

Primary Care

ACUTE PHARYNGITIS

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ACUTE pharyngitis is one of the most common illnesses for which patients visit primary care physicians. According to the National Ambulatory Medical Care Survey, upper respiratory tract infections, including acute pharyngitis, are responsible for 200 visits to a physician per 1000 population annually in the United States¹ — a rate more than double that for any other category of infectious disease. The sore throat, fever, and malaise associated with acute pharyngitis are distressing, but with few exceptions, these illnesses are both benign and self-limited.

Many bacterial and viral organisms are capable of inducing pharyngitis, either as a single manifestation or as part of a more generalized illness. A partial list of microorganisms that cause pharyngitis is presented in Table 1.² Strategies for diagnosis and treatment are directed at identifying those patients who require specific antimicrobial agents and attempting to minimize the unnecessary use of these agents. Pharyngitis as part of the common cold will not be considered in detail in this review.

STREPTOCOCCAL PHARYNGITIS

Clinical Manifestations

Group A streptococcus is by far the most common bacterial cause of acute pharyngitis, accounting for approximately 15 to 30 percent of cases in children and 5 to 10 percent of cases in adults.^{3,4} Moreover, group A streptococcal pharyngitis is the only common form of the disease for which antimicrobial therapy is definitely indicated. Therefore, when a clinician evaluates a patient with acute sore throat, the most important clinical task is to decide whether or not the patient has “strep throat.” This illness occurs predominantly, though not exclusively, in school-age children. In tem-

perate climates, the incidence is highest during the winter and early spring. The characteristic clinical findings are summarized in Table 2. Not all patients have the full-blown syndrome; many cases are milder and nonexudative, and patients who have undergone tonsillectomy may have milder symptoms. Children less than three years of age may have coryza and crusting of the nares; exudative pharyngitis is rare in this age group.

Diagnosis

The presence of such findings as tonsillopharyngeal exudate (Fig. 1) and anterior cervical lymphadenitis increases the statistical likelihood that the infectious agent is group A streptococcus.⁶ A number of algorithms incorporating epidemiologic and clinical factors have been devised; these improve diagnostic accuracy primarily by identifying patients with an exceedingly low risk of streptococcal infection.^{4,7,8} Indicators of low risk include the absence of fever (without the use of antipyretic agents), the absence of pharyngeal erythema, and the presence of obvious manifestations of the common cold.

Unless streptococcal infection can be ruled out with confidence on the basis of clinical and epidemiologic evidence, however, patients with acute pharyngitis should be tested for the presence of group A streptococci in the throat,^{5,9-11} by means of either a throat culture or a rapid test for group A streptococcal antigen. Physicians who rely on the clinical impression alone are likely to overtreat for fear of missing an infection that might result in acute rheumatic fever or in locally or systemically invasive disease.^{3,12}

A properly performed and interpreted throat culture remains the gold standard for the diagnosis of group A streptococcal pharyngitis. It has a sensitivity of 90 percent or higher, according to studies that used duplicate throat cultures. False negative results are likely in patients with small numbers of organisms in the pharynx, and many such patients are probably streptococcal carriers rather than acutely infected persons. The important factors involved in the throat culture (the proper method of swabbing; the optimal medium, time, and atmosphere for incubation; and an accurate reading of the plates) have been summarized in detail elsewhere.^{9,13,14}

Obtaining definitive results from the throat culture takes between 24 and 48 hours. Delaying antimicrobial therapy for this period will not diminish its efficacy in preventing rheumatic fever, but it is often difficult to explain to patients or their parents the need to withhold therapy, particularly from a sick child. Indeed, in patients who appear acutely ill and in whom

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TABLE 1. MICROBIAL CAUSES OF ACUTE PHARYNGITIS.*

PATHOGEN	SYNDROME OR DISEASE	ESTIMATED PERCENTAGE OF CASES†
Viral		
Rhinovirus (100 types and 1 subtype)	Common cold	20
Coronavirus (3 or more types)	Common cold	≥5
Adenovirus (types 3, 4, 7, 14, and 21)	Pharyngoconjunctival fever, acute respiratory disease	5
Herpes simplex virus (types 1 and 2)	Gingivitis, stomatitis, pharyngitis	4
Parainfluenza virus (types 1–4)	Common cold, croup	2
Influenzavirus (types A and B)	Influenza	2
Coxsackievirus A (types 2, 4–6, 8, and 10)	Herpangina	<1
Epstein–Barr virus	Infectious mononucleosis	<1
Cytomegalovirus	Infectious mononucleosis	<1
Human immunodeficiency virus type 1	Primary human immunodeficiency virus infection	<1
Bacterial		
<i>Streptococcus pyogenes</i> (group A β-hemolytic streptococci)	Pharyngitis and tonsillitis, scarlet fever	15–30
Group C β-hemolytic streptococci	Pharyngitis and tonsillitis	5
<i>Neisseria gonorrhoeae</i>	Pharyngitis	<1
<i>Corynebacterium diphtheriae</i>	Diphtheria	<1
<i>Arcanobacterium haemolyticum</i>	Pharyngitis, scarlatiniform rash	<1
Chlamydial		
<i>Chlamydia pneumoniae</i>	Pneumonia, bronchitis, and pharyngitis	Unknown
Mycoplasmal		
<i>Mycoplasma pneumoniae</i>	Pneumonia, bronchitis, and pharyngitis	<1

*Adapted from Gwaltney and Bisno² with the permission of the publisher. The list is not exhaustive.

†Estimates are of the percentage of cases of pharyngitis in persons of all ages that are due to the indicated organism.

TABLE 2. CHARACTERISTIC SIGNS AND SYMPTOMS OF STREPTOCOCCAL TONSILLOPHARYNGITIS AND UNCHARACTERISTIC FINDINGS.*

Symptoms	
Characteristic	Sudden onset of sore throat
	Pain on swallowing
	Fever
	Headache
	Abdominal pain
	Nausea and vomiting
Uncharacteristic	Coryza
	Hoarseness
	Cough
	Diarrhea
Signs	
Characteristic	Tonsillopharyngeal erythema
	Tonsillopharyngeal exudate
	Soft-palate petechiae (“doughnut” lesions)
	Beefy red, swollen uvula
	Anterior cervical lymphadenitis
	Scarlatiniform rash
Uncharacteristic	Conjunctivitis
	Anterior stomatitis
	Discrete ulcerative lesions

*These findings occur primarily in children more than three years old and in adults. Symptoms and signs in younger children may be different and less specific. Adapted from Dajani et al.⁵ with the permission of the publisher.

there is good reason to suspect streptococcal pharyngitis, it is not unreasonable to initiate antimicrobial therapy while one awaits the results of a culture. A negative throat culture, however, should dictate the prompt discontinuation of such therapy.

These problems may eventually be obviated by the rapid antigen-detection test, which can confirm the presence of group A streptococcal carbohydrate antigen on a throat swab in a matter of minutes. The test kits that are currently available commercially, which use enzyme-immunoassay methods, yield results that are highly specific for the presence of group A streptococci. Thus, a positive rapid test can be considered equivalent to a positive throat culture, and if the rapid test is positive, therapy can be initiated without further microbiologic confirmation. Unfortunately, the sensitivity of most of these tests ranges, at best, between 80 and 90 percent when the tests are compared with the blood agar plate culture. For this reason, national advisory committees recommend that negative results of rapid tests in children and adolescents be confirmed with a conventional throat culture.^{5,9,10}

Because most throat cultures obtained in ambulatory care settings are negative, the need to verify negative rapid tests with throat cultures is a disincentive for using this method of screening. One of the newer tests, the optical immunoassay, has been found by several investigators to be equivalent in sensitivity to



Figure 1. Acute Exudative Streptococcal Pharyngitis in an Adult.

the throat culture,^{15,16} but others have reported its sensitivity to be less than 80 percent.^{17,18} These discrepancies need to be explained. The recommendation to confirm negative results of rapid tests remains controversial, and some feel that the gain in sensitivity with the throat culture may not justify its cost and inconvenience and may not necessarily result in better outcomes in areas where the incidence of acute rheumatic fever is quite low.¹⁹ The development of more sensitive rapid diagnostic assays may render the issue moot. Meanwhile, physicians who elect to use optical immunoassay in children and adolescents without confirmation by culture should do so only after verifying that among the patients in their practice the assay has had a sensitivity similar to that of the standard throat culture.¹⁰ Moreover, practitioners must be certain enough of the equivalent sensitivity to withhold antimicrobial therapy for children and adolescents when rapid tests are negative.

Neither the conventional throat culture nor the rapid test reliably differentiates acutely infected patients from asymptomatic carriers with intercurrent viral pharyngitis. Indeed, the chief virtue of these tests in areas with a low incidence of rheumatic fever is that they allow physicians to withhold antibiotics from the majority of children and adolescents with sore throats, whose cultures will prove to be negative. This is very important in view of the fact that 70 percent of children and adolescents with sore throats who are seen in primary care settings in the United States receive prescriptions for antimicrobial agents.²⁰

Given the low incidence of streptococcal pharyn-

gitis and the minimal risk of acute rheumatic fever in persons over 20 years of age, it seems reasonable to rely on either a throat culture or a high-sensitivity rapid antigen-detection test without confirmation by culture in adults. The high specificity of the rapid tests (very few false positive results) should help prevent the needless use of antimicrobial agents in adults with acute pharyngitis.

Therapy

The objectives of therapy for group A streptococcal pharyngitis are to prevent suppurative complications (peritonsillar or retropharyngeal abscess, cervical lymphadenitis, mastoiditis, sinusitis, and otitis media), prevent rheumatic fever, decrease infectivity so that the patient can return to school or work, and shorten the clinical course of the disease.^{21,22} The last objective can usually be accomplished only if the patient is treated early in the course of the illness, because in the great majority of patients with streptococcal sore throats, the symptoms improve within three to four days even without therapy.²³ There is no firm evidence that treatment of the antecedent streptococcal throat infection can prevent the development of acute glomerulonephritis.

Penicillin, to which the organism is uniformly susceptible, remains the treatment of choice for group A streptococcal pharyngitis because of its proven efficacy, narrow spectrum, safety, and low cost. If oral therapy is elected, a full 10-day course of treatment is necessary to ensure the maximal rate of eradication of the infection from the pharynx²⁴ (Table 3). Recent

studies suggest that treatment for 10 days with a single daily dose of amoxicillin is as effective as treatment with multiple daily doses of penicillin V.²⁵ If this finding is confirmed, the amoxicillin regimen may be considered as a simple and economical alternative to penicillin. The slightly higher rate of eradication achievable with cephalosporins²⁶ may be due to the superior efficacy of these drugs in eradicating carriage²⁷ and does not justify the routine use of these more expensive and broader-spectrum antibiotics. Although erythromycin should be the drug of first choice in patients with an allergy to penicillin that is not of the immediate type, oral cephalosporins are a reasonable second choice in such cases.

Treatment with a number of antimicrobial agents, including azithromycin, cefuroxime, cefdinir, cefixime, and cefpodoxime, has been reported to result in rates of streptococcal eradication at 5 days that are similar to the rates achieved with penicillin at 10 days, but cost and effects on patterns of antimicrobial resistance must still be considered. Azithromycin has several appealing features: it can be given in a single daily dose, it is better tolerated than erythromycin in patients who are allergic to penicillin, and it may be effective in five-day courses. However, the current average wholesale price of a 5-day course of azithromycin tablets at the recommended dosage is \$40, as compared with \$1.75 for a 10-day course of penicillin V (250 mg three times a day). Moreover, streptococcal resistance to macrolides develops rapidly with extensive use of these drugs, which is not the case with penicillin²⁸; therefore, the use of newer macrolides, such as azithromycin, as first-line therapy should be avoided.

With rare exceptions,⁹ neither post-treatment throat

cultures of asymptomatic patients nor routine cultures of asymptomatic family contacts are necessary. The treatment of recurrent and relapsing pharyngitis, including suggested antimicrobial regimens, has recently been reviewed.^{9,14}

Pharyngitis Due to Non-Group A Streptococci

Streptococci of serogroups C and G have been responsible for foodborne and waterborne outbreaks of pharyngitis and for cases that led to acute glomerulonephritis. These organisms may also cause sporadic cases of pharyngitis that mimic group A streptococcal pharyngitis but are generally less severe.²⁹ Because group C and group G streptococci are often commensals of the upper respiratory tract, it is quite difficult to differentiate colonization from infection. The benefit, if any, of antimicrobial therapy is unknown. The antimicrobial agents used to treat group A streptococci (Table 3) would be appropriate for non-group A organisms; the duration of treatment should be shorter, however, since non-group A streptococci have never been shown to cause acute rheumatic fever.

DIPHTHERIA

Pharyngeal diphtheria is now extremely rare in the United States. A single probable case was reported to the Centers for Disease Control and Prevention in 1998. The disease occurs primarily among unimmunized or poorly immunized members of socioeconomically disadvantaged groups.³⁰ The most notable physical finding is the grayish brown diphtheritic pseudomembrane, which may involve one or both tonsils or may extend widely to involve the nares, uvula, soft palate, pharynx, larynx, and tracheobronchial tree. Involvement of the latter structures can cause

TABLE 3. ANTIMICROBIAL THERAPY FOR GROUP A STREPTOCOCCAL PHARYNGITIS.*

DRUG	DOSE	DURATION
Oral		
PenicillinV†	250 mg 2 or 3 times daily for children 250 mg 4 times daily or 500 mg 2 times daily for adolescents and adults	10 days
Intramuscular		
Penicillin G benzathine	600,000 units for patients weighing ≤ 27 kg (60 lb) 1,200,000 units for patients weighing > 27 kg	1 dose
Penicillin G benzathine combined with penicillin G procaine‡	1,200,000 units	1 dose
For patients allergic to penicillin§		
Erythromycin estolate	20–40 mg per kilogram of body weight orally per day, divided into 2 to 4 doses (maximum, 1 g/day)	10 days
Erythromycin ethylsuccinate	40 mg per kilogram per day, divided into 2 to 4 oral doses (maximum, 1 g/day)	10 days
Erythromycin stearate	1 g per day, divided into 2 or 4 oral doses for adolescents and adults	

*Data are from Dajani et al.⁵ and Bisno et al.⁹ and other sources.

†For the purpose of palatability, amoxicillin suspension may be used in children who are unable to swallow tablets.

‡This combination contains only 900,000 units of penicillin G benzathine and is not recommended for adolescents or adults.

§First- and second-generation cephalosporins are acceptable alternatives to erythromycin in patients who do not have immediate hypersensitivity to penicillin. Azithromycin is also an acceptable alternative to erythromycin.

life-threatening respiratory obstruction. Removal of the membrane reveals a bleeding and edematous submucosa. Soft-tissue edema and prominent cervical and submental adenopathy may create a bull-neck appearance. The potent toxin elaborated by *Corynebacterium diphtheriae* may produce cardiac toxicity and neurotoxicity. The diagnosis, which may be strongly suspected on epidemiologic and clinical grounds, should be confirmed by culture of the pseudomembrane in Loeffler's or tellurite selective medium. Pharyngeal diphtheria is treated with equine hyperimmune diphtheria antitoxin and penicillin or erythromycin.

OTHER BACTERIAL INFECTIONS

Arcanobacterium haemolyticum is a rarely diagnosed cause of acute pharyngitis and tonsillitis that tends to occur in adolescents and young adults. The symptoms of infection with this organism closely mimic those of acute streptococcal pharyngitis, including a scarlatiniform rash in many patients.^{31,32} *A. haemolyticum* infection should be suspected in patients with these findings in whom the throat culture is negative for group A streptococci. The organism may be detected more readily on human-blood agar plates than on those containing sheep's blood and thus may be missed on routine cultures. In rare cases, *A. haemolyticum* produces a membranous pharyngitis that can be confused with diphtheria. Erythromycin is the preferred drug for treatment.

Although colonization of the pharynx with *Neisseria gonorrhoeae* is usually asymptomatic, clinically apparent pharyngitis sometimes develops, and pharyngeal colonization may be associated with disseminated disease.³³ Gonococcal pharyngitis should be suspected, particularly in women and homosexual men who practice fellatio. The diagnosis should be confirmed by culture on Thayer-Martin medium. If the case is uncomplicated, treatment consists of either a single dose of intramuscular ceftriaxone (125 mg) or a single dose of an oral quinolone (ciprofloxacin, 500 mg, or ofloxacin, 400 mg), plus either a single dose of azithromycin (1 g) or doxycycline (100 mg) twice daily for seven days for possible chlamydial coinfection at genital sites.³⁴ Doxycycline and ofloxacin should not be prescribed for pregnant women.

VIRAL INFECTIONS

Infectious Mononucleosis

Infectious mononucleosis is caused by Epstein-Barr virus, a member of the Herpesviridae family. Most clinically apparent cases occur in persons between 15 and 24 years of age. After a prodromal period of chills, sweats, feverishness, and malaise, the disease presents with the classic triad of severe sore throat, fever (a temperature as high as 38°C to 40°C), and lymphadenopathy. The tonsils are enlarged, the pharynx is erythematous and often covered with a thick continuous exudate, and palatal petechiae may be evident.

Posterior and anterior cervical lymphadenopathy is most prominent, but axillary and inguinal nodes are also frequently enlarged. Splenomegaly is present in 50 percent of cases, hepatomegaly in approximately 10 to 15 percent, and jaundice in 5 percent.³⁵ About 5 percent of patients have a rash of variable morphology, and the administration of ampicillin will provoke a pruritic maculopapular eruption in nearly all patients.

The hematologic findings include relative and absolute lymphocytosis, with more than 10 percent atypical lymphocytes, and thrombocytopenia that is usually mild but may occasionally be severe. Heterophil antibodies that agglutinate sheep erythrocytes after absorption with guinea-pig kidney are present in approximately 90 percent of affected adolescents and adults within the first two to three weeks of illness. Horse red-cell agglutinins are more sensitive, although the results must be interpreted cautiously since heterophil antibodies may persist in serum for a year or more after the acute phase of the illness.³⁶ Spot and slide tests that use horse or purified bovine erythrocytes and allow rapid screening for heterophil antibodies are now commercially available.³⁷ These tests are highly specific, and a positive result in conjunction with clinically compatible illness may be considered diagnostic. False negative results of heterophil tests are common in children, particularly those less than four years of age. For heterophil-negative or atypical cases, specific antibodies to a number of viral antigens can be measured. The most useful of these for general clinical purposes is the IgM antibody to viral capsid antigen.

The most common entities that should be considered in the differential diagnosis of infectious mononucleosis are streptococcal pharyngitis (which it may closely mimic in the early stages), cytomegalovirus infection, and the acute retroviral syndrome. Less frequently, infection with hepatitis A virus, *Toxoplasma gondii*, human herpesvirus 6, or rubella virus may mimic some aspects of infectious mononucleosis. Although a number of antiviral drugs have activity against Epstein-Barr virus in vivo, none have proved useful in primary care practice.³⁸ Treatment should be focused on the control of symptoms, and patients should be cautioned against vigorous activities that might produce splenic rupture during at least the first month after the onset of illness.³⁹ Corticosteroids produce symptomatic improvement, but their use in this usually benign and self-limited illness is not generally recommended. They are indicated if the patient has tonsillar hypertrophy that threatens to obstruct the airway, severe thrombocytopenia, or hemolytic anemia.

Acute Retroviral Syndrome

The acute retroviral syndrome is an increasingly recognized manifestation of primary infection with the human immunodeficiency virus (HIV). After an incubation period that may be as short as six days but is

usually three to five weeks, symptoms develop that include fever, nonexudative pharyngitis, lymphadenopathy, and systemic symptoms such as arthralgia, myalgia, and lethargy. Maculopapular rash is present in 40 to 80 percent of patients. The illness sometimes resembles infectious mononucleosis, but it can be differentiated from mononucleosis by its more acute onset, the absence of exudate and of prominent tonsillar hypertrophy, and often the occurrence of a rash (which is rare in mononucleosis except after treatment with ampicillin) and mucocutaneous ulceration.⁴⁰ Tests for HIV antibodies are often negative during the acute phase of illness, but assays for HIV type 1 RNA or p24 antigen will confirm the diagnosis. Most authorities favor the initiation of maximally suppressive combinations of antiretroviral drugs during this acute phase of HIV infection.⁴¹

Other Viruses

In addition to nonspecific sore throats, some respiratory viruses produce more distinctive clinical syndromes. Adenoviruses can produce pharyngoconjunctival fever or an influenza-like syndrome known as the acute respiratory disease of military recruits.⁴² Coxsackieviruses are the most frequent causes of hand-foot-and-mouth disease and herpangina (Fig. 2).⁴³

Several studies have documented primary human herpesvirus 1 infection as a cause of pharyngitis, often exudative, in college students.^{44,45} Human herpesvirus 2 can occasionally cause a similar illness as a consequence of oral-genital sexual contact.⁴⁶ Although primary herpesvirus infections may involve the anterior portion of the oral cavity (gingivostomatitis), they do not routinely do so.



Figure 2. Palatal Lesions of Herpangina in a Teenager with Severe Throat Pain.

Multiple white papules and vesicles are present on an erythematous base. Reprinted from Read⁴³ with the permission of the publisher.

OTHER INFECTIOUS AGENTS

Mycoplasma pneumoniae is isolated with varying frequency from patients with symptomatic pharyngitis but also from controls. Although it probably causes some cases of acute pharyngitis, the frequency of such cases remains uncertain.⁴⁷⁻⁴⁹ *Chlamydia pneumoniae* has been reported to cause fever, cough, and sore throat, either as an isolated syndrome, or together with or preceding pneumonia.⁵⁰ When unassociated with lower respiratory tract disease, neither of these microbial agents is likely to be diagnosed during the acute phase of illness with the routine tests available to primary care physicians. Both organisms respond to therapy with tetracycline or erythromycin.

TREATMENT

During the acute phase of pharyngitis, patients with severe symptoms will benefit from rest, maintenance of an adequate fluid intake, antipyretic drugs, and gargling with warm salt water. Over-the-counter lozenges containing menthol and mild local anesthetics also provide temporary relief from severe throat pain. For bacterial pharyngitis, antimicrobial therapy should be administered according to the guidelines given above. For the great majority of cases of pharyngitis, which have nonbacterial causes, no further therapy is necessary. Although it can be difficult, primary care physicians have the responsibility to educate their patients about the self-limited nature of viral pharyngitis and the hazards of indiscriminate use of antimicrobial agents for both the patient and the community.

SUMMARY

The primary care physician needs to identify those patients with acute pharyngitis who require specific antimicrobial therapy and to avoid unnecessary and potentially deleterious treatment in the large majority of patients who have a benign, self-limited infection that is usually viral. In most cases, differentiating between these two types of infection can be accomplished easily if the physician considers the epidemiologic setting, the history, and the physical findings, plus the results of a few readily available laboratory tests. When antimicrobial therapy is required, the safest, narrowest-spectrum, and most cost-effective drugs should be used. Despite agreement on these principles by expert advisory committees,^{5,9,10} data from national surveys of ambulatory care indicate that antimicrobial agents continue to be prescribed indiscriminately for upper respiratory infections.

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