

festated by bilateral eye findings, high fevers, and meningeal signs. Intracranial extension, including epidural abscess, subdural abscess, brain abscess, and meningitis, requires the appropriate intravenous antibiotics as well as neurosurgical intervention.

STREPTOCOCCAL PHARYNGITIS

method of

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Sore throat is a common manifestation of many infectious syndromes and a frequent complaint of patients seeking acute medical care. The majority of cases of acute tonsillopharyngitis are caused by viral pathogens, including adenoviruses, enteroviruses, influenza and parainfluenza viruses, and Epstein-Barr virus. Group A beta-hemolytic streptococci (GABHS) are the most common cause of bacterial pharyngitis, with sporadic or epidemic cases due to Groups B, C, and G streptococci. Increasing attention has been given to other bacterial causes of pharyngitis recently, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Arcanobacterium haemolyticus*, and *Neisseria gonorrhoeae*, but these infections represent only a small percentage of cases of bacterial pharyngitis. A sore throat may also occur in patients with noninfectious illness, such as Behçet's syndrome, Kawasaki disease, or recurrent aphthous stomatitis.

Recommendations vary regarding the evaluation and management of the patient with acute tonsillopharyngitis. The situation is complicated by the fact that a diagnosis of GABHS pharyngitis cannot be made solely based on symptomatology or physical examination. Accurate diagnosis and appropriate treatment of the patient with GABHS infection is important due to the possibility of suppurative sequelae, such as retropharyngeal or peritonsillar abscess, or nonsuppurative sequelae, such as acute rheumatic fever or glomerulonephritis. Indiscriminate treatment of sore throat with antibiotics should be discouraged, particularly in this era of increasingly prevalent drug-resistant bacteria. The following discussion reviews the microbiology and epidemiology of GABHS as well as current diagnostic options and available therapeutic regimens for the patient with acute GABHS tonsillopharyngitis.

THE ORGANISM

Group A streptococci (*Streptococcus pyogenes*) are gram-positive cocci that typically form chains. Most strains form a zone of clear (beta) hemolysis on blood agar around each colony. Differentiation of group A from other hemolytic streptococci is typically done by looking for a zone of inhibition around a bacitracin disk. Group-specific identification of beta-hemolytic streptococci may also be performed, most commonly utilizing a latex agglutination method.

More than 80 types of GABHS have been characterized based on a surface component, the M protein. This protein provokes a serologically distinct immune response and is a major virulence factor, helping the organism evade phagocytosis. Some serotypes are associated with an increased risk of nonsuppurative sequelae following infection with

these strains. GABHS have a variety of other surface proteins that enhance virulence, and produce a remarkable number of biologically active extracellular toxins, including streptolysins O and S, erythrogenic toxins A, B, and C, DNAase, and hyaluronidase.

The immune response and host defense against GABHS pharyngitis are not well characterized, but there appears to be an early accumulation of monocytes and neutrophils with subsequent phagocytosis of bacteria. Antibody responses to a type-specific M protein are not detectable for several weeks after an infection and probably serve a protective role against reinfection by the same serotype.

EPIDEMIOLOGY

GABHS are primarily human pathogens and are rarely found in other species. Streptococcal pharyngitis is predominantly a disease of school-age children, with peak incidence occurring between age 5 and 15 years. Infants rarely develop pharyngitis but may develop a purulent rhinitis caused by GABHS known as streptococcosis. Infection is typically more frequent in winter and spring, but sporadic cases occur throughout the year. In cold or temperate climates, approximately one-third of children and 10% of adults who complain of sore throat during the peak winter season are actually infected with GABHS; the remainder of cases are usually viral in origin.

Transmission of GABHS is through close contact and from person to person. The organism is primarily spread through transfer of respiratory secretions or contact with large droplet nuclei containing streptococci. Spread through the air by dust particles or by fomites (environmental objects) does not appear to be involved. Infection among family members or classmates is common. Patients should be considered highly contagious in the acute stage of illness. Treatment with appropriate antibiotics rapidly suppresses growth of GABHS, and the patient may be considered much less contagious after 24 to 48 hours. Carriers of GABHS (to be discussed later) are infectious primarily in the first two weeks after acquisition of the organism. There appears to be little risk of spread after that time.

CLINICAL MANIFESTATIONS

The incubation period is short, with onset of symptoms within 12 hours to 4 days of exposure. Symptoms of GABHS tonsillopharyngitis generally occur suddenly, with the appearance of fever and sore throat. Parents may notice that the child has "bad breath" and that the throat and tonsils are red. The severity of illness may vary from very mild sore throat to severe pharyngitis with toxicity, high fever, nausea, vomiting, and collapse. Headache and abdominal pain are common complaints in children. Many patients will have at least some degree of tender anterior cervical adenopathy. Physical examination will often confirm pharyngitis, with pharyngeal erythema and enlarged tonsils. In 50% to 90% of cases, there is a whitish-yellow exudate over the tonsils or pharynx. It is important to note that unless suppurative sequelae occur, GABHS is a self-limited illness, with symptoms usually subsiding in 3 to 5 days.

DIAGNOSIS

The diagnosis of GABHS pharyngitis has been based on throat culture for many years, and it remains the "gold standard." Attempts to diagnose streptococcal infection

based solely on clinical grounds are fraught with error and lead to overtreatment in most cases. Breese and others have developed clinical scoring systems that may be helpful in some cases but generally will have no better than 60% to 70% sensitivity overall. Some clinical features may be helpful in excluding GABHS infection, such as the presence of cough, hoarseness, or conjunctivitis, but these findings are by no means conclusive. The situation is further complicated by the fact that many children are asymptomatic pharyngeal carriers of GABHS, so a positive throat culture result may be seen in a patient with a typical viral pharyngitis. Blood tests are generally not obtained, but leukocytosis is common in GABHS infection, as opposed to many viral etiologies of pharyngitis. The absence of an elevated white blood cell count decreases the likelihood of GABHS as the cause of pharyngitis. C-reactive protein may be elevated in some cases of GABHS but is usually normal with viral infection.

In recent years, rapid diagnostic tests for the detection of group A streptococci have allowed clinicians to make a quick diagnosis of GABHS pharyngitis before the patient leaves the office. While the specificity of most currently available assays is generally better than 90% to 95%, sensitivity is less than optimal. Up to 30% of cases of true GABHS infection will be missed by rapid tests. False-negatives typically occur if the relative numbers of streptococci in the oropharynx are low, or if the throat swab is improperly obtained. False-positives due to chronic carriage of GABHS also present a problem. Whereas these tests facilitate early treatment, this is not clearly a necessary or even desirable approach. Some studies suggest that early antibiotic treatment decreases the development of type-specific immunity and that treatment may be delayed for up to seven to nine days without any increase in risk of nonsuppurative sequelae such as rheumatic fever. The common practice of obtaining a throat culture and withholding treatment until the result is known can be justified early in the course of disease. However, it is also true that early treatment leads to more rapid resolution of symptoms and may limit spread of GABHS to others. A reasonable approach is to treat patients with positive rapid antigen assays and obtain throat cultures on patients with a negative test, deferring treatment until the culture results are known. Routine follow-up throat cultures are no longer recommended.

THErapy

Treatment of GABHS pharyngitis reduces the duration of symptoms, decreases the risk of suppurative and nonsuppurative sequelae, and limits the spread of illness to others. Although GABHS are susceptible to a variety of antimicrobials, penicillin remains the drug of choice in nonallergic individuals, based both on proven efficacy and low cost. Recent reports suggesting that penicillin has become less effective in eradicating GABHS from the pharynx have appeared, but this has not been substantiated. Speculation that treatment failures occur due to beta-lactamase production by oropharyngeal flora or because penicillin tolerance occurs in some strains of group A streptococci has been difficult to prove; published studies have provided conflicting results. The likely clinical significance of these problems is minor. By far the most common reason for therapeutic failure is noncompliance. Although most patients will improve

symptomatically within 24 to 48 hours of beginning treatment, complete eradication of GABHS from the pharynx is difficult and has led to recommendations for a full 10-day course of therapy. Many patients will discontinue treatment after they feel well, typically within three to four days. Re-exposure to friends or family members who are infected may also explain apparent treatment failures.

A variety of other agents have efficacy in the treatment of GABHS pharyngitis and may be useful when concerns exist about compliance, bacterial copathogenicity (beta-lactamase production by oral flora), penicillin tolerance, or in the face of treatment failure. These will be discussed next and are listed in Table 1. Inappropriate agents for treatment include sulfonamides (including trimethoprim-sulfamethoxazole [Bactrim, Septra]) and tetracyclines, which are not active enough against GABHS.

Penicillins

Oral penicillin V has traditionally been used to treat group A streptococcal infections. Twice-daily dosing is as efficacious as more frequent three or four times a day dosing in eradication of GABHS. Decreased dosing frequency clearly enhances patient compliance. Amoxicillin or ampicillin, while no more active in vitro than penicillin, is an acceptable alternative and may be more palatable than penicillin V for patients receiving an oral suspension. When concern exists about patient compliance or follow-up, a single dose of intramuscular benzathine G is appropriate. This is also the preferred strategy for treatment of epidemic infections due to GABHS. Amoxicillin/clavulanate (*Augmentin*) is generally not indicated unless concerns about bacterial copathogenicity exist; diarrhea is also a common side effect, making this a less attractive treatment option.

Macrolides

Erythromycin has long been advocated as the best alternative for patients with penicillin allergy or sensitivity who require treatment of GABHS infection. However, it has a higher failure rate than beta-lactam agents, and some strains of GABHS are resistant. Gastrointestinal (GI) side effects also occur frequently and lead to early discontinuation of therapy. Clarithromycin (*Biaxin*) is a new macrolide with excellent activity against GABHS; it allows the convenience of twice-daily dosing and has a much lower incidence of GI intolerance than erythromycin. Azithromycin (*Zithromax*) is an azalide drug with a long half-life; this agent may be given once daily for five days with equivalent efficacy to a ten-day treatment course of penicillin for GABHS pharyngitis. Both clarithromycin and azithromycin are available in an oral suspension and should be considered good alternatives to erythromycin in treatment of the penicillin-allergic patient with streptococcal pharyngitis.

TABLE 1. Antibiotic Dosing for GABHS Pharyngitis*

Antibiotic	Child < 40 Pounds	Adults and Children ≥ 40 Pounds
Penicillin VK	25–50 mg/kg/d divided bid	500 mg bid
Amoxicillin	20–40 mg/kg/d divided tid	500 mg bid
Cephalexin (Keflex)	25–50 mg/kg/d divided bid	250 mg qid
Cefadroxil (Duricef)	30 mg/kg/d qd	1 gm qd
Cefaclor (Ceclor)	20 mg/kg/d divided bid	250 mg tid
Cefuroxime axetil (Ceftin)	20 mg/kg/d divided bid	250 mg bid
Cefprozil (Cefzil)	15 mg/kg/d divided bid	500 mg qd
Cefpodoxime (Vantin)	10 mg/kg/d divided bid	100 mg bid
Loracarbef (Lorabid)	15 mg/kg/d divided bid	200 mg bid
Erythromycin estolate (Ilosone)	40 mg/kg/d divided bid	500 mg bid
Clarithromycin (Biaxin)	15 mg/kg/d divided bid	250 mg bid
Azithromycin (Zithromax)	12 mg/kg/d qd for 5 d	500 mg on day 1, 250 mg qd days 2–5
Clindamycin (Cleocin)	20 mg/kg/d divided tid	150 mg tid

*All treatment courses are 10 days unless otherwise specified.

Cephalosporins

Multiple clinical trials have demonstrated that the majority of currently available oral cephalosporins are at least as effective as penicillin in treatment of GABHS pharyngitis and in many cases have superior rates of clinical and bacteriologic cure. Many of these agents are resistant to a variety of beta-lactamases, eliminating concerns about bacterial copathogenicity. Cephalexin (Keflex) and cefadroxil (Duricef) are commonly prescribed agents; the former has the advantage of low cost, the latter has the advantage of once-daily dosing. Second-generation agents such as cefaclor (Ceclor), and cefuroxime (Ceftin), are also quite effective, but cefaclor may have a greater incidence of adverse side effects such as rash or serum sickness. Recently a variety of novel agents, including loracarbef (Lorabid), cefpodoxime (Vantin), and cefprozil (Cefzil), have been approved by the Food and Drug Administration. These agents are well tolerated and are usually dosed twice daily. Cefprozil has been shown to be efficacious in adults with GABHS pharyngitis when given once a day. Most oral cephalosporins are quite expensive and should generally be considered for use only when a patient has failed treatment with a standard penicillin regimen. A complete list of currently available cephalosporins and dosing regimens is included in Table 1.

RECURRENT STREPTOCOCCAL PHARYNGITIS AND THE CARRIER STATE

Patients who have persistently positive throat cultures for GABHS often provide a dilemma for practicing physicians; if this occurs in the setting of clinical pharyngitis, there is no easy way to determine whether the patient has a refractory group A streptococcus infection or is a chronic carrier of GABHS with a concomitant viral pharyngitis. The carrier state is a puzzling phenomenon in which patients harbor the organism for long periods of time without developing an immune response. Carriers appear to be at low risk for development of rheumatic fever.

Fortunately, spread of GABHS from carriers to close contacts is rare.

Patients who fail to improve rapidly on therapy or have a prompt recrudescence of symptoms following completion of a treatment course and have persistently positive throat cultures should be retreated. Retreatment with penicillin is inappropriate. Alternative agents such as cephalosporins or macrolides should be used. Other reasons for treatment failure, such as noncompliance or intrafamilial spread, should be considered. In some cases, culture of family members and treatment of positive results are indicated. If the throat culture remains positive after a second course of therapy, the benefit of more treatment is doubtful. However, if the patient is a persistent carrier and typically has frequent episodes of pharyngitis, interpretation of throat culture results will be difficult. In this setting, attempts at eradication of the carrier state can be considered. Clindamycin (Cleocin) has been demonstrated to be quite effective in this setting, although GI intolerance and concerns about increased risk of antibiotic-associated colitis have limited its use. A combined regimen of penicillin and rifampin (Rifadin), has also been shown to be effective at eradication of the carrier state.

TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIAL DISEASES

method of
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TUBERCULOSIS

Tuberculosis (TB) remains an important cause of disease in the United States and throughout the