CLINICAL PRACTICE

# Streptococcal Pharyngitis

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*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 10-year-old girl presents with a sore throat and fever that has lasted for 1 day. She appears flushed and moderately ill. Physical examination reveals a temperature of 39°C, tender bilateral anterior cervical lymph nodes that are 1 to 2 cm in the greatest dimension, and erythema and whitish-yellow exudate over enlarged tonsils and the posterior pharynx. A rapid antigen-detection test from a throat-swab specimen is positive for group A streptococcus. How should the patient be evaluated and treated?**

## THE CLINICAL PROBLEM

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Sore throat is an extremely common presenting symptom. Acute pharyngitis accounts for 1.3% of outpatient visits to health care providers in the United States, and it accounted for an estimated 15 million patient visits in 2006.[1] Group A streptococcus (*Streptococcus pyogenes*) is responsible for 5 to 15% of cases of pharyngitis in adults and 20 to 30% of cases in children.[2] Streptococcal pharyngitis occurs most commonly among children between 5 and 15 years of age. In temperate climates, the incidence is highest in winter and early spring. The economic burden of streptococcal pharyngitis among children in the United States has been estimated at $224 million to $539 million per year, with a substantial fraction of the associated costs attributable to parents' lost time from work.[3]

Streptococcal pharyngeal infection not only causes acute illness but also can trigger the postinfectious syndromes of poststreptococcal glomerulonephritis and acute rheumatic fever. Rheumatic fever is currently uncommon in most developed countries, but it remains the leading cause of acquired heart disease among children in many resource-poor areas such as sub-Saharan Africa, India, and parts of Australasia.[4]

## STRATEGIES AND EVIDENCE

### EVALUATION

The onset of symptoms in patients with streptococcal pharyngitis is often abrupt. In addition to throat pain, symptoms may include fever, chills, malaise, headache, and particularly in younger children abdominal pain, nausea, and vomiting.[5] Occasionally, streptococcal pharyngitis is accompanied by scarlet fever, which is manifested as a finely papular erythematous rash that spares the face, may be accentuated in skin folds, and may desquamate during convalescence. Cough, coryza, and conjunctivitis are not typical symptoms of streptococcal pharyngitis, and, if present, they suggest an alternative cause such as a viral infection. Throat pain may be severe, and it is often worse on one side. However, severe unilateral pain or an inability to swallow should raise concern about a local suppurative complication such as peritonsillar or retropharyngeal abscess, particularly if these symptoms arise or progress several days into the illness. Among children younger than 3 years of age, exudative pharyngitis due to streptococcal infection is rare. In this age group, streptococcal

infection may be manifested as coryza, excoriated nares, and generalized adenopathy.[5] In most persons, fever resolves within 3 to 5 days, and throat pain resolves within 1 week, even without specific treatment.[6,7]

The diagnosis of streptococcal pharyngitis on clinical grounds is notoriously unreliable.[8,9] Symptoms and signs are variable, and the severity of illness ranges from mild throat discomfort alone to classic exudative pharyngitis with high fever and prostration. The diagnosis is further complicated by the fact that infection due to many other agents may be indistinguishable clinically from streptococcal pharyngitis (Table 1).

Clinical scoring systems have been developed to predict the likelihood of streptococcal infection among children and adults presenting with sore throat. These systems are based on assessment for suggestive clinical findings: fever, tonsillar swelling or exudate, tender and enlarged anterior cervical lymph nodes, and the absence of cough. The probability of positive results of a throat culture or a rapid antigen-detection test ranges from 3% or less in patients with no suggestive clinical criteria to approximately 30 to 50% in those with all of them[8,10-12] (Table 2). Clinical prediction rules based on these criteria have been validated in both adults and children to help identify patients in whom evaluation with a throat culture or rapid antigen-detection test is warranted.[10] For example, in the absence of particular risk factors, such as known exposure to a person with streptococcal pharyngitis or a history of acute rheumatic fever or rheumatic heart disease, a throat culture or rapid antigen-detection test would not be indicated in a patient meeting only one or none of the criteria listed above.

Another consideration in deciding whether to perform a throat culture or rapid antigen-detection test is the fact that certain persons are asymptomatic carriers of *S. pyogenes*. The organism can be cultured from the pharynx in the absence of symptoms or signs of infection during winter months in approximately 10% of school-age children and less frequently in persons in other age groups. Carriage can persist for weeks or months and is associated with a very low risk of suppurative or nonsuppurative sequelae or of transmission to others. Therefore, in the absence of suggestive clinical findings, a positive culture or rapid antigen-detection test is likely to reflect incidental carriage of *S. pyogenes*.[13,14]

**Table 1. Infectious Causes of Acute Pharyngitis.**

| Organism | Clinical Manifestations |
|---|---|
| **Viruses** | |
| Rhinovirus | Common cold |
| Coronavirus | Common cold |
| Adenovirus | Pharyngoconjunctival fever |
| Influenza virus | Influenza |
| Parainfluenza virus | Cold, croup |
| Coxsackievirus | Herpangina, hand–foot–mouth disease |
| Herpes simplex virus | Gingivostomatitis (primary infection) |
| Epstein–Barr virus | Infectious mononucleosis |
| Cytomegalovirus | Mononucleosis-like syndrome |
| Human immunodeficiency virus | Acute (primary) infection syndrome |
| **Bacteria** | |
| Group A streptococci | Pharyngitis, scarlet fever |
| Group C and group G streptococci | Pharyngitis |
| Mixed anaerobes | Vincent's angina (necrotizing gingivostomatitis) |
| *Fusobacterium necrophorum* | Lemierre's syndrome (septic thrombophlebitis of the internal jugular vein) |
| *Arcanobacterium haemolyticum* | Pharyngitis, scarlatiniform rash |
| *Neisseria gonorrhoeae* | Pharyngitis |
| *Treponema pallidum* | Secondary syphilis |
| *Francisella tularensis* | Pharyngeal tularemia |
| *Corynebacterium diphtheriae* | Diphtheria |
| *Yersinia enterocolitica* | Pharyngitis, enterocolitis |
| *Yersinia pestis* | Plague |
| *Mycoplasma pneumoniae* | Bronchitis, pneumonia |
| *Chlamydophila pneumoniae* | Bronchitis, pneumonia |
| *Chlamydophila psittaci* | Psittacosis |

## LABORATORY TESTS

Because the presentation is nonspecific, the diagnosis of streptococcal pharyngitis should be based on the results of a specific test to detect the presence of the organism: a throat culture or a rapid antigen-detection test of a throat-swab specimen. Swabbing the posterior pharynx and tonsils and not the tongue, lips, or buccal mucosa increases the sensitivity of both the culture and rapid antigen-detection test.[15] Measurement of serum antibodies to streptolysin O or DNase B, although useful for retrospective diagnosis of streptococcal infection to provide support for the diagnosis of acute rheumatic fever or poststreptococcal glomerulonephritis, is not helpful in the

**Table 2. Clinical Scoring System and Likelihood of Positive Throat Culture for Group A Streptococcal Pharyngitis.***

| Criteria | Points† |
|---|---|
| Fever (temperature >38°C) | 1 |
| Absence of cough | 1 |
| Swollen, tender anterior cervical nodes | 1 |
| Tonsillar swelling or exudate | 1 |
| Age | |
| 3 to <15 yr | 1 |
| 15 to <45 yr | 0 |
| ≥45 yr | −1 |

* The information is adapted from McIsaac et al.[10]
† A score of 0 or a negative score is associated with a risk of 1 to 2.5%, 1 point is associated with a risk of 5 to 10%, 2 points is associated with a risk of 11 to 17%, 3 points is associated with a risk of 28 to 35%, and 4 or more points is associated with a risk of 51 to 53%.

management of pharyngitis, since titers do not begin to increase until 7 to 14 days after the onset of infection, reaching a peak in 3 to 4 weeks.

Because the results of throat cultures are not available for 1 or 2 days, rapid antigen-detection tests have been developed to detect *S. pyogenes* directly from throat swabs, generally within minutes.[16] These tests are based on acid extraction of cell-wall carbohydrate antigen and detection of the antigen with the use of a specific antibody. An alternative approach has been the rapid identification of *S. pyogenes*–specific DNA sequences by means of hybridization with a DNA probe or by means of a real-time polymerase-chain-reaction assay. A wide range of sensitivity (generally, 70 to 90%) has been reported for currently available rapid antigen-detection tests, and the measured sensitivity has been shown to depend on the clinical likelihood of streptococcal infection in the test population.[17,18] The specificity of rapid antigen-detection tests is 95% or greater, and thus a positive result can be considered to be definitive and to obviate the need for culture. A rapid antigen-detection test is less sensitive than culture, so most guidelines recommend obtaining a throat culture if the rapid antigen-detection test is negative.

### RATIONALE FOR ANTIBIOTIC TREATMENT

Since streptococcal pharyngitis is a self-limited illness in the vast majority of cases, a reasonable question is whether it is worthwhile to pursue diagnostic testing and to offer antibiotic treatment for suspected or confirmed cases. Although poststreptococcal glomerulonephritis does not appear to be prevented by antibiotic treatment of streptococcal pharyngitis, several other potential benefits have been suggested to justify treatment.

Studies largely involving military recruits in the 1950s have shown that antibiotic treatment reduces the risk of subsequent development of acute rheumatic fever.[7,19-21] In general, these trials involved study-drug assignment based on military record number (rather than true randomization) and were not consistently placebo-controlled, nor were they fully blinded. Despite these limitations, a meta-analysis that included nine such studies (involving 6702 patients) showed that administration of various regimens of intramuscular penicillin was associated with an 80% reduction in the incidence of acute rheumatic fever, as compared with no antibiotic treatment (relative risk, 0.20; 95% confidence interval [CI], 0.11 to 0.36).[22]

Antibiotic therapy also reduces the risk of suppurative complications of streptococcal infection. A Cochrane review of randomized, placebo-controlled trials showed that antibiotic therapy significantly reduced the risks of acute otitis media (in 11 studies; relative risk, 0.30; 95% CI, 0.15 to 0.58) and peritonsillar abscess (in 8 studies; relative risk, 0.15; 95% CI, 0.05 to 0.47).[23]

Without treatment, streptococcal pharyngitis is associated with persistence of positive throat cultures for up to 6 weeks in 50% of patients.[24] In contrast, treatment with an active antibiotic results in negative throat cultures within 24 hours in more than 80% of patients.[25,26] It is recommended that children receive treatment for streptococcal pharyngitis for 24 hours before they return to school because shorter intervals are associated with a higher rate of positive cultures.[27]

Antibiotic therapy also reduces the duration of streptococcal symptoms. In controlled trials, the rates of fever and sore throat were significantly lower at 24 hours among patients treated with antibiotics than among patients who received placebo.[6,7,25,26] Antibiotics may be less effective in ameliorating symptoms if treatment is delayed.[6]

### APPROACHES TO DIAGNOSIS AND TREATMENT

In the 1950s and 1960s, the most compelling reason for antibiotic treatment of streptococcal pharyngitis was to prevent acute rheumatic fever.

Although high rates persist in several areas of the world, the incidence of acute rheumatic fever in developed countries has declined dramatically, raising questions regarding whether the traditional approach to the diagnosis and treatment of streptococcal pharyngitis is still appropriate in such settings.[28]

In this context, several decision analyses have compared the cost-effectiveness of various strategies for diagnosis and treatment. These strategies include antibiotic treatment based on the results of a throat culture, no treatment, treatment of all patients with symptoms, treatment based on the results of a rapid antigen-detection test alone, treatment based on the results of a rapid antigen-detection test plus culture in patients with a negative rapid antigen-detection test, and treatment based on an algorithm of signs and symptoms alone or in combination with the selective use of culture, rapid antigen-detection test, or both. One analysis of four strategies for the management of pharyngitis in children (treatment of all patients with symptoms, rapid antigen-detection test alone, culture alone, or rapid antigen-detection test plus culture) concluded that a rapid antigen-detection test plus culture was most cost-effective when the costs of managing complications of streptococcal infection and treatment were included.[29] In this analysis, a relatively low sensitivity value (55%) was assigned to the rapid antigen-detection test, and the marginal benefit of culture decreased with increasing sensitivity of the rapid antigen-detection test. Another study involving children, which included these four strategies plus a "treat none" strategy and used a sensitivity of 80% for the rapid antigen-detection test, showed that the rapid antigen-detection test alone was the most cost-effective approach.[30] A similar study involving adults concluded that empirical treatment of all symptomatic patients was the least cost-effective strategy and that the other four strategies had similar cost-effectiveness. The strategy of treating only patients with a positive culture was the least expensive. However, a rapid antigen-detection test plus culture would be the most cost-effective strategy if the prevalence of streptococcal pharyngitis were greater than 20%.[31] A consistent finding is that empirical antibiotic treatment on the basis of symptoms alone results in overuse of antibiotics, increased costs, and an increased rate of side effects from antibiotics, as compared with other strategies.

### TREATMENT REGIMENS

Recommended treatment regimens are summarized in Table 3.

### FOLLOW-UP AFTER TREATMENT

Repeat culture is not generally recommended after treatment for uncomplicated streptococcal pharyngitis. A positive culture after appropriate treatment is of uncertain clinical significance if symptoms and signs of pharyngitis have resolved. Although such a result could imply failure of treatment, it also may mean that the patient is a streptococcal carrier who had an intercurrent episode of pharyngitis caused by another organism.

A rapid antigen-detection test, culture, or both should be performed if symptomatic pharyngitis recurs after treatment; if the result is positive, retreatment is indicated. If incomplete adherence to the initial regimen is a concern, intramuscular benzathine penicillin may be preferred for retreatment. Recurrence may also result from reinfection from a household contact who is a carrier. Although carriage is not an indication for treatment in most circumstances, many experts recommend cultures of throat-swab specimens from household contacts and treatment of all carriers if reinfection is suspected. Clindamycin and cephalosporins appear to be more effective than penicillin in eradicating carriage, and either of these agents is preferred in this situation.[39,40] *S. pyogenes* can persist for days on toothbrushes, but a role in reinfection has not been proved. There is no convincing evidence that household pets are a source of recurrent streptococcal infection.

## AREAS OF UNCERTAINTY

Several articles have suggested that bacteriologic cure rates associated with penicillin treatment of streptococcal pharyngitis have decreased in recent decades and that cephalosporins are more efficacious.[41,42] A meta-analysis of 51 studies showed no significant difference in the bacteriologic failure rate associated with penicillin treatment between the period from 1953 to 1979 and the period from 1980 to 1993 (10.5% and 12%, respectively).[43] A later meta-analysis of 35 comparative trials from 1970 through 1999, involving 7125 children, showed a small, but significant difference in the bacterial cure rate favoring cephalosporins over penicillin.[41] However, as in the earlier study, there was no significant change in the cure rate

**Table 3. Recommended Treatment Regimens for Group A Streptococcal Pharyngitis.***

| Drug | Dose, Route, and Duration | Comments | Reference |
|---|---|---|---|
| Penicillin V | Patient weight <27 kg: 250 mg orally two or three times a day for 10 days; patient weight ≥27 kg: 500 mg two or three times a day for 10 days | Narrow spectrum, inexpensive, vast clinical experience | |
| Benzathine penicillin G | Patient weight <27 kg: 600,000 units intramuscularly as a single dose; patient weight ≥27 kg: 1.2 million units intramuscularly as a single dose | Best evidence for prevention of acute rheumatic fever; obviates concerns about patient adherence | |
| Amoxicillin | 20 mg/kg/dose orally twice a day to maximum of 500 mg/dose for 10 days or 50 mg/kg orally once a day to maximum of 1 g once a day for 10 days | Oral suspension more palatable than penicillin; the only FDA-approved once-daily regimen (Moxatag, MiddleBrook Pharmaceuticals) is a timed-release formulation for patients ≥12 yr, 775 mg orally once a day for 10 days; although not FDA-approved, standard-formulation amoxicillin once daily has efficacy in children and adults similar to that of twice-daily amoxicillin or various penicillin regimens | Clegg et al.,[32] Lennon et al.[33] |
| **Alternatives for patients with penicillin allergy** | | | |
| Cephalexin | 20 mg/kg/dose orally twice a day to maximum of 500 mg/dose for 10 days | Cephalosporins considered acceptable alternative for patients who do not have a history of immediate hypersensitivity to penicillin; first-generation cephalosporins are preferred because of narrower spectrum and lower cost† | |
| Cefadroxil | 30 mg/kg orally once a day to maximum of 1 g once a day for 10 days | | |
| Azithromycin | 12 mg/kg orally once a day to maximum of 500 mg/dose for 5 days | FDA-approved for 5-day treatment course; lower doses associated with higher failure rate among children; resistance <8% in most areas of North America but higher in certain communities and >20% in parts of Europe and Asia‡ | Liu et al.,[35] Tamayo et al.,[36] Tanz et al.[37] |
| Clindamycin | 7 mg/kg/dose orally three times a day to maximum of 300 mg/dose for 10 days | Oral suspension has unpleasant taste; may be associated with higher incidence of *Clostridium difficile* colitis; resistance <2% in United States and Canada but up to 20% in some other countries | Tamayo et al.,[36] Tanz et al.,[37] Kim and Yong Lee[38] |

* FDA denotes Food and Drug Administration.

† A short course (usually 4 or 5 days) of some broad-spectrum cephalosporins appears to have efficacy similar to that of a 10-day course of penicillin, and a 5-day course of cefpodoxime or cefdinir has been approved by the FDA for this indication.[34] However, these agents are not recommended under most circumstances because they are more expensive and have an unnecessarily broad spectrum as compared with penicillin or first-generation cephalosporins.

‡ Erythromycin has been a standard choice for patients who are allergic to penicillin; however, alternative agents have become more popular in recent years because of reduced gastrointestinal side effects and simpler dosing regimens.

associated with penicillin from the 1970s to the 1990s. A proposed explanation for the varying rates of bacteriologic cure associated with penicillin treatment is the variation in the proportion of *S. pyogenes* carriers in the study populations.[44,45] Penicillin is less effective than cephalosporins or clindamycin in eradicating asymptomatic carriage of *S. pyogenes*. Accordingly, inclusion of a larger proportion of carriers in a trial would result in a lower bacteriologic cure rate. In one randomized trial comparing cefadroxil with penicillin in children with a positive throat culture or rapid antigen-detection test, overall rates of bacteriologic cure were 94% and 86%, respectively ($P<0.01$).[40] However, among patients classified clinically (before analysis of the bacteriologic results) as likely to have streptococcal pharyngitis (i.e., those with tender cervical lymphadenopathy, tonsillar exudate, or tonsillar petechiae and no cough, nasal congestion, or diarrhea), there was no significant difference in cure rates between the two treatment regimens. In contrast, among patients who were classified clinically as probable carriers, the rate of bacteriologic cure was 95% in the cefadroxil group and only 73% in the penicillin group.

Several explanations have been proposed for the occasional failure of penicillin treatment, but data are lacking to provide support for them. Potential mechanisms include local degradation of penicillin by beta-lactamases produced by other throat flora and the inhibitory effect of penicillin on competing flora. However, data in support of either mechanism are not conclusive.[40] There is no evidence that *S. pyogenes* has become more resistant to penicillin.

## GUIDELINES

Recommendations for the evaluation and treatment of streptococcal pharyngitis have been published or endorsed by the American College of Physicians (ACP), the American Academy of Family Physicians (AAFP), and the Centers for Disease Control and Prevention (CDC)[46,47]; the Infectious Diseases Society of America (IDSA)[48]; and the American Heart Association–American Academy of Pediatrics (AHA).[49] All these guidelines consider it reasonable not to perform a throat culture or rapid antigen-detection test in persons who have none of the clinical features suggestive of streptococcal infection (fever, tender cervical adenopathy, tonsillar or pharyngeal swelling or exudate, and absence of cough). The guidelines of the ACP, the AAFP, and the CDC endorse three alternative strategies for adults with two or more of the clinical criteria described above. The first strategy is to treat patients with a positive rapid antigen-detection test. The second strategy is to treat patients who meet all four clinical criteria without further testing and those who meet two or three clinical criteria and have a positive rapid antigen-detection test. The third strategy is to test no one and to treat patients who meet three or four clinical criteria. The IDSA and AHA do not endorse the second and third strategies of the ACP, the AAFP, and the CDC because these approaches result in higher rates of prescribing unnecessary antibiotics.

All guidelines recommend penicillin orally or intramuscularly as the preferred therapy for streptococcal pharyngitis. The more recently published AHA guidelines also endorse once-daily amoxicillin as first-line therapy. The ACP, the AAFP, the CDC, and the IDSA recommend the use of erythromycin in patients who are allergic to penicillin. The AHA recommends a first-generation cephalosporin in patients with penicillin allergy who do not have immediate hypersensitivity to beta-lactam antibiotics, with clindamycin, azithromycin, or clarithromycin as an alternative treatment option. Guidelines in some European countries are largely consistent with these approaches, whereas other European guidelines consider streptococcal pharyngitis to be a self-limited illness that does not require a specific diagnosis or antibiotic treatment except in high-risk patients (i.e., those with a history of acute rheumatic fever or rheumatic heart disease) or severely ill patients.[28] In contrast, guidelines from India, where the incidence of acute rheumatic fever remains high, list intramuscular benzathine penicillin G first among recommended therapies for streptococcal pharyngitis.[50]

## CONCLUSIONS AND RECOMMENDATIONS

In patients with symptoms and signs suggestive of streptococcal pharyngitis, such as the patient in the vignette, a specific diagnosis should be determined by performing a throat culture or a rapid antigen-detection test with a throat culture if the rapid antigen-detection test is negative, at least in children. Penicillin is the preferred treat-

ment, and a first-generation cephalosporin is an acceptable alternative unless there is a history of immediate hypersensitivity to a beta-lactam antibiotic. In the patient in the case vignette, the positive rapid antigen-detection test establishes a diagnosis of streptococcal infection. I would recommend ibuprofen or acetaminophen for symptomatic relief and would prescribe oral penicillin V for 10 days. Since the rapid antigen-detection test is positive, a throat culture is not needed for diagnosis, nor is one necessary after treatment, if symptoms resolve.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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