Management of Group A Beta-Hemolytic Streptococcal Pharyngitis

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Bacteria are responsible for approximately 5 to 10 percent of pharyngitis cases, with group A beta-hemolytic streptococci being the most common bacterial etiology. A positive rapid antigen detection test may be considered definitive evidence for treatment; a negative test should be followed by a confirmatory throat culture when streptococcal pharyngitis is strongly suspected. Treatment goals include prevention of suppurative and nonsuppurative complications, abatement of clinical signs and symptoms, reduction of bacterial transmission and minimizing of antimicrobial adverse effects. Antibiotic selection requires consideration of patients’ allergies, bacteriologic and clinical efficacy, frequency of administration, duration of therapy, potential side effects, compliance and cost. Oral penicillin remains the drug of choice in most clinical situations, although the more expensive cephalosporins and, perhaps, amoxicillin-clavulanate potassium provide superior bacteriologic and clinical cure rates. Alternative treatments must be used in patients with penicillin allergy, compliance issues or penicillin treatment failure. Patients who do not respond to initial treatment should be given an antimicrobial that is not inactivated by penicillinase-producing organisms (e.g., amoxicillin-clavulanate potassium, a cephalosporin or a macrolide). Patient education may help to reduce recurrence. (Am Fam Physician 2001;63:1557-64,1565.)
A positive rapid antigen detection test may be considered definitive evidence for treatment. A confirmatory throat culture should follow a negative test result.

According to the American Academy of Pediatrics and the American Heart Association, a positive rapid antigen detection test may be considered definitive evidence for treatment of streptococcal pharyngitis. A confirmatory throat culture should follow a negative rapid antigen detection test when the diagnosis of group A beta-hemolytic streptococcal infection is strongly suspected.

Investigators in one recent study recommended that cost-conscious physicians use well-validated prediction rules to help them make better use of rapid antigen tests and throat cultures. Clinical prediction rules take into account key elements of a patient's history and physical examination and allow physicians to predict the probability of group A beta-hemolytic streptococcal pharyngitis.

Therapeutic Goals

Treatment goals in patients with streptococcal pharyngitis, including the management of complications, are listed in Table 1.

TABLE 1
Treatment Goals in Patients with Group A Beta-Hemolytic Streptococcal Pharyngitis

Prevention of nonsuppurative and suppurative complications
Abatement of clinical signs and symptoms
Reduction of bacterial transmission to close contacts
Minimization of adverse effects of antimicrobial therapy

acute rheumatic fever was as high as 388 cases per 100,000 U.S. Army personnel. In the 1970s and early 1980s, the incidence of this illness fell to 0.23 to 1.14 cases per 100,000 school-aged children, most likely because of changes in nutrition, decreased crowding, alterations in the pathogen’s immune-stimulating potential, improved access to medical care and the introduction of effective antibiotics. However, important outbreaks of acute rheumatic fever in the late 1980s raised concern that virulent serotypes were on the rise. The reported annual incidence of acute rheumatic fever is now approximately one case per 1 million population.

Suppurative complications of streptococcal pharyngitis occur as infection spreads from pharyngeal mucosa to deeper tissues. Since the mid-1980s, an increase in the severity of streptococcal pharyngitis cases has been reported in the United States.

Group A beta-hemolytic streptococci can also cause invasive infections such as necrotizing fasciitis, myositis and streptococcal toxic shock syndrome. Although the skin is the most common portal of entry for these invasive infections, the pharynx has been documented as the point of entry in some cases.

Antibiotic Therapy

Multiple factors should be considered in selecting an antibiotic to treat streptococcal pharyngitis (Table 3). Potential antibiotic regimens are provided in Table 4. An algorithm for the suggested evaluation and treatment of patients with a sore throat is provided in Figure 1.

**TABLE 2**

**Complications of Group A Beta-Hemolytic Streptococcal Pharyngitis**

<table>
<thead>
<tr>
<th>Non supplicative complications</th>
<th>Rheumatic fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppurative complications</td>
<td>Cervical lymphadenitis</td>
</tr>
<tr>
<td></td>
<td>Peritonsillar or retropharyngeal abscess</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Mastoiditis</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Endocarditis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
</tbody>
</table>


Patients with streptococcal pharyngitis who remain symptomatic after initial therapy are considered clinical failures and must be retreated.

**TABLE 3**

**Factors in Selecting an Antibiotic for Streptococcal Pharyngitis**

| Bacteriologic and clinical efficacy |
| Patient allergies                  |
| Compliance issues                  |
| Frequency of administration        |
| Palatability                       |
| Cost                               |
| Spectrum of activity               |
| Potential side effects             |

proven efficacy and safety, a narrow spectrum of activity and low cost.

From the early 1950s into the 1970s, streptococcal pharyngitis was treated with a single intramuscular injection of penicillin G benzathine. Studies from the late 1960s and the 1970s revealed that streptococcal eradication was equal with intramuscularly and orally administered penicillins. Thus, since the early 1980s, oral treatment using penicillin V has been preferred. 

Although penicillin is effective, it does have drawbacks. About 10 percent of patients are allergic to penicillin, and compliance with a four-times-daily dosing schedule is difficult. Fortunately, cure rates are similar for 250 mg of penicillin V given two, three or four times daily. The use of intramuscularly administered penicillin may overcome compliance problems, but the injection is painful.

Bacteriologic and clinical treatment failures occur with penicillin, as with all antibiotics.

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### TABLE 4
Selected Antibiotic Regimens for Group A Beta-Hemolytic Streptococcal Pharyngitis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/dosage</th>
<th>Dosing frequency</th>
<th>Duration of therapy</th>
<th>Cost (generic)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V (Veetids)</td>
<td>Child: 250 mg</td>
<td>Two or three times daily</td>
<td>10 days</td>
<td>$1.50 (1.00 to 1.25)</td>
</tr>
<tr>
<td></td>
<td>Adult: 500 mg</td>
<td>Two or three times daily</td>
<td>10 days</td>
<td>$2.00 (1.75 to 2.00)</td>
</tr>
<tr>
<td>Penicillin G benzathine (Bicillin L-A)</td>
<td>Child: 600,000 units</td>
<td>Single injection</td>
<td>—</td>
<td>10.25</td>
</tr>
<tr>
<td></td>
<td>Adult: 1,200,000 units</td>
<td>Single injection</td>
<td>—</td>
<td>17.75</td>
</tr>
<tr>
<td>Amoxicillin (Amoxil)</td>
<td>Child: 40 mg per kg per day</td>
<td>Three divided doses</td>
<td>10 days</td>
<td>$5.25 (6.00 to 6.75)</td>
</tr>
<tr>
<td></td>
<td>Adult: 500 mg</td>
<td>Three times daily</td>
<td>10 days</td>
<td>$16.50 (11.75 to 17.50)</td>
</tr>
<tr>
<td>Erythromycin ethylsuccinate (E.E.S. 400)</td>
<td>Child: 40 mg per kg per day</td>
<td>Two to four divided doses</td>
<td>10 days</td>
<td>$8.50 (11.00 to 12.25)</td>
</tr>
<tr>
<td></td>
<td>Adult: 400 mg</td>
<td>Four times daily</td>
<td>10 days</td>
<td>$9.25 (11.00 to 12.50)</td>
</tr>
<tr>
<td>Erythromycin estolate</td>
<td>Child: 20 to 40 mg per kg per day</td>
<td>Two to four divided doses</td>
<td>10 days</td>
<td>$(15.00 to 31.50)</td>
</tr>
<tr>
<td></td>
<td>Adult: not recommended</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>Child: 12 mg per kg for 5 days</td>
<td>Once daily</td>
<td>5 days</td>
<td>$28.50¶</td>
</tr>
<tr>
<td></td>
<td>Adult: 500 mg on day 1; 250 mg on days 2 through 5</td>
<td>Once daily</td>
<td>5 days</td>
<td>$40.00</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate potassium (Augmentin)</td>
<td>Child: 40 mg per kg per day</td>
<td>Two or three divided doses</td>
<td>10 days</td>
<td>$45.75¶</td>
</tr>
<tr>
<td></td>
<td>Adult: 500 to 875 mg</td>
<td>Two times daily</td>
<td>10 days</td>
<td>$71.25</td>
</tr>
<tr>
<td>Cefadroxil (Duricef)</td>
<td>Child: 30 mg per kg per day</td>
<td>Two divided doses</td>
<td>10 days</td>
<td>$32.00¶</td>
</tr>
<tr>
<td></td>
<td>Adult: 1 g</td>
<td>Once daily</td>
<td>10 days</td>
<td>$162.50 (73.50 to 143.00)</td>
</tr>
<tr>
<td>Cephalexin (Keflex) (Keftab)</td>
<td>Child: 25 to 50 mg per kg per day</td>
<td>Two to four divided doses</td>
<td>10 days</td>
<td>$35.00 (11.25 to 26.00)</td>
</tr>
<tr>
<td></td>
<td>Adult: 500 mg</td>
<td>Two times daily</td>
<td>10 days</td>
<td>$65.50 (9.25 to 23.50)</td>
</tr>
</tbody>
</table>

* — Estimated cost to the pharmacist based on average wholesale prices for the lowest given dosages (rounded to the nearest quarter dollar) in Red book. Montvale, N.J.: Medical Economics Data, 2000. Cost to the patient will be greater, depending on prescription filling fee.
† — Price based on cost of 100-mL bottle in 250 mg per 5 mL strength.
‡ — Price based on cost of 100-mL bottle in 400 mg per 5 mL strength.
§ — Price based on cost of 150-mL bottle in 250 mg per 5 mL strength.
¶ — Price based on cost of all bottle sizes and strengths.
|| — Price based on cost of 100-mL bottle in 250 mg-62.5 mg per 5 mL strength; no generic liquid available.
“Bacteriologic failure” is failure to eradicate the streptococcal organism responsible for the original infection. Patients with this type of treatment failure may or may not remain symptomatic. Some infected but asymptomatic patients may be carriers. Patients who remain symptomatic despite treatment are considered “clinical failures” and must be retreated. Studies conducted over the past 40 years have reported penicillin V bacteriologic failure rates ranging from 10 to 30 percent and clinical failure rates ranging from 5 to 15 percent.13

### Patient with a Sore Throat

Number of signs and symptoms present:
1. Lack of cough
2. History of fever
3. Tonsillar exudate
4. Swollen, tender anterior lymph nodes

None or one present
- Symptomatic treatment; consider other causes.

Two or three present
- Perform rapid antigen detection test.
  - Negative test
  - Treat symptoms and send throat specimen for culture.

All four present
- Treat with antibiotics.

Negative culture
- Positive culture

- No penicillin allergy
  - First-line therapy: penicillin or amoxicillin
  - Clinical failure

- Penicillin allergy
  - First-line therapy: erythromycin
  - Second-line therapy: amoxicillin-clavulanate potassium (Augmentin), azithromycin (Zithromax) or a cephalosporin*
  - Questions about compliance

- Questions about compliance
  - Penicillin G benzathine

* — Patients with an immediate hypersensitivity reaction to penicillin should not be treated with a cephalosporin.

ALTERNATIVES TO PENICILLIN

Amoxicillin. In children, the cure rates for amoxicillin given once daily for 10 days are similar to those for penicillin V. The absorption of amoxicillin is unaffected by the ingestion of food, and the drug's serum half-life in children is longer than that of penicillin V. Amoxicillin is less expensive and has a narrower spectrum of antimicrobial activity than the presently approved once-daily antibiotics. Suspensions of this drug taste better than penicillin V suspensions, and chewable tablets are available. However, gastrointestinal side effects and skin rash may be more common with amoxicillin.

Macrolides. Erythromycin is recommended as a first alternative in patients with penicillin allergy. Because erythromycin estolate is hepatotoxic in adults, erythromycin ethylsuccinate may be used. Erythromycin is absorbed better when it is given with food. Although this antibiotic is as effective as penicillin, 15 to 20 percent of patients cannot tolerate its gastrointestinal side effects.

The extended spectrum of azithromycin (Zithromax) allows once-daily dosing and a shorter treatment course. The U.S. Food and Drug Administration (FDA) has labeled a five-day course of azithromycin as a second-line therapy for streptococcal pharyngitis. Azithromycin is associated with a low incidence of gastrointestinal side effects, and three- and four-day courses of this antibiotic have been shown to be as effective as a 10-day course of penicillin V. However, azithromycin is expensive, and its effectiveness in preventing acute rheumatic fever is unknown.

Cephalosporins. A 10-day course of a cephalosporin has been shown to be superior to penicillin in eradicating group A beta-hemolytic streptococci. A meta-analysis of 19 comparative trials found that the overall bacteriologic cure rate for cephalosporins was 92 percent, compared with 84 percent for penicillin (P <0.0001).

Cephalosporins have a broader spectrum of activity than penicillin V. Unlike penicillin, cephalosporins are resistant to degradation from beta-lactamase produced by copathogens. First-generation agents such as cefadroxil (Duricef) and cephalexin (Keftab, Keflex) are preferable to second- or third-generation agents, if used, because they offer a narrower spectrum of activity.

Because of the possibility of cross-reactivity, patients with immediate hypersensitivity to penicillin should not be treated with a cephalosporin. Cephalosporins are also expensive. Therefore, use of these agents is often reserved for patients with relapse or recurrence of streptococcal pharyngitis.

Amoxicillin-Clavulanate Potassium. The combination drug amoxicillin-clavulanate potassium (Augmentin) is resistant to degradation from beta-lactamase produced by copathogens that may colonize the tonsillopharyngeal area. Amoxicillin-clavulanate is often used to treat recurrent streptococcal pharyngitis. Its major adverse effect is diarrhea. Amoxicillin-clavulanate is also expensive.

MANAGEMENT ISSUES

Treatment Failure and Reinfection. A recent retrospective chart review found that recurrent group A beta-hemolytic streptococcal infections were more common in the 1990s than in the 1970s. Within days after completing antimicrobial therapy, a small percentage of patients redevelop symptoms of acute pharyngitis, with the infection confirmed by laboratory tests. These patients have either relapse or reinfection. Theories to explain apparent treatment failures include lack of antibiotic compliance, repeat exposure, beta-lactamase-producing copathogens, eradication of protective pharyngeal microflora, antibiotic suppression of immunity and penicillin resistance.

Not all treatment failures should be regarded in the same manner. Repeated episodes in a patient should prompt a search within the patient's family for an asymptomatic carrier who, if found, can be treated. Patients who do not comply with a 10-day course of penicillin
should be offered an alternative, such as intramuscularly administered penicillin or a once-daily orally administered macrolide or cephalosporin. Patients with clinical failure should be treated with an antimicrobial agent that is not inactivated by penicillinase-producing organisms. Amoxicillin-clavulanate potassium, cephalosporins and macrolides fall into this category.

Group A beta-hemolytic streptococci persist for up to 15 days on unrinsed toothbrushes and removable orthodontic appliances. The pathogens are not isolated from rinsed toothbrushes after three days. Instructing patients to rinse toothbrushes and removable orthodontic appliances thoroughly may help to prevent recurrent infections.

Pets. Transmission of group A beta-hemolytic streptococci occurs principally through contact with respiratory secretions from an infected person. Although anecdotes are numerous and a few cases have been reported, family pets are rare reservoirs of group A beta-hemolytic streptococci.3,9,26

Close Contacts. During epidemics, 50 percent of the siblings and 20 percent of the parents of infected children develop streptococcal pharyngitis.14 Asymptomatic contacts do not require cultures or prophylaxis. Symptomatic contacts may be treated with or without cultures.

Follow-up and Carriers. Routine post-treatment throat cultures are not necessary. About 5 to 12 percent of treated patients have a positive post-treatment culture, regardless of the therapy given.7 A positive post-treatment culture represents the asymptomatic chronic carrier state, and carriers are not a significant source for the spread of group A beta-hemolytic streptococci. Furthermore, they are not at risk of developing rheumatic fever.14 In general, asymptomatic carriers are not treated unless they are associated with treatment failure in a close-contact index patient.

Contagion. Patients with streptococcal pharyngitis are considered contagious until they have been taking an antibiotic for 24 hours.2 Children should not go back to their day-care center or school until their temperature returns to normal and they have had at least 24 hours of antibiotic therapy.

Streptococcal Necrotizing Fasciitis. Group A beta-hemolytic streptococci are the causative organisms in streptococcal necrotizing fasciitis. This infection, attributed to so-called “flesh-eating bacteria,” has been the subject of sensational journalistic reports. Invasive streptococcus strains usually have a cutaneous portal of entry and rarely enter via the tonsillopharyngeal area.2,28,29 Patients with streptococcal necrotizing fasciitis may develop streptococcal toxic shock syndrome.

Symptomatic Treatment. Antibiotic therapy for streptococcal pharyngitis shortens the duration of symptoms by less than one day.30 Therefore, measures to relieve symptoms are important. Salt-water gargles, lozenges, aspirin-containing gum, demulcents and other remedies all have proponents. No evidence confirms or denies the utility of these measures.

Acetaminophen or a nonsteroidal anti-inflammatory drug may be given to reduce temperature. Children and adolescents should not take aspirin.

The Future

In time, rapid tests such as optical immunoassay and chemiluminescent DNA may increase the accuracy and, unfortunately, the cost of diagnosing group A beta-hemolytic streptococcal infections. Current research on a vaccine, involving the streptococcal M protein, may allow prevention of the disease.31 However, the clinical studies that must follow basic research on a vaccine will require many years. A marker to identify susceptibility to rheumatic fever may make use of the vaccine in susceptible persons practical.4 More research on penicillin treatment fail-
Streptococcal Pharyngitis

ures would be useful. If a reported increase in recurrences after antibiotic treatment is confirmed elsewhere and streptococcal serotypes and drug sensitivities are, indeed, changing, penicillin will probably no longer be the drug of choice for the treatment of streptococcal pharyngitis.

REFERENCES


