hour delay to process the throat culture before antibiotic therapy is started does not increase the risk of rheumatic fever. However, early diagnosis (eg, by rapid antigen test) and therapy may reduce the period of infectivity and morbidity, which would allow the patient to return to normal activity sooner. Patients are considered no longer contagious after 24 hours of antibiotic therapy.[32]

Oral Penicillins

The oral antibiotics of choice are penicillin V and amoxicillin (Table 2). Comparative clinical trials used penicillin V dosages of 40 mg/kg (not to exceed 750 mg for those weighing <27 kg) per 24 hours, given in 3 equally divided doses. Generally, 250 mg 2 times daily is recommended for most children **(Class I, LOE B)**.[33,34] Little information is available about comparable penicillin doses in adults. A dose of 500 mg 2 to 3 times daily is recommended for adolescents and adults **(Class I, LOE B)**. All patients should continue to take penicillin regularly for an entire 10-day period, even though they likely will be asymptomatic after the first few days **(Class I, LOE A)**. Penicillin V is preferred to penicillin G because it is more resistant to gastric acid. An oral, time-released formulation of amoxicillin (Moxatag; Middle-Brook Pharmaceuticals, Westlake, Tex) was recently approved by the US Food and Drug Administration for once-daily therapy of GAS pharyngitis in those 12 years of age and older. In comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum 1000 mg) for 10 days has been shown to be effective for GAS pharyngitis **(Class I, LOE B)**.[35–38] This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence, and is relatively inexpensive, and amoxicillin suspension is considerably more palatable than penicillin V suspension.

Intramuscular Benzathine Penicillin G

Benzathine penicillin G should be considered particularly for patients who are unlikely to complete a 10-day course of oral therapy and for patients with personal or family histories of rheumatic fever or rheumatic heart disease or environmental factors (such as crowded living conditions or low socioeconomic status) that place them at enhanced risk for rheumatic fever **(Class IIa, LOE B)**.[39–42] Benzathine penicillin G (Bicillin L-A; King Pharmaceuticals, Bristol, Tenn) should be given as a single injection in a large muscle mass. This formulation is painful; injections that contain procaine penicillin in addition to benzathine penicillin G (Bicillin C-R) are less painful. Less discomfort is associated with intramuscular benzathine penicillin G if the medication is warmed to room temperature before administration.

The recommended dosage of benzathine penicillin G is 600 000 U IM for patients who weigh 27 kg (60 lb) or less and 1 200 000 U for patients who weigh more than 27 kg. The combination of 900 000 U of benzathine penicillin G and 300 000 U of procaine penicillin G (Bicillin C-R 900/300) is satisfactory therapy for most smaller children.[43] The efficacy of this combination for heavier patients such as large teenagers or adults requires further study.

Allergic reactions to penicillin are more common in adults than in children. Reactions occur in only a small percentage of patients, are more frequent after injection, and include urticaria and angioneurotic edema. A serum sickness–like reaction characterized by fever and joint pain may be mistaken for acute rheumatic fever. Anaphylaxis is rare, especially in children. A careful history regarding allergic reactions to penicillin should be obtained.

Other Antimicrobial Agents

Oral Cephalosporins

A 10-day course of a narrow-spectrum oral cephalosporin is recommended for most penicillin-allergic individuals **(Class I, LOE B)**. Several reports indicate that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx.[44–47] Analysis of these data suggest that the difference in eradication is due mainly to a higher rate of eradication of carriers included unintentionally in these clinical trials. Narrow-spectrum cephalosporins such as cefadroxil or cephalexin are much preferred to broad-spectrum cephalosporins such as cefaclor, cefuroxime, cefixime, cefdinir, and cefpodoxime. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should not be used in patients with immediate (anaphylactic-type) hypersensitivity to penicillin.[48]

Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin, and the former agents are more likely to select for antibiotic-resistant flora. Other reports suggest that a 5-day course with selected oral broad-spectrum cephalosporins is comparable to a 10-day course of oral penicillin in eradicating GAS from the pharynx.[49–52] Some of these regimens are not currently approved by the Food and Drug Administration, and further studies are warranted to expand and confirm these observations before these shorter-course regimens can be recommended.

Oral Clindamycin

Clindamycin resistance among GAS isolates in the United States is ≈1%, and this is a reasonable agent for treating penicillin-allergic patients (**Class IIa, LOE B**; Table 2).

Macrolides

The use of an oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is reasonable for patients allergic to penicillins **(Class IIa, LOE B)**. Ten days of therapy is indicated, except for azithromycin, which is given for 5 days (Table 2). Macrolides (erythromycin and clarithromycin), and to a much lesser extent azalides (azithromycin), can cause prolongation of the QT interval in a dose-dependent manner. Because macrolides are metabolized extensively by cytochrome P-450 3A, they should not be taken concurrently with inhibitors of cytochrome P-450 3A such as

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azole antifungal agents, HIV protease inhibitors, and some selective serotonin reuptake inhibitor antidepressants.[53,54] Erythromycin might be considered but is associated with substantially higher rates of gastrointestinal side effects than the other agents **(Class IIb, LOE B)**. Strains of GAS resistant to these agents have been highly prevalent in some areas of the world, which has resulted in treatment failures.[55] In recent years, macrolide resistance rates among pharyngeal isolates in most areas of the United States have been approximately 5% to 8%.[56]

Other Considerations

Studies suggesting that β-lactamase–producing upper respiratory tract flora may interfere with penicillin in the treatment of GAS pharyngitis have not been confirmed.[57] Antibiotic therapy directed against these organisms remains controversial and is not indicated in patients with acute pharyngitis **(Class III, LOE B)**.

Certain antimicrobials are not recommended for treatment of group A streptococcal upper respiratory tract infections. Tetracyclines should not be used because of the high prevalence of resistant strains **(Class III, LOE B)**. Sulfonamides and trimethoprim-sulfamethoxazole do not eradicate GAS in patients with pharyngitis and should not be used to treat active infections **(Class III, LOE B)**.[58] Older fluoroquinolones (eg, ciprofloxacin) have limited activity against GAS and should not be used to treat GAS pharyngitis **(Class III, LOE B)**.[59] Newer fluoroquinolones (eg, levofloxacin, moxifloxacin) are active in vitro against GAS but are expensive and have an unnecessarily broad spectrum of activity, and therefore, they are not recommended for routine treatment of GAS pharyngitis **(Class III, LOE B)**.[60]

Other Treatment Recommendations

Follow-Up Throat Cultures

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS are eradicated from the pharynx.[61] Posttreatment throat cultures 2 to 7 days after completion of therapy are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had rheumatic fever and are therefore at unusually high risk for recurrence **(Class I, LOE C)**.

Treatment Failures

Failure to eradicate GAS from the throat occurs more frequently after the administration of oral penicillin than after the administration of intramuscular benzathine penicillin G.[62] Repeated courses of antibiotic therapy are rarely indicated in asymptomatic patients who continue to harbor GAS after appropriate therapy **(Class IIb, LOE C)**. Many patients in whom treatment fails are chronic carriers who have prolonged periods of GAS colonization.[63] A second course of therapy in asymptomatic individuals should be considered only for those with previous rheumatic fever themselves or in members of their families. Symptomatic individuals who continue to harbor GAS in their pharynx after completion of a course of therapy can be retreated with the same antimicrobial agent, given an alternative oral agent, or given an intramuscular dose of benzathine penicillin G, especially if poor adherence to oral therapy is likely; however, expert opinions differ about the most appropriate therapy in this situation **(Class II, LOE C)**. Agents such as a narrow-spectrum cephalosporin, clindamycin, or amoxicillin–clavulanic acid, or the combination of penicillin with rifampin, are reasonable in the treatment of patients with GAS pharyngitis in whom initial penicillin treatment has failed **(Class IIa, LOE B)**.

Carriers

Chronic streptococcal carriers (defined as individuals with positive throat cultures for GAS without clinical findings or immunologic response to GAS antigens) usually do not need to be identified or treated with antibiotics.[18] Streptococcal carriage may persist for many months, and a difficult diagnostic problem arises when symptomatic upper respiratory tract viral infections develop in carriers. Because it is impossible in that setting to distinguish carriers from infected individuals, a single course of appropriate antibiotic therapy should be administered to any patient with acute pharyngitis and evidence of GAS by a throat swab culture or an antigen detection test **(Class I, LOE C)**. Streptococcal carriers appear to be at little risk for development of rheumatic fever. In general, chronic carriers are thought not to be important in the spread of GAS to individuals who live and work around them.[18]

Non-GAS Pharyngitis

Both group C and group G β-hemolytic streptococci can cause acute pharyngitis with clinical features similar to those of GAS pharyngitis. Group C streptococci are a relatively common cause of acute pharyngitis among college students and among adults who go to an emergency department for treatment.[64,65] Acute rheumatic fever has not been described as a complication of either group C or group G streptococcal pharyngitis; therefore, 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. However, there is currently no convincing evidence 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.

Prevention of Recurrent Attacks of Rheumatic Fever (Secondary Prevention)

General Considerations

An individual with a previous attack of rheumatic fever in whom GAS pharyngitis develops is at high risk for a recurrent attack of rheumatic fever. A recurrent attack can be associated with worsening of the severity of rheumatic heart disease that developed after a first attack, or less frequently with the new onset of rheumatic heart disease in individuals who did not develop cardiac manifestations during the first attack. Prevention of recurrent episodes of GAS pharyngitis is the most effective method to prevent the development of severe rheumatic heart disease. A GAS infection need not be symptomatic to trigger a recurrence. Furthermore, rheumatic fever recurrence can occur even when a symptomatic infection is treated optimally. For these reasons, prevention of recurrent rheumatic fever (secondary prophylaxis) requires continuous antimicrobial prophylaxis rather than recognition

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Table 3. Duration of Secondary Rheumatic Fever Prophylaxis

Category	Duration After Last Attack	Rating
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis (see text)	IC
Rheumatic fever with carditis but no residual heart disease (no valvular disease*)	10 years or until 21 years of age (whichever is longer)	IC
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)	IC

Rating indicates classification of recommendation and LOE (eg, IC indicates class I, LOE C).

*Clinical or echocardiographic evidence.

and treatment of acute episodes of streptococcal pharyngitis. Continuous prophylaxis is recommended for patients with well-documented histories of rheumatic fever (including cases manifested solely by Sydenham chorea) and those with definite evidence of rheumatic heart disease **(Class I, LOE A)**. Such prophylaxis should be initiated as soon as acute rheumatic fever or rheumatic heart disease is diagnosed. A full therapeutic course of penicillin (as outlined in Table 2) first should be given to patients with acute rheumatic fever to eradicate residual GAS, even if a throat culture is negative at that time. Streptococcal infections that occur in family members of patients with current or previous rheumatic fever should be treated promptly **(Class I, LOE B)**.

Duration of Prophylaxis

Continuous antimicrobial prophylaxis provides the most effective protection from rheumatic fever recurrences. Risk of recurrence depends on several factors. Risk increases with multiple previous attacks, whereas the risk decreases as the interval since the most recent attack lengthens.[4,6,66] In addition, the likelihood of acquiring a GAS upper respiratory tract infection is an important consideration. Individuals with increased exposure to streptococcal infections include children and adolescents, parents of young children, teachers, physicians, nurses and allied health personnel in contact with children, military recruits, and others living in crowded situations (eg, college dormitories). A higher risk of recurrences in economically disadvantaged populations has been demonstrated.[39,67]

Physicians must consider each individual situation when determining the appropriate duration of prophylaxis. In addition to the risk factors for recurrence described above, the presence of rheumatic heart disease also needs to be taken into consideration. The committee's recommendations are given in Table 3. The duration of prophylaxis depends on whether residual heart damage (valvular disease) is present or absent. Patients who have had rheumatic carditis, with or without valvular disease, are at a relatively high risk for recurrences of carditis and are likely to sustain increasingly severe cardiac involvement with each recurrence.[5,6,68] Therefore, patients who have had rheumatic carditis should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life **(Class I, LOE C)**. For patients with persistent valvular disease, the committee recommends prophylaxis for 10 years after the last episode of acute rheumatic fever or until 40 years of age (whichever is longer). After that time, the severity of the valvular disease and the potential for exposure to GAS should be discussed, and continued prophylaxis (potentially lifelong) should be considered for high-risk patients. Prophylaxis should continue even after valve surgery, including prosthetic valve replacement. For patients without persistent valvular disease, prophylaxis should continue for 10 years or until the patient is 21 years of age, whichever is longer **(Class I, LOE C)**.

Patients who have had rheumatic fever without rheumatic carditis are also at risk for cardiac involvement with recurrences, although the risk is lower. In general, prophylaxis should continue in these patients until the patient reaches 21 years of age or until 5 years has elapsed since the last rheumatic fever attack, whichever is longer **(Class I, LOE C)**. In all situations, the decision to discontinue prophylaxis or to reinstate it should be made after discussion with the patient of the potential risks and benefits and careful consideration of the epidemiological risk factors enumerated above.

Choice of Regimen for Prevention of Recurrent Rheumatic Fever

Intramuscular Benzathine Penicillin G (Bicillin L-A)

An injection of 1 200 000 U of this long-acting penicillin preparation every 4 weeks is the recommended regimen for secondary prevention in most circumstances in the United States **(Class I, LOE A**; Table 4). In populations in which the incidence of rheumatic fever is particularly high, the administration of benzathine penicillin G every 3 weeks is justified and recommended, because serum drug levels may fall below a protective level before the fourth week after administration of this dose of penicillin **(Class I,**

Table 4. Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

Agent	Dose	Mode	Rating
Benzathine penicillin G	600 000 U for children ≤27 kg (60 lb), 1 200 000 U for those >27 kg (60 lb) every 4 wk*	Intramuscular	IA
Penicillin V	250 mg twice daily	Oral	IB
Sulfadiazine	0.5 g once daily for patients ≤27 kg (60 lb), 1.0 g once daily for patients >27 kg (60 lb)	Oral	IB
For individuals allergic to penicillin and sulfadiazine			
Macrolide or azalide	Variable	Oral	IC

Rating indicates classification of recommendation and LOE (eg, IA indicates class I, LOE A).

*In high-risk situations, administration every 3 weeks is justified and recommended. See discussion of high-risk situations in the text.

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LOE A).[69,70] In the United States, the administration of benzathine penicillin G every 3 weeks is recommended only for those who have recurrent acute rheumatic fever despite adherence to an every-4-week regimen **(Class I, LOE C)**. Long-acting penicillin is of particular value in patients with a high risk of rheumatic fever recurrence, especially those with rheumatic heart disease, in whom the consequences of recurrence may be serious. The advantages of benzathine penicillin G must be weighed against the inconvenience to the patient and the pain of injection, which causes some individuals to discontinue prophylaxis. Although there has been concern about the risk of serious allergic reactions in patients receiving long-term intramuscular benzathine penicillin G prophylaxis for rheumatic fever, a large, international, prospective study determined that life-threatening allergic reactions are rare in these patients.[71] It has been demonstrated that the long-term benefits of such prophylaxis far outweigh the risk of serious allergic reactions.

Oral Agents

Successful oral prophylaxis depends primarily on patient adherence to prescribed regimens (compliance). Patients need careful and repeated instructions about the importance of continuing prophylaxis. Most failures of prophylaxis occur in nonadherent patients. Even with optimal patient adherence, the risk of recurrence is higher in individuals receiving oral prophylaxis than in those receiving intramuscular benzathine penicillin G.[62] Oral agents are more appropriate for patients at lower risk for rheumatic fever recurrence. Accordingly, some physicians may consider switching patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of rheumatic attacks for at least 5 years **(Class IIb, LOE C)**.

Penicillin V

The recommended oral agent is penicillin V **(Class I, LOE B)**. The dosage for children and adults is 250 mg twice daily (Table 4). There are no published data about the use of other penicillins, macrolides, azalides, or cephalosporins for the secondary prevention of rheumatic fever.

Sulfadiazine

For patients allergic to penicillin, sulfadiazine is recommended **(Class I, LOE B)**. Although sulfonamides are not effective in the eradication of GAS, they do prevent infection. The recommended dose of sulfadiazine is 0.5 g once per day for patients weighing 27 kg (60 lb) or less and 1 g once per day for patients weighing >27 kg. Sulfadiazine and sulfisoxazole appear to be equivalent; therefore, the use of sulfisoxazole is acceptable on the basis of extrapolation from data demonstrating that sulfadiazine has proven effectiveness in secondary prophylaxis **(Class IIa, LOE C)**. The recommended dose of sulfisoxazole is the same as that for sulfadiazine. Sulfonamide prophylaxis is contraindicated in late pregnancy because of transplacental passage of the drugs and potential competition with bilirubin for albumin-binding sites.

Macrolides

For the patient who is allergic to both penicillin and sulfisoxazole, an oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is recommended **(Class I, LOE C)**. Macrolides (erythromycin and clarithromycin), and to a much lesser extent azalides (azithromycin), can cause prolongation of the QT interval in a dose-dependent manner. Because macrolides are metabolized extensively by cytochrome P-450 3A, they should not be taken concurrently with inhibitors of cytochrome P-450 3A such as azole antifungal agents, HIV protease inhibitors, and some selective serotonin reuptake inhibitor antidepressants.[53,54]

Bacterial Endocarditis Prophylaxis

The AHA has recently published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis.[72] Because of the lack of published evidence indicating that the principle of prophylaxis is definitively valid as it has been applied to infective endocarditis prevention, the value of infective endocarditis prophylaxis has been called into question by the AHA, as well as by other international scientific bodies.[73] However, the AHA and others continue to recognize that certain conditions, such as patients with prosthetic valves, those with previous endocarditis, cardiac transplant recipients who develop cardiac valvulopathy, and specific forms of congenital heart disease, are associated with the highest risk of adverse outcome from endocarditis, and given that documented high risk, prophylaxis remains indicated. Notably, the current AHA recommendations no longer suggest prophylaxis for patients with rheumatic heart disease. However, the maintenance of optimal oral health care remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with prosthetic valves or prosthetic material used in valve repair, the current AHA recommendations should be followed.[72] These recommendations advise the use of an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for rheumatic fever, because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

Poststreptococcal Reactive Arthritis

The term "poststreptococcal reactive arthritis" (PSRA) was first used in 1959 to describe an entity in patients who had arthritis after an episode of GAS pharyngitis but lacked other major criteria of acute rheumatic fever.[74] Patients with PSRA and with acute rheumatic fever have arthritis that occurs after a symptom-free interval after an episode of GAS pharyngitis. However, the arthritis of rheumatic fever occurs 14 to 21 days after an episode of GAS pharyngitis and responds rapidly to acetylsalicylic acid, whereas PSRA occurs ≈10 days after the GAS pharyngitis and does not respond readily to acetylsalicylic acid. In addition, the arthritis of rheumatic fever is migratory and transient and usually involves only the large joints, whereas the arthritis of PSRA is cumulative and persistent and can involve large joints, small joints, or the axial skeleton. Although all patients with PSRA have serological evidence of a recent GAS infection, no more than half of these patients who have a throat culture performed have GAS isolated. Because a small proportion of patients with

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PSRA have been reported to subsequently develop valvular heart disease,[74,75] these patients should be observed carefully for several months for clinical evidence of carditis. Some experts recommend that these patients receive secondary prophylaxis for up to 1 year after the onset of their symptoms, but its effectiveness is not well established **(Class IIb, LOE C)**. If clinical evidence of carditis is not observed, the prophylaxis can be discontinued. If valvular disease is detected, the patient should be classified as having had acute rheumatic fever and should continue to receive secondary prophylaxis **(Class I, LOE C)**.

The term PSRA subsequently has been used inconsistently in the literature to refer to a variety of constellations of signs and symptoms. Most of the information about PSRA is based on case reports or small series.[76] Although criteria have been proposed to define a homogeneous syndrome,[75] the case reports of PSRA have been quite heterogeneous. It is still not clear whether this entity represents a distinct syndrome or is a manifestation of acute rheumatic fever.[76] Investigations are required to determine whether there is a true association between reactive arthritis after GAS pharyngitis and acute rheumatic fever and whether antimicrobial prophylaxis is needed after PSRA.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

In 1998, investigators proposed the hypothesis that childhood obsessive-compulsive disorder and/or tics may arise as a result of a poststreptococcal autoimmune process and suggested the acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).[77] They proposed that a subset of patients with obsessive-compulsive and tic disorders produce autoimmune responses that cross-react with brain tissue in response to a GAS infection, similar to the autoimmune response believed to be responsible for the manifestations of Sydenham chorea (a major manifestation of acute rheumatic fever). If this were correct, secondary prophylaxis that prevents recurrences of Sydenham chorea might also be effective in preventing recurrences of obsessive-compulsive and tic disorders in these patients. Because of the proposed autoimmune mechanism, it has also been suggested that these patients may benefit from immunoregulatory therapy such as plasma exchange or intravenous immunoglobulin infusions.

The PANDAS hypothesis has stimulated considerable research, as well as considerable controversy. The current state of knowledge dictates that the concept of PANDAS should be considered only as a yet-unproven hypothesis.[78,79] Until carefully designed and well-controlled studies have established a causal relationship between PANDAS and GAS infections, the committee does not recommend routine laboratory testing for GAS to diagnose, long-term antistreptococcal prophylaxis to prevent, or immunoregulatory therapy (eg, intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder **(Class III, LOE B)**.

Disclosures

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