

Chapter 2

Pharyngitis

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Introduction

One of the most common chief complaints in a primary care physician's office is sore throat. Although a broad variety of differential diagnoses must be considered, ranging from infectious or inflammatory etiology to traumatic or neoplastic processes, the vast majority of these symptoms derive from either a viral or bacterial source. The physician must narrow the differential, decide which clinical and laboratory data may be helpful, select the most appropriate management plan for the patient's symptoms and disease process, and prevent further complications. This chapter reviews the most common causes of pharyngitis, relevant available clinical information, appropriate laboratory tests, recommended treatment guidelines, possible complications, and general strategies for evaluating patients with acute pharyngitis.

In the 1990s, more than 6.7 million visits with a primary complaint of sore throat were made by adults to physicians' offices, emergency departments, or other primary care providers in the United States.² Currently, acute pharyngitis accounts for approximately 2% of all primary healthcare visits for adults and 6% for children annually (more than 10 million visits).^{7,10} Of these cases, approximately 30% are idiopathic, 30 to 60% have a viral etiology, and 5 to 15% are caused by bacteria.⁸ Of the possible bacterial sources, Group A β -hemolytic streptococci (GABHS) is the most frequently isolated pathogen, causing acute pharyngitis in 5 to 15% of adults and 15 to 36% of children in the USA.^{4,10} Although this chapter reviews the broad range of causes of pharyngitis, the emphasis is on the diagnosis and treatment of GABHS, because this is the only common cause of sore throat that warrants antibiotic treatment.

In recent years, fear of GABHS infection and its possible complications, and growing expectation of antibiotic prescriptions by patients has resulted in overuse of antibiotics for treatment of acute pharyngitis. Reportedly, 50 to 75% of all cases of pharyngitis are currently treated with antibiotic therapy, approximately 40% of which use broad-spectrum antibiotics or antibiotics that are not indicated.^{7,10,14} Spurred by efforts from the Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA), recent guidelines have been established to decrease the frequency of unnecessary antibiotic use, and to concentrate instead on clinical protocol and appropriate laboratory evaluation.

Pathophysiology

Pharyngitis is an inflammation of the pharynx that can lead to a sore throat. Etiologic agents are passed through person-to-person contact, most likely via droplets of nasal secretions or saliva. Symptoms often manifest after an incubation period ranging from 1 to 5 days, and occur most commonly in the winter or early spring. Outbreaks of pharyngitis may occur in households or classrooms, and, infrequently, may be linked to food or animal sources.

The most common bacterial cause of pharyngitis, GABHS, is also known as *Streptococcus pyogenes* and may exist as single, paired, or chained gram-positive cocci. These bacteria possess protein M, a potent virulence factor that inhibits bacterial phagocytosis, as well as a hyaluronic acid capsule that enhances its ability to invade tissues. Multiple exotoxins and two hemolysins (Streptolysin S and Streptolysin O) further enhance the virulence of GABHS. Cocci may be detected on cultures (grown on blood agar), latex agglutination tests, or rapid tests using labeled monoclonal antibodies.

The viruses and other nonstreptococcal bacteria that also can cause pharyngitis are discussed in greater detail below, in the “Differential Diagnosis” section.

Clinical Presentation

History

Pharyngitis can present with sudden onset of sore throat, fever, headache, tender anterior cervical lymphadenopathy or lymphadenitis, and, occasionally, abdominal pain, nausea, vomiting, fatigue, or rash. When GABHS is the etiologic agent, fevers are often $>38.5^{\circ}\text{C}$ (101.3°F), tonsillar exudates are common, and patients may experience fevers, chills, and myalgias.⁸ Children may sometimes present with atypical symptoms such as abdominal pain and emesis, regardless of the cause of their pharyngitis.

Physical Exam

On examination, the typical findings of acute pharyngitis may include an erythematous and swollen pharynx, tonsillar hypertrophy and inflammation (with or without tonsillar exudates), fever, edematous uvula, petechial rash along the palate, and tender anterior cervical lymphadenopathy. Occasionally, a scarlatiniform rash may be present, often seen in association with a GABHS infection.

Clinical Guidelines

Given the above historical and physical findings, a number of clinical tools have been established to help determine whether GABHS is the likely causative pathogen. The most widely accepted of these tools is the Centor Clinical Prediction Rules for the diagnosis of GABHS in adults, which uses the presence (or absence) of four main criteria (see Table 2.1).^{4,12}

If the patient has none or one of these symptoms, suspicion for GABHS is very low and no further testing or treatment is necessary. If the patient meets two, three, or four of the criteria, a diagnostic laboratory test is indicated. Some physicians will begin antibiotic therapy presumptively for patients with severe symptoms who meet three or four of the Centor criteria, and may not send a diagnostic test in addition to testing. The absence of three or four criteria has a negative predictive value near 80%.^{4,14} The Centor Clinical Prediction Rules are endorsed by the IDSA and listed currently among the CDC recommendations online at: www.cdc.gov/drugresistance/community/files/ads/Acute_Pharyngitis.pdf.

Ultimately, the usefulness of clinical prediction rules depends on the prevalence of disease in a given community. In a GABHS-dense population, a higher score on a GABHS prediction tool would convey a higher probability of actually having a bacterial infection than in regions where overall prevalence was lower.⁴

Laboratory Evaluation

There is significant debate surrounding the selection of which laboratory tests are necessary to establish the correct diagnosis and ensure the appropriate treatment course for pharyngitis. Aside from influenza and new-onset HIV, the viral causes of pharyngitis only require supportive care and do not necessitate extensive testing. Of the bacterial causes, only GABHS has an indication for antibiotic therapy. Therefore, the majority of laboratory diagnostics for pharyngitis concentrate on the presence or absence of GABHS.

The gold standard of pharyngitis testing remains the throat culture, collected by swabbing the pharynx and peritonsillar region, and growing the sample on a sheep's blood agar plate. Under ideal circumstances, and often using two samples, the sensitivity and specificity of such cultures reaches 97% and 99%, respectively.¹⁷ In most offices, however, those numbers vary widely, with a sensitivity between 30

Table 2.1 Centor Clinical Prediction Rules

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1. Fever (by history or exam)
 2. Tender anterior cervical lymphadenopathy
 3. Presence of tonsillar exudates
 4. Absence of cough
 - Presence of 0–1 of the above—no further testing indicated
 - Presence of 2–4 of the above—GABHS testing indicated
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and 90% and a specificity from 75 to 99%.⁸ Some false positive results can be expected with culture results because up to 20% of the US population may be chronic, asymptomatic GABHS carriers.

Another class of available tests are the rapid antigen detection (RAD) tests, which use enzyme or acid extraction from throat swabs, followed by latex agglutination, coagglutination, or enzyme-linked immunoabsorbent assay (ELISA) procedures to isolate GABHS antigen–antibody complexes.³ Although older models were not as reliable and variation still exists, newer techniques show a sensitivity ranging from 76 to 97% and a specificity >95%.^{8,17} Most modern RAD tests produce results within 10 minutes or less.

Serology may be collected for presence or absence of streptococcal antibody titers, but this information will not influence the immediate treatment of the patient's pharyngitis symptoms. Serum titers of deoxyribonuclease B, hyaluronidase, streptokinase, nicotinic acid, and antistreptolysin O (ASO) may rise quickly during acute streptococcal infection (a positive ASO result reflects a fourfold increase), and will peak within 2 to 3 weeks. This information is necessary to support a diagnosis of rheumatic fever, but treatment for pharyngitis needs to begin before the return of serology laboratory results.

Both the American Academy of Pediatrics (AAP) and the American Heart Association consider a positive RAD test definitive evidence for presence of GABHS and indication for antibiotic therapy.⁸ The AAP also contends that when GABHS is strongly suspected, a negative RAD test should be followed up with a confirmatory throat culture.^{7,8} In an adult patient, clinical suspicion should guide decisions regarding whether further confirmation of a negative RAD test is needed.

Differential Diagnosis

The differential diagnosis for sore throat symptoms is extensive. The most common viral pathogens causing pharyngitis include rhinovirus, coronavirus, adenovirus, herpes simplex virus (HSV), parainfluenza virus, influenza virus, Epstein–Barr Virus (EBV), and human immunodeficiency virus (HIV). Rhinoviruses and coronaviruses comprise more than 25% of viral cases. Acute influenza and HIV are the only viruses for which treatments with antiviral agents may improve symptoms. Otherwise, supportive treatment options are indicated for sore throat symptoms.

As discussed above in the pathophysiology section, the most common bacterial cause of pharyngitis is GABHS, occurring in 5 to 30% of cases. However, there are several other bacterial causes, including Group C streptococci, *Neisseria gonorrhoea*, *Corynebacterium diphtheriae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Arcanobacterium haemolyticus*.³ Clinical presentation and associated signs and symptoms are important for differentiating these bacterial infections.

The patients' clinical history and physical examination findings can help distinguish among the several viral, bacterial, and other causes of pharyngitis. Viral infections often include cough, coryza, conjunctivitis, fatigue, hoarseness, generalized body aches, abdominal pain, or diarrhea as additional symptoms. Patients with Epstein–Barr

Virus (EBV) often have severe pharyngitis with tonsillar exudates, but also complain of fatigue, body aches, and systemic complaints. EBV is also associated with posterior cervical lymph adenopathy, splenomegaly, and a classic maculopapular rash that develops if patients receive penicillin-derived antibiotics. A patient presenting with primary HIV may complain of sore throat as well as several other flu-like symptoms, but they are likely to have HIV risk factors in their history (e.g., unprotected intercourse, multiple sexual partners, previous blood transfusion, and intravenous drug use).

Bacterial infections also have particular defining characteristics. *Chlamydia pneumoniae* or *Mycoplasma pneumoniae* can cause lower respiratory symptoms that are more severe, such as bronchitis, pneumonitis, or pneumonia, in addition to pharyngitis. *Arcanobacterium haemolyticum*, formerly known as *Corynebacterium haemolyticum*, is seen more frequently in teenagers and young adults, and may be accompanied by a scarlatiniform rash. The clinical significance of an *A. haemolyticum* infection remains uncertain. Reported cases of *Corynebacterium diphtheriae* are very rare because of childhood vaccinations, but patients with this variety of pharyngitis will frequently complain of hoarseness and stridor caused by circulation of the diphtheria exotoxin, and may also experience cervical adenitis and edema. The defining characteristic of this bacteria is the development of a firmly adherent, gray, inflammatory pseudomembrane across the oropharynx. Group C streptococci also may cause pharyngitis, but would ultimately be distinguished by a RAD test or throat culture.

In addition to the more common viral and bacterial causes of pharyngitis, a number of other causes of sore throat exist. These include Kawasaki disease, trauma or exertional irritation, neoplastic processes, abscess (such as Ludwig's angina, parapharyngeal or retropharyngeal, and peritonsillar), thyroiditis, gastroesophageal reflux disease (GERD), or allergy-related postnasal drip.¹⁸ Pharyngitis secondary to GERD or allergies would likely accompany symptoms of dyspepsia or nasal congestion with postnasal drip, respectively. Trauma or throat strain caused by overuse (shouting, for example) should be elicited via the patient's history of symptom onset. Neoplastic processes can be more subtle, but may have accompanying weight loss, night sweats, fatigue, or dysphagia. An abscess would likely cause higher fevers, more discomfort, and persistent symptoms despite typical first-line antibiotic treatment. Airway compromise, hoarseness, or neck swelling may accompany abscesses depending on their location. Kawasaki disease is most common in children younger than 3 years of age, and is defined by a number of well-documented features, including pharyngeal erythema, strawberry tongue, nonpurulent conjunctivitis, fever, cervical lymphadenopathy, cracked red lips, and erythema and swelling of the hands and feet with desquamation of periungual regions several days after symptom onset.

Treatment

Therapeutic goals for treating pharyngitis include amelioration of symptoms, decrease in contagion and transmission, prevention of complications, and, to some extent, satisfying the patient's personal goals in the physician-patient interaction.

For the vast majority of pharyngitis cases, supportive therapy purely for symptom control is the most appropriate strategy. A typical viral pharyngitis should resolve within 5 to 10 days, if not sooner. For GABHS pharyngitis, if antibacterial therapy is begun within 3 days of symptom onset, the duration of fever and pain may be shortened by approximately 1 day.⁴ The primary purpose of using antibiotics in GABHS pharyngitis is to avoid the development of further complications (discussed in the section below). Children with GABHS should be kept home from school until 24 hours after the initiation of antibiotic therapy.

Supportive therapy for pharyngitis includes appropriately dosed analgesic and antipyretic medicines, proper oral hydration, and rest. Acetaminophen or ibuprofen are indicated for all ages for both pain and fever control, whereas aspirin should be avoided in the pediatric population because it can increase the risk of injury to hepatic and renal structures (Reye's Syndrome).¹³ Warm salt water gargles (1/4 teaspoon of salt with 8 ounces of water), soft foods, cool beverages, and frozen desserts can soothe irritated oropharyngeal tissues. Over-the-counter lozenges, sore throat drops, and throat sprays are also available to keep the affected area moisturized or anesthetized. For severe symptoms, viscous lidocaine preparations (e.g., "Magic Mouthwash"), stronger pain medicines or narcotics, or alternative modalities can be tried.

For GABHS, the above supportive measures should be combined with antibiotic therapy. Recommendations for treatment of GABHS pharyngitis have changed very little in the past decade. The CDC, the AAP, and the IDSA all agree that penicillin is the first-line agent to treat GABHS in children and adults.^{4,10,16} Treatment should continue for 10 days to eradicate the bacteria from the pharynx (dosing regimens are indicated in Table 2.2). Penicillin-allergic patients should be treated with erythromycin or a first-generation cephalosporin. Preferred antibiotics for recurrent GABHS infection or initial treatment failure include clindamycin, amoxicillin-clavulanic acid, and penicillin G.

Complications

For patients with acute pharyngitis, complications can develop when a bacterial source of infection is not managed properly. Most notably, GABHS is associated with suppurative complications, such as cervical lymphadenitis, peritonsillar or retropharyngeal abscess, mastoiditis, sinusitis, otitis media, bacteremia, endocarditis, and meningitis, as well as nonsuppurative complications, such as poststreptococcal glomerulonephritis and rheumatic fever.⁸ Suppurative complications develop as bacteria spreads from pharyngeal mucosal layers to deeper tissue, either directly or via hematogenous or lymphatic routes. Nonsuppurative complications are reflective of streptococcal toxins, streptolysins, and inflammatory processes involving antibodies targeted at the bacteria. GABHS is also linked to scarlet fever, myositis, impetigo, erysipelas or cellulitis, necrotizing fasciitis, and streptococcal toxic shock syndrome.

Peritonsillar and retropharyngeal abscesses form in <1% of patients complaining of sore throat who are treated with antibiotics. The overall incidence would be

Table 2.2 Dosing regimens for GAHBS**Dosing strategies, initial treatment of GAHBS**

1. Penicillin VK (every 250 mg of penicillin VK = 400,000 U of penicillin)
 - Children <12 years of age: 25–50 mg/kg/day orally divided three to four times daily for 10 days (maximum, 3 g/day)
 - Children >12 years of age: 250–500 mg orally three or four times daily for 10 days (maximum, 3 g/day)
 - Adults: 250 mg orally three or four times daily or 500 mg orally twice daily for 10 days
2. Penicillin G
 - Children: 0.3–0.6 million units intramuscularly (IM) once for children lighter than 27 kg, or 0.9 million units IM once for children heavier than 27 kg
 - Adults: 0.6–1.2 million units IM once
3. Erythromycin stearate
 - Children: 30–50 mg/kg/day orally divided three to four times daily for 10 days
 - Adults: 250–500 mg orally three to four times daily for 10 days
4. Erythromycin ethyl succinate
 - Children: 30–50 mg/kg/day orally divided three to four times daily for 10 days
 - Adults: 400 mg orally four times daily for 10 days
5. Cephalexin
 - Children: 25–50 mg/kg/day orally divided twice daily for 10–14 days (maximum, 4 g/day)
 - Adults: 500 mg orally twice daily for 10–14 days
6. Cefadroxil
 - Children: 30 mg/kg/day orally divided twice daily for 10 days (maximum, 2 g/day)
 - Adults: 1–2 g orally divided once or twice daily for 10 days
7. Amoxicillin
 - Children >3 months: 25–45 mg/kg/day orally divided twice daily or 20–40 mg/kg/day orally divided three times daily for 10 days
 - Adults: 500–875 mg orally twice daily for 10 days

Dosing strategies, recurrent infection or treatment failure

1. Clindamycin
 - Children: 20–30 mg/kg/day orally divided three times daily for 10 days (maximum, 1.8 g/day)
 - Adults: 150 mg orally four times daily or 300 mg orally twice daily for 10 days
2. Amoxicillin–clavulanic acid
 - Children >3 months old, but < 40 kg: 25–45 mg/kg/day orally divided twice daily or 20–40 mg/kg/day divided three times daily for 10 days
 - Children > 40 kg: dosing similar to adults
 - Adults: 500–875 mg orally twice daily for 10 days
3. Penicillin G
 - Dosing identical to initial treatment options

even less, but patients do not always present for evaluation until complications have begun.⁴ Signs and symptoms related to abscess formation include a more ill-appearing patient with a “hot potato” voice, deviation of the uvula or uneven palate, and occasionally a visible fluctuant peritonsillar mass. Surgical drainage, airway management, and broader-spectrum antibiotic coverage is sometimes necessary to manage these problems effectively.

Poststreptococcal glomerulonephritis is thought to result from a reaction between circulating antibody complexes that may inappropriately bind laminin, type IV collagen, and certain proteoglycans found in the kidneys. Patients can present after a recent streptococcal illness, with hematuria, edema, and an elevated ASO titer.

There is no evidence to suggest that antibiotic therapy decreases the incidence of this complication, and it occurs very infrequently.

Rheumatic fever tends to affect genetically predisposed individuals after a GABHS infection, and occurs in <1 in 100,000 cases of GABHS pharyngitis in the United States and other developed countries.^{12,17} Symptoms may present within weeks and are thought to be caused by cross reactivity between antistreptococcal antibodies and sarcolemmal muscle and kidney antigens. The resultant inflammatory process can damage heart muscle and valves (especially, mitral valves), connective tissue, joints, and the central nervous system. Rheumatic fever is a clinical diagnosis made using the Jones Criteria, where either two major or one major and one minor criterion are fulfilled. Major criteria include carditis, migratory polyarthritis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum. Minor criteria include fever, arthralgia, elevated acute phase reactants, and a prolonged PR interval on EKG. Treatment involves GABHS antibiotic coverage for any subsequent pharyngitis attacks and therapy for all clinical manifestations.

Scarlet fever presents as a characteristic erythematous, blanchable "sandpaper-like" rash formed by tiny papules, and is caused by streptococcal pyrogenic exotoxins A, B, and C. Along with typical pharyngitis symptoms, the scarlatiniform rash begins on day 2 or 3 of illness on the trunk and spreads to the extremities, sparing the palms and soles. Patients may also present with circumoral pallor, strawberry tongue, and Pastia's lines, an accentuation of the rash within skin creases. Desquamation of the palms and soles sometimes follows resolution of the scarlet fever rash on day 6 to 9 of illness.

Suggestions for Evaluation and Management

When evaluating a patient with pharyngitis and outlining a treatment plan, the initial goals of sore throat management must be kept in mind:

1. First, the differential must be addressed through history and physical exam.
2. Second, based on the above assessment, the physician must determine which laboratory tests, if any, should be carried out to ensure the proper diagnosis. The Centor Criteria is an effective clinical tool that may help guide this decision. Offering a RAD test or throat culture to those patients with two, three, or four of these criteria will help delineate which patients may need antibiotic treatment. Whether or not a second RAD or throat culture is to be used as back up to initial testing should depend on the level of clinical suspicion and prevalence of GABHS in the region. Differences in individual clinical routines will dictate whether empiric treatment is used for patients with three or four Centor Criteria, or if treatment is based on subsequent laboratory test results. Physicians must be mindful of the growing problem of antibacterial resistance in this country—patients who only fulfill one of the Centor Criteria do not need further testing and should not be given antibiotics.

3. Third, the patient's symptoms should be alleviated. The entire range of supportive therapies, including analgesic and antipyretic medicines, oral hydration, and rest, should be considered for every patient whose symptoms warrant them. These modalities are inexpensive, easy to use, and provide an appreciable degree of comfort relief.
4. Fourth, physicians need to be vigilant for possible complications. If a patient has GABHS pharyngitis, a full 10-day course of PCN or other appropriate antibiotic must be completed to eradicate the bacteria from the pharynx and prevent rheumatic fever. One must be suspicious of symptoms that worsen or persist beyond clinical expectations.
5. Last, physicians should ensure that patients understand the medical course of their illness, and are satisfied with the assessment and treatment plan.

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