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59 Pharyngitis

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SHORT VIEW SUMMARY

Definition
- Pharyngitis is defined as the triad of sore throat, fever, and pharyngeal inflammation.
- Generally a primary disease, pharyngitis may be associated with systemic disorders.

Epidemiology
- Pharyngitis is one of the most common disorders in adults and children, with more than 10 million ambulatory visits per year.
- The highest burden of disease is found in children and young adults, with 50% of cases identified between the ages of 5 to 24 years.
- In temperate climates, most cases occur in winter months, corresponding with peaks in respiratory viruses

Microbiology
- Viruses are the single most common cause of pharyngitis, with adenovirus being the most commonly identified (see Table 59-1).
- Group A *Streptococcus* (GAS) is the bacterial cause for which ample evidence exists for antibiotic therapy to prevent postinfectious sequelae.
- *Fusobacterium necrophorum* has been recently recognized as a cause of pharyngitis with potential severe complications (i.e., Lemierre syndrome), especially in young adults.

Diagnosis
- Essential to diagnosis is the identification of treatable causes (e.g., GAS) to prevent complications.
- Signs and symptoms of GAS pharyngitis include acute onset of sore throat with tonsillar or pharyngeal exudates, tender anterior cervical lymphadenopathy, and fever (see Table 59-2).
- Signs and symptoms consistent with viral etiologies include conjunctivitis, coryza, oral ulcers, cough, and diarrhea.
- Testing for GAS pharyngitis should not be pursued in those with signs and symptoms indicative of a viral etiology (see Table 59-3).
- Rapid antigen detection tests (RADTs) alone are sufficient for the diagnosis of GAS in adults, but negative results should be backed up by throat culture in children.
- Specific techniques should be used to identify other causes where appropriate.

Therapy
- Treatment of pharyngitis is focused on prevention of postinfectious sequelae (e.g., acute rheumatic fever) from GAS.
- Penicillin and its derivatives remain the primary treatment for GAS pharyngitis (see Table 59-4).
- Antimicrobial therapy should not be used to prevent GAS pharyngitis except in special circumstances.
- Given the potential severity of complications from pharyngitis caused by *F. necrophorum*, signs of bacteremia or neck swelling warrant expansion of antibiotic therapy and further evaluation.

Acute pharyngitis is typically described as the triad of sore throat, fever, and pharyngeal inflammation characterized by erythema and edema, although exudates, vesicles, or ulcerations may also be present.[1] Although pharyngitis may be a primary disorder, sore throat and pharyngeal erythema may also be prominent in systemic disorders, such as the acute retroviral syndrome, or part of a more generalized upper respiratory tract infection. Most cases of acute pharyngitis are due to common viral infections and are benign, self-limited processes. The appropriate recognition of patients with more complicated infections that require diagnostic evaluations and treatment is one of the challenges of primary care medicine.

ETIOLOGY

Viruses are the single most common cause of pharyngitis and account for 25% to 45% of all cases, often occurring with other signs or symptoms of upper respiratory tract infection (URI).[2-4] Essentially all viruses known to cause URIs have been described in both adults and children with pharyngitis (Table 59-1). Although the methodology between different studies is highly variable, adenovirus is frequently identified as the most prevalent viral cause of pharyngitis, reported in 12% to 23% of cases.[2,3,5,6] Other respiratory viruses that cause pharyngitis include rhinoviruses, enteroviruses, influenza A and B, parainfluenza viruses, respiratory syncytial virus, coronaviruses, human metapneumovirus, and human bocavirus.[3-5,7-9] Several human herpesviruses, such as Epstein-Barr virus, herpes simplex virus (HSV), and human cytomegalovirus (CMV), have also been reported to cause pharyngitis, as well as human immunodeficiency virus type 1 (HIV-1).

Streptococcus pyogenes, group A *Streptococcus* (GAS), is the bacterial etiology of greatest concern in cases of acute pharyngitis because of the association between GAS and acute rheumatic fever (ARF). GAS is responsible for approximately 10% to 15% of cases of pharyngitis in adults[10,11] and 15% to 30% of cases in children.[12] *Fusobacterium necrophorum*, a gram-negative, non–spore-forming anaerobe, is a bacterial cause of sore throat in as many as 10% of cases of pharyngitis[13] and the etiologic agent in up to 23% of cases of peritonsillar abscess.[14] The organism has also been implicated in recurrent or chronic sore throat syndromes and may be identified in up to 21% of such cases.[15] *Arcanobacterium haemolyticum* (formerly *Corynebacterium haemolyticum*), a gram-positive bacillus, has been recognized as a cause of pharyngitis for more than 60 years. *A. haemolyticum* has an incidence ranging from 0.2% to 0.5%, with the highest frequency of infection in adolescents and young adults.[16,17] *Corynebacterium diphtheriae* is also a cause of pharyngitis and is of particular concern for travelers to areas where vaccination programs are not well established or have failed.[18] Nontoxigenic strains of *C. diphtheria* have been reported with increasing frequency in individuals with sore throat, but their contribution as a causative agent of pharyngitis remains in question.[19] Pharyngitis caused by gonorrhea should be considered in sexually active adolescents and young adults. Throat cultures yield *Neisseria gonorrhoeae* in as many as 1% to 6% of individuals in sexually transmitted disease clinics.[20,21] *Mycoplasma pneumoniae,* identified in 3% to 14% of cases of pharyngitis, and *Chlamydia pneumoniae*, less frequently detected at 3% to 8%, should also be considered as potential etiologic agents of pharyngitis.[4,5,22]

EPIDEMIOLOGY

Pharyngitis is a common disorder in adults and children. In a prospective family study, 16% of adults and 41% of children reported an illness with sore throat over a 1-year time frame.[23] The incidence rate of medically attended tonsillitis in children has been estimated at 15 to 25 cases per 1000 children per year.[24] The National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey have documented 6.2 to 9.7 million visits to primary care physicians, clinics, and emergency departments each year for children with pharyngitis and more than 5 million visits per year for adults.[25-27]

KEYWORDS

adenovirus; *Arcanobacterium hemolyticum: Fusobacterium;* group A *Streptococcus*; non–group A *Streptococcus*; pharyngeal exudate; sore throat; tonsillitis; viral upper respiratory tract infection

TABLE 59-1 Microbial Causes of Acute Pharyngitis

PATHOGEN	ASSOCIATED DISORDER(S)
Bacteria	
Streptococcus, group A	Pharyngitis, tonsillitis, scarlet fever
Streptococcus, groups C and G	Pharyngitis, tonsillitis
Mixed anaerobes	Vincent's angina
Fusobacterium necrophorum	Pharyngitis, tonsillitis, Lemierre syndrome
Neisseria gonorrhoeae	Pharyngitis, tonsillitis
Corynebacterium diphtheria	Diphtheria
Arcanobacterium haemolyticum	Pharyngitis, scarlatiniform rash
Yersinia pestis	Plague
Francisella tularensis	Tularemia, oropharyngeal form
Treponema pallidum	Secondary syphilis
Viruses	
Rhinovirus	Common cold
Coronavirus	Common cold
Adenovirus	Pharyngoconjunctival fever
Herpes simplex type 1 and 2	Pharyngitis, gingivostomatitis
Parainfluenza	Cold, croup
Enteroviruses	Herpangina, hand-foot-mouth disease
Epstein-Barr virus	Infectious mononucleosis
Cytomegalovirus	CMV mononucleosis
Human immunodeficiency virus	Primary HIV infection
Influenza A and B	Influenza
Respiratory syncytial virus	Cold, bronchiolitis, pneumonia
Human metapneumovirus	Cold, bronchiolitis, pneumonia
Mycoplasma	
Mycoplasma pneumoniae	Pneumonia, bronchitis, pharyngitis
Chlamydia	
Chlamydia psittaci	Acute respiratory disease, pneumonia
Chlamydia pneumoniae	Pneumonia, pharyngitis

CMV, cytomegalovirus; HIV, human immunodeficiency virus.
Modified from Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. Infect Dis Clin North Am. *2007;21:449-469, vii; with permission.*

Four factors affect the epidemiology of pharyngitis reported in the literature. These include the age of the population studied, laboratory methods used to identify the causative microorganisms, season of the year, and the clinical severity of the illness. Despite these caveats, the highest burden of disease from pharyngitis is consistently found in children and young adults, with approximately 50% of cases diagnosed in patients from 5 to 24 years of age.[28] School-aged children from 5 to 18 years of age usually account for the greatest overall number of cases of pharyngitis, similar to disease from GAS.[23] The reported prevalence of GAS pharyngitis is influenced both by the age of the patient and the examination setting, with higher rates found in younger people evaluated in urgent care and emergency centers.[29] The most recent studies show GAS prevalence in cases of pharyngitis as high as 37% in children[30] and 17% in adults.[31] Population-based data demonstrate that serologically proven GAS pharyngitis occurs at a rate of 0.14 cases per child-year in the developed world and is estimated to be 5 to 10 times greater in developing communities.[32]

In temperate climates, most cases of pharyngitis occur in the winter and early spring, corresponding to peak times of respiratory virus activity. This is also true for GAS pharyngitis, where up to half of the cases in children may be due to this agent during these peak months.[22,33]

Between 49% and 57% of children and 64% of adults evaluated for pharyngitis receive an antibiotic prescription, a rate much higher than the prevalence of GAS infection for which treatment is indicated.[25-27] In addition, recent surveys have demonstrated a significant increase in the use of broad-spectrum antibiotics for the treatment of pharyngitis, a practice that is thought to contribute to the growing problem of antibiotic resistance and the "medicalization" of a generally benign illness.[27]

PATHOGENESIS

The exact mechanisms responsible for the development of the signs and symptoms of pharyngitis have not been fully delineated. Early studies have demonstrated that bradykinin is induced in symptomatic rhinovirus infections and that bradykinin challenge in healthy volunteers produces significant sore throat when delivered either to the oropharynx or the nasal mucosa.[34,35] Other inflammatory mediators, including prostaglandins, have been postulated to play a role with bradykinin via their actions on sensory nerve endings in the pharynx.[36] Several randomized controlled trials have demonstrated a beneficial effect of either nonsteroidal anti-inflammatory drugs or corticosteroids on throat pain, also suggesting that inflammatory mediators play a key role in the pathophysiology of sore throat.[37-39]

Among bacterial causes of pharyngitis, the pathogenesis of GAS has been studied most extensively. Multiple virulence factors have been identified that ultimately lead to the manifestation of acute pharyngitis. Despite this growing fund of knowledge, major gaps exist regarding the events leading to tonsillopharyngeal disease. Furthermore, the mechanism underlying asymptomatic carriage has been the subject of much speculation. The role the immune system and possible molecular genetic changes in GAS play in asymptomatic carriage remains elusive. Proteins involved in immune avoidance (M protein, hyaluronic acid capsule, C5a peptidase), adherence to epithelial cells (pilus, fibronectin binding proteins, lipoteichoic acid), spread through host tissues (hyaluronidase, streptokinase, deoxyribonucleases [DNases]), and numerous exotoxins (streptolysins, superantigenic toxins) have been described[40,41] but are beyond the scope of this chapter. Expression of these virulence factors leads to symptomatic pharyngitis and complications such as invasive disease, acute rheumatic fever, and acute glomerulonephritis. The mechanism by which GAS pharyngitis results in acute rheumatic fever is unknown. However, autoimmunity through molecular mimicry is suspected. A growing body of evidence supports the existence of rheumatogenic GAS serotypes. Comparing M-type distribution between two periods separated by 40 years, Shulman and co-workers[42] were able to demonstrate that decreases or complete disappearance of certain M types were associated with the decline in incidence of acute rheumatic fever. Whether other strain-specific GAS virulence factors are involved is unknown.

CLINICAL MANIFESTATIONS

Although it is well documented that the etiology of pharyngitis in individual patients cannot be accurately discerned based on clinical characteristics alone, certain pathogens may cause more readily recognizable syndromes as outlined below.

Group A *Streptococcus*

Pharyngitis attributable to GAS is sudden in onset in older children and adults. Sore throat associated with GAS may result in difficulty swallowing. Fever, headache, and gastrointestinal symptoms (nausea, vomiting, abdominal pain) are also associated with strep throat but are not always present. Physical examination generally reveals pharyngeal erythema, tonsillar enlargement, and a gray-white exudate covering the posterior pharynx and tonsillar pillars. Petechiae are sometimes observed on the soft palate, with erythema and edema of the uvula. Anterior cervical lymphadenopathy, often at the angle of the jaw, is typical of GAS pharyngitis, and nodes may be quite large and tender. Patients may also present with a characteristic scarlatiniform rash that typically begins on the trunk, spreads to the extremities, and spares the palms and soles. The rash is usually described as confluent with a sandpaper-like quality. Scarlet fever is caused by one or more of the pyrogenic exotoxins produced by pharyngeal strains of GAS. Signs and symptoms most indicative of GAS pharyngitis are tonsillar or pharyngeal exudates, tender anterior cervical nodes, fever or history of fever, and absence of cough.[29]

Non–group A *Streptococcus*

Group C and G streptococci are commonly found as normal microbiota in the human pharynx; however, they have also become increasingly recognized as potential causes of pharyngitis. *S. dysgalactiae* subsp. *equisimilis* (group C) is the most commonly isolated non-GAS associated with sore throat,[43] although recently, *S. equi* subsp.

zooepidemicus has emerged as a potentially important human pathogen.[44] Group C streptococci are known to cause endemic,[45] whereas group G is more frequently associated with epidemic pharyngitis[46] after ingestion of contaminated food, including salads (especially those with eggs) and milk products. Signs and symptoms from pharyngitis caused by group C and G streptococci may be indistinguishable from GAS infection. The need for treatment in these cases is unclear because they have not been associated with the development of acute rheumatic fever.

Fusobacterium necrophorum

Although current guidelines emphasize the identification of GAS in the diagnosis and management of acute pharyngitis, *F. necrophorum* is being more frequently recognized as an agent of endemic pharyngitis in young adults. The clinical signs and symptoms of pharyngitis caused by *F. necrophorum* may be indistinguishable from those causing GAS pharyngitis. However, the clinician should maintain a high index of suspicion because of the potential for the severe complication of the Lemierre syndrome. Patients with Lemierre syndrome may initially present with symptoms of pharyngitis, tonsillitis, or peritonsillar abscess and show initial clinical improvement. A recent study from Denmark identified *F. necrophorum* as the most frequently detected bacteria in peritonsillar abscess.[14] Approximately 4 days after clinical improvement of pharyngitis, the signs and symptoms of bacteremia (e.g., rigors) associated with the Lemierre syndrome may appear. It has been suggested that *F. necrophorum* be a major consideration in the treatment of pharyngitis in adolescents and young adults based on the severity of complications caused by *F. necrophorum,*[47] in contrast to the markedly decreased incidence of acute rheumatic fever.

Arcanobacterium haemolyticum

Throat findings in patients with *A. haemolyticum* infection include pharyngeal erythema and exudate, fever, and cervical lymphadenopathy, similar to GAS pharyngitis. The distinguishing clinical feature of pharyngitis caused by *A. haemolyticum* is the rash that may occur in up to one half of infected individuals. The rash is scarlatiniform, macular or maculopapular and is most frequently seen in adolescents and young adults.[17] The rash begins on the distal extremities, typically involving the extensor surfaces but sparing the palms and soles, followed by centripetal spread.[48] Rarely, *A. haemolyticum* may cause more severe infection (e.g., pneumonia and pyomyositis) but in these cases is most often a coinfecting agent.[49]

Corynebacterium diphtheriae

Diphtheria is rare in developed countries because of widespread vaccination. The majority of respiratory infections caused by *C. diphtheriae* are tonsillopharyngeal. Sore throat is one of the most common symptoms of diphtheria and is usually accompanied by low-grade fever and malaise.[50] Formation of a membrane on the tonsil or pharyngeal surface is the hallmark of diphtheria but occurs in only one third of patients. A relative lack of fever and the formation of a membrane distinguish diphtheria from pharyngitis caused by group A β-hemolytic streptococci and viral etiologies. The membrane that forms in diphtheria is described as white early in the course of the illness, becomes dark gray, and leather-like, with attempts to dislodge the membrane potentially causing bleeding.[51] Membrane formation is the result of local toxin production, and spreading of the membrane indicates more systemic toxicity. Extensive spreading of the membrane may lead to tonsillar, anterior cervical, and submandibular lymphadenopathy, as well as swelling of the neck (so-called bull neck). Continued progression may lead to respiratory distress and death.

Neisseria gonorrhoeae

Although pharyngeal infection with *N. gonorrhoeae* is often asymptomatic, sore throat is reported by patients with tonsillar involvement. A review of published cases of oropharyngeal gonorrhea found that more than 10% were classified as tonsillitis.[52] Fever is uncommon, as is cervical lymphadenopathy. Among patients with tonsillitis, a whitish-yellow exudate was observed in 20%.[52] Because the clinical presentation of pharyngitis caused by *N. gonorrhoeae* is nonspecific and symptoms may be mild, a thorough history, including risk factors for sexually transmitted infections, should be obtained in adolescents and young adults with pharyngitis to make this diagnosis.

Atypical Bacteria

Both *Mycoplasma pneumoniae* and *C. pneumoniae* have been identified as a cause of pharyngitis in all age groups, with a higher prevalence generally noted for *M. pneumoniae.*[5,53] Disease occurs year round, but seasonal peaks and community outbreaks occurring every few years have also been described.[54] Most adult cases appear to present as an undifferentiated acute respiratory infection or an influenza-like illness; however, isolated pharyngitis has also been noted.[55] In an outbreak of respiratory disease caused by *M. pneumoniae* within a military unit, sore throat was reported in 35% to 70% of patients, with fatigue, headache, and cough noted more commonly. The only risk factor for symptomatic disease identified after the outbreak was cigarette smoking.[56] Esposito and colleagues[5] have described several case series of children with pharyngitis caused by *M. pneumoniae* or *C. pneumoniae* and identified dysphagia in 25% to 36%, tonsillar hypertrophy in 76% to 83%, cervical adenopathy in approximately half, and exudate in 25% to 39%. Although these findings were not specific to pharyngitis caused by atypical bacterial infection compared with common viral causes of pharyngitis, children with infection caused by *M. pneumoniae* or *C. pneumoniae* were significantly more likely to have a history of recurrent pharyngitis.[57] In addition, children with pharyngitis caused by atypical bacterial infections treated with azithromycin had lower rates of subsequent respiratory infections, including lower tract disease, compared with children given symptomatic treatment alone.[58]

Epstein-Barr Virus

Infectious mononucleosis (IM) is a multisystem disorder caused by primary infection with Epstein-Barr virus (EBV) and defined by the triad of fever, pharyngitis, and adenopathy.[59] Among 150 young adults with serologically confirmed acute EBV infection, three quarters reported sore throat and fatigue, with approximately half noting fever, painful cervical adenopathy, and headache at their initial visit.[60] Other symptoms included cough, myalgia, arthralgia, and nausea. Rash was uncommon and is typically described as a diffuse maculopapular eruption in patients given ampicillin or related compounds. On examination, pharyngitis with mildly painful anterior and posterior cervical lymphadenopathy was detected in 75% of patients, whereas splenomegaly and hepatomegaly were uncommon despite minimally elevated transaminase levels in more than half of the group.[60] The pharyngitis that accompanies IM is subacute in onset and may be accompanied by mild-to-moderate enlargement of the tonsils as well as exudates and palatal petechiae.[59] Symptoms substantially improve over the first month of illness and after 6 months are almost completely resolved.[60]

Although IM has been traditionally described in adolescents and young adults, children also commonly develop fever, exudative pharyngitis, and painful cervical adenopathy during primary infection with EBV.[61] In addition, rash and splenomegaly are more common in young children with primary EBV infection than in adolescents or adults.[61] Periorbital or eyelid edema, as a symptom of primary EBV infection, appears to be unique to children.[61] A mononucleosis-like illness caused by primary infection with CMV, human herpesvirus 6, HSV-1, and HIV-1 has also been described.

Human Immunodeficiency Virus

Symptoms associated with primary HIV-1 infection develop in 40% to 90% of infected individuals and are referred to as the acute retroviral syndrome.[1,62,63] This illness is a multisystem disorder, typically occurring 5 to 29 days after infection, and is characterized by the acute onset of one or more of the following complaints: fever, rash, pharyngitis, fatigue, weight loss, myalgia, arthralgia, headache, night sweats, cervical adenopathy, nausea, vomiting, or diarrhea.[62] Hecht and co-workers[64] identified 145 patients with either primary HIV-1 infection or recent seroconversion and found that the most sensitive symptoms of primary infection were fever (80%) and malaise (68%), with the majority of patients reporting an illness lasting 1 to 2 weeks. The combination of fever and rash were identified as significant independent predictors of primary HIV-1 infection, with the rash described most commonly as a nonpruritic polymorphous eruption beginning on the face and

chest and spreading outward.[1,59] Pharyngitis is recognized in 50% to 70% of patients, whereas cervical adenopathy is noted in 25% to 50%.[63,64] Although extensive descriptions of the pharyngeal findings associated with primary HIV infection are lacking, exudates appear to be present in a minority of patients.[1,64] In addition, the adenopathy tends to be nontender and may be generalized.[59] Painful oral ulcerations are one of the least common symptoms in patients with primary HIV-1 infection, identified in only 10% to 35%, but they are highly specific.[64] Ulcerations can be found almost anywhere in the mouth, including the floor of the mouth, inner lips, buccal mucosa, gingiva, hard and soft palate, as well as the esophagus, anus, and penis.[63,65] Concomitant oral thrush has also been described.

Based on the common presenting symptoms of fever, pharyngitis, rash, and lymphadenopathy, it is easy to understand how primary HIV-1 infection may be confused with infectious mononucleosis, secondary syphilis, acute hepatitis A or B, toxoplasmosis, or other viral syndromes. In fact, Schacker and co-workers[62] noted that only one quarter of patients with symptoms of primary HIV-1 infection had the diagnosis suspected at the initial medical evaluation. A recent report estimating the prevalence of primary HIV-1 infection in symptomatic adolescent and adult ambulatory patients found that pharyngitis was due to primary HIV-1 infection in 1.3 patients per 1000 cases.[66] Because up to one half of all new HIV-1 infections occur in adolescents, physicians who care for adults and children should be familiar with the clinical characteristics of primary HIV-1 infection to maintain a high index of suspicion for this disorder.[65] Early diagnosis via virus-specific tests, such as p24 antigen or the detection of plasma HIV-1 RNA, reliably identify people with primary HIV-1 infection before seroconversion and can potentially aid in both the control of virus transmission as well as treatment decisions for individual patients (see Chapter 122).

Enteroviruses

Enteroviruses classically cause an undifferentiated febrile illness but are also recognized as a cause of pharyngitis and upper respiratory tract infections, with most disease occurring in the summer and fall. Non-polio enteroviruses have been identified in 8% to 29% of cases of pharyngitis in children by using reverse-transcriptase polymerase chain reaction (RT-PCR).[67,68] Fever is common, but the throat examination typically reveals only mild erythema without significant adenopathy. Although exudates are not generally described, in a recent report, enteroviruses were found in 16% of children with exudative pharyngitis.[6]

Two specific pharyngeal syndromes typically associated with enterovirus infections are herpangina and hand-foot-mouth disease (HFM). Among children with fever and clinical signs of pharyngeal or tonsillar infection, 24 were identified with herpangina, of whom 75% had an enterovirus detected in their throat swab.[67] The majority of cases of herpangina are due to group A coxsackieviruses; however, group B coxsackieviruses, echoviruses, enterovirus 71, adenovirus, and HSV have also been detected.[69,70] Both endemic and epidemic herpangina are well described, with young children affected more commonly than newborns and adults. The clinical manifestations include hyperemia of the pharynx, with discrete 1- to 4-mm erythematous-based vesicles or ulcerations sparsely distributed on the tonsillar pillars, uvula, soft palate, or posterior pharynx.[71] Sore throat and fever are invariably present, but symptoms typically resolve spontaneously in about a week. Similar to herpangina, HFM is characterized by the presence of erythematous-based vesicles and ulcerations in the pharynx in a patient with significant sore throat. In contrast to herpangina, vesicles are also noted on the hands, feet, and buttocks in patients with HFM, and the fever tends to be less prominent.[71] Although most cases are self-limited, severe multisystem disease, particularly involving the central nervous system, accompanying HFM and herpangina has been described during outbreaks associated with enterovirus 71 (see Chapter 174).[72,73]

Adenovirus

Respiratory infections with adenovirus are well described in children and young adults, occur year round, and cause both upper and lower tract disease. Examining sore throat or pharyngitis specifically, adenovirus infections are identified as the etiologic agent in up to 25% of cases in children and in 3% of ambulatory adults.[4-6,74] Not only are adenoviruses a common cause of pharyngitis, but infections with adenovirus also commonly cause pharyngitis. Retrospective reviews have demonstrated that pharyngitis or tonsillitis is reported in 40% to 88% of children with adenovirus infections.[75,76] Exudates are noted in about half of the cases and are often described as thick and white with marked throat pain. In addition, almost three quarters of children with adenovirus infections have fever higher than 39° C that persists for a mean of 6 days.[77] Among military recruits followed prospectively, approximately 35% of those with culture-confirmed adenovirus infection had sore throat, and 29% were febrile.[78] Bilateral cervical lymphadenopathy (32%), conjunctivitis (17%), and rash (12%) have also been described in patients with adenovirus respiratory tract infections.[76]

Pharyngoconjunctival fever is a specific syndrome caused by adenovirus infections, often occurring in outbreaks and associated with swimming or bathing.[79] Patients typically present with fever, conjunctivitis, pharyngitis, and cough but may also complain of headache, myalgia, and malaise. Lymphadenopathy is found on examination in about half of the patients, whereas one quarter also have coryza.[80] This disorder is highly contagious, with an attack rate of approximately 50% and spread via direct inoculation into the conjunctiva. Although the conjunctivitis may be quite intense and last for 1 to 2 weeks, there is invariably complete resolution of all symptoms with no sequelae.[80]

Herpes Simplex Virus

Primary infection with HSV commonly causes gingivostomatitis in young children, whereas pharyngitis is noted among adolescents and young adults. In a series of 35 college students with HSV pharyngitis, infections occurred year round, with the majority of patients presenting with fever, pharyngeal erythema, exudates, and enlarged tender cervical adenopathy.[81] Approximately one third also had symptoms more characteristic of HSV, including either ulcerations of the mouth; lips; or pharynx; or swollen, tender, erythematous gingiva. One clue to the diagnosis of HSV pharyngitis is that esophagitis may also be present in immunocompetent adolescents and young adults and should be considered in patients complaining of substernal chest pain and dysphagia in addition to sore throat.

DIAGNOSIS

Because pharyngitis is one of the most common complaints a physician may encounter, diagnosis of treatable etiologies is paramount. The prevention of rheumatic fever requires antimicrobial treatment and eradication of GAS from the pharynx.[82] Certain clinical findings help to distinguish GAS from viral causes of pharyngitis (Table 59-2). As noted, tonsillar or pharyngeal exudates, tender anterior cervical lymphadenopathy, and fever are commonly associated with GAS. Alternatively, symptoms such as conjunctivitis, coryza, oral ulcers, cough, and diarrhea suggest a viral cause.

Multiple clinical prediction rules have been developed to aid in the diagnosis of GAS pharyngitis. Scoring systems attempt to use clinical and epidemiologic data to assign a probability that acute pharyngitis is attributable to GAS (Table 59-3).[11,83,84] Prediction rules for the diagnosis of GAS pharyngitis are limited because the signs and symptoms of many viral causes of acute pharyngitis overlap with infection caused by GAS, and the rules are best at identifying patients with a low probability for GAS infection. A large-scale study evaluating the modified clinical prediction rule (see Table 59-3) confirmed that even in subjects with all clinical features, streptococcal pharyngitis could only be confirmed in 57% of cases.[85] For these reasons, the most recent guidelines from the Infectious Disease Society of America (IDSA) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) recommend confirmation of GAS infection by rapid antigen detection testing (RADT), throat culture, or both.[86,87] In contrast, the guidelines issued by the Centers for Disease Control and Prevention and the American College of Physicians–American Society of Internal Medicine suggest empirical treatment based on a pharyngitis score alone with or without microbiologic confirmation.[88]

The difference in these guidelines has been the subject of intense debate, and empirical therapy based on the use of predication rules has been implicated in the overuse of antibiotics for the treatment of

TABLE 59-2 Clinical and Epidemiologic Findings Associated with Group A *Streptococcus* Pharyngitis

Suggestive of Group A *Streptococcus*
Sudden onset
Sore throat
Fever
Headache
Nausea, vomiting, and abdominal pain
Inflammation of pharynx and tonsils
Patchy discrete exudates
Tender, enlarged anterior cervical nodes
Patient aged 5-15 yr
Presentation in winter or early spring
History of exposure
Suggestive of Viral Etiology
Conjunctivitis
Coryza
Cough
Diarrhea
Discrete ulcerative lesions
Suggestive of Complications of Pharyngitis
Dysphagia
Stridor
Drooling
Dysphonia
Marked neck swelling
Respiratory distress
Pharyngeal pseudomembrane
Hemodynamic instability
HIV behavioral risk
Travel to or exposure to individuals from a region endemic for diphtheria
Lack of diphtheria immunization

HIV, human immunodeficiency virus.

Modified from Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis. *2012;55: e86-e102; and Kociolek LK, Shulman ST. In the clinic. Pharyngitis.* Ann Intern Med. *2012;157:ITC3-1-ITC3-16; with permission.*

TABLE 59-3 Modified Centor Score and Culture Management Approach for Pharyngitis

CRITERIA	POINTS
Temperature > 38° C	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age	
3-14 yr	1
15-44 yr	0
45 yr or older	–1

SCORE	RISK OF STREPTOCOCCAL INFECTION	SUGGESTED MANAGEMENT
≤0	1%-2.5%	No further testing or antibiotic
1	5%-10%	
2	11%-17%	Culture all: antibiotics only for positive culture results
3	28%-35%	
≥4	51%-53%	Treat empirically with antibiotics and/or culture

From McIsaac WJ, Kellner JD, Aufricht P, et al. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. *2004;291:1587-1595; with permission.*

pharyngitis.[84] A study on the effectiveness of these strategies showed that empirical treatment is a reasonable strategy for those least likely to have GAS pharyngitis, but microbiologic confirmation was the most effective and least expensive when all factors were considered.[89] In addition, in 78% of cases, physicians did not adhere to any guidelines, leading to overuse of antibiotics for the treatment of pharyngitis.[90] More recently, improved accuracy of the Centor score[83] was achieved by adding real-time local biosurveillance for GAS pharyngitis. However, real-time biosurveillance is impractical in most settings. At this time, the evidence supports the practice of obtaining microbiologic confirmation of GAS as the cause of pharyngitis before antibiotic therapy.

Assaying for the presence of GAS by throat culture on sheep blood agar plate (BAP), as first described by Breese and Disney,[91] has been accepted practice for diagnosing streptococcal pharyngitis for more than 50 years. Selective streptococcal media are used by some laboratories and reduce the number of contaminating normal flora and may increase the sensitivity and specificity of culture.[92] However, the use of selective media may also reduce the likelihood of recovery of other bacterial etiologic agents. Ideally, specimens should be obtained from bilateral tonsillar surfaces and the posterior pharynx while avoiding the mouth, tongue, and other surfaces of the pharynx. The major disadvantage of throat culture for the confirmation of GAS pharyngitis is the 24 to 48 hours required for accurate detection. RADT has become more readily available and, in some instances, has been reported to equal or exceed the sensitivity and specificity of throat culture. Rapid testing may lead to more timely treatment and, in so doing, can reduce the spread of GAS, time missed from school or work, overtreatment of viral causes of pharyngitis, and minimize suppurative and nonsuppurative sequelae of GAS. The original RADTs were based on the detection of GAS cell wall carbohydrate antigen by enzyme immunoassays. Newer assays use molecular biology methods to detect DNA specific to GAS by using chemiluminescence or real-time PCR but are restricted because of the need to batch specimens and the specialized equipment required. The sensitivity of RADTs is 70% to 90% when compared with BAP culture, with a specificity of approximately 95% and with all of the tests performing essentially the same.[93] Of importance, RADT specimens must be collected in a manner similar to BAP culture. Swabs obtained from the mouth and subjected to RADT have a sensitivity of less than 20% versus 80% for those obtained properly from the posterior pharynx and tonsils.[94] Currently, it is recommended that a negative RADT be confirmed by BAP culture for all children.[86,87] Because the incidence of a first attack of rheumatic fever is low in adults in the United States and the prevalence of GAS pharyngitis is minimal, the need to back up a negative RADT in adults is not universally recommended.[84]

The diagnosis of non-GAS pharyngitis is specific to the etiologic agent involved. A high index of suspicion must be maintained for alternative diagnoses in the appropriate epidemiologic setting because many pathogens are not screened, even in large clinical laboratories. Culture on either standard BAP or selective streptococcal media will identify both group C and G *Streptococcus;* however, they may be identified only as non–group A β-hemolytic *Streptococcus. Arcanobacterium haemolyticum* also grows on standard blood agar or selective streptococcal media but may be missed because colonies generally take up to 72 hours to appear and are small and dry.

Specific media and techniques are necessary to identify other causes of pharyngitis. If diphtheria is suspected, the laboratory must be notified so that selective media are used for isolation. Recently, multiplex PCR has been used for the identification of *C. diphtheriae* and to differentiate toxin-producing from nontoxigenic strains[95] but requires further investigation before use in a clinical setting. The diagnosis of *Fusobacterium* pharyngitis can be made by isolating the organism in anaerobic culture media, although most clinical laboratories rely on commercial kits and automated systems for identification. The accuracy of these systems is variable and may lead to initial misidentification. Molecular detection of *Fusobacterium* has been used in some studies[96] but currently is not commercially available. The diagnosis of pharyngitis caused by *Neisseria gonorrhoeae* is confirmed by isolation of the organism from a throat swab on selective media. Nucleic acid amplification tests are both sensitive and specific for urogenital

specimens. Ease of testing pharyngeal samples may be simplified by nucleic acid amplification of salivary samples, but this is still in an investigational stage.[97]

Serologic testing of acute and convalescent serum samples is the standard procedure for diagnosing pharyngitis caused by *M. pneumoniae* or *C. pneumoniae*; however, PCR and culture are commonly used in addition to serology for research purposes. The diagnosis of primary EBV infection is also confirmed by serology, either via a heterophil antibody test (monospot or monoslide) or detection of immunoglobulin M (IgM) antibodies to EBV viral capsid antigen in an acute serum specimen. Although 85% of adolescents and adults develop heterophil antibodies, usually at about 1 week into illness, specific serology for EBV is usually necessary to make the diagnosis in children, especially those younger than 4 years.[59,61] Common respiratory viruses that cause pharyngitis can be identified either by viral culture of a nasopharyngeal swab or molecular detection techniques such as PCR or RT-PCR.

THERAPY

Prescribing antibiotics for patients with sore throat is a common practice and is often done in an effort to prevent potential complications of pharyngitis. A systematic review of the use of antibiotics for sore throat that included almost 13,000 patients found that antibiotics did reduce the incidence of otitis media, acute sinusitis, peritonsillar abscess, and acute rheumatic fever.[98] However, only 7 of the 58 studies included in the review were published since 1996, and the populations included were very heterogeneous, including those with and without GAS. A more recent evaluation used a national database of more than one million cases of sore throat and found that although there was a decrease in the incidence of quinsy (peritonsillar abscess) after the use of antibiotics, the number needed to treat to prevent one case was 4300, suggesting that the small decrease in risk of an uncommon complication did not warrant the widespread use of antibiotics for a self-limited disease.[99]

The goal of therapy for GAS pharyngitis is to decrease the time to resolution of symptoms, reduce risk of transmission, and reduce the incidence of suppurative and nonsuppurative sequelae. This is achieved by the elimination of GAS from the pharynx. Penicillin has been the mainstay of therapy for GAS pharyngitis for more than 60 years. Despite this long-term use, there has yet to be a confirmed instance of penicillin resistance in GAS. A 10-day course of penicillin or amoxicillin is the treatment of choice and is recommended by the IDSA and AAP for the treatment of pharyngitis caused by GAS (Table 59-4).[86,87]

TABLE 59-4 Antimicrobial Therapy for Group A Streptococcal Pharyngitis

DRUG	DOSE	DURATION
Oral Regimens		
Penicillin V	Children: 250 mg bid or tid Adolescents and adults: 250 mg tid or qid or 500 mg bid	10 days
Amoxicillin	50 mg/kg once daily (maximum 1000 mg) Alternative: 25 mg/kg bid (maximum 500 mg)	10 days
For Penicillin-Allergic Patients		
Erythromycin	Varies with formulation	10 days
First-generation cephalosporins	Varies with agent	10 days
Intramuscular Regimens		
Benzathine penicillin G	600,000 units for patients <27 kg	1 dose
	1.2 million units for patients ≥27 kg	1 dose
Mixtures of benzathine and procaine penicillin G	Varies with formulation	1 dose

Modified from Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. Infect Dis Clin North Am. *2007;21:449-469, vii; with permission.*

Penicillin-allergic patients should be given a macrolide (erythromycin) or first-generation cephalosporin for non–IgE-mediated allergy. Currently, the use of broad-spectrum cephalosporins, such as cefixime and ceftibuten, although approved by the U.S. Food and Drug Administration for the treatment of GAS pharyngitis, is not endorsed.

The use of amoxicillin for the treatment of GAS pharyngitis has increased because of improved taste and less frequent dosing intervals compared with penicillin, leading to better patient compliance. Two relatively small studies have shown that treatment of GAS pharyngitis with once-daily amoxicillin for 10 days achieved similar clinical and bacteriologic outcomes compared with traditional penicillin dosing.[100,101] Furthermore, a larger study confirmed a once-daily amoxicillin regimen as noninferior to twice-daily penicillin.[102] Given the evidence, the most recent guidelines endorse the use of amoxicillin if greater compliance is anticipated.[87]

Antimicrobial therapy should not be used for the prevention of GAS pharyngitis except in special circumstances. Culture or RADT for diagnosis, coupled with treatment is indicated in those with a previous episode of rheumatic fever, during an outbreak of acute rheumatic fever or poststreptococcal glomerulonephritis, or in close contacts of persons with invasive infections, such as necrotizing fasciitis or streptococcal toxic shock syndrome.[86,87] There is also no need to routinely obtain throat cultures at the end of treatment in asymptomatic patients, to document clearance of GAS except in those situations noted above.

Recommendations for treatment of *Fusobacterium* infections include a penicillin in combination with a β-lactamase inhibitor (e.g., ampicillin/sulbactam) together with metronidazole.[103] Resistance to penicillin has been reported, but this is not widespread. Penicillin and erythromycin are the only two agents recommended for treatment of *C. diphtheriae,* although newer macrolides, such as azithromycin, are commonly used in clinical practice. Treatment of *Arcanobacterium haemolyticum* should include either a macrolide or β-lactam antibiotic. Penicillin resistance has been reported and appears to be more common in cases of pharyngitis.[104] Treatment of pharyngitis caused by *N. gonorrhoeae* is problematic because pharyngeal eradication of the organism is more difficult than eradication from the urogenital tract. As such, it is recommended that repeat cultures be obtained at the end of therapy to confirm eradication. Specific treatment regimens for gonorrhea are discussed elsewhere.[105]

COMPLICATIONS

The potential suppurative complications of pharyngitis (see Table 59-2) include peritonsillar abscess, parapharyngeal space abscess, lymphadenitis, sinusitis, otitis media, mastoiditis, and invasive infections (e.g., necrotizing fasciitis and toxic shock syndrome with GAS). Peritonsillar abscess typically occurs in adolescents and young adults but has been described in all age groups. Patients present with fever, malaise, sore throat, and dysphagia. There may be trismus or ipsilateral ear pain. Physical examination reveals drooling and a muffled voice ("hot potato voice") with tender cervical adenopathy and swelling of the anterior tonsillar pillar and soft palate on the affected side. The uvula is displaced to the contralateral side by the abscess.[106] In older adults, the signs and symptoms of a peritonsillar or parapharyngeal space abscess may be subtle, and disease appears to be more common in those with underlying immunocompromising conditions.[107] In a series of 14 patients older than 50 years, fever, trismus, and voice changes each were present in less than one third of patients with peritonsillar abscess or parapharyngeal space abscess.[107] Drainage of purulent material coupled with antibiotics are the standard of treatment.[108] Because peritonsillar and parapharyngeal abscesses are often polymicrobial, involving aerobic and anaerobic bacteria, one suggested agent for treatment is ampicillin/sulbactam.[106]

Acute rheumatic fever (ARF) and acute glomerulonephritis are potential nonsuppurative complications of pharyngitis caused by GAS. Rheumatic heart disease and its complications affect almost two million individuals each year, primarily in developing countries.[32] Acute rheumatic fever has become rare in the United States except for sporadic outbreaks of rheumatogenic strains of GAS.[109] Acute glomerulonephritis is associated with GAS skin infections and uncommonly associated with pharyngitis caused by GAS. Rarely, acute

glomerulonephritis occurs after group C or G streptococcal pharyngitis, but these organisms have never been associated with ARF.

Lemierre syndrome is an uncommon complication of pharyngitis in adolescents and young adults, characterized by septic thrombophlebitis of the internal jugular vein and metastatic lesions (septic emboli) of distant sites after acute sore throat, most commonly caused by *F. necrophorum*.[103] The clinical characteristics of pharyngitis caused by *Fusobacterium* are nonspecific and similar to GAS, and systemic illness may present after pharyngeal symptoms have subsided.

Key References

The complete reference list is available online at Expert Consult.

1. Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. *Infect Dis Clin North Am*. 2007;21:449-469, vii.
4. Huovinen P, Lahtonen R, Ziegler T, et al. Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. *Ann Intern Med*. 1989;110:612-616.
5. Esposito S, Blasi F, Bosis S, et al. Aetiology of acute pharyngitis: the role of atypical bacteria. *J Med Microbiol*. 2004;53:645-651.
6. Hsieh TH, Chen PY, Huang FL, et al. Are empiric antibiotics for acute exudative tonsillitis needed in children? *J Microbiol Immunol Infect*. 2011;44:328-332.
9. Louie JK, Hacker JK, Gonzales R, et al. Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center Clinic during the influenza season. *Clin Infect Dis*. 2005;41:822-828.
11. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ*. 1998;158:75-83.
12. Kaplan EL, Top FH Jr, Dudding BA, Wannamaker LW. Diagnosis of streptococcal pharyngitis: differentiation of active infection from the carrier state in the symptomatic child. *J Infect Dis*. 1971;123:490-501.
14. Ehlers Klug T, Rusan M, Fuursted K, Ovesen T. *Fusobacterium necrophorum:* most prevalent pathogen in peritonsillar abscess in Denmark. *Clin Infect Dis*. 2009;49:1467-1472.
17. Mackenzie A, Fuite LA, Chan FT, et al. Incidence and pathogenicity of *Arcanobacterium haemolyticum* during a 2-year study in Ottawa. *Clin Infect Dis*. 1995;21:177-181.
21. Wiesner PJ, Tronca E, Bonin P, et al. Clinical spectrum of pharyngeal gonococcal infection. *N Engl J Med*. 1973;288:181-185.
23. Danchin MH, Rogers S, Kelpie L, et al. Burden of acute sore throat and group A streptococcal pharyngitis in school-aged children and their families in Australia. *Pediatrics*. 2007;120:950-957.
25. Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic treatment of children with sore throat. *JAMA*. 2005;294:2315-2322.
26. Nash DR, Harman J, Wald ER, Kelleher KJ. Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Arch Pediatr Adolesc Med*. 2002;156:1114-1119.
27. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991-1999. *Ann Intern Med*. 2003;138:525-533.
29. Ebell MH, Smith MA, Barry HC, et al. The rational clinical examination. Does this patient have strep throat? *JAMA*. 2000;284:2912-2918.
30. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics*. 2010;126:e557-e564.
31. Llor C, Madurell J, Balague-Corbella M, et al. Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: a randomised clinical trial. *Br J Gen Pract*. 2011;61:e244-e251.
32. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5:685-694.
33. Martin JM, Green M, Barbadora KA, Wald ER. Group A streptococci among school-aged children: clinical characteristics and the carrier state. *Pediatrics*. 2004;114:1212-1219.
38. Wing A, Villa-Roel C, Yeh B, et al. Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. *Acad Emerg Med*. 2010;17:476-483.
39. Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract*. 2000;50:817-820.
42. Shulman ST, Stollerman G, Beall B, et al. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clin Infect Dis*. 2006;42:441-447.
45. Meier FA, Centor RM, Graham L Jr, Dalton HP. Clinical and microbiological evidence for endemic pharyngitis among adults due to group C streptococci. *Arch Intern Med*. 1990;150:825-829.
47. Centor RM. Expand the pharyngitis paradigm for adolescents and young adults. *Ann Intern Med*. 2009;151:812-815.
48. Miller RA, Brancato F, Holmes KK. *Corynebacterium hemolyticum* as a cause of pharyngitis and scarlatiniform rash in young adults. *Ann Intern Med*. 1986;105:867-872.
56. Klement E, Talkington DF, Wasserzug O, et al. Identification of risk factors for infection in an outbreak of *Mycoplasma pneumoniae* respiratory tract disease. *Clin Infect Dis*. 2006;43:1239-1245.
57. Esposito S, Cavagna R, Bosis S, et al. Emerging role of *Mycoplasma pneumoniae* in children with acute pharyngitis. *Eur J Clin Microbiol Infect Dis*. 2002;21:607-610.
58. Esposito S, Bosis S, Begliatti E, et al. Acute tonsillopharyngitis associated with atypical bacterial infection in children: natural history and impact of macrolide therapy. *Clin Infect Dis*. 2006;43:206-209.
59. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. *Am J Med*. 2007;120:911.e1-.e8.
61. Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003-1010.
62. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. 1996;125:257-264.
64. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. 2002;16:1119-1129.
71. Rotbart HA, Hayden FG. Picornavirus infections: a primer for the practitioner. *Arch Fam Med*. 2000;9:913-920.
73. Jiang M, Wei D, Ou WL, et al. Autopsy findings in children with hand, foot, and mouth disease. *N Engl J Med*. 2012;367:91-92.
74. Chi H, Chiu NC, Li WC, Huang FY. Etiology of acute pharyngitis in children: is antibiotic therapy needed? *J Microbiol Immunol Infect*. 2003;36:26-30.
76. Dominguez O, Rojo P, de Las Heras S, et al. Clinical presentation and characteristics of pharyngeal adenovirus infections. *Pediatr Infect Dis J*. 2005;24:733-734.
81. McMillan JA, Weiner LB, Higgins AM, Lamparella VJ. Pharyngitis associated with herpes simplex virus in college students. *Pediatr Infect Dis J*. 1993;12:280-284.
82. Catanzaro FJ, Rammelkamp CH Jr, Chamovitz R. Prevention of rheumatic fever by treatment of streptococcal infections. II. Factors responsible for failures. *N Engl J Med*. 1958;259:53-57.
83. Centor RM, Witherspoon JM, Dalton HP, et al. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making*. 1981;1:239-246.
84. McIsaac WJ, Kellner JD, Aufricht P, et al. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA*. 2004;291:1587-1595.
85. Fine AM, Nizet V, Mandl KD. Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. *Arch Intern Med*. 2012;172:847-852.
86. Committee on Infectious Diseases. Group A streptococcal infections. In: Pickering LK, ed. *Red Book*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:668-680.
87. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55:e86-e102.
88. Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *Ann Intern Med*. 2001;134:506-508.
89. Neuner JM, Hamel MB, Phillips RS, et al. Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis. *Ann Intern Med*. 2003;139:113-122.
90. Linder JA, Chan JC, Bates DW. Evaluation and treatment of pharyngitis in primary care practice: the difference between guidelines is largely academic. *Arch Intern Med*. 2006;166:1374-1379.
98. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2006;4:CD000023.
102. Lennon DR, Farrell E, Martin DR, Stewart JM. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. *Arch Dis Child*. 2008;93:474-478.
103. Riordan T. Human infection with *Fusobacterium necrophorum* (Necrobacillosis), with a focus on Lemierre's syndrome. *Clin Microbiol Rev*. 2007;20:622-659.
110. Kociolek LK, Shulman ST. In the clinic. Pharyngitis. *Ann Intern Med*. 2012;157:ITC3-1-ITC3-16.

References

1. Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. *Infect Dis Clin North Am*. 2007;21:449-469, vii.
2. Putto A. Febrile exudative tonsillitis: viral or streptococcal? *Pediatrics*. 1987;80:6-12.
3. Bastien N, Robinson JL, Tse A, et al. Human coronavirus NL-63 infections in children: a 1-year study. *J Clin Microbiol*. 2005;43:4567-4573.
4. Huovinen P, Lahtonen R, Ziegler T, et al. Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. *Ann Intern Med*. 1989;110:612-616.
5. Esposito S, Blasi F, Bosis S, et al. Aetiology of acute pharyngitis: the role of atypical bacteria. *J Med Microbiol*. 2004;53:645-651.
6. Hsieh TH, Chen PY, Huang FL, et al. Are empiric antibiotics for acute exudative tonsillitis needed in children? *J Microbiol Immunol Infect*. 2011;44:328-332.
7. Choi JH, Chung YS, Kim KS, et al. Development of real-time PCR assays for detection and quantification of human bocavirus. *J Clin Virol*. 2008;42:249-253.
8. Dollner H, Risnes K, Radtke A, Nordbo SA. Outbreak of human metapneumovirus infection in Norwegian children. *Pediatr Infect Dis J*. 2004;23:436-440.
9. Louie JK, Hacker JK, Gonzales R, et al. Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center Clinic during the influenza season. *Clin Infect Dis*. 2005;41:822-828.
10. Komaroff AL, Pass TM, Aronson MD, et al. The prediction of streptococcal pharyngitis in adults. *J Gen Intern Med*. 1986;1:1-7.
11. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ*. 1998;158:75-83.
12. Kaplan EL, Top FH Jr, Dudding BA, Wannamaker LW. Diagnosis of streptococcal pharyngitis: differentiation of active infection from the carrier state in the symptomatic child. *J Infect Dis*. 1971;123:490-501.
13. Amess JA, O'Neill W, Giollariabhaigh CN, Dytrych JK. A six-month audit of the isolation of *Fusobacterium necrophorum* from patients with sore throat in a district general hospital. *Br J Biomed Sci*. 2007;64:63-65.
14. Ehlers Klug T, Rusan M, Fuursted K, Ovesen T. *Fusobacterium necrophorum:* most prevalent pathogen in peritonsillar abscess in Denmark. *Clin Infect Dis*. 2009;49:1467-1472.
15. Batty A, Wren MW, Gal M. *Fusobacterium necrophorum* as the cause of recurrent sore throat: comparison of isolates from persistent sore throat syndrome and Lemierre's disease. *J Infect*. 2005;51:299-306.
16. Carlson P, Renkonen OV, Kontiainen S. *Arcanobacterium haemolyticum* and streptococcal pharyngitis. *Scand J Infect Dis*. 1994;26:283-287.
17. Mackenzie A, Fuite LA, Chan FT, et al. Incidence and pathogenicity of *Arcanobacterium haemolyticum* during a 2-year study in Ottawa. *Clin Infect Dis*. 1995;21:177-181.
18. Dittmann S, Wharton M, Vitek C, et al. Successful control of epidemic diphtheria in the states of the Former Union of Soviet Socialist Republics: lessons learned. *J Infect Dis*. 2000;181(suppl 1):S10-S22.
19. Reacher M, Ramsay M, White J, et al. Nontoxigenic corynebacterium diphtheriae: an emerging pathogen in England and Wales? *Emerg Infect Dis*. 2000;6:640-645.
20. Stolz E, Schuller J. Gonococcal oro- and nasopharyngeal infection. *Br J Vener Dis*. 1974;50:104-108.
21. Wiesner PJ, Tronca E, Bonin P, et al. Clinical spectrum of pharyngeal gonococcal infection. *N Engl J Med*. 1973;288:181-185.
22. Glezen WP, Clyde WA, Senior RJ, et al. Group A streptococci, mycoplasmas, and viruses associated with acute pharyngitis. *JAMA*. 1967;202:119-124.
23. Danchin MH, Rogers S, Kelpie L, et al. Burden of acute sore throat and group A streptococcal pharyngitis in school-aged children and their families in Australia. *Pediatrics*. 2007;120:950-957.
24. Uijen JH, Bindels PJ, Schellevis FG, van der Wouden JC. ENT problems in Dutch children: trends in incidence rates, antibiotic prescribing and referrals 2002-2008. *Scand J Prim Health Care*. 2011;29:75-79.
25. Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic treatment of children with sore throat. *JAMA*. 2005;294:2315-2322.
26. Nash DR, Harman J, Wald ER, Kelleher KJ. Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. *Arch Pediatr Adolesc Med*. 2002;156:1114-1119.
27. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991-1999. *Ann Intern Med*. 2003;138:525-533.
28. Andre M, Odenholt I, Schwan A, et al. Upper respiratory tract infections in general practice: diagnosis, antibiotic prescribing, duration of symptoms and use of diagnostic tests. *Scand J Infect Dis*. 2002;34:880-886.
29. Ebell MH, Smith MA, Barry HC, et al. The rational clinical examination. Does this patient have strep throat? *JAMA*. 2000;284:2912-2918.
30. Shaikh N, Leonard E, Martin JM. Prevalence of streptococcal pharyngitis and streptococcal carriage in children: a meta-analysis. *Pediatrics*. 2010;126:e557-e564.
31. Llor C, Madurell J, Balague-Corbella M, et al. Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: a randomised clinical trial. *Br J Gen Pract*. 2011;61:e244-e251.
32. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5:685-694.
33. Martin JM, Green M, Barbadora KA, Wald ER. Group A streptococci among school-aged children: clinical characteristics and the carrier state. *Pediatrics*. 2004;114:1212-1219.
34. Proud D, Reynolds CJ, Lacapra S, et al. Nasal provocation with bradykinin induces symptoms of rhinitis and a sore throat. *Am Rev Respir Dis*. 1988;137:613-616.
35. Rees GL, Eccles R. Sore throat following nasal and oropharyngeal bradykinin challenge. *Acta Otolaryngol*. 1994;114:311-314.
36. Eccles R. Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis*. 2005;5:718-725.
37. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann Pharmacother*. 2010;44:489-506.
38. Wing A, Villa-Roel C, Yeh B, et al. Effectiveness of corticosteroid treatment in acute pharyngitis: a systematic review of the literature. *Acad Emerg Med*. 2010;17:476-483.
39. Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract*. 2000;50:817-820.
40. Bisno AL, Brito MO, Collins CM. Molecular basis of group A streptococcal virulence. *Lancet Infect Dis*. 2003;3:191-200.
41. Olsen RJ, Shelburne SA, Musser JM. Molecular mechanisms underlying group A streptococcal pathogenesis. *Cell Microbiol*. 2008;11:1-12.
42. Shulman ST, Stollerman G, Beall B, et al. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the United States. *Clin Infect Dis*. 2006;42:441-447.
43. Turner JC, Hayden FG, Lobo MC, et al. Epidemiologic evidence for Lancefield group C beta-hemolytic streptococci as a cause of exudative pharyngitis in college students. *J Clin Microbiol*. 1997;35:1-4.
44. Balter S, Benin A, Pinto SW, et al. Epidemic nephritis in Nova Serrana, Brazil. *Lancet*. 2000;355:1776-1780.
45. Meier FA, Centor RM, Graham L Jr, Dalton HP. Clinical and microbiological evidence for endemic pharyngitis among adults due to group C streptococci. *Arch Intern Med*. 1990;150:825-829.
46. Gerber MA, Randolph MF, Martin NJ, et al. Community-wide outbreak of group G streptococcal pharyngitis. *Pediatrics*. 1991;87:598-603.
47. Centor RM. Expand the pharyngitis paradigm for adolescents and young adults. *Ann Intern Med*. 2009;151:812-815.
48. Miller RA, Brancato F, Holmes KK. *Corynebacterium hemolyticum* as a cause of pharyngitis and scarlatiniform rash in young adults. *Ann Intern Med*. 1986;105:867-872.
49. Therriault BL, Daniels LM, Carter YL, Raasch RH. Severe sepsis caused by *Arcanobacterium haemolyticum:* a case report and review of the literature. *Ann Pharmacother*. 2008;42:1697-1702.
50. Naiditch MJ, Bower AG. Diphtheria; a study of 1,433 cases observed during a ten-year period at the Los Angeles County Hospital. *Am J Med*. 1954;17:229-245.
51. Farizo KM, Strebel PM, Chen RT, et al. Fatal respiratory disease due to *Corynebacterium diphtheriae:* case report and review of guidelines for management, investigation, and control. *Clin Infect Dis*. 1993;16:59-68.
52. Balmelli C, Gunthard HF. Gonococcal tonsillar infection—a case report and literature review. *Infection*. 2003;31:362-365.
53. Meijer A, Dagnelie CF, De Jong JC, et al. Low prevalence of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* among patients with symptoms of respiratory tract infections in Dutch general practices. *Eur J Epidemiol*. 2000;16:1099-1106.
54. Layani-Milon MP, Gras I, Valette M, et al. Incidence of upper respiratory tract *Mycoplasma pneumoniae* infections among outpatients in Rhône-Alpes, France, during five successive winter periods. *J Clin Microbiol*. 1999;37:1721-1726.
55. Thom D, Grayston JT, Campbell LA, et al. Respiratory infection with *Chlamydia pneumoniae* in middle-aged and older adult outpatients. *Eur J Clin Microbiol Infect Dis*. 1994;13:785-792.
56. Klement E, Talkington DF, Wasserzug O, et al. Identification of risk factors for infection in an outbreak of *Mycoplasma pneumoniae* respiratory tract disease. *Clin Infect Dis*. 2006;43:1239-1245.
57. Esposito S, Cavagna R, Bosis S, et al. Emerging role of *Mycoplasma pneumoniae* in children with acute pharyngitis. *Eur J Clin Microbiol Infect Dis*. 2002;21:607-610.
58. Esposito S, Bosis S, Begliatti E, et al. Acute tonsillopharyngitis associated with atypical bacterial infection in children: natural history and impact of macrolide therapy. *Clin Infect Dis*. 2006;43:206-209.
59. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. *Am J Med*. 2007;120:911.e1-.e8.
60. Rea TD, Russo JE, Katon W, et al. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract*. 2001;14:234-242.
61. Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003-1010.
62. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. 1996;125:257-264.
63. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998;339:33-39.
64. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. 2002;16:1119-1129.
65. Aggarwal M, Rein J. Acute human immunodeficiency virus syndrome in an adolescent. *Pediatrics*. 2003;112:e323.
66. Coco A, Kleinhans E. Prevalence of primary HIV infection in symptomatic ambulatory patients. *Ann Fam Med*. 2005;3:400-404.
67. Hosoya M, Ishiko H, Shimada Y, et al. Diagnosis of group A coxsackieviral infection using polymerase chain reaction. *Arch Dis Child*. 2002;87:316-319.
68. Sharland M, Hodgson J, Davies EG, et al. Enteroviral pharyngitis diagnosed by reverse transcriptase-polymerase chain reaction. *Arch Dis Child*. 1996;74:462-463.
69. Nakayama T, Urano T, Osano M, et al. Outbreak of herpangina associated with Coxsackievirus B3 infection. *Pediatr Infect Dis J*. 1989;8:495-498.
70. Tsai HP, Kuo PH, Liu CC, Wang JR. Respiratory viral infections among pediatric inpatients and outpatients in Taiwan from 1997 to 1999. *J Clin Microbiol*. 2001;39:111-118.
71. Rotbart HA, Hayden FG. Picornavirus infections: a primer for the practitioner. *Arch Fam Med*. 2000;9:913-920.
72. Chen K-T, Chang H-L, Wang S-T, et al. Epidemiologic features of hand-foot-mouth disease and herpangina caused by enterovirus 71 in Taiwan, 1998-2005. *Pediatrics*. 2007;120:e244-e252.
73. Jiang M, Wei D, Ou WL, et al. Autopsy findings in children with hand, foot, and mouth disease. *N Engl J Med*. 2012;367:91-92.
74. Chi H, Chiu NC, Li WC, Huang FY. Etiology of acute pharyngitis in children: is antibiotic therapy needed? *J Microbiol Immunol Infect*. 2003;36:26-30.
75. Chang SY, Lee CN, Lin PH, et al. A community-derived outbreak of adenovirus type 3 in children in Taiwan between 2004 and 2005. *J Med Virol*. 2008;80:102-112.
76. Dominguez O, Rojo P, de Las Heras S, et al. Clinical presentation and characteristics of pharyngeal adenovirus infections. *Pediatr Infect Dis J*. 2005;24:733-734.
77. Lin CH, Huang YC, Chiu CH, et al. A cluster of adenovirus serotype 3 infections in children in northern Taiwan: clinical features and laboratory findings. *J Microbiol Immunol Infect*. 2007;40:302-309.
78. McNamara MJ, Pierce WE, Crawford YE, Miller LF. Patterns of adenovirus infection in the respiratory diseases of naval recruits: a longitudinal study of two companies of naval recruits. *Am Rev Respir Dis*. 1962;86:485-497.
79. Centers for Disease Control and Prevention. Outbreak of pharyngoconjunctival fever at a summer camp—North Carolina, 1991. *MMWR Morb Mortal Wkly Rep*. 1992;41:342-344.
80. Nakayama M, Miyazaki C, Ueda K, et al. Pharyngoconjunctival fever caused by adenovirus type 11. *Pediatr Infect Dis J*. 1992;11:6-9.
81. McMillan JA, Weiner LB, Higgins AM, Lamparella VJ. Pharyngitis associated with herpes simplex virus in college students. *Pediatr Infect Dis J*. 1993;12:280-284.
82. Catanzaro FJ, Rammelkamp CH Jr, Chamovitz R. Prevention of rheumatic fever by treatment of streptococcal infections. II. Factors responsible for failures. *N Engl J Med*. 1958;259:53-57.
83. Centor RM, Witherspoon JM, Dalton HP, et al. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making*. 1981;1:239-246.
84. McIsaac WJ, Kellner JD, Aufricht P, et al. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA*. 2004;291:1587-1595.
85. Fine AM, Nizet V, Mandl KD. Large-scale validation of the Centor and McIsaac scores to predict group A streptococcal pharyngitis. *Arch Intern Med*. 2012;172:847-852.
86. Committee on Infectious Diseases. Group A streptococcal infections. In: Pickering LK, ed. *Red Book*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:668-680.
87. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious

Diseases Society of America. *Clin Infect Dis*. 2012;55:e86-e102.
88. Snow V, Mottur-Pilson C, Cooper RJ, Hoffman JR. Principles of appropriate antibiotic use for acute pharyngitis in adults. *Ann Intern Med*. 2001;134:506-508.
89. Neuner JM, Hamel MB, Phillips RS, et al. Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis. *Ann Intern Med*. 2003;139:113-122.
90. Linder JA, Chan JC, Bates DW. Evaluation and treatment of pharyngitis in primary care practice: the difference between guidelines is largely academic. *Arch Intern Med*. 2006;166:1374-1379.
91. Breese BB, Disney FA. The accuracy of diagnosis of beta streptococcal infections on clinical grounds. *J Pediatr*. 1954;44:670-673.
92. Bellon J, Weise B, Verschraegen G, De Meyere M. Selective streptococcal agar versus blood agar for detection of group A beta-hemolytic streptococci in patients with acute pharyngitis. *J Clin Microbiol*. 1991;29:2084-2085.
93. Gerber MA, Shulman ST. Rapid diagnosis of pharyngitis caused by group A streptococci. *Clin Microbiol Rev*. 2004;17:571-580.
94. Fox JW, Marcon MJ, Bonsu BK. Diagnosis of streptococcal pharyngitis by detection of *Streptococcus pyogenes* in posterior pharyngeal versus oral cavity specimens. *J Clin Microbiol*. 2006;44:2593-2594.
95. Pimenta FP, Hirata R Jr, Rosa AC, et al. A multiplex PCR assay for simultaneous detection of *Corynebacterium diphtheriae* and differentiation between non-toxigenic and toxigenic isolates. *J Med Microbiol*. 2008;57:1438-1439.
96. Aliyu SH, Marriott RK, Curran MD, et al. Real-time PCR investigation into the importance of *Fusobacterium necrophorum* as a cause of acute pharyngitis in general practice. *J Med Microbiol*. 2004;53:1029-1035.
97. Papp JR, Ahrens K, Phillips C, et al. The use and performance of oral-throat rinses to detect pharyngeal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections. *Diagn Microbiol Infect Dis*. 2007;59:259-264.
98. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2006;4:CD000023.
99. Petersen I, Johnson AM, Islam A, et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ*. 2007;335:982.
100. Feder HM Jr, Gerber MA, Randolph MF, et al. Once-daily therapy for streptococcal pharyngitis with amoxicillin. *Pediatrics*. 1999;103:47-51.
101. Shvartzman P, Tabenkin H, Rosentzwaig A, Dolginov F. Treatment of streptococcal pharyngitis with amoxycillin once a day. *BMJ*. 1993;306:1170-1172.
102. Lennon DR, Farrell E, Martin DR, Stewart JM. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. *Arch Dis Child*. 2008;93:474-478.
103. Riordan T. Human infection with *Fusobacterium necrophorum* (Necrobacillosis), with a focus on Lemierre's syndrome. *Clin Microbiol Rev*. 2007;20:622-659.
104. Nyman M, Banck G, Thore M. Penicillin tolerance in *Arcanobacterium haemolyticum*. *J Infect Dis*. 1990;161:261-265.
105. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*. 2006;55:1-94.
106. Galioto NJ. Peritonsillar abscess. *Am Fam Physician*. 2008;77:199-202.
107. Franzese CB, Isaacson JE. Peritonsillar and parapharyngeal space abscess in the older adult. *Am J Otolaryngol*. 2003;24:169-173.
108. Brook I. Microbiology and management of peritonsillar, retropharyngeal, and parapharyngeal abscesses. *J Oral Maxillofac Surg*. 2004;62:1545-1550.
109. Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med*. 1987;316:421-427.