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Diagnosis and Treatment of Group A Streptococcal Pharyngitis

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In 1990, throat complaints brought nearly 18.9 million patients to office-based physicians.[1] Pediatricians diagnosed acute pharyngitis, acute tonsillitis, and streptococcal sore throat more than 7 million times in 1989.[2] Most of these illnesses are nonbacterial and do not require or benefit from antibiotic therapy, but a minority are caused by group A streptococci and should be treated.

When evaluating a patient with sore throat, the primary concern is accurate diagnosis and appropriate treatment of pharyngitis caused by group A streptococci, which accounts for approximately 15% of all episodes of pharyngitis. Acute streptococcal pharyngitis requires accurate diagnosis and subsequent therapy to prevent its suppurative and nonsuppurative complications. The sequelae of streptococcal pharyngitis, especially acute rheumatic fever (ARF) and acute glomerulonephritis (AGN), formerly resulted in considerable morbidity and mortality in the United States and continue to do so in many parts of the world. Prevention of ARF in particular depends on accurate, timely diagnosis of streptococcal tonsillopharyngitis and on prompt antibiotic treatment.

Diagnosis

The reality of clinical practice in North America in the 1990s emphasizes a dichotomous differential diagnosis for acute pharyngitis: group A streptococcal pharyngitis or not. Most nonstreptococcal syndromes and causes of acute pharyngitis are either very rare or self-limited and benign (Tables 1 and 2). Only group A streptococcal pharyngitis is common, acutely responsive to specific therapy, and requires treatment to prevent complications. Thus, accurate diagnosis of streptococcal pharyngitis and appropriate therapy are essential. Diagnosis begins with recognition of the spectrum of clinical features of streptococcal pharyngitis, the signs and symptoms suggestive of nonstreptococcal (usually viral) disease, and the clinical epidemiology of various pharyngitis syndromes.

Clinical Features

The classic patient with acute streptococcal pharyngitis is a school-aged child with sudden onset of fever and sore throat in the late winter or early spring (Table 3). Headache, malaise, abdominal pain, nausea, and vomiting are commonly associated. Cough, rhinorrhea, stridor, hoarseness, conjunctivitis, and diarrhea are distinctly unusual. Pharyngeal erythema, sometimes with palatal petechiae, is found on examination. Tonsils are enlarged and red, with patchy exudates on their surfaces. The papillae of the tongue may be red and swollen, leading to the designation, "strawberry tongue." Tender, enlarged anterior cervical lymph nodes often are found. Combinations of these signs assist in diagnosis; tonsillar exudates in association with palatal petechiae and tender anterior cervical adenitis strongly suggest group A streptococcal pharyngitis. Very often, some or all of these classic characteristics are absent in patients with streptococcal pharyngitis. Younger children may have coryza with crusting below the nares, more generalized adenopathy, and a more chronic course, a syndrome known as streptococcosis.

Scarlet Fever

Scarlet fever, so-called because of its fine, diffuse red rash, usually indicates infection with group A streptococci. It rarely is seen in children younger than 3 years or in adults. The rash of scarlet fever is caused by infection with a group A strain that contains a bacteriophage encoding for the production of an erythrogenic toxin, usually erythrogenic (or pyrogenic) exotoxin A. The scarlet fever rash has a texture that feels similar to sandpaper and blanches with pressure. Beginning on the face, it becomes generalized after 24 hours. The area around the mouth often appears pale in comparison to the extremely red cheeks, giving the appearance of circumoral pallor. Accentuation of erythema occurs in flexor skin creases, especially in the antecubital fossae (Pastia's sign or Pastia's lines). The erythema begins to fade within a few days, and within a week of onset desquamation occurs, first on the face, progressing downward, and often resembling that seen subsequent to a mild sunburn. Occasionally, sheetlike desquamation occurs around the free margins of the finger nails, usually more coarse than the desquamation seen with Kawasaki disease. Differential diagnosis of scarlet fever includes Kawasaki disease, measles, and staphylococcal toxic shock syndrome (Table 2).

Recent publicity has highlighted invasive toxin-producing group A streptococcal infection that includes necrotizing fasciitis. Although many patients with the so-called "streptococcal toxic shock syndrome" also are infected with streptococci that produce erythrogenic toxin A, most infections caused by such group A streptococci are not associated with unusual severity. Streptococcal toxic shock syndrome is associated more commonly with a primary cutaneous focus of infection rather than a pharyngeal focus of infection.[3] Scarlet fever can still be explained in simple terms to patients and their families as streptococcal pharyngitis with a rash.

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Table 1. Etiology of Pharyngitis

Definite Causes
Streptococcus pyogenes (Group A streptococcus)
Corynebacterium diphtheriae
Arcanobacterium hemolyticum
Neisseria gonorrhoeae
Epstein-Barr virus
Parainfluenza viruses
Influenza viruses
Rhinoviruses
Coronavirus
Adenovirus
Respiratory syncytial virus
Herpes simplex virus
Probable Causes
Group C streptococci
Group G streptococci
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

Clinical Epidemiology

Streptococcal pharyngitis was identified mainly in well-defined epidemics before World War II, but has been endemic in the United States since then. Cases generally peak in the late winter and early spring. Children from 5 to 11 years old have the highest rates of streptococcal pharyngitis, but infection occurs at all ages; an outbreak has been documented in a day care center.[4]

Spread of group A streptococci in classrooms and within families is common. Crowded living conditions increase spread; military units have been common sites for streptococcal research because of frequent epidemics and their devastating effect on troop training and availability.[5] Transmission occurs primarily by inhalation of organisms in large droplets or by direct contact with respiratory secretions. Pets do not seem to be a significant reservoir of group A streptococci. Untreated streptococcal pharyngitis is particularly contagious early in the acute illness and for the first 2 weeks after the organism has been acquired. Appropriate antibiotic therapy eliminates contagiousness within 24 hours after institution of therapy, and children can return to school.[6]

Diagnosis of Group A Streptococcal Pharyngitis

Many patients with *bona fide* group A streptococcal pharyngitis do not have classic signs and symptoms, and their symptoms overlap substantially with pharyngitis caused by other agents. However, the presence of typical features of viral pharyngitis when there are low rates of streptococcal disease in the community very strongly suggests a nonstreptococcal etiology, and laboratory testing is optional. When signs and symptoms suggest acute streptococcal pharyngitis (including patients with scarlet fever), laboratory diagnosis is strongly recommended (Fig 1). Clinical scoring systems for diagnosing acute streptococcal pharyngitis have been developed but have not proved very useful.[7] Using clinical criteria alone, physicians tend to overestimate the likelihood that patients have streptococcal infection.[8]

The throat culture has been used in physicians' offices to diagnose streptococcal pharyngitis since the early 1950s.[9] Plating a swab of the posterior pharynx and tonsils on sheep blood agar, identifying β-hemolytic colonies, and testing them for sensitivity to a bacitracin-impregnated disc is the "gold standard" diagnostic test, but requires 24 to 48 hours. More recently, a number of rapid diagnostic tests that require less than 30 minutes have been developed. When performed by experienced personnel, these rapid diagnostic tests (rapid strep antigen tests) are highly specific (generally >95%), using the throat culture as the standard. Specificity reflects the percentage of positive results that come from patients who truly harbor group A streptococci. Unfortunately, the sensitivity (the percentage of true-positives that are identified by group A antigen detection) of most of these rapid tests is problematic. Although the sensitivities of these tests are typically 80% to 85%, they can

Table 2. Differential Diagnosis of Scarlet Fever

	Scarlet Fever	*KD*	*Measles*	*STSS*
Agent	Group A streptococci	?	Measles virus	*S aureus*
Age range	All (peak 5-11 yr)	Usually <5 yr	<2, 10-20 yr	All (esp > 10 yr)
Prodrome	No	No	Fever, coryza	Usually no
Enanthem	No	Occasionally	Koplik spots	No
Mouth	"Strawbery tongue" exudative pharyngitis, palatal petechiae	Erythema; red, cracked lips	Diffusely red	Usually normal
Rash	Fine, red, "sandpaper," desquamates, circumoral pallor, Pastia's lines	Variable, esp hands and feet, desquamates	Maculopapular, progressing from forehead to feet	Diffuse erythroderma, desquamates
Other	Cervical adenitis, gall bladder hydrops	Cervical adenopathy, thrombocytosis, pyuria (sterile), conjunctival injection, gall bladder hydrops, coronary artery disease	Cough, coryza, conjunctivitis "toxic" appearance, dehydration, encephalitis, pneumonia	Shock, encephalopathy

Abbreviations: KD, Kawasaki disease; STSS, staphylococcal toxic shock syndrome.

Table 3. Classic Features of Acute Streptococcal Pharyngitis

Season
Late winter or early spring
Age
5 to 11 years
Symptoms (sudden onset)
Sore throat
Fever
Headache
Abdominal pain, nausea, vomiting
Signs
Pharyngeal erythema and exudation
Tender, enlarged anterior cervical nodes
Palatal petechiae
Tonsillar hypertrophy
Absence of cough, coryza, laryngitis, stridor, conjunctivitis, diarrhea

be much lower, resulting in frequent false-negative results and failure to diagnose acute streptococcal pharyngitis.[10-14] The accuracy of the rapid tests seems to be highly dependent on the experience and skill of the individuals performing them.[12,14]

Rapid strep tests usually employ latex agglutination or enzyme immunoassay (EIA) methodologies to detect the presence of the group A carbohydrate cell wall antigen of group A streptococci after acid extraction of organisms obtained by throat swab. EIA tests generally produce less ambiguous end points and are easier to interpret. A newer test based on the optical immunoassay (OIA) technology has not been evaluated sufficiently to be recommended at this time.

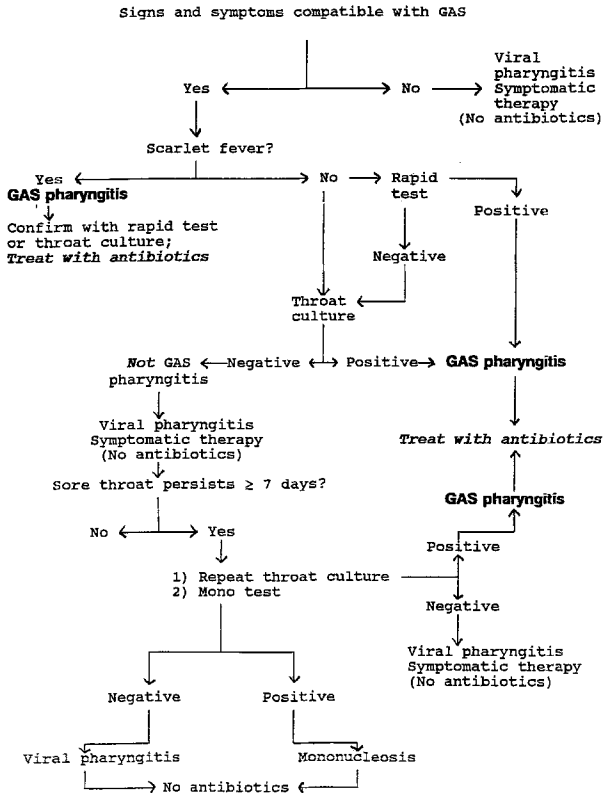

Figure 1. Management of patients with sore throat. GAS, group A streptococcus.

The inadequate sensitivity of most rapid tests, coupled with their excellent specificity, requires a two-step approach when rapid streptococcal antigen tests are used. Two swabs should be obtained from patients with suspected streptococcal pharyngitis. One swab is used for a rapid test. When the rapid antigen detection test is positive, it is highly likely that the patient has group A streptococci in the throat, and the extra swab can be discarded. When the rapid test is negative, group A streptococci may still be present; thus, the extra swab should then be processed for culture in routine fashion. In general, patients with negative rapid tests do not require treatment before culture verification. When there is a particularly high index of suspicion that group A streptococci are involved (eg, several of the following: tonsillar exudates, cervical adenopathy, palatal petechiae, scarlet fever, and recent exposure to a person with streptococcal pharyngitis) presumptive treatment may be appropriate.

Rapid tests are intended for the diagnosis of acute streptococcal pharyngitis and should not be used to evaluate the effectiveness of therapy. A positive result in an asymptomatic patient does not distinguish among infection, colonization (carriage), or the presence of nonviable organisms, and a negative result must be confirmed by throat culture.

Several surveys have examined the actual strategies used by physicians to diagnose streptococcal pharyngitis. Cochi et al[15] surveyed primary care physicians in December 1982 and January 1983, before rapid tests became available, and found that approximately 25% of the respondents always or nearly always obtained throat cultures from patients with sore throat. Cultures were never or almost never obtained by 23% of the physicians surveyed. This survey also found that pediatricians were more likely than internists or family/general practitioners to use throat cultures. In 1993, Schwartz et al[16] surveyed pediatricians about their diagnostic approaches to children with pharyngitis. An optimal approach, defined as use of culture alone or as a backup to a negative rapid antigen test for at least 80% of patients, was used by 44% of pediatricians who responded to the survey. Seventeen percent reported using clinical findings or rapid test without culture for most children with pharyngitis. We obtained similar results from a recent national survey of U.S. pediatricians; 64% used rapid tests at least some of the time, 42% used throat cultures whenever the rapid test was negative, 38% used cultures alone, and 20% used strategies that are not recommended.[17] Thus, it appears that many physicians do not follow recommended guidelines for diagnosing streptococcal pharyngitis.

Testing patients for serological evidence of an antibody response to extracellular products of group A streptococci (such as streptolysin O) is not useful during the acute pharyngitis episode. Because serum antibody levels require at least 10 to 14 days to increase, streptococcal antibody tests are valid only for determining past infection. Antibodies often measured include anti–streptolysin O (ASO), anti–DNase B, and anti–hyaluronidase (AHT). When antibody testing is desired to evaluate a possible poststreptococcal illness, more than one of these tests should be performed to improve sensitivity. However, the Streptozyme test (Wampole Laboratories, Cranbury, NJ), an

assay that uses latex particles coated with group A streptococcus broth culture supernates, has been shown to be poorly standardized and therefore cannot be recommended.[18]

Treatment

The primary goal of therapy for acute streptococcal pharyngitis is to prevent the development of ARF. Treatment begun within 9 days after the onset of acute pharyngitis and continued for 10 days is effective in preventing ARF.[19] Therapy does not seem to affect the risk of poststreptococcal AGN. Antibiotic therapy also reduces the suppurative sequelae of streptococcal pharyngitis, such as peritonsillar abscess and cervical adenitis.

In addition to preventing ARF, signs and symptoms of pharyngitis resolve somewhat more rapidly in patients treated early, a fact documented most recently by studies published in the 1980s[20,21] but first noted several decades ago.[22,23] Since antibiotic therapy also terminates contagiousness within 24 hours, institution of appropriate antibiotic therapy generally should be undertaken as soon as the diagnosis is supported by laboratory tests. Although some studies have suggested that early treatment may increase the rate of recurrent streptococcal pharyngitis by stunting the immune response,[24,25] the most carefully performed investigation refutes this concept.[26] Unnecessarily delaying therapy risks losing the patient to follow-up (a particular problem among patients without an established source of primary health care), may prolong symptoms leading to loss of additional time from school and/or work, and extends the period of contagiousness. Antimicrobial therapy can be started before the results of cultures are available, especially if the rash of scarlet fever is present or other clinical features are highly suggestive of streptococcal infection. Therapy should be stopped if group A streptococci are not confirmed by rapid test or throat culture, although many physicians unfortunately continue antibiotic therapy despite negative tests.[15]

The drug of choice for treating streptococcal pharyngitis has been penicillin for more than 40 years. Despite the widespread use of penicillin to treat streptococcal and other infections, penicillin resistance among group A streptococci has not developed.[27] Penicillin usually is given by mouth for 10 days (125 to 250 mg of penicillin V three or four times each day) or intramuscularly as a single injection of benzathine penicillin (600,000 units for patients weighing less than 60 pounds [27 kg], 1.2 million units for those weighing 60 pounds [27 kg] or more). In efforts to improve compliance, twice-daily dosing has been tried with some success.[28,29] Shorter courses of therapy also have been tried, but the bacteriologic results of 5 or 7 days of therapy have not been promising.[30,31] Use of intramuscular benzathine penicillin also alleviates concern about patient compliance but is quite painful. A less painful alternative is 900,000 units of benzathine penicillin in combination with 300,000 units of procaine penicillin for all patients. Intramuscular procaine penicillin alone is insufficient because adequate levels of penicillin are short-lived. Other β-lactams, including semisynthetic derivatives of penicillin and cephalosporins, have been used to treat streptococcal pharyngitis. The decreased frequency of administration of some of these agents may improve patient compliance and makes them attractive in selected circumstances.

Patients who are allergic to penicillin should receive erythromycin or another non–β-lactam antibiotic, such as clindamycin. Resistance of group A streptococci to erythromycin has been reported in countries such as Japan, France, Spain, and Finland, where erythromycin is widely used.[32] This has not emerged as a problem in the United States. Sulfa drugs, including sulfamethoxasole/trimethoprim, tetracyclines, and chloramphenicol are not effective in eradicating group A streptococci from the pharynx and should not be used for treatment of acute pharyngitis.

Treatment Failure and Chronic Carriage

Despite universal susceptibility of group A streptococci to penicillin, treatment fails to eradicate streptococci from the pharynx in as many as 25% of patients.[33] Penicillin resistance is not the cause of treatment failure; therefore, treatment failure is a puzzling phenomenon. A small proportion of these patients remain symptomatic and are thus characterized as "clinical treatment failures." Reinfection with the same or a different strain of group A streptococcus is possible, as is intercurrent viral pharyngitis. Some patients may have been noncompliant with therapy, but apparent treatment failure occurs even among patients treated with intramuscular benzathine penicillin.[34,35] Some of these patients are chronic pharyngeal carriers of group A streptococci and suffer from a new superimposed viral infection (Fig 2).

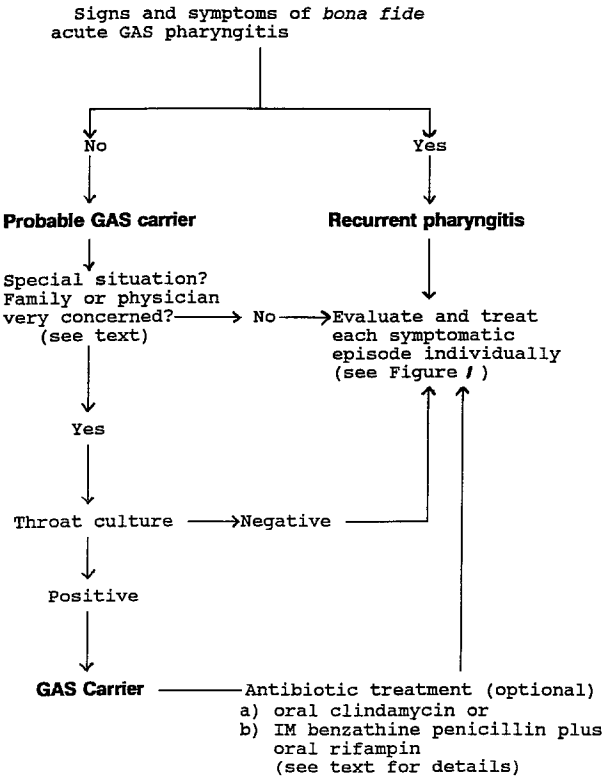

Figure 2. Management of patients with repeated or frequent positive rapid test or throat culture results. GAS, group A streptococcus.

Most patients with bacteriologic treatment failure are asymptomatic and are identified when follow-up cultures are obtained, a practice that generally is unnecessary. Patients who are compliant with therapy are at minimal risk for ARF.[36] There is some evidence that bacteriologic failure rates may be somewhat lower when antibiotics other than penicillin are used, especially the cephalosporins.[37-39] Although numerous studies of various cephalosporins have been published, few studies have been large enough or have been performed rigorously enough to prove that this class of antimicrobials is superior to penicillin; all of the antibiotics have treatment failure associated with their use. Published metanalyses suffer from the poor quality of many of the included studies.[39] Semisynthetic derivatives of penicillin (such as dicloxicillin), rifampin given with oral penicillin, amoxicillin-clavulanate, clindamycin, and other drugs also have been used. At this time, it is fair to say that these antimicrobials are at least as effective as penicillin for treating streptococcal pharyngitis but that their broader spectrum, their much greater cost, and the lack of formal data concerning prevention of ARF currently relegate them to second-line status. Routine use of these agents is not warranted.

Several theories have been advanced to explain bacteriologic treatment failure. These include protection of group A streptococci by β-lactamase–producing oral flora,[40-42] tolerance of group A streptococci to penicillin,[43] streptococci "hiding" in tonsils,[44] and the absence of oral flora (particularly alpha streptococci) inhibitory to group A streptococci.[45-46] None of these theories has been proven, but several deserve mention. Numerous reports on efficacy of β-lactamase–resistant antibiotics suggest a possible role for β-lactamase–producing flora in penicillin treatment failure.[37,47-49] However, the patient populations studied, the bacteriologic methods used, and the follow-up differ greatly among these studies. Few of these studies actually isolated β-lactamase–producing bacteria from the pharynx and tried to correlate their presence with the bacteriologic outcome of treatment. Our study that evaluated the presence of β-lactamase producers with outcome of treatment of acute streptococcal pharyngitis does not support the β-lactamase theory.[50] Tolerance to penicillin (inhibition of bacterial growth without killing) has been discussed widely but does not seem to play a role in treatment failure.[49,51] Perhaps the best explanation for asymptomatic persistence of group A streptococci after appropriate treatment is that these patients are chronically colonized with group A streptococci and develop symptoms because of an intercurrent viral pharyngitis (ie, in retrospect, they did not have *bona fide* acute streptococcal pharyngitis).[33]

Patients who are colonized chronically with group A streptococci are called chronic carriers. Chronic carriers do not seem to be at risk for ARF or for development of suppurative complications, and they rarely spread group A streptococci in the community.[36] There is no reason to exclude chronic carriers from school or other activities. Careful, controlled studies of the causes of chronic pharyngeal carriage of group A streptococci are few. At present, the precise mechanisms that lead to this phenomenon remain obscure, but theories include those advanced to explain bacteriologic treatment failure.

Chronic streptococcal carriage is fairly common; in one study, 8.3% of children 5 to 7 years old who presented for well child care had asymptomatic colonization with group A streptococci.[52] Even higher rates of carriage are sometimes documented. Carriage poses problems for the clinician because there is no easy way to identify chronic carriers prospectively among patients with symptoms of acute pharyngitis. Streptococcal antibody titers often are elevated in carriers, but neither these elevated titers nor quantitative throat cultures have proved useful.[36] The clinician should consider the possibility of chronic streptococcal carriage when a patient has multiple culture-positive episodes of pharyngitis, especially when symptoms are mild or atypical. A culture obtained when the suspected carrier is symptom-free or is receiving treatment with penicillin (intramuscular benzathine penicillin is recommended to eliminate the possibility of noncompliance) usually is positive for group A streptococci. Chronic carriers sometimes receive multiple unsuccessful courses of antibiotic therapy in attempts to eliminate streptococci. Physician and patient anxiety is common and can develop into "streptophobia" on the part of both. Unproven and generally untested therapies for carriers often are encountered. These include tonsillectomy, prolonged administration of antibiotics, use of β-lactamase–resistant antibiotics, and culture and/or treatment of pets. None of these approaches can be justified at this time for treating chronic carriers of group A streptococci.

Several treatment options *are* available for the physician faced with a chronic streptococcal carrier: (1) Ignore the problem and stop obtaining throat cultures, even for new symptomatic attacks of pharyngitis; (2) obtain a rapid test and/or throat culture each time the patient has symptoms and signs suggestive of streptococcal pharyngitis, and avoid obtaining throat cultures when patients have symptoms more typical of viral illnesses (cough, rhinorrhea, stridor, hoarseness, conjunctivitis, diarrhea), and treat with penicillin each time a test is positive; or (3) treat with one of the regimens established to be effective for terminating chronic carriage.[34,53] Of these three options, the first is the most risky because a patient could become infected with a new strain of group A streptococcus and be at risk for ARF if left untreated. The second option is simple, as safe as penicillin, and appropriate for many patients. The third option should be reserved for particularly anxious patients and families, individuals with a history of ARF or living with someone who had ARF, or those living or working in nursing homes, chronic care facilities, and hospitals, and in families exhibiting "ping-pong" spread, ie, streptococcal pharyngitis bouncing among family members for a long time. The two treatment regimens that have been demonstrated to be effective are: (1) intramuscular benzathine penicillin plus oral rifampin (10 mg/kg/dose up to 300 mg, administered twice daily for 4 days beginning on the day of the penicillin injection)[34]; and (2) oral clindamycin given for 10 days (20 mg/kg/day up to 450 mg, divided into three equal doses).[53] We currently prefer clindamycin because it is easier to use than intramuscular penicillin plus oral rifampin and may be somewhat more effective. No other antibiotic regimens have been demonstrated in controlled, comparative trials to reliably terminate the chronic streptococcal carrier state. Successful eradication of the carrier state makes evaluation of subsequent episodes of pharyngitis much easier, although we have seen chronic carriage recur on reexposure to group A streptococci.

Recurrent Acute GAS Pharyngitis

Some patients seem remarkably susceptible to streptococcal pharyngitis. Appropriate antibiotic treatment of each episode results in resolution of symptoms and eradication of the microorganism. Follow-up throat culture may be needed to distinguish recurrent acute streptococcal pharyngitis from frequent nonstreptococcal pharyngitis in patients who are chronic carriers. The reasons for frequent episodes of *bona fide* acute streptococcal pharyngitis are obscure, but lack of flora, especially alpha streptococci, capable of inhibiting group A streptococci, or unusual mucosal adherence to group A streptococci, are intriguing concepts. Studies of nasal spraying of alpha streptococci to prevent recurrent acute pharyngitis are ongoing in Sweden.[54]

The role of tonsillectomy in managing patients with multiple episodes of streptococcal pharyngitis remains controversial. Paradise et al[55] demonstrated fewer episodes of sore throat among children treated with tonsillectomy (compared to patients treated without surgery) but only during the first 2 years after the operation. The patients enrolled in that study had experienced numerous episodes of pharyngitis, but not all episodes of sore throat were caused by group A streptococci (a fact often missed when this study is cited). Of particular concern are the reported tonsillectomy complication rate of 14% and the improvement over time noted among the patients who did not undergo tonsillectomy. Finally, it is clear that the presence of tonsils is not necessary for streptococci to infect the throat. Tonsillectomy cannot be recommended at present except in unusual circumstances.

Differential Diagnosis of Pharyngitis

Most episodes of pharyngitis are caused by viruses. Distinguishing between viral and streptococcal pharyngitis on clinical grounds alone can be difficult, but certain clues may help the physician. Accompanying symptoms of rhinitis, croup, laryngitis, hoarseness, conjunctivitis, or diarrhea are common with viral infection but rare in streptococcal pharyngitis.

Many viral agents can produce pharyngitis (Table 1). Some viruses cause distinct clinical syndromes that can be diagnosed without laboratory testing. Parainfluenza and influenza viruses, rhinoviruses, coronaviruses and respiratory syncytial virus typically produce symptoms of coryza and cough as well as mild pharyngitis. Influenza virus infections may cause fever, cough, headache, malaise, myalgias, and cervical adenopathy, in addition to pharyngitis. Adenoviruses can cause fever, cervical lymph node enlargement, pharyngeal erythema, follicular hyperplasia of the tonsils, and exudate. When conjuctivitis occurs in association with adenoviral pharyngitis the resulting syndrome is called pharyngoconjunctival fever. The enteroviruses (Coxsackie viruses and echovirus) can cause sore throat, especially in the summer. The throat may be slightly red, but tonsillar exudate and cervical adenopathy are unusual. Symptoms resolve within a few days. Enteroviruses cause two specific syndromes that involve the oropharynx. Herpangina caused by Coxsackie viruses A and B or echovirus is characterized by distinctive discrete, painful, gray-white papulovesicular lesions distributed over the posterior oropharynx. The vesicles are 1 to 2 mm in diameter and are surrounded initially by a halo of erythema, then ulcerate. Fever may reach 39.5°C. Coxsackie virus A16 causes hand-foot-mouth disease. Painful vesicles that may ulcerate can occur throughout the oropharynx. Vesicles also develop on the palms and soles and sometimes on the trunk or extremities. Fever is present in most cases, but many children do not appear ill. Primary infection with herpes simplex virus usually produces high fever with acute gingivostomatitis in young children. Vesicles (which become ulcers) develop throughout the anterior portion of the mouth, including the lips, but the posterior pharynx is spared. High fever is common and pain is intense; intake of oral fluids often is impaired and may lead to dehydration. Herpetic gingivostomatitis may last up to 2 weeks.

Experience with infants and toddlers during a measles epidemic in Chicago highlighted the prominence of early oral findings. In addition to high fever, cough, coryza, and conjunctivitis, the pharynx may be intensely and diffusely erythematous, without tonsillar enlargement or exudate. The presence of Koplik's spots, the pathognomonic white or blue-white enanthem of measles, on the buccal mucosa near the mandibular molars provides evidence of measles before the rash develops.

Acute exudative pharyngitis often occurs with infectious mononucleosis (IM) caused by primary infection with Epstein-Barr virus (EBV). IM usually is associated with hepatosplenomegaly, generalized lymphadenopathy, and pharyngitis of variable severity. The latter may be quite severe, with significant tonsillar hypertrophy, erythema, and impressive tonsillar exudates, closely resembling streptococcal pharyngitis. Regional lymph nodes may be particularly enlarged and tender.

IM occurs most prominently in adolescents and young adults and is frequently milder or is subclinical among preadolescents. After a 2- to 4-week incubation period, patients typically experience abrupt onset of malaise, fatigue, fever, and headache, followed closely by pharyngitis with enlarged tonsils with exudates and cervical adenopathy. More generalized adenopathy with hepatosplenomegaly often follows quickly. Fever and pharyngitis typically last 1 to 3 weeks, whereas lymphadenopathy and hepatosplenomegaly subside over 3 to 6 weeks. Malaise and lethargy can persist for up to several months, leading to impaired school or work performance.

Acute exudative pharyngitis associated with hepatomegaly, splenomegaly, and generalized lymphadenopathy strongly suggest IM. Early in the disease, IM may be difficult to distinguish from other causes of pharyngitis, including streptococcal pharyngitis. Laboratory findings include atypical lymphocytosis, heterophile antibodies that react with bovine erythrocytes (most often detected by the monospot test), and specific antibody against EBV viral capsid antigen (VCA), early antigen (EA), and Epstein-Barr nuclear antigen (EBNA). Acute IM usually is associated with a positive heterophile test and antibody to VCA and EA. Serological evidence of IM should be sought when splenomegaly or other features are present or if symptoms persist beyond 7 days, regardless of throat culture results.

Several bacteria other than group A streptococci have been associated with pharyngitis. These bacteria include *Arcanobacterium hemolyticum, Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydia* species, *Mycoplasma pneumoniae,* and non–group A streptococci.

Arcanobacterium (formerly *Corynebacterium*) *hemolyticum* is a gram-positive rod that causes a scarlet fever–like illness with acute pharyngitis and rash, most often in teenagers and young

adults.[56] This agent requires special methods for culture. The clinical features of *A hemolyticum* pharyngitis are very similar to those of group A streptococcal pharyngitis. Nearly all patients have pharyngeal erythema, about 70% have patchy white or gray tonsillar exudates, 50% have cervical adenitis, and 40% have moderate fever. Palatal petechiae and "strawberry tongue" have not been described. Erythromycin appears to be the preferred treatment.[56]

Diphtheria, usually caused by pharyngeal infection by toxigenic strains of *C diphtheriae,* is now very rare in the United States and other developed countries because of immunization with diphtheria toxoid. The handful of diphtheria cases recognized annually in the United States usually occur in unimmunized individuals, and the fatality rate is about 5%. A recent large outbreak of diphtheria in Russia, with infection documented in several travelers to Western Europe, emphasizes the need to support immunization programs.[57,58] Acute tonsillar and pharyngeal diphtheria is characterized by anorexia, malaise, low-grade fever, and sore throat. The classic grayish membrane forms within 1 to 2 days over the tonsils and pharyngeal walls and may extend into the larynx and trachea. Cervical adenopathy may be associated with the appearance of a "bull neck." In mild cases, the membrane sloughs after 7 to 10 days, and the patient recovers. In severe cases, the disease may progress to prostration, stupor, coma, and death within 6 to 10 days. Toxin-mediated palatal paralysis, laryngeal paralysis, ocular palsies, diaphragmatic palsy, and myocarditis may occur. Accurate diagnosis requires isolation of *C diphtheriae* on culture of material from beneath the membrane, with confirmation of toxin production by the organism isolated.

Acute symptomatic pharyngitis caused by *N gonorrhoeae* occurs occasionally in sexually active individuals as a consequence of oral-genital contact. In children, sexual abuse must be suspected. The infection usually presents as an ulcerative exudative tonsillopharyngitis but may be asymptomatic and resolve spontaneously. Gonococcal pharyngitis occurs in homosexual men and heterosexual women after fellatio, and is less readily acquired after cunnilingus. Gonorrhea rarely is transmitted from the pharynx to a sex partner, but pharyngitis can serve as a source for gonococcemia. Diagnosis requires culture on appropriate selective media (eg, Thayer-Martin).

Chlamydia trachomatis has been implicated serologically in as many as 20% of adults with pharyngitis, but isolation of the organism from the pharynx is difficult. Recently *Chlamydia pneumoniae* (formerly named TWAR) also was identified as a cause of pharyngitis. Diagnosis of chlamydial pharyngitis is difficult, whether by culture or serologically, and neither method is readily available to the clinician. *M pneumoniae* probably causes pharyngitis. Serological or culture methods can be used to identify this agent.[59,60] Chlamydial or mycoplasmal pharyngitis are diagnosed only in research studies of nonstreptococcal pharyngitis. The efficacy of antibiotic treatment for these illnesses is not known, but both appear to be self-limited.

Certain β-hemolytic streptococci other than group A are capable of causing acute pharyngitis. Well-documented epidemics of foodborne group C and group G streptococcal pharyngitis have been reported in young adults.[61,62] The role of these non–group A streptococcal organisms as etiologic agents of endemic acute pharyngitis has been more difficult to establish. There are data suggesting group C and group G β-hemolytic streptococci are responsible for acute pharyngitis, particularly in adolescents. Gerber et al[63] reported an outbreak of group G streptococcal pharyngitis among suburban children. However, the exact role of these agents, which can be carried asymptomatically in the pharynx, remains to be fully characterized. When implicated as agents of acute pharyngitis, group C or G organisms do not appear to require treatment because they cause self-limited infections. Acute rheumatic fever is not a sequel to these infections, although poststreptococcal nephritis has occurred rarely after epidemic group C and group G streptococcal pharyngitis.

Complications

Suppurative complications

Antibiotic therapy has greatly reduced the suppurative complications of acute group A streptococcal pharyngitis caused by spread from the pharynx to adjacent structures. Peritonsillar abscess ("quinsy") presents with fever, severe throat pain, dysphagia, "hot potato voice," pain referred to the ear, and bulging of the peritonsillar area with asymmetry of the tonsils and displacement of the uvula. Occasionally, peritonsillar cellulitis without a well-defined abscess occurs. When an abscess is found clinically or by an imaging study such as computed tomography scan, surgical drainage is indicated. Retropharyngeal abscess represents extension of infection from the pharynx or peritonsillar region into the retropharyngeal (prevertebral) space, which is rich in lymphoid structures. Fever, dysphagia, drooling, stridor, extension of the neck, and a mass in the posterior pharyngeal wall may be noted. Surgical drainage is required if frank suppuration has occurred. Spread of streptococci via pharyngeal lymphatics to regional nodes can cause cervical lymphadenitis that can suppurate. Otitis media, mastoiditis, and sinusitis also may occur as complications of streptococcal pharyngitis (Table 4).

Nonsuppurative Sequelae

These complications include acute rheumatic fever, acute poststreptococcal glomerulonephritis, and probably reactive arthritis/synovitis. As noted above, preventing ARF and subsequent rheumatic heart disease is the principle reason to treat streptococcal pharyngitis. Therapy with an appropriate antibiotic

Table 4. Complications of Streptococcal Pharyngitis

Suppurative
Retropharyngeal abscess
Peritonsillar abscess
Cervical adenitis
Otitis media
Sinusitis
Mastoiditis
Streptococcal toxic shock syndrome (rare)
Nonsuppurative
Acute rheumatic fever
Acute glomerulonephritis
Reactive arthritis (?)

begun within 9 days after onset of symptoms is highly effective in preventing this complication.[19]

Acute rheumatic fever is diagnosed using the clinical criteria first formulated by T. Duckett Jones in 1944. The latest (1992) revised Jones Criteria are found in Table 5. In addition to evidence of antecedent infection with group A streptococci, the diagnosis of ARF requires one major plus two minor criteria or two major criteria. Proof of infection is a positive throat culture or rapid test, or an elevated antibody titer to at least one extracellular product of the group A streptococcus. Long-term, chronic therapy with penicillin or sulfa (perhaps for life) is recommended for patients with a history of ARF or rheumatic heart disease to prevent recurrent attacks of ARF.

Poststreptococcal reactive arthritis analogous to other postinfectious reactive syndromes without other features of ARF probably occurs. The relationship of this entity to ARF is unclear. Those patients who fulfill the Jones criteria should be considered to have ARF after other diagnoses are excluded and managed accordingly.

The incidence and severity of ARF in the United States and many developed countries began to decline in the early 1900s. Advances in living conditions, sanitation, and nutrition probably account for this early decline. Since the 1950s, greater access to medical care, presumably leading to prompt diagnosis and treatment, contributed to further decline in ARF.[64] Since the late 1980s, unexpected local and regional clusters of ARF have been reported, beginning with an outbreak near Salt Lake City.[65,66] Many of the patients in these outbreaks have been suburban, middle-class children with only mild symptoms of antecedent pharyngitis, and the incidence of carditis among them has been high. There is evidence that group A streptococcus strains that are heavily encapsulated and produce mucoid-appearing colonies on blood agar are associated with some outbreaks.[67] Although it was once thought that all group A streptococci had equal potential to cause acute rheumatic fever, certain strains now appear particularly rheumatogenic. The reasons for the local resurgences of ARF remain to be fully elucidated but may be related to local presence of these highly rheumatogenic strains of group A streptococci.

Poststreptococcal AGN is the other major sequela of group A streptococcal infection. In contrast to ARF, AGN does not appear to be prevented by prompt treatment of the antecedent streptococcal infection. Pharyngitis caused by a nephritogenic strain of group A streptococci precedes symptoms by about 10 days. Unlike ARF, which only occurs after pharyngitis, AGN also can follow skin infection. AGN is characterized by sudden onset of edema, oliguria, hematuria, proteinuria, and hypertension. Diagnosis of poststreptococcal AGN requires evidence of prior infection with group A streptococci by culture, rapid test, or serological means. Hypocomplementemia, especially decreased C3, supports the diagnosis.

Table 5. Guidelines for Diagnosing the Initial Attack of Acute Rheumatic Fever

Major Criteria
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules
Minor Criteria
Clinical
Arthralgia
Fever
Laboratory
Elevated acute phase reactants
Erythrocyte sedimentation rate
C-reactive protein
Prolonged P-R interval

NOTE. Jones criteria, revised 1992; two major or one major and two minor criteria suffice for diagnosis if supported by evidence of antecedent infection with GAS (positive throat culture or rapid strep test or elevated or rising antibody titer).

Summary

Pharyngitis caused by the group A streptococcus requires accurate diagnosis and timely treatment to prevent acute rheumatic fever. Clinical signs and symptoms often do not distinguish pharyngitis caused by group A streptococci from pharyngitis caused by other microorganisms. Rapid antigen detection or throat culture are recommended for diagnosis except when viral signs and symptoms are prominent. Therapy with penicillin, the drug of choice, is associated with prevention of rheumatic fever, more rapid clinical improvement, and prompt loss of contagiousness. Bacteriologic treatment failure occurs despite universal sensitivity of group A streptococci to penicillin. The causes of treatment failure (and of chronic carriage) remain to be determined. Newer, more expensive antibiotics do not substantially enhance treatment success and need not be prescribed for most patients.

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