Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Diagnosis and Treatment of Group A Streptococcal Pharyngitis

Robert R. Tanz and Stanford T. Shulman

In 1990, throat complaints brought nearly 18.9 million patients to office-based physicians. Pediatricians diagnosed acute pharyngitis, acute tonsillitis, and streptococcal sore throat more than 7 million times in 1989. 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 papilla 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 streptococcal toxic shock syndrome.

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 fascitis. 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. Scarlet fever can still be explained in simple terms to patients and their families as streptococcal pharyngitis with a rash.
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. 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. 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

Table 2. Differential Diagnosis of Scarlet Fever

| Agent            | Scarlet Fever | KD | Measles | STSS |
|------------------|---------------|----|---------|------|
| Age range        | All (peak 5-11 yr) | Usually <5 yr | Measles virus | <2, 10-20 yr | S aureus |
| Prodrome         | No            | No | Fever, coryza | Usually no | All (esp > 10 yr) |
| Enanthem         | No            | Occasionally Koplik spots | No | |
| Mouth            | "Strawberry tongue" | Erythema; red, cracked lips | Diffusely red | |
| 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.
experience and skill of the individuals performing them.\textsuperscript{12,14} The accuracy of the rapid tests seems to be highly dependent on the failure to diagnose acute streptococcal pharyngitis.\textsuperscript{13} The sensitivity of rapid strep tests often 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.

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 (carrier), 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\textsuperscript{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\textsuperscript{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.\textsuperscript{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

\textbf{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 |
|                 | 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.\textsuperscript{10,14} The accuracy of the rapid tests seems to be highly dependent on the experience and skill of the individuals performing them.\textsuperscript{12,14}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.pdf}
\caption{Management of patients with sore throat. GAS, group A streptococcus.}
\end{figure}
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.\(^\text{18}\)

**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.\(^\text{19}\) 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\(^\text{20,21}\) but first noted several decades ago.\(^\text{22,23}\) 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,\(^\text{24,25}\) the most carefully performed investigation refutes this concept.\(^\text{26}\) 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.\(^\text{13}\)

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.\(^\text{27}\) 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.\(^\text{26,29}\) Shorter courses of therapy also have been tried, but the bacteriologic results of 5 or 7 days of therapy have not been promising.\(^\text{30,31}\) 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 andcephalexin, 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.\(^\text{32}\) This has not emerged as a problem in the United States. Sulfa drugs, including sulfamethoxazole/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.\(^\text{33}\) 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.\(^\text{34,35}\) Some of these patients are chronic pharyngeal carriers of group A streptococci and suffer from a new superimposed viral infection (Fig 2).

![Figure 2](image)

**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. There is some evidence that bacteriologic failure rates may be somewhat lower when antibiotics other than penicillin are used, especially the cephalosporins. 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 antibiotics is superior to penicillin; all of the antibiotics have treatment failure associated with their use. Published metaanalyses suffer from the poor quality of many of the included studies. 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, tolerance of group A streptococci to penicillin, streptococci “hiding” in tonsils, and the absence of oral flora (particularly alpha streptococci) inhibitory to group A streptococci. 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. 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.

Tolerance to penicillin (inhibition of bacterial growth without killing) has been discussed widely but does not seem to play a role in treatment failure. 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).

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 supplicative complications, and they rarely spread group A streptococci in the community. 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. 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. 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. 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); and (2) oral clindamycin given for 10 days (20 mg/kg/day up to 150 mg, divided into three equal doses). 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.33

The role of tonsillectomy in managing patients with multiple episodes of streptococcal pharyngitis remains controversial. Paradise et al33 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 conjunctivitis 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 enamel 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. 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.

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. 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, oculopalpebral 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 pharyngeal diphtheria 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 gonococcal meningitis, which can be very serious. 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. The role of these organisms in pharyngeal abscesses is not characterized. When implicated as agents of acute pharyngitis, group C or G streptococcal pharyngitis has occurred rarely after epidemic group C and group G streptococcal pharyngitis.

### Complications

#### Suppurative complications

Antibiotic therapy has greatly reduced the suppurrative complications of acute group A streptococcal pharyngitis caused by spread from the pharynx to adjacent structures. Peritonsillar abscesses ("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).

#### Non-suppurative sequelae

These complications include acute rheumatic fever, acute post-streptococcal 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)             |
| Non-suppurative                                      |
| Acute rheumatic fever                                |
| Acute glomerulonephritis                             |
| Reactive arthritis (?)                               |

There are data suggesting group C and group G β-hemolytic streptococci are responsible for acute pharyngitis, particularly in adolescents. Gerber et al 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 streptococcal pharyngitis 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.
Advances in living conditions, sanitation, and nutrition probably considered to have ARF after other diagnoses are excluded and unclear. Those patients who fulfill the Jones criteria should probably occur. The relationship of this entity to ARF is heart disease to prevent recurrent attacks of ARF. Recommended for patients with a history of ARF or rheumatic 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. Since the late 1980s, unexpected local and regional clusters of ARF have been reported, beginning with an outbreak near Salt Lake City. 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. 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 | Minor Criteria | Laboratory |
|----------------|---------------|------------|
| Carditis       | Clinical      | Elevated acute phase reactants | Prolonged P-R interval |
| Polyarthritis  | Arthralgia    | Erythrocyte sedimentation rate |     |
| Chorea         | Fever         | C-reactive protein |     |
| Erythema marginatum |             |            |     |
| Subcutaneous nodules |           |            |     |

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).

### References

1. Schappert SM: National Ambulatory Medical Care Survey: 1990 Summary. Advance data from vital and health statistics; no. 213. Hyattsville, MD, National Center for Health Statistics, 1992
2. Woodwell D: Office visits to pediatric specialists, 1989. Advance data from vital and health statistics; no. 208. Hyattsville, MD, National Center for Health Statistics, 1992
3. Stevens DL, Tanner MH, Winship J, et al: Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 321:1-7, 1989
4. Smith TD, Wilkinson V, Kaplan EL: Group A streptococcus-associated upper respiratory tract infections in a day care center. Pediatrics 83:380-384, 1989
5. Wannamaker LW, Denny FW, Perry WD, et al: The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state. N Engl J Med 249:1-7, 1953
6. Randolph MF, Gerber MA, DeMao KK, et al: Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. J Pediatr 106:870-875, 1985
7. Breese BB: A simple scorecard for the tentative diagnosis of streptococcal pharyngitis. Am J Dis Child 131:514-517, 1977
8. Poses RM, Cebul RD, Collins M, et al: The accuracy of experienced physicians' probability estimates for patients with sore throats: Implications for decision making. JAMA 254:925-929, 1985
9. Breese BB, Disney FA: The accuracy of diagnosis of beta streptococcal infections on clinical grounds. J Pediatr 44:670-673, 1954

### 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.
10. Gerber MA, Spadaccini IJ, Wright LL, et al: Latex agglutination tests for rapid identification of group A streptococci directly from throat swabs. J Pediatr 105:702-705, 1984

11. Berkowitz CD, Anthony BF, Kaplan EL, et al: Cooperative study of latex agglutination to identify group A streptococcal antigen on throat swabs in patients with acute pharyngitis. J Pediatr 107:89-92, 1985

12. Lieu TA, Fleisher GR, Schwartz JS: Clinical performance and effect on treatment rates of latex agglutination testing for streptococcal pharyngitis in an emergency department. Pediatr Infect Dis J 5:655-659, 1986

13. Gerber MA, Randolph MF, Chanatry J, et al: Antigen detection test for streptococcal pharyngitis: Evaluation of sensitivity with respect to true infections. J Pediatr 108:654-657, 1986

14. Dobkin D, Shulman ST: Evaluation of an ELISA for group A streptococcal antigen for diagnosis of pharyngitis. J Pediatr 110:666-659, 1987

15. Cochi SL, Fraser DW, Hightower AW, et al: Diagnosis and treatment of streptococcal pharyngitis: Survey of U.S. practitioners, in Shulman ST (ed): Pharyngitis: Management in an Era of Declining Rheumatic Fever. New York, NY, Praeger, 1984, pp 73-94

16. Schwartz B, Fries S, Fitzgibbon AM, et al: Pediatricians' diagnostic approach to pharyngitis and impact of CLIA 1988 on office diagnostic tests. JAMA 271:229-232, 1994

17. Tanz RR, Hofer C: A survey of U.S. pediatricians' strategies for managing group A streptococcal (GABs) pharyngitis. Abstracts of the XII Lancefield International Symposium on Streptococci and Streptococcal Diseases, St. Petersburg, Russia, 1993 (abstr L3)

18. Kaplan EL, Huwe BB: The sensitivity and specificity of an agglutination test for antibodies to streptococcal extracellular antigens: A quantitative analysis and comparison of the Strepzyme test with the anti-streptolysin O and anti-deoxyribonuclease B tests. J Pediatr 96:367-73, 1980

19. Catanzaro FJ, Stetson CA, Morris LJ, et al: Symposium on rheumatic fever and rheumatic heart disease: The role of streptococci in the pathogenesis of rheumatic fever. Am J Med 17:749-76, 1954

20. Randolph MF, Gerber MA, DeMecoo KK, et al: The effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. J Pediatr 106:870-875, 1985

21. Krober MS, Bass JW, Michels GN: Streptococcal pharyngitis: Placebo-controlled double-blind evaluation of clinical response to penicillin therapy. JAMA 233:1271-1274, 1978

22. Hall CB, Breese BB: Does penicillin make Johnny's strep throat better? Pediatr Infect Dis J 1:3-2-9, 1984

23. Denny FW: Current problems in managing streptococcal pharyngitis. J Pediatr 111:797-406, 1987

24. Breese BB, Disney FA, Talpey WB: The prevention of type-specific immunity to streptococcal infections due to the therapeutic use of penicillin. Am J Dis Child 74:333-359, 1960

25. Pichichero ME, Disney FA, Talpey WB, et al: Adverse and beneficial effects of immediate treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin. Pediatr Infect Dis J 6:603-634, 1987

26. Gerber MA, Randolph MF, DeMecoo KK, et al: Lack of impact of early antibiotic therapy for streptococcal pharyngitis on recurrence rates. J Pediatr 117:833-858, 1990

27. Coogan KM, Kaplan EL: In vitro susceptability of recent North American group A streptococcal isolates to eleven oral antibiotics. Pediatr Infect Dis J 13:630-635, 1994

28. Gerber MA, Spadaccini IJ, Wright LL, et al: Twice-daily penicillin in the treatment of streptococcal pharyngitis. Am J Dis Child 139:1145-1148, 1985

29. Breese BB, Disney FA, Talpey WB: Penicillin in streptococcal infections: Total dose and frequency of administration. Am J Dis Child 110:125-130, 1965

30. Gerber MA, Randolph MF, Chanatry J, et al: Five vs ten days of penicillin V therapy for streptococcal pharyngitis. Am J Dis Child 141:224-227, 1987

31. Schwartz RJ, Wienzen RL, Jr, Pedreira E, et al: Penicillin V for group A streptococcal pharyngitis: A randomized trial of seven vs ten days therapy. JAMA 246:1790-1793, 1981

32. Soppala H, Nissen A, Jarvinen H, et al: Resistance to erythromycin in group A streptococci. N Engl J Med 326:292-297, 1992

33. Gastanaduy AS, Kaplan EL, Huwe BB, et al: Failure of penicillin to eradicate group A streptococci during an outbreak of pharyngitis. Lancet 2:49-50, 1980

34. Tanz RR, Shulman ST, Barthel MJ, et al: Penicillin plus rifampin eradicates pharyngeal carriage of group A streptococci. J Pediatr 106:876-880, 1985

35. Feldman S, Bisno AL, Lott L, et al: Efficacy of benzathine penicillin G in group A streptococcal pharyngitis: Reevaluation. J Pediatr 116:783-787, 1987

36. Kaplan EL: The group A streptococcal upper respiratory tract carrier state: An enigma. J Pediatr 97:337-345, 1980

37. Pichichero ME, Margolis PA: A comparison of cephalosporins and penicillin in the treatment of group A beta-hemolytic streptococcal pharyngitis: A metaanalysis supporting the concept of microbial copathogenicity. Pediatr Infect Dis J 10:275-281, 1991

38. Pichichero ME: Cephalosporins are superior to penicillin for treatment of streptococcal tonsillitis/pharyngitis: Is the difference worth it? Pediatr Infect Dis J 12:268-274, 1993

39. Shulman ST, Gerber MA, Tanz RR, et al: Streptococcal pharyngitis: The case for penicillin therapy. Pediatr Infect Dis J 13:1-7, 1994

40. Simon HJ, Sakai W: Staphylococcal antagonism to penicillin-G therapy of hemolytic streptococcal pharyngeal infection: Effect of oxacillin. Pediatriatrics 31:463-469, 1963

41. Brook I: Role of beta-lactamase-producing bacteria in the failure of penicillin to eradicate group A streptococci. Pediatr Infect Dis J 4:491-495, 1985

42. Brook I: The role of beta-lactamase-producing bacteria in the persistence of streptococcal tonsillar infection. Rev Infect Dis 5:601-607, 1988

43. Kim KS, Kaplan EL: Association of penicillin tolerance with failure to eradicate group A streptococci from patients with pharyngitis. J Pediatr 107:681-684, 1985

44. Brook I, Yousem P, Shah K: Surface s cell-tonsillar aerobic and anaerobic flora in recurrent tonsillitis. JAMA 244:1698-1698, 1990

45. Roos K, Graham E, Holm SE: Evaluation of beta-lactamase activity and microbial interference in treatment failures of acute streptococcal tonsillitis. Scand J Infect Dis 18:313-319, 1986

46. Graham E, Holm SE: The effect of penicillin on bacterial interference in vivo. Scand J Infect Dis 19:333-359, 1987

47. Chaudary S, Bilinsky SA, Hennessy JL, et al: Penicillin V and rifampin for the treatment of group A streptococcal pharyngitis: A randomized trial of 10 days penicillin v 10 days penicillin with rifampin during the final 4 days of therapy. J Pediatr 106:481-486, 1985

48. Kaplan EL, Johnson DR: Eradication of group A streptococci from the upper respiratory tract by amoxicillin with clavulanate after oral penicillin V treatment failure. J Pediatr 113:400-403, 1988

49. Smith TD, Huskins WC, Kim KS, et al: Efficacy of beta-lactamase-resistant penicillin and influence of penicillin tolerance in eradicating streptococci from the pharynx after failure of penicillin therapy for group A streptococcal pharyngitis. J Pediatr 110:778-782, 1987

50. Tanz RR, Shulman ST, Sroka PA, et al: Lack of influence of beta-lactamase-producing flora on recovery of group A streptococci after treatment of acute pharyngitis. J Pediatr 117:859-863, 1990
51. Stjernquist-Desatnik A, Orrling A, Schalen C, et al: Penicillin tolerance in group A streptococci and treatment failure in streptococcal tonsillitis. Acta Otolaryngol 68:71, 1992 (Suppl 492)

52. Ginsburg CM, McCracken GH, Crow SD, et al: Seroepidemiology of the group A streptococcal carriage state in a private pediatric practice. Am J Dis Child 139:614-617, 1985

53. Tanz RR, Poncher JR, Corydon KE, et al: Clindamycin treatment of chronic pharyngeal carriage of group A streptococci. J Pediatr 119:123-128, 1991

54. Roos K, Grahn E, Lind L, et al: Treatment of recurrent tonsillitis by recolonization with alpha-streptococci. Eur J Clin Microbiol Infect Dis 8:318-319, 1989

55. Paradise JL, Bluestone CD, Bachman RZ, et al: Efficacy of tonsillectomy for recurrent throat infection in severely affected children: Results of parallel randomized and nonrandomized clinical trials. N Engl J Med 310:674-683, 1984

56. Waagner DC: *Arcanobacterium haemolyticum*: Biology of the organism and diseases in man. Pediatr Infect Dis J 10:933-939, 1991

57. WHO: Expanded program of immunization: Outbreak of diphtheria, update. Wkly Epidemiol Rec 68:134-138, 1993

58. Lumio J, Jahkola M, Vuento R, et al: Diphtheria after visit to Russia. Lancet 342:53-54, 1993 (letter)

59. Komaroff AL, Aronson MD, Pass TM, et al: Serologic evidence of chlamydial and mycoplasmal pharyngitis in adults. Science 222:927-929, 1983

60. Komaroff AL, Branch WT Jr, Aronson MD, et al: Chlamydial pharyngitis. Ann Intern Med 111:537-538, 1989

61. Hill HR, Caldwell GG, Wilson E, Hager G, Zimmerman RA: Epidemic of pharyngitis due to streptococci of Lancefield group G. Lancet 2(616):371-374, 1969

62. Group C streptococcal infections associated with eating home made cheese. New Mexico Morbid Mortal Weekly Rept pp. 510, 515-516, October 7, 1983

63. Gerber MA, Randolph MF, Martin NJ, et al: Community-wide outbreak of group C streptococcal pharyngitis. Pediatrics 87:598-603, 1991

64. Massel BF, Chute CG, Walker AM, Kurland GS: Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. N Engl J Med 318:280-286, 1988

65. Veasy LG, Wiedmeier SE, Orsmond GS, et al: Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med 316:421-427, 1987

66. Veasy LG, Tami LY, Hill HR: Persistence of acute rheumatic fever in the intermountain area of the United States. J Pediatr 124:9-16, 1994

67. Bisno AL: Group A streptococcal infections and acute rheumatic fever. N Engl J Med 323:783-785, 1991