## Staphylococcal Toxic Shock Syndrome

TSS is an acute febrile illness characterized by a generalized erythematous eruption that is due to in vivo production of a toxin at the site of localized, often relatively asymptomatic or unnoticed infection by *S. aureus* strains capable of toxin production.[188–192] The multisystem effects observed in TSS patients are induced by TSST-1 and, to a lesser extent, other staphylococcal enterotoxins. The toxins act as superantigens binding directly to the Vβ chain of the T-cell receptor and to the major histocompatibility complex molecule, which triggers clonal expansion of the T cells and an unregulated outpouring of proinflammatory cytokines.[175,193] Although staphylococcal TSS has been most commonly linked to *S. aureus,* TSST-1–producing coagulase-negative staphylococci have also been described.[194]

Although in the early 1980s most cases of TSS occurred in menstruating females, often in association with tampon use, nonmenstrual staphylococcal TSS is now more common.[191] Nonmenstrual TSS has been associated with a variety of infections, including postoperative wounds, cutaneous infections, burn wounds, postpartum complications, and *S. aureus* respiratory infections, often after viral influenza.[195] Recurrent nonmenstrual toxic shock has been described.[196]

TSS may range in severity from a relatively mild disease, often misdiagnosed as a viral syndrome, to a severe life-threatening illness. The most common symptoms include a temperature greater than 40°C (104°F), hypotension, and diffuse erythroderma with desquamation 1 to 2 weeks after the onset of illness. Additional early features include conjunctival, oropharyngeal, and vaginal hyperemia; vomiting and diarrhea; and myalgias. Most patients have abnormalities in three or more organ systems: (1) muscular: rhabdomyolysis, (2) central nervous system: toxic encephalopathy, (3) renal: azotemia, (4) liver: abnormal aminotransferase levels, and (5) hematologic: thrombocytopenia. The rash of TSS is almost always noted within the first 24 hours of illness. Desquamation occurs after 7 to 10 days, most prominently on the hands and feet. Histologically, the epidermis exhibits cleavage in the basilar layers, which differentiates TSS from SSSS and from viral and drug eruptions. *S. aureus* septicemia may be associated with erythematous, petechial, or pustular lesions. In addition, lesions associated with endocarditis, such as Osler nodes, Janeway lesions, and splinter hemorrhages, may occur. Such skin lesions have been reported in 10% to 64% of patients with staphylococcal septicemia. Purpuric lesions may in some cases be so extensive as to suggest meningococcemia or RMSF. Gram-stained smears of the material in these lesions usually demonstrate gram-positive cocci.

## Streptococcal Infections

The group A streptococci *(S. pyogenes)* cause a wide variety of local (e.g., impetigo, erysipelas, cellulitis, lymphangitis) and invasive syndromes (e.g., bacteremia, necrotizing soft tissue infections, streptococcal TSS) associated with cutaneous manifestations.[197,198] These manifestations of streptococcal infection occur via three distinct mechanisms[199]: (1) direct infection of the skin, (2) immunologically mediated disease, and (3) toxin-mediated disease. Rheumatic fever affects up to 3% of people with untreated group A hemolytic streptococcal infections of the nasopharynx. Cutaneous manifestations include erythema marginatum (occurring in 10%–20% of cases), subcutaneous nodules (in up to 30%), and erythema papulatum (rare).

Scarlet fever is a diffuse erythematous eruption that results from the production of pyrogenic exotoxin (erythrogenic toxin) produced by *S. pyogenes,* most commonly in the setting of pharyngitis. There appear to be three distinct exotoxins (types A, B, and C) produced by approximately 90% of group A strains. The rash of scarlet fever requires both the presence of pyrogenic exotoxin and the existence of delayed-type skin reactivity to streptococcal products. The latter requires prior exposure to organism. The pharynx is usually beefy red with edema involving the tonsillar area extending anteriorly to the soft palate and uvula. The rash of scarlet fever usually starts on the head and neck and then rapidly expands to cover the trunk and finally the extremities. The palms and soles are usually spared. The rash is a diffuse erythema, blanching on pressure, with numerous small (1–2 mm) papular elevations, giving a "sandpaper" quality to the skin. The rash is most marked in the skin folds of the inguinal, axillary, antecubital, and abdominal areas and about pressure points (e.g., buttocks). The rash often exhibits a linear petechial character in the antecubital fossae and axillary folds (Pastia lines). The rash of scarlet fever may be confused with rashes due to erythema infectiosum (fifth disease), rubella, rubeola, EBV, hepatitis B, HIV, enteroviruses, and *Streptobacillus moniliformis* (rat-bite fever). The cutaneous eruptions of TSS and secondary syphilis may also appear similar to that of scarlet fever, but vasomotor instability in the former and positive serology in the latter should suffice to differentiate them from scarlet fever. Noninfectious syndromes that should be considered include Kawasaki disease, acute systemic lupus erythematosus, and juvenile rheumatoid arthritis.

In the later part of the 1990s an increased incidence of severe group A streptococcal infections was reported.[197] Invasive group A streptococcal infections are life threatening, especially when associated with streptococcal TSS. Similar to staphylococcal TSS, this syndrome is due to the production of highly potent exoproteins that act as superantigens. The term *streptococcal toxic shock syndrome* is now used for those patients with hypotension and organ dysfunction as a result of toxin-mediated streptococcal disease (Table 57.4).[191,198,200] Many, but not all, patients have a rash at the time of presentation. Skin manifestations include generalized erythroderma with desquamation and localized cellulitis with vesiculation or bulla formation. The differential diagnosis of a desquamative rash includes Kawasaki disease, EM, toxic epidermal necrolysis, leptospirosis, and RMSF. Unlike staphylococcal TSS, a focus of pyogenic inflammation is usually present, and a large proportion of the patients have documented bacteremia. Commonly, the local focus of infection results in necrotizing fasciitis manifest by diffuse swelling and tenderness, a peau d'orange appearance, and erythema with subsequent formation of bullae. Later the skin color changes from red to purple or black as the skin becomes necrotic. However, initially the clinical symptom of the local site of infection often is only severe pain, with tenderness and other physical findings appearing later. Rarely, group B[201] and group G[202] streptococci have been reported to cause myositis with TSS.

## Rickettsial Infections

Rickettsiae comprise several important pathogens transmitted by ticks in the United States. Cutaneous manifestations often provide important and early clues in the diagnosis of tick-borne diseases.[203–206] Rickettsiae are obligate intracellular parasites whose primary target in humans appears to be the endothelial cell. After parasitization of the endothelial cell, necrosis of the media and intima results in thrombosis, formation of microinfarcts, and extravasation of blood. The end result is increased vascular permeability and vasculitis.

**TABLE 57.4 Staphylococcal Versus Streptococcal Toxic Shock Syndrome**

| FEATURE | STAPHYLOCOCCAL | STREPTOCOCCAL |
|---|---|---|
| Age | Primarily 15–35 yr | Primarily 20–50 yr |
| Gender | Higher frequency in women | Men and women equally affected |
| Severe pain | Rare | Common |
| Hypotension | 100% | 100% |
| Erythroderma rash | Very common | Less common |
| Renal failure | Common | Common |
| Bacteremia | Low frequency | 60% |
| Tissue necrosis | Rare | Common |
| Predisposing factors | Tampons, surgery | Cuts, burns, varicella |
| Thrombocytopenia | Common | Common |
| Mortality rare | <3% | 30%–70% |

*Data from Stevens DL. The toxic shock syndromes.* Infect Dis Clin North Am. *1996;10:727–746.*

Rash is a hallmark of RMSF,[207,208] the most common serious rickettsial disease in the United States. Initially, a maculopapular rash develops. Subsequently, the rash becomes more petechial. Characteristically, the rash appears between the second and sixth days of illness (average, 4 days). However, the rash may be absent in 5% to 17% of patients, and in up to 50% it may not appear within the first 3 days of illness.[209–211] Failure to initiate proper therapy within 5 days of onset of symptoms[212] and failure to use a tetracycline[213] have been associated with an increased mortality rate. Independent predictors of failure by the physician to initiate therapy the first time a patient was seen include absence of a rash, presentation between August 1 and April 30, and presentation within 3 days of illness.[213] Most commonly, the rash begins on the extremities, often around the wrists and ankles, and spreads centripetally to the trunk, with relative sparing of the face. However, the rash may begin on the trunk (10%) and spread centrifugally or may have a diffuse distribution at the time of onset (10%). Characteristically, the rash involves the palms or soles or both in the later stages of infection (Fig. 57.8). Over time the rash, which begins as maculopapular lesions, may progress to become petechial or ecchymotic. Rarely, gangrene or skin necrosis that requires amputation occurs.[214] The rash may rarely be urticarial or pruritic. Because the mortality rate for infection may be decreased from 15% to 3% with appropriate treatment, institution of antibiotic therapy should never be delayed in the absence of rash. Signs and symptoms similar to those of RMSF may occur with ehrlichiosis and anaplasmosis (see later discussion). The rash of rickettsialpox typically begins as maculopapular and in its early phase may be confused with that of RMSF, but it quickly becomes papulovesicular, which is not characteristic of the RMSF eruption. The rash of RMSF may also be confused with measles, mononucleosis, viral hepatitis, streptococcal infection, primary HIV infection, secondary syphilis, parvovirus infection (fifth disease), Kawasaki disease, and roseola. If a penicillin or cephalosporin is administered before the appearance of the rash, the subsequent rash may be incorrectly diagnosed as a drug eruption rather than the rash of RMSF.

## *Ehrlichia* and *Anaplasma* Species

Important tick-borne diseases that occur in the United States include RMSF, Lyme disease, tick-borne viral encephalitis, babesiosis, and tularemia (see Chapter 296). Recently, *Ehrlichia* spp. and *Anaplasma* spp. have emerged as important and potentially life-threatening pathogens.[215–220]

In the United States ehrlichiosis caused by *Ehrlichia chaffeensis* (human monocytotropic ehrlichiosis) is most common in the southern and mid-Atlantic, and north- and south-central states and in isolated areas of New England. Common early signs and symptoms of infection include fever, headache, malaise, and myalgia. Rash occurs in approximately 60% of children but in less than 30% of adults. The rash pattern varies from petechial to maculopapular to diffuse erythema and typically occurs late in the course of the disease (median, 5 days after onset). The rash pattern might involve the extremities, trunk, face, or rarely, the palms and soles. A newly recognized human pathogen, *Ehrlichia ewingii*, also may cause rash, but it is uncommon.

Anaplasmosis is caused by *Anaplasma phagocytophilum* (human granulocytotropic anaplasmosis). In the United States it is most common in New England and the north-central and Pacific coastal states. Common signs and symptoms include fever, headache, malaise, myalgia, and vomiting. Rash is reported in less than 10% of cases. The clinical and epidemiologic features of anaplasmosis and ehrlichiosis overlap with those of RMSF. Rash is less common with ehrlichiosis and anaplasmosis than with RMSF, but it is important to remember that at presentation less than 50% of patients with RMSF will have a rash, and 15% will never demonstrate a rash (i.e., so-called Rocky Mountain spotless fever). As with RMSF, the rash of these other tick-borne diseases may resemble that of mononucleosis, thrombotic thrombocytopenic purpura, hepatitis A, and drug eruptions.

**FIG. 57.8 Rocky Mountain spotted fever.** An example of late stage rash in an RMSF patient. *(From Lin L, Decker CF. Rocky Mountain spotted fever.* Dis Mon. *2012;58:361–369.)*

## *Borrelia burgdorferi* Infection

Lyme disease is a tick-borne borreliosis with broad distribution and myriad manifestations.[221–224] In early localized or disseminated Lyme disease, fever is present in approximately 15% of patients, although it is usually low grade. Skin lesions are prominent clinical manifestations of all stages of Lyme disease.[225–228] Clinically, the disease is divided into three stages of illness: early localized disease, early disseminated disease, and persisting late disease. The most common manifestation of early localized Lyme disease is EM, which usually appears at the site of the tick bite within 7 to 10 days (range, 3–30 days). Seventy percent to 80% of infected patients will demonstrate EM.[203] Most patients (75%–80%) who exhibit EM in the United States have only a single (primary) lesion. EM initially begins as a red macule or papule that is usually homogeneous in its redness and may remain so until it heals. More commonly, the lesion partly or totally clears centrally, leaving an annular erythema that spreads centrifugally. The EM skin lesions are typically 5 cm or more in their largest diameter. EM may develop anywhere but is most frequently located around the knees, in the axillae, and in the groin. Although the lesion may last from a few days to about 1 year, it usually disappears within a few weeks to months. In about half of the patients, itching, dysesthesia/hyperesthesia, or sensations of heat may develop at the site of erythema. Many patients who develop early disseminated disease exhibit EM-like lesions. The disseminated lesions are usually smaller than the primary lesion and often multiple. These lesions may be ring shaped but are often homogeneous and nonmigrating.

## Syphilis

Physicians should be familiar with the cutaneous manifestations of syphilis because primary and secondary syphilis and congenital syphilis continue to occur in the United States, especially in the southern states. The primary skin lesion (chancre) typically develops about 21 days after exposure. The differential diagnosis of patients with a genital ulcer in addition to syphilis includes genital herpes and chancroid. Secondary syphilis (Fig. 57.9) is often accompanied by a rash with highly variable morphology. Lesions may be macular, papular, maculopapular, papulosquamous, or pustular. On occasion, all types of lesions may be present in the same patient. A characteristic presentation of secondary syphilis is that of a pityriasis rosea–like eruption appearing as numerous, tan to reddish brown, scaly macules, usually distributed along skin tension lines on the trunk and, to a lesser extent, other body sites. Typically, no herald patch (a hallmark feature of pityriasis rosea) is present when this eruption is caused by syphilis, and usually the patient with secondary syphilis lacks associated pruritus and may have concurrent "copper penny" macules or plaques on the palms or soles. The differential diagnosis for secondary syphilis skin manifestations includes RMSF, pityriasis rosea, psoriasis, lichen planus, and exanthematous drug/viral eruptions. Condylomata lata, which are grayish, raised, broad, flat-appearing papular lesions, may occur in skin folds or apposed skin in

**FIG. 57.9 Secondary syphilis.** Rash of secondary syphilis on patient's sole. *(From Miller AC, Rashid RM, Khachemoune A. Secondary syphilis.* J Emerg Med. *2008;35:83–85.)*

moist areas, such as the anus, vulva, and scrotum. Condylomata lata need to be distinguished from condylomata acuminata (genital warts), squamous cell carcinoma, molluscum contagiosum, and micropapillomatosis of the vulva.

### Candidiasis

The incidence and relative frequency of health care–associated infections due to *Candida* has risen dramatically in the recent past, and this increase has been accompanied by a shift in the infecting pathogen away from *Candida albicans* to non–*C. albicans* spp.[229–231] The most recent data from the CDC (2011–14) reported that non-*glabrata,* non-*albicans Candida* spp. accounted for 4.9%, *C. glabrata* for 3.4%, and *C. albicans* for 6% of central line–associated bloodstream infections.[232] Predisposing factors for disseminated or invasive infection are mucosal colonization with *Candida;* malignancy with cytotoxic therapy; neutropenia; antimicrobial therapy, especially with broad-spectrum agents; parenteral hyperalimentation; severe burn injuries; very low birth weight; use of IV catheters; systemic administration of adrenocortical corticosteroids; acute renal failure; prolonged care in an intensive care unit; and complicated intraabdominal surgery.[229–231]

An older study reported that 13% of patients with disseminated candidiasis have skin lesions,[233] whereas a more recent study reported 35.8%.[234] Typical skin lesions are 5 to 10 mm, erythematous or purpuric, nontender, firm, deep dermal papules that characteristically do not develop a central eschar or necrosis.[234,235] The lesions may have the appearance of papules, nodules, or plaques. In about half of the cases, they show characteristic central pale vesicular or pustular centers. Uncommonly, they may have necrotic centers. Usually the lesions are diffuse, involving the trunk and proximal extremities, but they may be localized to a small area. The face is usually spared. The diagnosis of systemic candidiasis may be confirmed by punch biopsy for touch preparation, histology, and culture in approximately 70% of patients.[234,236] Congenital candidiasis is a rare disease with fewer than 100 cases reported that result from acquisition of infection in utero.[237] It is characterized by a diffuse erythematous skin eruption with or without vesicles and pustules. Systemic infection, including pneumonia, may occur with or without skin lesions.

Many other fungi produce nodular lesions identical to those caused by *Candida* and must be considered as possible pathogens in immunocompromised patients. In patients with acquired immunodeficiency syndrome (AIDS), cryptococci may cause umbilicated nodules that mimic the lesions of molluscum contagiosum.

### Measles

Measles remains endemic in multiple regions of the world. However, in recent years we have seen increases in the numbers of cases in countries where there have been decreases in the frequency of measles vaccination.[238] Thus physicians need to become reacquainted with the skin manifestations of the disease. Measles is characterized by a prodrome of fever (as high as 105°F) and malaise; cough, coryza, and conjunctivitis (the three "C"s); and a pathognomonic enanthem (Koplik spots, tiny white spots that appear inside the mouth), followed by a maculopapular rash. The classic morbilliform rash associated with measles typically occurs at the end of the prodromal phase of disease (see Fig. 57.1). The rash typically develops on the face and then proceeds to spread down the body to involve extremities, including the palms and soles. The rash usually lasts 5 days and will become confluent, especially on the face. During the healing phase, the rash may desquamate and typically clears first from the regions initially involved. Typically, measles patients are most ill during the first 1 to 2 days of the rash.

Measles also presents in an atypical form, usually associated with inactivated measles vaccination.[239,240] The atypical measles syndrome is characterized by pneumonia, often with lobular infiltrates, hilar lymphadenopathy, and pleural effusion. The pulmonary syndrome is associated with a maculopapular rash that progresses to vesicular petechial or purpuric lesions. Despite appearing ill, spontaneous recovery is expected with atypical measles syndrome.

## NEW AND EMERGING INFECTIOUS DISEASES

The Institute of Medicine defines *new and emerging diseases* as "new, reemerging or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future."[241] Many would also include infections whose geographic range is increasing. The factors leading to the development of new and emerging diseases have been reviewed in the literature.[241–244] Approximately 75% of emerging or reemerging diseases are known to be zoonotic.[245] It is important for infectious disease clinicians to realize that international travel has dramatically increased; in accordance, patients may present with diseases only rarely seen in the United States. Many of these diseases may be associated with either local or generalized skin lesions, including dengue fever, yellow fever, viral hemorrhagic fevers, Zika virus, malaria, and leptospirosis.

### Dengue, Chikungunya, and Zika Viruses

The etiologic agents of dengue fever are four serologically related RNA viruses belonging to the family Flaviviridae.[246–248] Dengue is widely distributed with endemic transmission in Africa, Asia, and South and Central America. Most cases in the continental United States have involved travelers, but transmission has been reported in Hawaii and Texas. Classic dengue fever begins after an incubation period of 3 to 15 days (average, 5–8 days) with an abrupt onset of fever that may be accompanied by chills, headache, and general malaise. The fever usually lasts 3 to 7 days and may be biphasic. Dermatologic findings do not occur in all patients with classical dengue. When they occur, erythema may appear shortly before the onset of fever, concurrently with fever onset or 24 to 48 hours later. This rash may be noted as a flushing or erythematous mottling beginning on the trunk and spreading centrifugally to the face, neck, and extremities. Flushing may disappear after 1 or 2 days or may blend into an erythematous macular or maculopapular rash that develops at any time during the course of illness. Pruritus and desquamation, especially on the palms and soles, may follow termination of the eruption. Dengue hemorrhagic fever/dengue shock syndrome, a more severe disease, has more pronounced dermatologic findings, including petechiae, purpura, ecchymoses, epistaxis, and gum bleeding.

Chikungunya virus is an arbovirus (genus *Alphavirus*, family Togaviridae) that is prevalent in Africa and Asia, especially in India and islands in the Indian Ocean and has recently spread to the Caribbean and South America.[249] Disease has been reported in the United States in travelers returning from endemic areas, with local transmission in Puerto Rico and Florida.[250] After an incubation period of 2 to 4 days, patients have an abrupt onset of high fever, headache, back pain, myalgia, and arthralgia that may be intense. Skin involvement is present in 20% to 50% of cases and consists of a pruriginous maculopapular rash mostly located on the face, trunk, and extremities. The rash is transient. Facial edema and pruritus may accompany the rash. In children a bullous rash with pronounced sloughing may occur.

Hemorrhagic fever has been reported in Chikungunya-infected patients from Thailand.

The rash from Zika virus is morphologically very similar to that of dengue virus, with the majority of Zika virus infections presenting with a morbilliform rash with islands of sparing.[251–253] The rash can be pruritic[254–255], descending,[256] and/or blanching.[257–258] The rash typically occurs after the initial 3 to 4 days of symptoms, with reports of the rash occurring as early as the first day of illness or even preceding other symptoms.[259–261] The rash typically lasts for an average of 6 days (range, 2–14 days) and can spread to any part of the body, including the torso, extremities, palms, soles, and face.[259,262] Fever tends to be less prominent than with dengue virus infection, often occurring in less than 50% of individuals.[256]

## Viral Hemorrhagic Fever

Hemorrhagic fever may be caused by viruses belonging to several families, including the Arenaviridae (e.g., New World arenaviruses, such as Argentine hemorrhagic fever, Bolivian hemorrhagic fever, Venezuelan hemorrhagic fever; Lassa fever), Bunyaviridae (hantaviruses, Crimean-Congo fever, Rift Valley fever), Filoviridae (Ebola, Marburg), and Flaviviridae (yellow fever, dengue hemorrhagic fever, Omsk hemorrhagic fever).[263–265]

Hantaviruses are RNA viruses that belong to the family Bunyaviridae and include Hantaan, Seoul, Puumala, Dobrava, Sin Nombre, Bayou, Black Creek Canal, and New York viruses.[266–268] Hemorrhagic fever with renal syndrome (HFRS) may be caused by seven hantaviruses (e.g., Hantaan, Seoul, Dobrava, Saaremaa, Amur, Puumala, and Far East).[267] Severe forms of HFRS have characteristic phases that may not be seen with milder disease. After an incubation period of 2 to 3 weeks, patients present with abrupt onset of fever in association with malaise, headache, myalgias, back pain, abdominal pain, nausea, and vomiting. Conjunctival injection or hemorrhage with palatal and upper torso petechiae is commonly seen on physical examination. During this phase, a characteristic erythematous flush that blanches with pressure may be observed, usually affecting the face, neck, and upper torso. After the 3- to 7-day febrile phase, a period of hypotension and severe shock ensues that is characterized by hemorrhagic manifestations. Overall, about 20% of the patients manifest severe disease, with death from shock and renal failure in 5% to 10% of cases. The hantavirus pulmonary syndrome may be caused by multiple hantaviruses, including Sin Nombre virus.[267] Some forms of hantavirus pulmonary syndrome (e.g., Andes) can present as conjunctivitis, facial flushing, and variable numbers of fine petechiae on the trunk, axillary folds, soft palate, or neck.

Filoviruses include the agents that cause Marburg and Ebola hemorrhagic fever.[269–272] Ebola virus is more virulent than Marburg virus and causes more severe clinical disease, with an accelerated course and high morbidity and mortality rates. Patients present with an acute onset of fever, severe frontal headache, anorexia, malaise, and myalgias. These signs and symptoms are followed 2 to 3 days later by clinical deterioration heralded by pharyngitis, conjunctivitis, severe nausea and vomiting, abdominal pain, and watery diarrhea. Five days later, patients develop a maculopapular rash on the trunk and back that is followed by the appearance of petechiae, ecchymoses, subconjunctival hemorrhages, epistaxis, hemoptysis, hematemesis, and melena. Hemorrhagic shock may progress to death. Patients with Marburg virus infection may develop a scarlatiniform rash rather than a maculopapular rash. Considerations in the differential diagnosis of African hemorrhagic fevers also include yellow fever and Lassa fever, but these illnesses are not accompanied by a rash.

## Bacterial Diseases Due to *Bartonella* Species

*Bartonella* are small, fastidious, intracellular gram-negative bacteria.[273–275] The genus now includes more than 20 distinct species, several of which are capable of causing human disease. Most of our current knowledge on *Bartonella* infections is restricted to *B. henselae, B. quintana,* and *B. tribocorum*. *Bartonella* spp. that cause human disease are generally associated with well-defined reservoirs, usually domestic and wild animals.

Infection with *B. henselae* results in disease syndromes of variable severity, ranging from lymphadenopathy to systemic disease. Cat-scratch disease occurs primarily in children and young adults and is generally a benign self-limited disease. Cat-scratch disease typically begins with a cutaneous lesion at the site of inoculation.[276–278] The lesion that develops 3 to 10 days after introduction of the organism evolves through erythematous, vesicular, and papular crusted stages. Less commonly, it can be pustular or nodular. Approximately 2 weeks after inoculation, regional adenopathy develops proximal to the skin lesion. The nodes are usually tender, often have overlying erythema, and may suppurate. Low-grade fever and malaise occur in about 30% of children. Uncommon cutaneous manifestations include a transient maculopapular rash, EM, erythema nodosum, and purpura. The differential diagnosis includes other diseases associated with regional lymphadenopathy and cutaneous inoculation lesions (e.g., nontuberculous mycobacteria, *Nocardia, Y. pestis, Bacillus anthracis, Francisella tularensis, Erysipelothrix rhusiopathiae*), pyogenic infections due to streptococci and staphylococci, viral-associated lymphadenopathy (e.g., CMV, HIV, EBV), and lymphoma.

*B. henselae* and *B. quintana* are capable of causing a variety of diseases in immunocompromised patients, principally patients with late-stage HIV-1 infection, including bacillary angiomatosis, bacillary peliosis, splenitis, osteomyelitis, and bacteremia. On occasion, bacillary angiomatosis has been reported in immunocompetent individuals.[279] Skin lesions are the most frequent clinical manifestation of bacillary angiomatosis, with a prevalence of 55% to 90%. The typical lesion is solitary or disperses all over the body. The reddish purple papules may be difficult to distinguish clinically from Kaposi sarcoma and pyogenic granuloma. The lesions of bacillary angiomatosis may appear as smooth, warty, and pedunculated papules; subcutaneous nodules; and hyperkeratotic plaques. They rarely ulcerate or bleed.

## Orthopoxviruses

The genus *Orthopoxvirus* contains multiple species that infect humans, including variola, monkeypox, vaccinia (includes buffalopox), and cowpox.[280] Variola and monkeypox are often life-threatening diseases, whereas vaccinia and cowpox generally are associated with local lesions. The eradication of smallpox represents one of the greatest public health achievements of the 20th century. After the successful eradication of smallpox, the routine use of vaccinia vaccine was discontinued. However, the threat of bioterrorism raises the prospect for an intentional use of smallpox.[281–283] Given the threat of bioterrorism, all health care personnel should be familiar with the skin manifestations of the category A bioterrorist agents (i.e., anthrax, plague, tularemia, Ebola, Marburg, Lassa, Machupo).[284] Multiple outbreaks of monkeypox in humans have been reported,[285,286] including a 2003 outbreak in the United States traced back to a consignment of rodents (giant Gambian rats) from Ghana. Thus the clinician is now confronted with having to distinguish the skin lesions of several possible poxvirus infections, including smallpox, complications of vaccinia (i.e., generalized or progressive vaccinia, eczema vaccinatum), and monkeypox. These lesions must be distinguished from varicella, disseminated herpes simplex, and other disorders characterized by a similar eruption, including meningococcal septicemia, coagulation disorders, and typhus.

After a 12- to 14-day incubation period (range, 7–17 days), the patient with smallpox typically develops high fever, malaise, and prostration with headache and backache. A maculopapular rash then appears on the mucosa of the mouth and pharynx, face, and forearms and spreads to the trunk and legs. Within 1 to 2 days, the rash becomes vesicular and later pustular. The pustules are characteristically round, firm, and deeply embedded in the skin. Crusts begin to form after 7 to 9 days; the eschars later separate, leaving pits and scars. Bacterial superinfection of skin lesions may complicate smallpox. The rash of variola differs from that of varicella in several ways. First, the lesions of variola appear during a 1- to 2-day period and evolve at the same time, whereas the lesions of varicella demonstrate different stages of maturation and generally appear in crops every few days. Second, the lesions of variola tend to involve the extremities and face, whereas the lesions of varicella have a centripetal predilection with a greater concentration of lesions on the trunk than on the face and extremities.

Also, varicella lesions are almost never found on the palms and soles. Finally, the lesions of variola are much more deeply embedded than the rash of varicella, where the lesions are more superficial. The rash of smallpox may be confused with SJS, measles, and coxsackievirus infections.

Vaccinia vaccine is still being provided to members of the US military. Recognition and management of the complications of vaccinia vaccination have been summarized.[287,288] Vaccinia vaccination leads to the local lesion at the site of immunization. Local complications include satellite lesions, lymphangitis, secondary bacterial infections, lesions from inadvertent remote inoculation, and progressive vaccinia at the site of the vaccination most commonly in immunosuppressed persons. Disseminated lesions include generalized vaccinia and eczema vaccinatum. Generalized vaccinia refers to a relatively benign generalized eruption in which each lesion is identical to its primary smallpox vaccination. The incidence has been reported to range from 23 to 242 per 1 million first-time vaccinees. Severe cases can be treated with variola immune globulin, cidofovir, or both. After vaccinia vaccination, patients also may develop a generalized EM-like rash. This is a benign condition and does not require therapy.

Eczema vaccinatum occurs in persons with a history of eczema or atopic dermatitis regardless of disease activity or severity. It has also been reported in persons without a history of dermatologic conditions. Eczema vaccinatum is characterized by high fever and generalized lymphadenopathy with an extensive vesicular and pustular eruption. The syndrome begins concurrently or shortly after the onset of local vaccinial lesions in the vaccinee. It may also occur in contacts 5 to 19 days after exposure. There is a significant risk for secondary bacterial or fungal infections. This adverse reaction is associated with a poor prognosis and high mortality. Therapy consists of multiple doses of variola immune globulin, hemodynamic support, and treatment of secondary infections. Cidofovir might be useful for therapy, but there are no published clinical data on its efficacy. Historically, the rate of eczema vaccinatum per 1 million vaccinees was reported as 10.4 to 41.5.

Monkeypox is enzootic in squirrels and monkeys in the rain forests of western and central Africa. The disease appears to be endemic in these regions of Africa, but multiple outbreaks have been described. Clinical signs of monkeypox include respiratory distress, lymphadenopathy, and a centrifugally distributed vesiculopustular rash (Fig. 57.10). The case-fatality rate has been reported to be approximately 10% in persons not vaccinated against smallpox.

## Skin Lesions in Immunocompromised Patients

The diagnosis of skin lesions in the immunocompromised patient is complex because of the wide range of potential microbial pathogens that may cause disease in patients with abnormal immune responses (Table 57.5).[289–297] In addition, in immunocompromised persons, common infections may have unusual manifestations, and such patients often have an insufficient response to conventional therapy. Johnson[289] recommends the following approach to cutaneous lesions suspected to be infectious. First, the most rapid and sensitive methods for detecting

**FIG. 57.10 Monkeypox.** Patient with pox during a monkeypox outbreak in the Democratic Republic of the Congo. *(From Jahrling PB. Smallpox and related orthopoxviral infections. In: Guerrant RL, Walker DH, Weller PF, eds.* Tropical Infectious Diseases: Principles, Pathogens and Practice. *3rd ed. Philadelphia: Saunders Elsevier; 2011:369–377.)*

**TABLE 57.5 Types of Skin Infections in Immunocompromised Hosts by Pathophysiologic Events**

| TYPE OF INFECTION | PATHOGEN | SITE OF INFECTION | HEALTHY HOST | COMPROMISED HOST |
|---|---|---|---|---|
| Primary skin infections (common pathogens) | Group A *Streptococcus* | Epidermis, hair follicles | Impetigo, ecthyma, folliculitis | Soft tissue infection, necrotizing |
| Cellulitis, abscess | *Staphylococcus aureus* | Dermis | Abscesses, intertrigo | Soft tissue infection |
| Unusually widespread cutaneous infection | Dermatophytes, *Candida* spp.<br>*Candida* spp.<br><br>HSV<br><br>VZV<br>EBV<br>MCV<br>HPV | Epidermis, intertriginous sites, hair follicles<br>Oropharynx, esophagus, genitalia | Dermatophytosis; epidermal (limited), folliculitis<br>Candidiasis; intertrigo, genital<br>Localized herpes, resolves spontaneously<br>Herpes zoster (mild)<br><br>MCV (localized, nonfacial)<br>Common and mucosal warts | Dermatophytosis; epidermal (extensive), folliculitis<br>Candidiasis; intertrigo, folliculitis, mucosal<br>Chronic herpetic ulcers<br><br>Herpes zoster (extensive)<br>Hairy leukoplakia<br>Widespread MCV, resistant to therapy<br>Widespread warts; squamous cell carcinoma in situ |
| Opportunistic primary cutaneous infection | NTM<br>*Nocardia*<br>Molds<br>*Prototheca* | Dermis, hypodermis | Swimming pool granuloma | Soft tissue infection ± necrosis<br>Septicemia |
| Systemic infection metastatic to cutaneous and subcutaneous sites | Bacteria, fungal pneumonitis with fungemia | Dermis, hypodermis | Soft tissue infection ± necrotic nodules | Soft tissue infection ± necrotic nodules |

*EBV,* Epstein-Barr virus; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *MCV,* molluscum contagiosum virus; *NTM,* nontuberculous mycobacteria; *VZV,* varicella-zoster virus.

*Data from Johnson RA. The immune compromised host in the twenty-first century: management of mucocutaneous infections.* Semin Cutaneous Med Surg. *2000;19:19–61.*

microbes both histologically and immunologically should be used. Second, appropriate cultures and stains should be obtained to optimize the chance for identifying the pathogen. A 6- or 8-mm punch biopsy is usually adequate. Half of the tissue is sent for histopathologic evaluation by routine methods and by special stains for fungi, mycobacteria, and bacteria. The other half is sent to the microbiology laboratory for culture of aerobic and anaerobic bacteria, mycobacteria, and fungi (at 25° and 37°C) and for Gram stain, acid-fast, modified acid-fast, and direct fungal stains of touch preparations or ground tissue. Recommendations for processing specimens have been published.[292]

Solid-organ transplant recipients are at high risk for disease due to opportunistic bacterial, viral, and fungal pathogens. The risk for infection and the most likely infecting pathogen depend on the type of transplant; type and dose of immunosuppressive medications; time since transplantation; presence of coexisting diseases, including viral infections; and epidemiologic exposures.

Cutaneous infections in immunocompromised persons may be categorized into four groups based on pathophysiology: (1) infection originating in skin that is typical of those occurring in immunocompetent persons, albeit with the potential for more serious illness; (2) extensive cutaneous involvement with pathogens that normally produce trivial or well-localized disease in immunocompetent patients; (3) infection originating from a cutaneous source that is caused by opportunistic pathogens that rarely cause disease in immunocompetent patients but may cause either localized or widespread disease in immunocompromised patients; and (4) cutaneous or subcutaneous infection that represents metastatic spread from a noncutaneous site. Only life-threatening infections with cutaneous manifestations are discussed further here. In general, most cases of skin infection result from secondary dissemination after initial infection of the lungs or other organ systems. Primary cutaneous infection resulting from direct inoculation is less common. In transplant patients infections with viruses and fungi are probably more common than skin infections caused by bacteria.

Immunocompromised patients are at increased risk for the development of cellulitis due to *S. pyogenes* and *S. aureus*. Neutropenic patients are also susceptible to more unusual pathogens, such as members of the family Enterobacteriaceae and *Pseudomonas* spp. Patients with leukemia or impaired cell-mediated immunity may develop erysipelas-like lesions due to *Candida* spp. or *Cryptococcus neoformans*. Both local and diffuse skin infections with herpesviruses, especially HSV and VZV, are very common. Cutaneous CMV infection has a highly variable appearance that may include nodules, ulcers, indurated plaques, maculopapular eruptions, vesicles, and petechiae.

In immunocompromised patients cutaneous lesions resulting from hematogenous spread of infection are caused by three classes of organisms: (1) *P. aeruginosa* and other bacteria; (2) the endemic systemic mycoses caused by *Histoplasma capsulatum, Coccidioides* spp., and, rarely, *Blastomyces dermatitidis;* and (3) the opportunistic organisms *Aspergillus, C. neoformans, Candida, Rhizopus,* and *Nocardia. P. aeruginosa* may cause either cellulitis or ecthyma gangrenosum, which may develop in the absence of bacteremia. Patients with malignancy may develop sepsis associated with a variety of uncommon bacteria that are also associated with skin lesions (e.g., *A. hydrophila, C. canimorsus, Clostridium septicum,* mycobacteria, and *Salmonella enterica* serovar Typhimurium). Most commonly, *H. capsulatum* causes cellulitis, but it may also cause papules, nodules, pustules, and hemorrhagic lesions. Metastatic spread to the skin from noncutaneous sites of infection most commonly occurs with *Aspergillus* spp., *C. neoformans, Candida* spp., *Rhizopus* spp., and *Nocardia.* With the exception of *Candida,* the initial portal of entry is the respiratory tract. However, the respiratory tract infection may be asymptomatic, with the initial signs of illness seen in the skin. In neutropenic patients cutaneous lesions due to *Aspergillus* spp. are often found in association with the sino-orbital form of disease. Neutropenic patients may also develop disseminated infection with other fungi, such as *Fusarium* spp. and *Trichosporon beigelii.*

HIV infection commonly results in dermatologic disorders in both adults and children.[298–302] Clinically, the skin lesions associated with HIV infection may be classified by morphologic appearance, stage of HIV infection, pathophysiology (infectious, neoplastic, vascular, miscellaneous), and, for infectious diseases, etiologic agent. Skin eruptions are observed in greater than 50% of patients with primary HIV infection, generally developing on day 1 to 5 of the acute illness. The rash characteristically consists of 10 to hundreds of 5- to 10-mm, oval or round, pink to deep-red macules or slightly raised papules. Other skin manifestations have included diffuse urticaria, vesicular and pustular exanthema, desquamation of palms and soles, and alopecia. Like other immunocompromised patients, individuals with AIDS develop infections with opportunistic pathogens that rarely, if ever, cause infection in immunocompetent people. These include unusually severe or persistent herpes viral infections (HSV, VZV, CMV), staphylococcal infections including CA-MRSA, nontuberculous mycobacterial infections, disseminated candidiasis, infections with endemic fungi, ectoparasites, and soil-dwelling fungi.

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*The complete reference list is available online at Expert Consult.*

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# B Upper Respiratory Tract Infections

# 58 The Common Cold

*Yehuda Z. Cohen*


## SHORT VIEW SUMMARY

**Definition**
- The common cold is a clinical syndrome of mild to moderate severity that includes sore throat, sneezing, rhinorrhea, nasal congestion, and cough.
- A precise definition of the common cold is difficult because numerous viruses serve as etiologic agents, and there can be significant variability in symptoms and severity of illness.

**Microbiology**
- Rhinoviruses are responsible for approximately half of common colds.
- Coronavirus, adenovirus, respiratory syncytial virus, parainfluenza virus, influenza, and metapneumovirus also cause the common cold.

**Epidemiology and Transmission**
- Common colds occur four to six times per year in children and one to three times per year in adults.
- There is a seasonality to the viruses that cause the common cold. In temperate climates, rhinovirus infections peak in the spring and fall.
- The nasal and conjunctival mucosa are reliable portals of entry for rhinoviruses, in contrast to the mouth and throat.

**Diagnosis**
- The diagnosis of the common cold is a clinical diagnosis.

**Therapy**
- Directed symptomatic therapy is the mainstay of treatment.
- Vitamin C and *Echinacea* have not been shown to be effective for treatment of the common cold. Zinc lozenges may reduce the duration of the common cold.

**Prevention**
- No currently available interventions, including hand hygiene, have been shown to consistently prevent the common cold.


The common cold is a clinical syndrome of mild-to-moderate severity that includes sore throat, sneezing, rhinorrhea, nasal congestion, and cough. The common cold is universally experienced and easy to self-diagnose, although there may be significant variability in the prominence of symptoms and severity. Infection with any of numerous viruses causes the illness, and the frequency of each virus can vary over time and geographic site. Although there has been great progress in understanding the etiology of the common cold, efforts to prevent and treat the common cold have had little success.

## ETIOLOGY

The common cold has been ubiquitous since at least ancient times, and references to common cold syndromes appear in early Chinese and Egyptian medical texts. The use of the term *common cold* first appeared in the 1530s, and derives from the similarity of these symptoms to symptoms that occur on exposure to cold weather.[1] The notion that the common cold was related to a chilling of the body persisted into the 20th century. In the early 20th century, evidence began to accumulate that a nonbacterial "filterable agent" was the likely agent of the common cold. Experiments in which bacteria-free filtrates of nasal secretions transferred cold symptoms from one person to another demonstrated that these filterable agents, later known as viruses, caused the common cold.[2]

Epidemiologic studies conducted in New York and Seattle in the 1960s began to provide some information about which viruses were responsible for the common cold, but the laboratory techniques needed to reliably identify these viruses were still being developed.[3] A large epidemiologic study performed in Tecumseh, Michigan, was the first large prospective study to make extensive use of serology to diagnose respiratory infections. Approximately 1000 people were followed longitudinally over several years in the 1960s and 1970s. The study found that the most frequent cause of respiratory illness was rhinovirus.[4] Coronavirus, influenza, parainfluenza virus, respiratory syncytial virus (RSV), and adenovirus were also associated with upper respiratory infections.

With the emergence of polymerase chain reaction (PCR) and other molecular techniques, additional respiratory pathogens such as human bocavirus and human metapneumovirus have been discovered. Human bocavirus was first reported in children with wheezing and pneumonia.[5,6] The role of human bocavirus as a cause of the common cold remains uncertain. Although it is often detected by PCR, particularly in young children, concurrent respiratory illness is often not present (see Chapter 147).[7,8] Human metapneumovirus infects most children by 5 years of age and accounts for a small but significant proportion of respiratory infections in children and adults (see Chapter 159).[9–11]

Longitudinal, community-based studies using PCR have confirmed rhinovirus as the cause of approximately half of respiratory illnesses. The next leading cause is often influenza, adenovirus, or coronavirus.[8,12–16] There are more than 156 rhinovirus antigen types, with 15 to 30 types typically circulating simultaneously at a given site, although up to 74 rhinovirus types have been found to cocirculate.[17–19] There does not appear to be a correlation between particular rhinovirus antigen types and severity of illness.[18] Influenza is frequently found to be a significant cause of respiratory illness in epidemiologic studies, but it is not generally associated with the common cold. Nonetheless, symptoms of influenza can range from mild to severe and may manifest similarly to symptoms of the common cold.[20]

In early epidemiologic studies that relied solely on cell culture or serology, an infectious agent could not be detected in the vast majority of cases.[3] With the use of PCR, however, multiple respiratory viruses are often found in individuals with respiratory infections.[21–23] When PCR was performed on 225 children in childcare centers during episodes of respiratory illnesses, more than one virus was detected in most children.[13] PCR has also been shown to detect high rates of infection

with respiratory viruses among asymptomatic individuals.[8,24,25] The detection of multiple pathogens appears to be at least partially related to prolonged shedding of some respiratory viruses. The significance of the detection of multiple viruses in the etiology of respiratory illnesses and the common cold remains uncertain.

## EPIDEMIOLOGY

The Cleveland Family Study, conducted in the 1940s and 1950s, was the first study to reliably demonstrate that the incidence of respiratory infections is highest in children younger than 4 years of age. The study also found that there was an increased risk of illness when another family member was sick and that children were most often responsible for introducing the infection to the family.[26] In the Tecumseh, Michigan, study, children 4 years of age and younger experienced an average of four to six respiratory illnesses per year, and adults experienced an average of one to three respiratory illnesses per year. Common cold incidence was also found to decline with age, with persons older than 60 years of age having the lowest incidence.[27] Daycare attendance significantly increases the frequency of respiratory illnesses in children, although this difference diminishes the longer the child remains in daycare.[28–30]

There is a seasonality to the viruses that cause the common cold, the reasons for which are not completely understood. In temperate climates, rhinovirus infections peak in the fall but occur year-round. Influenza and RSV infections occur mainly in winter and early spring, and parainfluenza peaks in the spring and fall.[31,32] In tropical climates, influenza and RSV infections peak in the rainy season.[33] Hypotheses for the seasonality of these and other viral infections have included seasonal changes in effective contact rates (e.g., the start of the school year) and seasonal changes in the durability of the pathogen in the environment.[34]

It has been estimated that 500 million noninfluenza viral respiratory infections occur each year in the United States. Although the common cold is typically a mild-to-moderate illness, its economic impact is enormous. The total economic impact of the common cold approaches $40 billion annually, with most of these costs due to days missed from work. Based on these estimates, the economic burden of the common cold is greater than conditions such as hypertension, chronic obstructive pulmonary disease, and heart failure.[35]

### Transmission

Early studies demonstrated that very low doses of rhinovirus deposited in the nose reliably produced a cold.[36] The conjunctival mucosa also serves as a good portal of entry, in contrast to the mouth or throat.[37] Following inoculation, virus is typically first recovered in the nasopharynx and subsequently spreads anteriorly. Virus can be recovered from the nasal mucosa for up to 3 weeks.[38] Close contact is needed for efficient transmission of rhinovirus. Transmission is infrequent between childless couples, unless the infected individual sheds large amounts of virus and spends many hours with his or her partner.[17] Additionally, there is poor transmission in office settings.[39] The predominant mode of transmission for rhinovirus infection is not fully established. There is debate in the literature regarding whether the aerosol route or direct contact (self-inoculation after contact with the environment) is the most important mode of transmission, although direct contact appears to be most efficient. Surprisingly, low yields of rhinovirus are recovered from the coughs and sneezes of individuals with rhinovirus colds. In a number of studies in which uninfected individuals were placed in close proximity to infected individuals, few infections were observed, suggesting that direct contact was the primary mode of transmission.[40] However, another experiment found high rates of transmission via the aerosol route and no transmissions after contact with fomites.[41] It is worth noting that there is significant variability among individuals in the amount of aerosolized droplets that are produced during coughing or even quiet breathing.[42,43] This variability may account for at least some of the conflicting findings reported from transmission studies.

The optimal conditions for transmission differ among the numerous viruses that cause the common cold. Influenza and RSV, which are enveloped viruses, are more susceptible to degradation and remain infectious on surfaces for only minutes to hours. Rhinoviruses, which are nonenveloped, can be recovered from contaminated surfaces for days.[44] Rhinoviruses and adenoviruses survive best at high humidity, whereas survival is increased for RSV, parainfluenza, and influenza A at low humidity.[45,46]

### Predisposing Factors

Exposure to children is the most significant risk factor for spread of the common cold. Early community-based studies found consistently higher frequencies of respiratory illness in women compared with men, which was likely a consequence of the women having more frequent exposure to children.[3] Cold weather has long been thought to be a risk factor for the common cold, but this idea was mostly dismissed in the 20th century. Although some studies have supported an association between cold weather and the common cold, others have not.[47] The possibility that cold weather directly contributes to the pathogenesis of the common cold has continued to intrigue some investigators, who generally hypothesize that cold weather decreases respiratory immune defenses.[48] It has been shown that antiviral defenses are reduced in the nasal cavity as a result of its reduced temperature (compared with core body temperature) and that rhinovirus preferentially replicates in the nasal cavity for this reason.[49] However, there is currently no evidence that exposure to cold weather further reduces these defenses.

Crowding and poor ventilation are frequently cited as risk factors for respiratory infection. Severe crowding is associated with an increased rate of respiratory infection, and outbreaks of respiratory infection have been reported in crowded shelters following natural disasters.[50] It is less clear that the "crowding" that occurs in schools or other common indoor settings significantly increases the risk of the common cold. Little evidence exists that poor ventilation is a risk factor for the common cold. In one experiment, there was no difference in rates of the common cold between poorly ventilated and well-ventilated offices.[51] Recirculation of aircraft cabin air on 2-hour flights, as opposed to ventilation with fresh air, does not increase the risk of the common cold.[52]

Respiratory infections occur most frequently in children, yet there is significant variability in incidence among children, suggesting genetic risk factors. A number of studies have found that polymorphisms that result in low levels of mannose-binding lectin, a pattern recognition receptor, increase susceptibility to respiratory infections, particularly in young children.[53–55] Pattern recognition receptors recognize conserved molecular structures of particular pathogens and play a key role in the innate immune system. Polymorphisms in Toll-like receptors, another pattern recognition receptor, have also been associated with increased or decreased risk of respiratory infection in children.[55] However, associations between pattern recognition receptor deficiencies and risks of viral and bacterial infections have been inconsistent, and the significance of these findings remains uncertain. Mutations in the viral RNA-sensing protein MDA5 appeared to increase susceptibility to rhinovirus infection in a child with recurrent respiratory infections.[56]

Unique attributes of the common cold have allowed for studies that examine risk factors not typically associated with infectious diseases. Because the common cold is a mild, self-limiting illness, experimental challenge studies can readily be performed. Additionally, the common cold recurs on a frequent basis, which facilitates the conduct of observational studies. For these reasons, a significant body of work has been published on how factors such as stress, social ties, and sleep duration contribute to the risk and severity of the common cold. In a study in which 294 healthy participants were challenged with common cold viruses, psychological stress was associated with increased rates of both viral infection and clinical colds in a dose-response manner.[57] The duration of stress has also been shown to be important, with severe chronic stress, as opposed to acute stress, associated with an increased risk of colds in a challenge study.[58] In other challenge studies, participants with greater social ties to family, friends, work, and community and sociability in general (a combination of traits including extraversion) had a decreased risk of developing a cold.[59,60] In challenge studies that measured sleep duration, individuals who slept on average fewer than 7 hours a night had a significantly greater risk of developing a cold.[61,62] The physiologic mechanisms by which these factors increase or decrease susceptibility to the common cold are yet to be fully elucidated but may be related to inappropriate regulation of inflammation.[63]

## Immunity

The common cold recurs on a frequent basis. This is in contrast to many other viral infections in which protective immunity, typically mediated by neutralizing antibodies, is conferred after a single infection. The frequent recurrence of the common cold is primarily a result of the fact that the common cold is caused by different viruses, each with numerous viral antigenic types. (Table 58.1) Rhinovirus alone consists of at least 156 types, and there are at least 57 adenovirus types. Neutralizing antibodies produced against one virus or serotype will not prevent infection with another. Another factor is that the antibody response generated following respiratory virus infection is often not fully protective, even on rechallenge with the same serotype.

Rhinovirus infection induces neutralizing antibodies in both nasal secretions and serum after a period of 1 to 2 weeks.[64] These antibodies are extremely type-specific and can persist for years.[65,66] The fact that the incidence of the common cold decreases with age supports the notion that seroconversion confers some protection against infection. Challenge studies have confirmed that high levels of serotype-specific neutralizing antibody titers can be protective. In a rhinovirus serotype 39 challenge study, 70% of participants with high baseline serum antibody titers (>1:16) against this serotype became infected, compared with greater than 95% of participants with low or intermediate titers. The participants with high baseline serum titers who became infected demonstrated the lowest degree of viral shedding and the fewest symptoms, whereas participants with low titers demonstrated the greatest viral shedding and the most symptoms.[66] In another study, protection on reinfection with rhinovirus serotype 2 was associated with higher levels of rhinovirus serotype 2–specific immunoglobulin A in nasal secretions or serum.[64] Trials of inactivated rhinovirus vaccines conducted in the 1960s demonstrated that such vaccines could provide protection against homologous virus.[67,68] However, no protection was conferred against heterologous serotypes.

It is not clear why respiratory virus infection does not typically induce protective immunity. With regard to rhinovirus, one possibility may be that the antibody response is primarily directed against a nonprotective epitope located inside the viral capsid, which is exposed only on binding of rhinovirus to its cellular receptor intracellular adhesion molecule-1.[69] Evasion of the host immune system by these viruses likely plays a role in the failure of the host to establish protective immunity.[70,71] Human metapneumovirus, which is known to have only two genotypes, also exhibits high reinfection rates.[72,73] Although reinfection with respiratory viruses is common, the subsequent infection is typically of reduced severity.

## CLINICAL MANIFESTATIONS

Incubation periods vary for the different viruses that cause the common cold.[74] The incubation period for rhinovirus is typically 2 to 4 days. The common cold can manifest with a wide variety of symptoms based on the causative virus and the age and immune status of the host.

**TABLE 58.1 Viruses Associated With the Common Cold**

| VIRUS GROUP | ANTIGENIC TYPES |
|---|---|
| Rhinoviruses | >156 types |
| Coronaviruses | 5 types |
| Parainfluenza virus | 5 types |
| Respiratory syncytial virus | 2 types |
| Influenza virus | 3 types[a] |
| Adenovirus | 57 types |
| Metapneumovirus | 2 types |
| Other viruses: enteroviruses, bocavirus | |

[a]Multiple subtypes.

*Modified from Turner R. Rhinovirus. In: Bennett J, Dolin R, Blaser M, eds.* Principles and Practice of Infectious Diseases. *8th ed. Philadelphia: Elsevier; 2013:2113–2121.*

Common cold symptoms often begin with a sore or scratchy throat. Rhinorrhea and sneezing typically follow and persist for several days, after which nasal congestion and cough become the dominant symptoms.[75] Mucus color often changes from clear to yellow or green during the course of a cold. This does not represent the development of a bacterial infection but is a result of myeloperoxidase and other enzymes produced by neutrophils.[76] The mean duration of symptoms is 7 to 10 days, but nasal congestion and cough can persist for weeks. Other symptoms that may be experienced include headache, hoarseness, chilliness, and malaise. Fever is uncommon in adults but common in children.[77,78]

## PATHOGENESIS

The symptoms of a common cold caused by rhinovirus infection are a result of the host innate immune response and not virus-induced tissue damage. Although influenza is known to damage epithelial cells, the nasal epithelium remains intact during rhinovirus infection, and the only distinguishing feature on biopsy is an increased number of neutrophils in the submucosa and epithelium.[79,80] Additionally, very few cells in the nasal epithelium and nasopharynx are infected during rhinovirus colds.[81] The role of neutrophils in the pathogenesis of the common cold and viral infections in general remains unclear.[82,83] Following rhinovirus infection of human epithelial cells in vitro, levels of cytokines increase,[84] and elevated levels of inflammatory mediators and cytokines, including interleukin-1β (IL-1β), IL-6, and IL-8, have been found in nasal secretions during colds.[85,86] In rhinovirus challenge studies, symptom severity has been correlated with IL-8 and bradykinin levels in nasal secretions.[87,88] The roles of particular cytokines in the pathogenesis of the common cold have not been fully elucidated. Production of bradykinin appears to contribute to both sore throat and rhinorrhea, and administration of intranasal bradykinin has been shown to cause sore throat and rhinorrhea in healthy participants.[89,90] Histamine does not play a role in the pathogenesis of the common cold.[89]

The watery nasal discharge that is characteristic of the early phase of rhinorrhea is derived from a mix of nasal glandular secretions and plasma transudate. Nasal glands are activated to produce secretions through cholinergic stimulation.[91,92] The nasal congestion that occurs later in the course of the common cold is a result of the dilation of large capacitance veins (sinuses) in the nasal epithelium that can swell and block the nose.[93] Sympathetic stimulation of these venous sinuses results in vasoconstriction and decreased swelling. Interestingly, the nasal venous sinuses are similar to erectile tissue, with some data suggesting that they may have once played a role in sexual behavior.[94,95] Even in healthy individuals, the nasal venous sinuses undergo phases of congestion and decongestion, known as the nasal cycle. During this cycle, resistance increases in each nasal airway on a cyclical basis. In the setting of the inflammation and increased mucus secretion that occurs with the common cold, the effects of this cycle are amplified, resulting in restricted airflow and nasal obstruction.[96] As a result of the nasal cycle, it is common during a cold for one nasal airway to be patent while the other is obstructed.

The pathogenesis of cough as part of the common cold is not well understood. A dry cough may be the result of virus-induced hypersensitivity of airway sensory nerves. This increased sensitivity may be mediated by bradykinin and tachykinin.[97,98] Also, rhinovirus can invade the lower respiratory tract, causing lower respiratory tract symptoms in some individuals.[99] In the later phase of a cold, cough is often a result of irritation of the larynx with mucus.

## DIFFERENTIAL DIAGNOSIS

The common cold is a straightforward diagnosis, and the vast majority of patients will not seek medical care. Sometimes patients may seek medical care for the sore throat that occurs at the start of a cold, which may persist for days in the absence of other common cold symptoms. As opposed to bacterial pharyngitis, patients with pharyngitis as part of a cold generally feel otherwise well and do not have fever or tonsillar exudates. A rapid streptococcal antigen test will be negative. Rhinorrhea can occur in some noninfectious syndromes, particularly allergic and nonallergic rhinitis, but patients will frequently differentiate these syndromes from the common cold on their own. Patients with allergic

rhinitis typically have concomitant allergic conjunctivitis, which is characterized by itching, tearing, and conjunctival edema. Nonallergic rhinitis is a chronic condition in which the most prominent symptoms are nasal blockage and postnasal drip.[100]

Multiplex PCR assays for the diagnosis of upper respiratory tract infections have been adopted in many hospitals. These assays can test for more than 20 respiratory pathogens at once including viruses and bacteria. Multiplex PCR assays are used in emergency departments and hospital wards to guide treatment decisions and do not have a place in the diagnosis of the typical common cold. Even in the hospital setting, the optimal implementation strategy for these assays has been a matter of debate.[101]

## COMPLICATIONS

The common cold is a self-limiting illness. However, infection with common cold viruses may increase the risk for bacterial infection. Otitis media in particular is highly associated with upper respiratory viral infections, with one study finding that 37% of upper respiratory tract infections in young children were complicated by acute otitis media.[102] The most important factor in the development of acute otitis media in the setting of viral respiratory infections is congestion, which results in eustachian tube dysfunction. This dysfunction has a number of consequences, including decreased drainage of secretions produced in the middle ear and loss of protection of the middle ear from nasopharynx secretions.[103] Other factors also appear be involved in the development of otitis media, including an alteration of host immune defenses (see Chapter 61).[104] Specific viruses may differ in their propensity to cause otitis media,[102] and the risk for otitis media may be increased by certain combinations of viruses and bacteria.[105]

Sinusitis, which typically manifests as nasal congestion, purulent nasal discharge, and facial pain or pressure, is a common complication of the common cold. The vast majority of these cases are viral and typically resolve after approximately 10 days.[106,107] Bacterial sinusitis is suggested by symptoms that persist for longer than 10 days or a biphasic illness that begins to resolve but then worsens. Bacterial sinusitis comprises only 0.5% to 2% of episodes of sinusitis in adults[108] but may complicate 8% of upper respiratory tract infections in young children.[109]

A clear association exists between viral respiratory infections and asthma and chronic obstructive pulmonary disease exacerbations. In both adults and children with a history of asthma, approximately 85% of colds were associated with asthma symptoms.[110,111] Rhinovirus infections in particular have also been associated with the onset of wheezing illness in children and may play a direct role in the pathogenesis of asthma.[112,113]

Cough may persist for weeks after the resolution of other cold symptoms. This persistent cough has been referred to as a postviral or postinfectious cough. The pathogenesis of postinfectious cough is unclear but may be related to increased cough sensitivity as a result of inflammation. Postinfectious cough does not typically last longer than 8 weeks.[114] There is no specific treatment.

## THERAPY

### Symptomatic Therapy

The symptoms of the common cold evolve over the course of the illness. Therefore treatment should be directed at specific symptoms (Table 58.2). Studies that have demonstrated the effectiveness of symptomatic treatments have been performed in adults, and the few studies conducted in children have failed to show benefit. For this reason, the US Food and Drug Administration has recommended against the use of antihistamines, decongestants, and cough medicines in children younger than 4 years of age.

Treatment of sore throat includes the use of acetaminophen, nonsteroidal antiinflammatory drugs, or a topical anesthetic such as benzocaine. Anticholinergics are used to treat rhinorrhea. Anticholinergics block the cholinergic stimulation that causes nasal glandular secretion, and intranasal administration of the anticholinergic agent ipratropium is effective at reducing rhinorrhea.[115–117] The most common side effects of intranasal ipratropium are nasal dryness and nasal bleeding.

**TABLE 58.2 Symptomatic Treatment for the Common Cold**

| SYMPTOM | ETIOLOGY | TREATMENT | EXAMPLES |
|---|---|---|---|
| Sore throat | Bradykinin? | Analgesics, topical anesthetics | NSAIDs<br>Acetaminophen<br>Benzocaine lozenges |
| Rhinorrhea | Nasal glandular secretions | Anticholinergics | Diphenhydramine<br>Doxylamine<br>Ipratropium nasal spray |
| Nasal obstruction | Engorgement of nasal venous sinuses | Adrenergic agents | Pseudoephedrine<br>Oxymetazoline nasal spray |

*NSAIDs,* Nonsteroidal antiinflammatory drugs.

First-generation antihistamines are frequently used for treatment of the common cold. Their use developed from the mistaken idea that common cold symptoms are mediated by histamine.[118] Nevertheless, the anticholinergic properties of first-generation antihistamines make them effective for the treatment of rhinorrhea.[119–121] The most common side effect of first-generation antihistamines is sedation. This attribute can be useful in the setting of the common cold, and first-generation antihistamines are typically included in nighttime cold medicine formulations. Second-generation antihistamines such as loratidine and cetirizine lack anticholinergic properties and are not effective for treatment of the common cold.[122–124]

Adrenergic agents effectively constrict the nasal venous sinuses and thereby relieve congestion. The nasal veins are five times more sensitive than the heart to the effects of epinephrine,[125] which allows for the treatment of nasal congestion with adrenergic agents without pronounced cardiovascular side effects. Both oral and topical adrenergic agents have been shown to be effective treatments for nasal congestion,[126–129] but topical agents such as oxymetazoline are more potent and reliable.[130] Phenylephrine, which has gained prominence in over-the-counter preparations in recent years, does not appear to be as effective as pseudoephedrine.[131,132] Dextromethorphan is commonly used for the treatment of cough, although it has not been specifically studied in the setting of the common cold. There is insufficient evidence regarding the utility of expectorants such as guaifenesin.

### Homeopathic Remedies

Many remedies are marketed for the prevention and treatment of the common cold including vitamin C, *Echinacea*, and zinc as well as a host of "immune-boosting" formulations, which often contain vitamins and herbal supplements. There is no evidence to support the use of vitamin C or other vitamins in otherwise healthy individuals for the treatment or prevention of the common cold.[133,134] *Echinacea* has similarly been shown to be of no benefit.[135,136] The efficacy of zinc, administered as zinc gluconate or zinc acetate lozenges, is controversial. Zinc has been shown to have antiviral properties against a number of respiratory viruses in vitro,[137–140] but the results of clinical trials have been mixed, with some trials demonstrating benefit and others showing no effect.[141–144] Systematic reviews and meta-analyses have generally concluded that zinc lozenges may shorten the duration of the common cold by about 2 days.[145–147]

### Antiviral Therapy

Studies conducted in the 1980s found that intranasal administration of interferon could reduce the risk of developing a cold by 78% to 88% when administered prophylactically following rhinovirus challenge or in the setting of an ill family member.[148–150] However, when intranasal interferon was begun after the start of symptoms, it was ineffective.[151] Additionally, after taking interferon for 1 to 2 weeks, participants developed nasal stuffiness and bleeding. For these reasons, further development of interferon for the treatment or prevention of the common cold was abandoned.[152] Other efforts to develop antiviral therapies for the common cold have focused specifically on rhinovirus. Strategies have included blockade of the intracellular adhesion molecule-1 receptor, capsid-binding agents, and 3C protease inhibitors. Pleconaril, a

capsid-binding agent, was found to reduce the duration of common cold symptoms by 1 day in two trials.[153] However, pleconaril was not granted US Food and Drug Administration approval in 2002 due to safety concerns. An intranasal formulation of pleconaril failed to show efficacy for the prevention of rhinovirus infection (ClinicalTrials.gov Identifier: NCT00394914).

## Hand Hygiene

Hand hygiene is universally recommended to reduce the transmission of infectious diseases. However, the efficacy of hand hygiene for the prevention of the common cold has not been consistently demonstrated in clinical trials. The implementation of hand hygiene programs was shown to reduce rates of the common cold in individuals in daycare centers and military trainees.[154–156] In a randomized controlled trial conducted in the homes of families with children in daycare, however, a hand hygiene intervention did not reduce the rates of respiratory illness.[157] In another randomized trial that enrolled university students, the use of an alcohol lotion previously shown to be highly effective in removing rhinovirus from the hands was not found to reduce the incidence of rhinovirus infection.[158] As most colds are self-limited, the use of any potential therapy should assess the benefit-risk ratio as well as the cost.

## Key References


*The complete reference list is available online at Expert Consult.*

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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 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* is now recognized as a cause of pharyngitis in adolescents and young adults with potential severe complications (i.e., Lemierre syndrome).
- *Arcanobacterium haemolyticum* may cause pharyngitis associated with a rash, seen particularly in adolescents and 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) or throat culture should be used to confirm the diagnosis of GAS in adults; a negative RADT 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.

## DEFINITION

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).[2,3,4] Depending on patient characteristics, including age and the presence of documented pharyngitis versus sore throat, rates up to approximately 60% have been identified, primarily in children and young adults.[5,6] 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 and rhinovirus are frequently identified as the most prevalent viral cause of pharyngitis, reported in 12% to 27% of all cases.[2,5,6,7,8] Other respiratory viruses that cause pharyngitis include enteroviruses, influenza A and B, parainfluenza viruses, respiratory syncytial virus, coronaviruses, human metapneumovirus, and human bocavirus.[2,3,7,9,10,11] Several human herpesviruses, such as Epstein-Barr virus, herpes simplex virus (HSV) 1 and 2, 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[12,13] and 15% to 30% of cases in children.[14] *Fusobacterium necrophorum*, a gram-negative, non–spore-forming anaerobe, is a bacterial cause of sore throat in 10% to 20% of cases of pharyngitis in adolescents and young adults[15,16,17] and the etiologic agent in up to 23% of cases of peritonsillar abscess.[18] The organism has also been implicated in recurrent or chronic sore throat syndromes and may be identified in up to 21% of such cases.[19] *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.[20,21] *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.[22] Nontoxigenic strains of *C. diphtheriae* have been reported with increasing frequency in individuals with sore throat, but their contribution as a causative agent of pharyngitis remains in question.[23] Pharyngitis caused by gonorrhea should be considered in sexually active adolescents and adults. Throat cultures yield *Neisseria gonorrhoeae* in as many as 1% to 6% of individuals in sexually transmitted disease clinics.[24,25] *Mycoplasma pneumoniae,* identified in 3% to 14% of cases of pharyngitis, and *Chlamydia pneumoniae*, less frequently detected at

**TABLE 59.1 Microbial Causes of Acute Pharyngitis**

| PATHOGEN | ASSOCIATED DISORDER(S) |
|---|---|
| **Bacteria** | |
| *Streptococcus,* group A | Pharyngitis, tonsillitis, scarlet fever |
| *Streptococcus,* group C and G | Pharyngitis, tonsillitis |
| Mixed anaerobes | Vincent angina |
| *Fusobacterium necrophorum* | Pharyngitis, tonsillitis, Lemierre syndrome |
| *Neisseria gonorrhoeae* | Pharyngitis, tonsillitis |
| *Corynebacterium diphtheriae* | 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 types 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; reproduced with permission.*

3% to 8%, should also be considered as potential etiologic agents of pharyngitis.[3,7,26]

## 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.[27] The incidence rate of medically attended tonsillitis in children has been estimated at 15 to 25 cases per 1000 children per year.[28] 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.[29–31]

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.[32] 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.[27] 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.[33] The most recent studies show GAS prevalence in cases of pharyngitis approaching 40% in children[34,35] and 17% in adults.[36] 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.[37]

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.[26,38]

Between 49% and 62% of children[39] and 66% to 78% of adults[4,39] evaluated for sore throat or pharyngitis receive an antibiotic prescription, a rate much higher than the prevalence of GAS infection for which treatment is indicated.[29–31] 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.[31]

## 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.[40,41] Other inflammatory mediators, including prostaglandins, have been postulated to play a role with bradykinin via their actions on sensory nerve endings in the pharynx.[42] Several randomized controlled trials have demonstrated a beneficial effect of either nonsteroidal antiinflammatory drugs or corticosteroids on throat pain, also suggesting that inflammatory mediators play a key role in the pathophysiology of sore throat.[43–47]

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.[48] Despite this growing fund of knowledge, major gaps exist regarding the events leading to tonsillopharyngeal disease. Furthermore, the contribution and mechanism of underlying asymptomatic carriage has been the subject of much speculation.[49,50] 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), and numerous exotoxins (streptolysins, superantigenic toxins) have been described[48] but are beyond the scope of this chapter. Expression of these virulence factors leads to symptomatic pharyngitis and complications, including 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.[51] 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 coworkers[52] 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.

## MICROBIOLOGY

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 as follows.

### 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.[33]

## 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,[53] although recently, *S. equi* subsp. *zooepidemicus* has emerged as a potentially important human pathogen.[54] Group C streptococci are known to cause endemic,[55] whereas group G is more frequently associated with epidemic pharyngitis[56] 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. A recent study in a university health clinic found *F. necrophorum* in 20.5% of patients with pharyngitis and in 9.4% of asymptomatic students.[16] An accompanying editorial pointed out the challenges in interpretation of these findings.[57] A study from the Children's Hospital Los Angeles[17] showed a similarly high proportion of *F. necrophorum* in patients 14 to 20 years (13.5%) compared with younger children (1.9%). 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 Lemierre syndrome. Patients with Lemierre syndrome may initially present with symptoms of pharyngitis, tonsillitis, or peritonsillar abscess and show initial clinical improvement (see Chapter 64). A recent study from Denmark identified *F. necrophorum* as the most frequently detected bacteria in peritonsillar abscess.[18] Approximately 4 days after clinical improvement of pharyngitis, the signs and symptoms of bacteremia (e.g., rigors) associated with 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,*[58] 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.[21] The rash begins on the distal extremities, typically involving the extensor surfaces but sparing the palms and soles, followed by centripetal spread.[59] Rarely, *A. haemolyticum* may cause more severe infection (e.g., pneumonia and pyomyositis) but in these cases is most often a coinfecting agent.[60]

### *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.[61] 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.[62] 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.[63] Fever is uncommon, as is cervical lymphadenopathy. Among patients with tonsillitis, a whitish-yellow exudate was observed in 20%.[63] 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 *Chlamydia pneumoniae* have been identified as a cause of pharyngitis in all age groups, with a higher prevalence generally noted for *M. pneumoniae.*[7,64] Disease occurs year-round, but seasonal peaks and community outbreaks occurring every few years have also been described.[65] Most adult cases appear to present as an undifferentiated acute respiratory infection or an influenza-like illness; however, isolated pharyngitis has also been noted.[66] 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.[67] Esposito and colleagues[7] 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.[68] 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.[69] A more recent study of older adolescents and young adults at a University Health Clinic did not identify *M. pneumoniae* as a substantial cause of pharyngitis.[16]

## Epstein-Barr Virus

Infectious mononucleosis (IM) is a multisystem disorder caused by primary infection with Epstein-Barr virus (EBV) and defined by the classic symptoms of fever, fatigue, pharyngitis, and adenopathy.[70,71] Among more than 200 young adults with serologically confirmed acute EBV infection, three-quarters reported sore throat with approximately half noting cervical adenopathy at their initial visit.[71,72] Fatigue was common and noted in 65% to 75%. Other symptoms included fever, headache, 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/or hepatomegaly were detected in approximately 35% of patients during the first two weeks of the illness with minimally elevated transaminase levels in more than half of the group.[71,72] 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.[70] Symptoms substantially improve over the first month of illness and after 6 months are almost completely resolved.[72]

Although IM has been traditionally described in adolescents and young adults, children also commonly develop fever, exudative pharyngitis, and cervical adenopathy during primary infection with EBV.[73,74] In addition, rash and splenomegaly are more common in young children with primary EBV infection than in adolescents or adults.[74] Periorbital or eyelid edema, as a symptom of primary EBV infection, appears to be unique to children.[74] 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.[1,75,76] 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.[75] Hecht and coworkers[77] 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.[1,70] Pharyngitis is recognized in 50% to 70% of patients, whereas cervical adenopathy is noted in 25% to 50%.[76,77] Although extensive descriptions of the pharyngeal findings associated with primary HIV infection are lacking, exudates appear to be present in a minority of patients.[1,77] In addition, the adenopathy tends to be nontender and may be generalized.[70] 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.[77] 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.[76,78] 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 coworkers[75] noted that only one-quarter of patients with symptoms of primary HIV-1 infection had the diagnosis suspected at the initial medical evaluation. A 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.[79] 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.[78] 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 aid in both the control of virus transmission and treatment decisions for individual patients (see Chapter 120).

## 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).[6,80,81] Fever is common, but the throat examination typically reveals only mild erythema without significant adenopathy. Although exudates are not generally described, enteroviruses were found in 16% of children with exudative pharyngitis in one report.[8]

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.[80] 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.[82,83] Both endemic and epidemic herpangina are well described, with young children affected more commonly than newborns, older children, 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.[84] 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 classic HFM, and the fever tends to be less prominent.[84] Recently, cases of atypical HFM have been described with widespread vesiculobullous lesions involving the extremities, trunk, buttocks, face, hands, and feet.[85,86] Crusting of the lesions followed by acral desquamation and nail changes, including onychomadesis (nail shedding) approximately 4 to 6 weeks after the illness, are also described.[87] Most cases have been identified in young children, but adults with atypical HFM have also been reported and almost all have been attributed to infection with coxsackie A6.[88] 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 172).[89,90]

## 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 3% of ambulatory adults.[3,7,8,91] 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.[92,93] 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.[94] Among military recruits followed prospectively, approximately 35% of those with culture-confirmed adenovirus infection had sore throat, and 29% were febrile.[95] Bilateral cervical lymphadenopathy (32%), conjunctivitis (17%), and rash (12%) have also been described in patients with adenovirus respiratory tract infections.[93]

Pharyngoconjunctival fever is a specific syndrome caused by adenovirus infections, often occurring in outbreaks and associated with swimming or bathing.[96] 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.[97] 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.[97]

## Herpes Simplex Virus

Primary infection with HSV-1 commonly causes gingivostomatitis in young children, whereas pharyngitis is noted among adolescents and young adults due to both HSV-1 and HSV-2. 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.[98] Approximately

**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; reproduced 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; reproduced with permission.*

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. Acyclovir treatment is often used in severe cases.

## 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.[99] 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).[13,100,101] 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 be confirmed in only 57% of cases.[102] Further studies demonstrate that with the presence and increasing number of viral features (e.g., cough, rhinorrhea, oral ulcers/vesicles) GAS was progressively less prevalent.[35] Thus the most recent guidelines from the Infectious Diseases 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.[103,104] In contrast, the 2001 guidelines issued by the Centers for Disease Control and Prevention (CDC) and the American College of Physicians (ACP)-American Society of Internal Medicine suggested empirical treatment based on a pharyngitis score alone with or without microbiologic confirmation.[105]

The difference in these guidelines had 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 pharyngitis.[101] 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.[106] In addition, in 78% of cases, physicians did not adhere to any guidelines, leading to overuse of antibiotics for the treatment of pharyngitis.[107] More recently, improved accuracy of the Centor score[100] was achieved by adding real-time local biosurveillance for GAS pharyngitis. However, real-time biosurveillance is impractical in most settings. In 2016 the CDC and the ACP updated their guidelines to recommend that only patients with confirmed GAS pharyngitis by RADT and/or throat culture be treated with antibiotics.[108]

### Culture for Group A Streptococci

Assaying for the presence of GAS by throat culture on sheep blood agar plate (BAP), as first described by Breese and Disney,[109] 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.[110] 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.

## Rapid Antigen Detection Test

RADT is 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, and overtreatment of viral causes of pharyngitis and can 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. A recent meta-analysis assessing the sensitivity and specificity of RADT among 48 studies showed an overall sensitivity of 86% and specificity of 96%.[111] Highest sensitivity and specificity has been observed in molecular tests, with most recent PCR-based assays taking as little as 15 minutes.[112] 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.[113] Currently, it is recommended that a negative RADT be confirmed by BAP culture for all children.[103,104] 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 continues to be questioned.[101] In a study assessing the utility of a reflexive culture after a negative RADT in adolescents and young adults with pharyngitis, RADT failed to identify 55% of patients with modified Centor score ≥2, suggesting that in the absence of a backup method, many patients who may benefit from treatment would be missed.[114]

## Other Diagnostic Tests

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*. *A. 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[115] 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,[17,116] and has the advantage of detecting low concentrations of bacteria, but 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.[117]

Serologic testing of acute and convalescent serum samples has been the standard procedure for diagnosing pharyngitis caused by *M. pneumoniae* or *C. pneumoniae*; however, PCR is becoming readily available. The diagnosis of primary EBV infection is 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.[70,74] 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. Ultimately, as new technologies evolve it is likely that pharyngitis molecular panels will become available, allowing rapid diagnosis of a broad range of bacterial and viral etiologies analogous to those that have been developed for patients with respiratory symptoms, diarrheal illness, and meningitis/encephalitis.[118]

# 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.[119] 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.[120]

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).[103,104] 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 US 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.[121,122] Furthermore, a larger study confirmed a once-daily amoxicillin regimen as noninferior to twice-daily penicillin.[123] Given the evidence, the most

**TABLE 59.4 Antimicrobial Therapy for Group A Streptococcal Pharyngitis**

| DRUG | DOSE | DURATION |
|---|---|---|
| **Oral Regimens** | | |
| Penicillin V | Children: 250 mg bid or tid<br>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<br>1.2 million units for patients ≥27 kg | 1 dose<br>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; reproduced with permission.*

recent guidelines endorse the use of amoxicillin if greater compliance is anticipated.[104]

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 contact with persons with invasive infections, such as necrotizing fasciitis or streptococcal toxic shock syndrome.[103,104] 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 earlier.

Recommendations for treatment of *Fusobacterium* infections include a penicillin in combination with a β-lactamase inhibitor (e.g., ampicillin/sulbactam) together with metronidazole.[124] *Fusobacterium* species are universally resistant to macrolide antibiotics (e.g., azithromycin)[125] and have been increasingly noted to show resistance to clindamycin. In addition, up to one-quarter of *Fusobacterium* species isolates will produce a β-lactamase.[126] 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 *A. 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.[127] 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 in Chapter 212.[128]

Symptomatic treatment is the mainstay for most cases of viral pharyngitis. Significant improvement in pain relief with the use of 25 mg ibuprofen lozenges compared with placebo has recently been reported in a large double-blind randomized control trial of adults with sore throat not requiring antibiotics.[43] The use of a single dose of oral corticosteroids along with antibiotics was associated with a modest reduction in duration of throat pain by a mean time of 14 hours, as reported in a meta-analysis of studies.[45] A more recent meta-analysis reported a mean reduction of pain of 11 hours in patients with pharyngitis treated with a single dose of corticosteroids without antibiotics.[129] The IDSA guidelines[130] and the UK National Institute for Health Care Excellence do not recommend the routine treatment of pharyngitis with corticosteroids.[131]

## 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.[132] 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.[133] 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.[133] Drainage of purulent material coupled with antibiotics are the standard of treatment.[134] Because peritonsillar and parapharyngeal abscesses are often polymicrobial, involving aerobic and anaerobic bacteria, one suggested agent for treatment is ampicillin/sulbactam.[132]

Acute rheumatic fever (ARF) and acute glomerulonephritis are potential nonsuppurative complications of pharyngitis caused by GAS (see Chapter 198). Rheumatic heart disease and its complications affect almost two million individuals each year, primarily in developing countries.[37] Acute rheumatic fever has become rare in the United States except for sporadic outbreaks of rheumatogenic strains of GAS.[135] 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.*[124] The clinical characteristics of pharyngitis caused by *Fusobacterium* are nonspecific and similar to GAS, and systemic illness may present after pharyngeal symptoms have subsided.

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*The complete reference list is available online at Expert Consult.*

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# 60 Acute Laryngitis

*Brenda L. Tesini and Mary T. Caserta*

## SHORT VIEW SUMMARY

### Definition
- Acute laryngitis is a clinical syndrome characterized by a hoarse voice with decreased phonation and voice projection, usually occurring after an upper respiratory tract infection with cough.

### Epidemiology
- Approximately 1% of medical care claims are due to dysphonia, with 42% of those classified as acute laryngitis.
- Two percent of individuals with acute respiratory symptoms are diagnosed with acute laryngitis.
- Acute laryngitis is diagnosed more frequently in women (mean age, 36 years) than men (mean age, 41 years).
- More cases are diagnosed in the colder months of the year.

### Microbiology
- A viral upper respiratory tract infection is often associated (see Table 60.1).
- Bacterial infections of the upper respiratory tract have also been implicated.
- Unusual causes include tuberculosis, blastomycosis, histoplasmosis, coccidioidomycosis, cryptococcosis, and herpesvirus infections of the larynx.

### Diagnosis
- Clinical diagnosis is based on the appropriate history and changes in the voice.
- Visualization of the larynx reveals edema and vascular engorgement of the mucous membranes with hyperemic and erythematous vocal folds.

### Therapy
- Treatment is based on the underlying cause of the laryngeal pathologic process.
- Often, symptomatic therapy with voice rest, analgesics, and humidification is sufficient.

## DEFINITION

Acute laryngitis is a clinical syndrome commonly encountered by primary care physicians. The symptoms are often described as the recent onset of hoarseness or a husky voice with decreased voice projection often associated with a dry cough.[1] There may be voice breaks or episodes of aphonia that frequently occur in the context of an upper respiratory tract infection with rhinorrhea and sore throat. The duration of symptoms is difficult to discern from the literature; however, in a study of 80 adults with the common cold, hoarseness was reported for a median of 3 days, and 5.5 days represented the 75th percentile.[2] Although most reports describe acute laryngitis as a mild and self-limited syndrome, a survey of intercollegiate athletes found substantial morbidity associated with laryngitis.[3] These students reported laryngitis significantly more often as a cause of missed practice, compared with cough, nasal discharge, or myalgia, and as having an adverse effect on their athletic performance.

## EPIDEMIOLOGY

The incidence of acute laryngitis reported in the literature varies and is highly dependent on the research methods used. A study using a large medical claims database found that approximately 1% of people presenting for care did so because of dysphonia, with 42% receiving a diagnosis of acute laryngitis.[4] Further study of the same database found that over 20% of adults aged 65 years or older were diagnosed with acute laryngitis at least once during a 5-year period.[5] When the National Health Interview Survey was used to inquire regarding voice problems in the preceding year, approximately 18 million adults or 7.6% of the US population reported a voice disturbance. Acute laryngitis secondary to a respiratory infection was the most common diagnosis in 17.8%.[6] In reports including almost 5000 children and adults with acute respiratory symptoms, 2% were given a primary diagnosis of laryngitis.[7,8] In other studies, 38% of patients with pneumonia reported hoarseness as a symptom, as did 53% of adults with colds and 67% of children with bacterial tracheitis.[2,9,10] Laryngitis has also been noted in approximately 22% of adolescents or school-aged children with nonstreptococcal sore throat.[11] Despite this demonstration that laryngitis affects patients of all ages, a report of more than 800 patients seen in an ear, nose, and throat clinic showed that most patients with acute laryngitis presenting for care were women with a mean age of 36 years.[12] In addition, the study showed that the frequency of laryngitis during the colder months was almost double that observed in the warmer seasons.

## MICROBIOLOGY

All of the major respiratory viruses have been etiologically associated with laryngitis. In the study of patients older than 5 years of age with a primary diagnosis of laryngitis, 21% had infection with parainfluenza virus, 15% had rhinovirus, 3% had influenza virus, and 3% had adenovirus.[7] The risk of developing laryngitis with a particular type of respiratory tract infection is summarized in Table 60.1. McMillan and colleagues[11] reported that laryngitis and cough were noted significantly more often among patients with influenza (29%) than among patients with group A β-hemolytic streptococcal infection (2.3%). In a retrospective review of an epidemic of influenza in the United Kingdom, the rate of laryngitis or tracheitis reported by general practitioners peaked at approximately 100 per 100,000 population, coincident with the peak of influenza illness.[13] Overall 10% of children with human parainfluenza virus (HPIV) infection noted hoarseness in a retrospective review from a large medical center in Taiwan. The symptom was more commonly associated with human parainfluenza virus 2 infection, with hoarseness noted at presentation of 23.9% of children with HPIV2 infection versus only 5.5% of children with HPIV3 disease.[14] Younger patients were significantly more likely to report hoarseness than elderly subjects in a study of human metapneumovirus infection.[15] Hoarseness was reported in 91% of young adults with human metapneumovirus infection compared with 42% of similar-age subjects with respiratory syncytial virus infection. Acute laryngitis was the primary diagnosis in 3.3% of children from 1 month to 14 years of age hospitalized with acute respiratory symptoms and infection with human metapneumovirus.[8] Among older adults admitted to the hospital for respiratory disorders, hoarseness was reported by 25% of subjects with illness resulting from rhinovirus or coronavirus.[16] Hoarseness or laryngitis has not been reported as a symptom in patients

**TABLE 60.1 Frequency of Laryngitis Associated With Common Respiratory Pathogens**

| PATHOGEN | FREQUENCY (%) | REFERENCES |
|---|---|---|
| Rhinovirus | 25–29 | 16, 46 |
| Influenza | 28–35 | 11, 16, 46 |
| Parainfluenza | 5–25 | 14, 47 |
| Adenovirus | 22–35 | 48 |
| Coronavirus | 25 | 16 |
| *Mycoplasma pneumoniae* | 3–37 | 9, 16 |
| *Chlamydophila pneumoniae* | 12–30 | 21, 49 |
| Group A β-hemolytic streptococcus | 2.3–19 | 11, 46 |
| Human metapneumovirus | 3–91 | 8, 15, 50 |

with severe acute respiratory syndrome secondary to human pneumonia–associated coronavirus.[17]

Bacterial respiratory infections have also been associated with acute laryngitis. Several authors have noted the presence of hoarseness in patients with acute streptococcal pharyngitis (see Table 60.1). Laryngitis secondary to diphtheria has been virtually eliminated in the United States, although diphtheria continues to be an important cause of laryngeal disease worldwide. The possible etiologic role of *Moraxella catarrhalis* (formerly *Branhamella catarrhalis*) in adults with acute laryngitis was investigated in several reports from Sweden. In a case-control study of 40 adults with hoarseness and symptoms of upper respiratory tract infection, 55% of the patients and 14% of controls had *M. catarrhalis* isolated from a nasopharyngeal culture.[18] *Haemophilus influenzae* was the second most frequently recovered bacterial pathogen from patients with laryngitis (8%–20%), which suggests that the organism may also play a role in this condition. However, treatment of patients with *M. catarrhalis* with oral penicillin or erythromycin for 5 days failed to show any objective clinical benefit over placebo, despite a significant rate of bacteriologic eradication, casting doubt on the significance of the association.[19,20] Laryngitis was diagnosed in 12.2% of children presenting with real-time polymerase chain reaction–confirmed *Chlamydophila pneumoniae* acute respiratory infections in a study from Egypt.[21] Infection with *Bordetella pertussis* or *Mycoplasma pneumoniae* has been suggested as a cause of chronic laryngitis in a single report of adults with symptoms of hoarseness and throat clearing for more than 6 weeks.[22] Methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa,* and *Serratia marcescens* were also identified as possible causes of infectious laryngitis at laryngeal biopsy of patients with over 3 weeks of voice changes and evidence of laryngeal inflammation in a small retrospective review.[23]

Uncommon causes of acute laryngitis include herpesviruses, parvovirus B19, mucosal candidiasis, *Coccidioides immitis, Anncaliia algerae, Cryptococcus neoformans, Sporothrix schenckii*, mucormycosis, leishmaniasis, MRSA, actinomycosis, *Clinostomum complanatum,* and group G β-hemolytic streptococci in normal and immunocompromised patients.[2,4–29,30,31,32,33,34,35] Clinical findings in patients with laryngitis secondary to herpes simplex virus types 1 or 2, varicella-zoster virus, or cytomegalovirus include edema and inflammation of the glottic or supraglottic region with vesicles or ulcerative lesions with or without vocal cord paralysis.[33]

Laryngitis secondary to tuberculosis (TB) and blastomycosis is usually a chronic complication of pulmonary infection.[30,36] Although in the past laryngeal TB was frequently detected in young patients with recognized pulmonary TB, more recent reports have described changes in the epidemiology and clinical features of TB of the larynx. In a study of 31 patients with biopsy-confirmed laryngeal TB, only 55% were referred because of a previous diagnosis of pulmonary TB, whereas 33% had odynophagia or a suspicion of carcinoma.[37] Historically, patients with laryngeal TB had a large burden of organisms in their sputum. In a more recent study from India, patients with laryngeal TB were no more likely to have positive sputum results than patients with pulmonary TB without laryngeal disease.[36] Clinical findings reported in laryngeal TB range from the classic description of cranial nerve palsies with ulcerative lesions of the posterior larynx to anterior tumor-like masses. Given this changing clinical picture, a high degree of diagnostic suspicion is warranted in order to make a diagnosis of laryngeal TB.

Laryngeal histoplasmosis is usually a complication of disseminated infection but may be primary and manifests as hoarseness of indolent onset without cough[38] Blastomycosis and histoplasmosis of the larynx can be mistaken for squamous carcinoma because of the indolent onset, gross appearance at laryngoscopy, and pseudoepitheliomatous hyperplasia at biopsy. Fever is low grade or absent. Diagnosis depends on demonstration of the fungi in the submucosa. Hoarseness may also be noted as a component of other laryngeal infections, such as croup, acute epiglottitis, or supraglottitis. The latter conditions are discussed separately in Chapters 63 and 158. Other noninfectious causes of acute laryngitis include voice abuse, gastroesophageal reflux disease, and laryngeal malignancy.

## DIAGNOSIS AND THERAPY

The diagnosis of acute laryngitis caused by an upper respiratory tract infection can often be made from the history alone. Examination of the larynx reveals hyperemic and erythematous true and ventricular vocal folds resulting from edema and vascular engorgement of the mucous membranes.[39] Treatment needs to be directed at the underlying infectious cause of hoarseness but generally is symptomatic, with voice rest, analgesic therapy, and humidification.[39] Occasionally resection or laser ablation may be required for lesions resulting from uncommon pathogens.[40] As noted previously, studies evaluating the use of antibiotics for patients with acute laryngitis have not shown objective benefit, and a Cochrane review in 2013 concluded that antibiotics should not be prescribed for patients with typical laryngitis.[41] An updated Cochrane review in 2015 similarly concluded that antibiotics did not "appear to be effective in treating acute laryngitis when assessing objective outcomes."[42] Despite these findings, antibiotics are still prescribed with some frequency for acute laryngitis.[43]

## COMPLICATIONS

Long-term sequelae of laryngitis are uncommon, but prolonged hoarseness has been noted most frequently after infection with uncommon pathogens. Superior laryngeal neuralgia has also been described as a rare complication of acute laryngitis.[44] This disorder is characterized by painful paroxysms of the throat induced by head turning, swallowing, or voice straining and is associated with a trigger point on the lateral aspect of the neck overlying the thyrohyoid membrane. Various treatments, including injections of local anesthetic, have been used to treat this complication. An additional unusual complication of acute laryngitis is idiopathic ulcerative laryngitis.[45] Criteria for diagnosing this condition include a history of a preceding upper respiratory tract infection with cough, the presence of bilateral ulcerations at the midmembranous vocal folds at physical examination, and a lack of response to treatment with corticosteroids, antibiotics, and antireflux medications. Healing usually occurs over a minimum of 6 weeks with complete resolution of symptoms.

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*The complete reference list is available online at Expert Consult.*


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# 61 Otitis Externa, Otitis Media, and Mastoiditis

*Stephen I. Pelton*

## SHORT VIEW SUMMARY

### DEFINITION

#### Otitis Externa

- Otitis externa is an infection and inflammation of the external auditory canal.
- Infections of the pinna may occur with piercing ornaments.

#### Otitis Media

- Acute otitis media (AOM) is an acute illness defined by moderate-to-severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa, accompanied by acute signs of illness and signs or symptoms of middle ear inflammation.[1]

#### Mastoiditis

- Mastoiditis is infection and inflammation of the mastoid air cells and usually evolves from an episode of severe AOM.

### EPIDEMIOLOGY

#### Otitis Externa

- Acute diffuse otitis externa or swimmer's ear occurs in hot humid weather.
- Invasive or malignant otitis externa occurs in diabetic, immunocompromised, and debilitated patients.
- Children are prone to place foreign objects in the external ear canal, which may cause maceration and infection of the skin lining the external canal and herald the development of acute otitis externa.

#### Otitis Media

- Otitis media (OM) occurs at all ages, but the peak age group is children in the first 3 years of life.
- Children at risk for severe and recurrent OM are more frequently male, have a genetic predisposition to ear infections, and may be in large-group daycare exposed to frequent respiratory viruses and bacterial pathogens.

#### Mastoiditis

- The epidemiology of mastoiditis parallels that of OM.

### MICROBIOLOGY

#### Otitis Externa

- The microbial microbiota of the external ear canal responsible for otitis externa is predominantly staphylococcal species, and anaerobic bacteria.
- *Pseudomonas aeruginosa* is a frequent cause of swimmer's ear, infections of the pinna, and malignant otitis externa.

#### Otitis Media

- *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae* are the most frequent bacterial pathogens in all age groups.
- *Moraxella catarrhalis* has become more frequent after universal immunization with pneumococcal conjugate vaccine; group A streptococci and *Staphylococcus aureus* are less frequent causes of AOM.
- Respiratory viruses are frequent causes of AOM, most often associated with bacterial pathogens.

#### Mastoiditis

- The microbiology of mastoiditis is dominated by *S. pneumoniae* but includes group A streptococci, *S. aureus,* and anaerobic bacteria.
- Patients with persistent perforation of the TM may have invasion of the mastoid by organisms present in the external ear canal, including *S. aureus* and *P. aeruginosa.*

### DIAGNOSIS

#### Otitis Externa

- Acute localized otitis externa may occur as a pustule or furuncle that is visualized in the canal.
- Swimmer's ear is identified by edema, swelling, and erythema of the canal wall, the auricle, or both.
- Infections of the pinna may be associated with piercing ornaments to cartilaginous portions of the ear.
- Malignant otitis externa is associated with severe pain and tenderness of the tissues around the pinna and mastoid; pus may be present in the canal.

#### Otitis Media

- AOM is an acute illness with fluid in the middle ear space and bulging or decreased mobility and inflammation of the TM.

#### Mastoiditis

- The signs of mastoiditis include swelling, redness, and tenderness over the mastoid bone.
- The pinna is often displaced downward and outward, and a purulent discharge may emerge through a perforation of the TM.

### THERAPY

#### Otitis Externa

- The primary approach to treatment involves cleaning the external canal, managing pain, and treating infection and inflammation.
- Initial cleaning involves removal of cerumen and debris under direct observation and irrigation with 3% hydrogen peroxide (when the TM is intact).
- Topical therapy, including fluoroquinolone eardrops, is indicated for mild and moderate disease; a topical preparation of acetic acid and hydrocortisone can be used in mild cases.
- Systemic antimicrobial therapy, including activity against *P. aeruginosa,* is necessary to manage invasive external otitis.

#### Otitis Media

- The American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) recommend that infants younger than 6 months receive antibacterial therapy for AOM. Children aged 6 months to 2 years should receive antibacterial therapy if the diagnosis is certain, or if the diagnosis is uncertain and disease is severe. If the diagnosis is uncertain and disease is not severe, observation is an option.
- Children 2 years of age or older should receive antibacterial therapy if disease is severe. If disease is not severe or if the diagnosis is uncertain, observation is an option. See Table 61.1.
- Management of pain should be part of the approach to treatment.
- High-dose amoxicillin is the preferred drug for patients with AOM without recent exposure to antimicrobial treatment or concomitant conjunctivitis.
- If amoxicillin fails, amoxicillin-clavulanate or parenteral ceftriaxone is preferred.
- Most children with AOM improve without use of antimicrobial agents; initial observation may be warranted in children older than 2 years of age with mild or moderate symptoms as noted earlier.
- Placement of tympanostomy tubes may be warranted for children with OM, those who are unresponsive to antimicrobial therapy, or those with severe and recurrent episodes of AOM.

#### Mastoiditis

- Parenteral antimicrobial therapy is indicated for initial management of mastoiditis, and targets primarily *S. pneumoniae,* group A streptococci, and anaerobic bacterial species.
- Incision and drainage may be necessary when abscess is present in the mastoid air cells.

## SHORT VIEW SUMMARY—cont'd

### PREVENTION

#### Otitis Externa

- Patients should be dissuaded from placing foreign objects, including cotton-tipped applicators, in the external canal.
- Use of earplugs, shaking ears dry after swimming, or use of drops with acetic acid, alcohol, or both may be of benefit in individuals with recurrent disease associated with bathing or swimming.

#### Otitis Media

- Chemoprophylaxis may be of value for prevention of episodes of AOM in children with severe and recurrent disease.
- Pneumococcal conjugate vaccines have been effective in reducing episodes of AOM due to vaccine serotypes.
- Influenza virus vaccines reduce the incidence of AOM during the winter respiratory season.

#### Mastoiditis

- Prevention is similar to that of AOM.

# OTITIS EXTERNA

Infection of the external auditory canal (otitis externa) results most often from fluid (water) being trapped in the external canal and causing irritation and maceration of the superficial tissues, permitting local invasion of skin flora. The pain and itching that result may be severe because of the limited space for expansion of the inflamed tissue. Infections of the external canal may be subdivided into four categories: acute localized otitis externa, acute diffuse otitis externa, chronic otitis externa, and malignant otitis externa. Reviews by Senturia and coworkers,[2] Hirsch,[3] and Rubin and Yu[4] provide more complete information.

## Pathogenesis

The external auditory canal is approximately 2.5 cm long from the concha of the auricle to the tympanic membrane (TM). The outer half of the canal is cartilaginous; the medial half tunnels through the temporal bone. A constriction, the isthmus, present at the juncture of the osseous and cartilaginous portions, limits the entry of wax and foreign bodies to the area near the TM. The skin of the canal is thicker in the cartilaginous portion and includes a well-developed dermis and subcutaneous layer. The skin lining the osseous portion is thinner and firmly attached to the periosteum and lacks a subcutaneous layer. Hair follicles are numerous in the outer third and sparse in the inner two-thirds of the canal. Cerumen and debris from epithelial cells accumulate in the canal and are extruded by normal cleansing mechanisms. On occasion, the material may become inspissated and obstruct the canal.

The microbial flora of the external canal is similar to the flora of skin elsewhere. There is a predominance of *Staphylococcus epidermidis, Staphylococcus aureus,* corynebacteria, and, to a lesser extent, anaerobic bacteria such as *Propionibacterium acnes*.[5,6] Pathogens responsible for infection of the middle ear (*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis*) are rarely found in cultures of the external auditory canal when the TM is intact.

The epithelium absorbs moisture from the environment. Desquamation and denuding of the superficial layers of the epithelium may follow. In this warm moist environment, the organisms in the canal may flourish and invade the macerated skin. Inflammation and suppuration follow. Invasive organisms include those of the normal skin flora and gram-negative bacilli, particularly *Pseudomonas aeruginosa.* Invasive otitis externa is a necrotizing infection frequently associated with *P. aeruginosa.* The organism gains access to the deeper tissues of the ear canal and causes a localized vasculitis, thrombosis, and necrosis of tissues. Diabetic microangiopathy of the skin overlying the temporal bone results in poor local perfusion and a milieu for invasion by *P. aeruginosa.*

## Clinical Manifestations and Management

Acute localized otitis externa may occur as a pustule or furuncle associated with hair follicles; the external ear canal is erythematous, edematous, and may be filled with pus and flakes of skin debris. *S. aureus* is the most frequent pathogen. Erysipelas caused by group A streptococcus (GAS) may involve the concha and the canal. Pain may be severe. Bluish-red hemorrhagic bullae may be present on the osseous canal walls and also on the TM. Adenopathy in the lymphatic drainage areas is often present. Local heat and systemic antibiotics are usually curative. Incision and drainage may be necessary to relieve severe pain.

Acute diffuse otitis externa (swimmer's ear) occurs mainly in hot humid weather. The ear itches and becomes increasingly painful. The skin of the canal is edematous and red. Gram-negative bacilli, mainly *P. aeruginosa,* may play a significant role. A severe hemorrhagic external otitis caused by *P. aeruginosa* has been associated with mobile redwood hot tub use.[7] Gentle cleansing to remove debris, including irrigation with warm tap water, should reduce symptoms; alternatively, hypertonic saline (3%) and cleansing with mixtures of alcohol (70% to 95%) and acetic acid may be used. Hydrophilic solutions, such as 50% Burow solution, may be used for 1 to 2 days to reduce inflammation. A cotton wick may be of value in enhancing distribution of the ototopical agent when the canal is significantly swollen. A 10-day regimen of a fluoroquinolone otic solution, such as ofloxacin[8] or ciprofloxacin-dexamethasone otic[9] or eardrops of neomycin alone or with polymyxin combined with hydrocortisone, is effective in reducing local inflammation and infection.

Chronic otitis externa is caused by irritation from drainage through a perforated TM. The underlying cause is chronic suppurative otitis media (OM). Itching may be severe. Management is directed to treatment of the middle ear disorder. Rare causes of chronic otitis externa include tuberculosis, syphilis, yaws, leprosy, and sarcoidosis.

Invasive ("malignant") otitis externa is a severe, necrotizing infection that spreads from the squamous epithelium of the ear canal to adjacent areas of soft tissue, blood vessels, cartilage, and bone.[4,10] Severe pain and tenderness of the tissues around the ear and mastoid are accompanied by the drainage of pus from the canal. Older, diabetic, immunocompromised, and debilitated patients are at particular risk. Life-threatening disease may result from spread to the temporal bone and then on to the sigmoid sinus, jugular bulb, base of the skull, meninges, and brain. Permanent facial paralysis is frequent, and cranial nerves IX, X, and XII may also be affected.[11] *P. aeruginosa* is almost always the causative agent (see Chapter 219). The extent of damage to soft tissue and bone may be identified and monitored with the use of computed tomography and magnetic resonance imaging.[4] Diagnostic testing for comorbid disease should be routine. The canal should be cleansed, and devitalized tissue removed. Topical eardrops with antipseudomonal activity combined with a steroid are instilled into the external auditory canal. Systemic therapy with regimens including activity for *Pseudomonas* spp. should be used for 4 to 6 weeks, in combination with topical therapy. The combination of ceftazidime, cefepime, or piperacillin with an aminoglycoside (gentamicin or tobramycin) should be considered.[11] Oral quinolones with activity against *Pseudomonas* spp., such as ciprofloxacin, have been effective therapy early in the course of invasive external otitis.[12]

*Aspergillus* species, particularly *Aspergillus niger,* may grow in the cerumen and desquamated keratinaceous debris in the external auditory canal, sometimes forming a visible greenish or blackish fluffy colony. Role of the mold in acute otitis externa is usually modest, if it has any role at all, although in the severely immunocompromised patient *Aspergillus* can cause necrotizing otitis externa.[13] *Candida albicans* is also a frequent cause of external otitis in children with chronic mucocutaneous candidiasis.

Infections of the pinna may arise from placement of piercing ornaments in the cartilaginous portions of the ear, unlike the ear lobule where earrings are placed. This may result in chronic infection of the cartilage, often with *P. aeruginosa,* and can lead to severe cosmetic damage to the pinna unless treated early and effectively. Treatment involves removal of the ornament, drainage of fluctuant swelling, and administration of systemic antibiotics. Consultation with an otolaryngologist is advised, and reconstructive surgery may be required.

## OTITIS MEDIA

Acute otitis media (AOM) is an acute illness defined by moderate-to-severe bulging of the TM or new onset of otorrhea not due to acute otitis externa, accompanied by acute signs of illness and signs or symptoms of middle ear inflammation.[1] Otitis media with effusion (OME) is defined by the presence of middle ear fluid without acute signs of illness or inflammation of the middle ear mucosa. It usually follows AOM but may also occur as a result of barotrauma or allergy. The peak incidence occurs in the first 3 years of life. The disease is less common in school-aged children, in adolescents, and in adults. Nevertheless, infection of the middle ear may be the cause of fever, significant pain, and impaired hearing in all age groups. In addition, adults experience the sequelae of OM of childhood: hearing loss, cholesteatoma, adhesive OM, and chronic perforation of the TM.

Three recent factors have altered the incidence, microbiology, and management of OM:

1. Introduction of the 7-valent conjugate pneumococcal vaccine (PCV7) in the United States in 2000 and subsequently the 13-valent vaccine (PCV13) in 2010 has reduced the number of episodes of vaccine serotype pneumococcal AOM and has decreased the incidence of severe and recurrent disease, in addition to altering the distribution of pathogens recovered from the middle ear in children with AOM.
2. Developed in 2004 and updated in 2013, management guidelines from the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) for initial management of AOM are available, including observation without antimicrobial agents in selected cases[1,14] (Table 61.1).
3. These guidelines also emphasize the management of pain as part of the initial approach to treatment of AOM. Further details of the AAP/AAFP guidelines for the management of AOM and OME are discussed in the therapy section and in the accompanying references.[1,14,15,16]

### Epidemiology

The epidemiology of AOM has been altered by the universal immunization of birth cohorts of children with pneumococcal conjugate vaccine (PCV) in the United States since 2000. An overall decline in AOM and complex OM has been observed in children.[17,18] Recently, the cumulative incidence of OM at 7 years was reported to be 60.6% in Danish children, with 16.2% reporting their first OM episodes at 0 to 6 months of age, 44.3% at 7 to 18 months, and 39.5% at 19 months to 7 years. Four or more OM episodes by age 7 years were reported by 64.0% of those who had their OM debut at 0 to 6 months, supporting the concept of "early and often" as a strong predictor of the child at risk for recurrent or complex disease.[19] OM is infrequent in adults, but the bacteriologic characteristics and therapy are similar to those in children.[20]

Longitudinal studies have provided information about the characteristics of children at greatest risk for recurrent and severe episodes of AOM. The vast majority of children have no obvious anatomic defect or immunologic deficiency responsible for severe and recurrent OM, but a small number have anatomic changes (cleft palate, cleft uvula, submucous cleft), alteration of normal physiologic defenses (patulous eustachian tube), or congenital or acquired immunologic deficiencies. An increased incidence of AOM occurs in children with Down syndrome.[21] Children with acquired immunodeficiency syndrome have a higher age-specific incidence of OM, beginning at 6 months of age.[22] Pichichero and colleagues have reported subtle T-cell and B-cell defects in children with recurrent OM manifesting as reduced responses to vaccine antigens.[23]

AOM occurs more often in males than in females and is observed more frequently when a family history (sibling or parent) is present. Concurrence in development of recurrent OM among identical twins supports a likely genetic susceptibility. Proinflammatory cytokine gene polymorphisms and polymorphisms in immunoresponse genes were also associated with recurrent AOM.[24,25] The age at the time of the first episode of AOM appears to persist as one of the most powerful predictors of recurrent middle ear infections. Breast-feeding for 3 or more months is associated with a decreased risk of AOM in the first year of life. Native Americans, Alaskan and Canadian Eskimos, and Aboriginals have an extraordinary high incidence and severity of OM.

The role of increased exposure to infectious agents and the importance of environmental pollutants have been identified in studies of the incidence of infection in group daycare and the effects of passive smoking on children. The introduction of infants into large daycare groups increases the incidence of respiratory infections, including OM. The daycare risk of infection is associated with the number of children in the facility. Children in daycare not only have more episodes of AOM than children in home care but have more complex disease, as measured by the need for more surgical procedures. A study of Pittsburgh children observed from birth through the second year of life noted that myringotomy and tympanostomy tube placements were performed in 21% of children in group daycare and in only 3% of children in home care.[26] Exposure to tobacco smoke documented by measuring a nicotine metabolite, cotinine, in saliva and urine was correlated with an increased incidence of new episodes of OME and the duration of effusion.[27] Kim and coworkers[28] have identified an association of invasive pneumococcal disease and OM with atmospheric conditions, air pollution (identified by levels of sulfur dioxide), and the isolation of respiratory viruses.

### Pathogenesis

The middle ear is part of a continuous system that includes the nares, nasopharynx, and eustachian tube medially and anteriorly and the mastoid air cells posteriorly. These structures are lined with a respiratory epithelium that contains ciliated cells, mucus-secreting goblet cells, and cells capable of secreting local immunoglobulins.

Anatomic or physiologic dysfunction of the eustachian tube appears to play a critical role in the development of OM. The eustachian tube has at least three physiologic functions with respect to the middle ear: protection of the ear from nasopharyngeal secretions, drainage into the nasopharynx of secretions produced within the middle ear, and ventilation of the middle ear to equilibrate air pressure with that in the external ear canal. When one or more of these functions is compromised, the results may be the development of fluid and infection in the middle ear. Most episodes of AOM occur in the following sequence: congestion of the mucosa of the upper respiratory tract, most often caused by a

**TABLE 61.1 Criteria for Initial Antibacterial-Agent Treatment or Observation in Children With AOM**

| AGE | UNILATERAL/BILATERAL AOM[a] WITH SEVERE SYMPTOMS[b]; AOM WITH OTORRHEA[a] | BILATERAL, NONSEVERE AOM[a] WITHOUT OTORRHEA | UNILATERAL, NONSEVERE AOM WITHOUT OTORRHEA[a] |
|---|---|---|---|
| < 6 mo | Antibiotic treatment | Antibiotic treatment | Antibiotic treatment |
| 6 mo to 2 yr | Antibiotic treatment | Antibiotic treatment | Antibiotic treatment or initial observation[c] |
| 2 yr | Antibiotic treatment | Antibiotic treatment or initial observation[c] | Antibiotic treatment or initial observation |

*AOM,* Acute otitis media.
[a]Applies only to children with well-documented AOM with high certainty of diagnosis.
[b]A toxic-appearing child, or persistent otalgia more than 48 hours, or temperature ≥39°C (102.2°F) in the past 48 hours, or if there is uncertain access to follow-up after the visit.
[c]This plan of initial management provides an opportunity for shared decision-making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48 to 72 hours of AOM onset.
Modified from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013;131:e964.

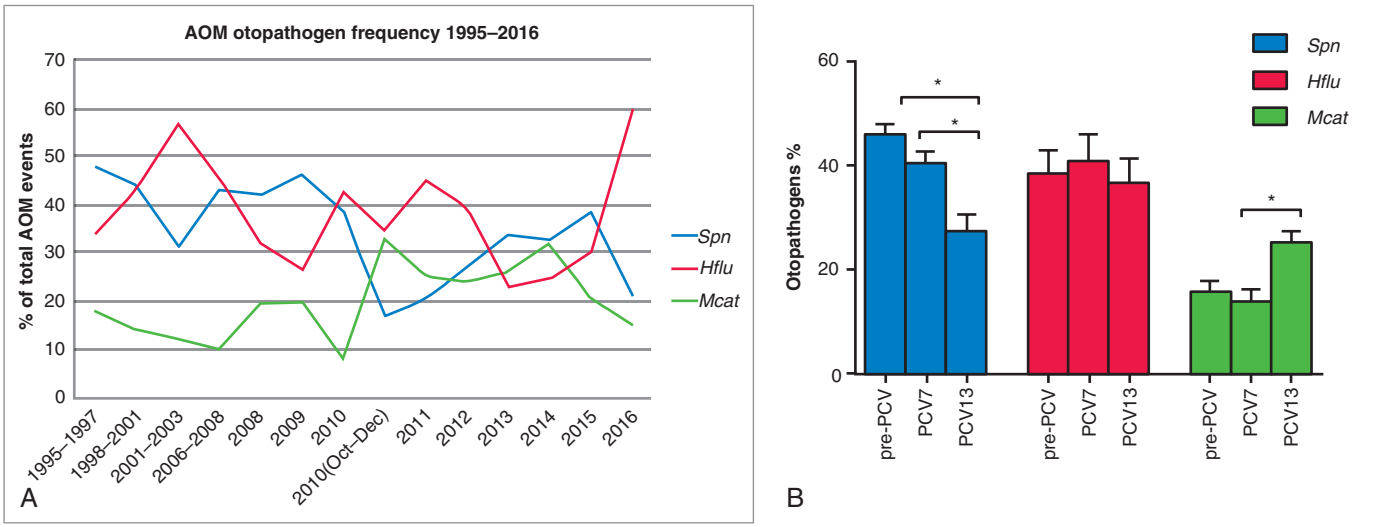


**FIG. 61.1 Bacterial pathogens isolated from middle ear fluid in children with acute otitis media (AOM).** (A) Frequency of otopathogens from MEF during AOM from 1995 to 2016. (B) Changes in otopathogen prevalence in different vaccine eras. *Hflu, Haemophilus influenzae; Mcat, Moraxella catarrhalis; PCV,* pneumococcal conjugate vaccine; *Spn, Streptococcus pneumoniae. (From Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era.* Pediatrics. *2017;140:e2070181.)*

respiratory viral infection and swelling of the mucosa of the eustachian tube, progressing to obstruction of the tube at its narrowest section, the isthmus. Persistence of fluid for weeks to months after episodes of adequately treated AOM is commonplace. Recent evidence supports the presence of bacterial biofilms on the middle ear mucosa as playing a major role in development of OME and complex OM.[29]

## Microbiology

**Bacteria.** The bacteriology of OM has been documented through appropriate cultures of middle ear effusions obtained with needle aspiration. Many studies of the bacteriology of AOM have been performed. The results are remarkably consistent in demonstrating the importance of *S. pneumoniae* and *H. influenzae* in all age groups. Initial studies after the introduction of PCV suggest that *H. influenzae* had replaced *S. pneumoniae* as the most frequently isolated pathogen of AOM in children (Fig. 61.1).[30,31] The most recent studies[32] report a nearly equal distribution of bacterial pathogens—*S. pneumoniae,* nontypable *H. influenzae,* and *M. catarrhalis*. *S. pneumoniae* remains an important cause of bacterial OM in most regions of the world.[33] Wherever PCV has been introduced, a decline in disease due to vaccine serotypes has been observed and serotypes 15A, 15B, 15C, 21, 23A, 23B, and 11A have emerged as most common.[34,35]

OM caused by *H. influenzae* is associated with nontypeable strains in the vast majority of patients. Before the introduction of *H. influenzae* type B conjugate vaccines, 10% of otitis cases were caused by *H. influenzae* type B; the condition was frequently severe and accompanied by bacteremia or meningitis. Type B is now rare because of the efficacy of the conjugate polysaccharide vaccine. Nontypeable strains of *H. influenzae* are a significant cause of OM in patients of all ages.[20] *H. influenzae* is the primary pathogen in the common conjunctivitis-AOM syndrome.[36]

*M. catarrhalis* was isolated from approximately 10% of children with AOM[37] in the past and was usually associated with a mild form of disease; however, recent studies have suggested that an increased proportion of cases are due to this pathogen. It is unclear, though, whether the incidence has increased. Today, most strains produce β-lactamase and are resistant to penicillin G, ampicillin, and amoxicillin.

*S. aureus,* including methicillin and multidrug-resistant strains, is an uncommon cause of AOM but is common in cases with persistent otorrhea that follows insertion of tympanostomy tubes.[38]

During the preantibiotic era, AOM caused by GAS was a frequent cause of severe AOM, frequently complicated by mastoiditis and often associated with scarlet fever. For reasons unknown, AOM caused by GAS is now uncommon. A survey in Israel identified GAS as being responsible for 3.1% of 11,311 episodes of AOM.[39] There is an increased proportion of cases due to GAS in children with otorrhea.

### Viruses

Virologic and epidemiologic studies have suggested that viral infection is frequently the initial event in the development of AOM.[40,41,42,43,44,45] Respiratory viruses have been isolated from the nasopharynx in up to 50% of children with AOM and have been detected in approximately 25% of middle ear fluids of children with AOM. Respiratory syncytial virus (RSV), influenza virus, enteroviruses, coronaviruses, and rhinoviruses were the most common viruses found in middle ear fluids.[40,41,42,43] Combined viral and bacterial infections are frequent and may be more severe than bacterial infection alone.[43,44,45] Chonmaitree and coworkers[44] noted that in a higher proportion of patients with viruses and bacteria in middle ear fluids, the bacteria had failed to clear 2 to 4 days after initiation of therapy, compared with the group in which bacteria alone were present.

### *Mycoplasma, Chlamydia,* and Unusual Organisms

*Mycoplasma pneumoniae* was responsible for hemorrhagic bullous myringitis in a study of nonimmune volunteers inoculated with the organism.[46] However, the middle ear fluid of a large number of patients (771) has been studied, and *M. pneumoniae* was isolated in only one case.[47,48] Although mycoplasmas do not appear to play a significant role in AOM, some patients with lower respiratory tract disease caused by *M. pneumoniae* may have concomitant OM.

*Chlamydia trachomatis* is associated with acute respiratory infections in infants younger than 6 months and is a cause of acute infection of the middle ear in this age group. The organism has been isolated from middle ear fluid of infants with acute infection.[49]

Uncommon forms of otitis include diphtheritic otitis, tuberculous otitis, otogenous tetanus, otitis caused by *Mycobacterium chelonae,*[50] and otitis caused by *Ascaris lumbricoides* or Wegener granulomatosis. Fungi are frequently associated with external otitis but rarely cause AOM; *Candida* and *Aspergillus* spp. have been isolated from middle ear fluids of immunodeficient patients who develop chronic suppurative OM.

## Immunology

The importance of host defenses in protecting the middle ear is supported by the observations that AOM is more common in children with immune deficiency and may be the presenting complaint, especially when the defect is related to antibody production against encapsulated

bacterial pathogens.[51] Protection against bacterial OM has been observed after passive immunization with immune globulin and after immunization with polysaccharide conjugate vaccines, further demonstrating the role of host defense in protecting the middle ear from bacterial infection.[52,53–54]

## Diagnosis and Clinical Course

AOM is an acute illness defined by moderate-to-severe bulging of the TM or new onset of otorrhea not due to acute otitis externa, accompanied by acute signs of illness and signs of middle ear inflammation. Signs and symptoms may be specific, such as ear pain, ear drainage, or hearing loss, or nonspecific, such as fever, lethargy, or irritability. Vertigo, nystagmus, and tinnitus may occur. Redness of the TM is an early sign of OM, but erythema alone is not diagnostic of middle ear infection because it may be caused by inflammation of the mucosa throughout the upper respiratory tract. However, AOM may manifest with intense erythema of the TM as the only otoscopic finding.[1]

The presence of fluid in the middle ear is determined by the use of pneumatic otoscopy, a technique that permits an assessment of the mobility of the TM. The motion of the TM is proportional to the pressure applied by gently squeezing and then releasing the rubber bulb attached to the head of the otoscope. Normal mobility is apparent when positive pressure is applied and the TM moves rapidly inward; with release of the bulb and the resulting negative pressure, the membrane moves outward. Fluid or high negative pressure in the middle ear dampens the mobility of the TM. Adjunctive techniques are available to confirm the results of otoscopic examinations and assist in the accuracy of diagnosis. Tympanometry uses an electroacoustic impedance bridge to record compliance of the TM and middle ear pressure. This technique presents objective evidence of the status of the middle ear and the presence or absence of fluid.[55] Acoustic reflectometry measures sound reflectivity from the middle ear and is able to distinguish an air- or fluid-filled space. Spatial gradient analysis is correlated with the probability of middle ear effusion in children.[56] In addition to a professional model, a consumer model (Innovia Medical, Omaha, NE) is available that permits home monitoring of the development or persistence of middle ear fluid.

Fluid persists in the middle ear for prolonged periods after the onset of AOM, even though symptoms usually resolve within a few days after the initiation of antimicrobial therapy. About 70% of children with OM have fluid in the middle ear 2 weeks after the onset of disease, 40% still have fluid 1 month after the onset, and 10% still have fluid 3 months after the first signs of middle ear infection.[15]

Patients with middle ear effusion develop hearing loss of variable severity. On average, a patient with fluid in the middle ear has a 25-dB (pure-tone average) loss.[57] Because the development of speech, language, and cognitive skills is dynamic during infancy, when the incidence of AOM is highest, there is concern that any impediment to reception or interpretation of auditory stimuli might have an adverse effect. Children with histories of recurrent episodes of AOM score lower in tests of speech, language, and cognitive abilities than their disease-free peers.[58,59]

The results of microbiologic studies of middle ear effusions in patients with AOM are so consistent that the choice of antimicrobial agents may be based on knowledge of the bacteriologic characteristics of OM acquired from the many investigations, rather than on the results of cultures from other sites, such as the throat or nasopharynx (see Fig. 61.1). If the patient is in a toxic condition or has focal infection elsewhere, cultures of samples of the blood and of the focal infection are warranted. Needle aspiration of the middle ear effusion (tympanocentesis) to define the microbiologic characteristics of the infection should be considered in select patients—the patient who is critically ill at the onset, the patient who has not responded to initial antimicrobial therapy in 48 to 72 hours and is in a toxic condition, and the patient with altered host defenses (e.g., an immunologic defect, including the newborn infant).

## Management

### Acute Otitis Media

#### Systemic and Topical Treatment of Otalgia

Pain is a common feature of AOM and may be severe. The AAP recommends treatment to reduce ear pain in children with AOM whether or not they are treated with antibiotics. Acetaminophen or ibuprofen is effective analgesia for mild-to-moderate pain. Topical procaine, or lidocaine preparations (if available) are an alternative for children 2 years of age or older but should not be used in children with TM perforation. Performance of incision and drainage of the middle ear abscess by means of tympanostomy or myringotomy usually requires otolaryngologic support but provides immediate relief.[1]

#### Antibiotic Therapy Versus Observation

In addition to pain control, there are two strategies for initial management of AOM: (1) immediate treatment with antibiotics and (2) observation with initiation of antibiotic therapy if the symptoms and signs worsen or fail to improve after 48 to 72 hours.

The choice of strategy depends on the age of the child, the severity of illness, and parental preference (Table 61.1). AAP guidelines recommend that children younger than 6 months with AOM be treated with an appropriate antibiotic at the time of diagnosis. In addition, those younger than 60 days or with high fever or severe irritability may require additional diagnostic evaluation for systemic illness.

Randomized trials support initial treatment for children 6 months to 2 years old with unilateral or bilateral AOM.[60,61] In children 2 years of age or older who are otherwise healthy children with mild symptoms and signs and no otorrhea, AAP guidelines support initial observation as an appropriate option; initial antibiotic treatment is recommended for those who appear toxic, have had persistent otalgia for more than 48 hours, have had a temperature of 102.2°F (39°C) or higher in the past 48 hours, or have bilateral AOM or otorrhea.

#### Selection of Antimicrobial Agents

The preferred antimicrobial agent for the patient with AOM must be active against *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. GAS and *S. aureus* are infrequent causes of AOM and need not be considered in initial therapeutic decisions. Gram-negative enteric bacilli and methicillin-resistant *S. aureus* must be considered when OM occurs in the newborn infant, in the patient with a depressed immune response, and in the patient with a tympanostomy tube in place. The antimicrobial agent should achieve concentrations in middle ear fluid above the expected minimal inhibitory concentration of the likely pathogens. Craig and Andes[62] have examined the relationship between bacteriologic cure in OM and serum and middle ear fluid concentrations for various antimicrobial agents. For β-lactam antibiotics, they found that a bacteriologic cure required the presence of serum concentrations above the minimal inhibitory concentration for at least 40% of the dosing interval.

There are now 19 antimicrobial agents approved by the U.S. Food and Drug Administration (FDA) for AOM. Amoxicillin remains the drug of choice for initial treatment because of its 25-year record of clinical success, acceptability, limited side effects, and relatively low cost. The drug is ineffective against β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*. In situations such as the otitis conjunctivitis syndrome or in children recently treated with amoxicillin, the likelihood of disease due to β-lactamase–producing nontypeable *H. influenzae* is increased (in the United States), and initial therapy with amoxicillin clavulanate may be warranted.

The recommendation of increasing the dose of amoxicillin to 90 mg/kg/day achieves higher concentrations in middle ear fluid and further reduces the number of children in whom amoxicillin therapy will fail because of resistant pneumococci. Alternatives to amoxicillin include amoxicillin-clavulanate, sulfa-containing regimens or trimethoprim-containing preparations (erythromycin plus sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole), two macrolides (azithromycin and clarithromycin), nine oral cephalosporins (cephalexin, cefaclor, cefixime, ceftibuten, cefprozil, cefpodoxime, cefuroxime axetil, loracarbef, and cefdinir), and one parenteral cephalosporin (ceftriaxone). Two topical fluoroquinolones, ofloxacin and ciprofloxacin-dexamethasone otic, are effective in children who have tympanostomy tubes and develop acute otorrhea. Currently only high-dose amoxicillin and amoxicillin-clavulanate and parenteral administration of ceftriaxone achieve sufficient middle ear concentrations to be effective against penicillin-resistant *S. pneumoniae*.

If amoxicillin therapy fails, preferred regimens include the increased dose of amoxicillin clavulanate (90 mg/kg/day in two doses) or intramuscular ceftriaxone (50 mg/kg once a day for 1 to 3 days). For children with severe and recurrent AOM, the use of tympanocentesis to identify the bacterial pathogen and susceptibility pattern may be necessary in order to choose the most effective drug. For children with known and severe allergy to β-lactam antibiotics, a macrolide (erythromycin plus sulfisoxazole, azithromycin, or clarithromycin) is preferred, but trimethoprim-sulfamethoxazole may be useful in regions where pneumococcal resistance to this combination is not a concern.

Some children with AOM caused by a bacterial pathogen improve without the use of antimicrobial agents.[63,64–65] Howie and Ploussard[65] performed sequential aspirations of middle ear fluid in children with AOM 2 to 7 days apart, with placebo given instead of an antibacterial drug. They found that 19% of middle ear fluids infected initially with pneumococci became sterile, and 48% of middle ear fluids infected initially with *H. influenzae* became sterile. The discrepancy between the proportions of infections becoming sterile after infection with the two bacterial species indicates that a simple mechanical effect (drainage of the infected fluid via a patent eustachian tube or a perforated TM) was unlikely to be responsible for the microbiologic effect. It is more likely that host defenses, probably based on humoral or cellular immunity, act preferentially to rid the infected ear of *H. influenzae* more frequently than *S. pneumoniae*.

The microbiologic results indicating that many children have AOM caused by a viral pathogen, and that some of the episodes of bacterial OM resolve without antibacterial drugs, prompted some European physicians to withhold initial antibiotic therapy from children with ear infections.[66,67] The option of observation of children with AOM rather than initial antimicrobial therapy is practiced extensively in Western Europe.[68] Two randomized controlled studies of initial antimicrobial therapy with amoxicillin-clavulanate compared with initial observation for children younger than 2 years with AOM demonstrated increased rates of treatment failure and TM perforation in those assigned initial observation.[60,61]

With appropriate antimicrobial therapy, most children with AOM are significantly improved within 48 to 72 hours. In children with persistent fever or bulging of the TM after 48 hours, antimicrobial treatment should be initiated in those managed with initial observation, or a change in antimicrobial treatment should be considered for those initially managed with amoxicillin.

## Treatment of Otitis Media With Effusion

OME is defined as fluid in the middle ear without signs or symptoms of acute illness. Most episodes resolve spontaneously within months; however, some patients have persistent disease that may last for 3 to 6 months, or longer. Persistent middle ear effusion may be associated with hearing loss, balance problems, sleep disorders, or poor school performance. The American Academy of Otolaryngology–Head and Neck Surgery Foundation, the AAP, and the AAFP have updated the 2004 guidelines for the management of OME.[69] The guidelines support improved diagnostic criteria including use of pneumatic otoscopy and observation in otherwise healthy children with middle ear effusion for a minimum of 3 months, and recommend against the use of antihistamines and decongestants, intranasal and systemic steroids, and antibiotics for treatment of persistent of middle ear effusion. The guidelines recommend that special consideration be given to children with underlying speech and language disorders; tympanostomy tubes be placed only (in the absence of other indications for tonsillectomy or adenoidectomy such as sleep apnea) when surgery is performed in children younger than 4 years; and adenoidectomy with tympanometry tubes be considered when surgery is indicated in children older than 4 years.[69]

## Surgical Management

Surgical management of recurrent episodes of AOM and persistent effusion of the middle ear includes use of myringotomy, adenoidectomy, and the placement of tympanostomy tubes. Myringotomy, or incision of the TM, is a method of draining middle ear fluid. Before the introduction of antimicrobial agents, myringotomy was the primary method of managing suppurative OM. Today, the use of myringotomy is limited to the relief of intractable ear pain, hastening resolution of mastoid infection, and drainage of persistent middle ear effusion that is unresponsive to medical therapy.

Tympanostomy tubes resemble small collar buttons. They are placed through an incision in the TM to provide drainage of fluid and ventilation of the middle ear. The placement of these tubes is now one of the most common surgical procedures in children. Hearing improves dramatically after placement of the ventilating tubes. Placement of tympanostomy tubes has also been part of the management of children with AOM due to multidrug-resistant *S. pneumoniae*.[74] The major complication of tympanostomy tube insertion is persistent otorrhea.[81] This may involve staphylococcal species and biofilm formation on the tube.

## Prevention of Acute Otitis Media

Prevention of severe and recurrent episodes of AOM includes chemoprophylaxis, use of bacterial and viral vaccines, and surgery.

## Chemoprophylaxis

Chemoprophylaxis has been shown to be of value for the prevention of acute illness in children who have had recurrences of middle ear infections. A variety of studies, including various antimicrobial agents and a placebo, have documented the efficacy of an antimicrobial agent in modified dosage in reducing the number of episodes of acute febrile illnesses caused by OM.[70,71] However, a modified dosage form of an antimicrobial agent may select resistant strains in the nasopharynx, and chemoprophylaxis should be considered only for children with severe and recurrent infections. Children should be considered for prophylaxis if they have had two episodes of AOM in the first 6 months of life or, in older children, three episodes in 6 months or four episodes in 1 year. Amoxicillin, 20 to 40 mg/kg, or sulfisoxazole, 50 mg/kg, may be administered once daily. Chemoprophylaxis may suppress symptoms of OM, but asymptomatic middle ear effusion may persist. The physician who chooses to use chemoprophylaxis to prevent acute recurrent disease must examine the patient at approximately 1-month intervals for middle ear effusion.

Because of concern for development of multidrug-resistant bacteria in patients receiving chemoprophylaxis, the 2013 guidelines of the AAP and the AAFP discourage chemoprophylaxis. The guidelines suggest prevention by placement of tympanostomy tubes, although it necessitates a surgical procedure and anesthesia.[1] Physicians must discuss with the parent the risk-benefit ratio of antibiotic prophylaxis versus surgery for prevention of further severe AOM.

## Pneumococcal Vaccines

Pneumococcal polysaccharide vaccines were inconsistently immunogenic and demonstrated limited protection against pneumococcal OM.[72,73] However, PCVs have had a significant impact on manifestations of OM associated with pneumococcal serotypes represented in the vaccine (Fig. 61.2).

A 7-valent conjugate pneumococcal polysaccharide vaccine, using a diphtheria toxin mutant (CRM197) as the protein carrier (Prevnar; Wyeth Pharmaceuticals [a subsidiary of Pfizer], Madison, NJ), demonstrated efficacy and effectiveness against vaccine-type invasive disease and resulted in a 60% decline in overall invasive pneumococcal disease. PCV7 was also efficacious in reducing vaccine serotype pneumococcal OM but had a more modest effect on overall AOM.[52] The vaccine reduced the number of episodes of AOM by 7% and reduced the number of procedures for placement of ventilating tubes by 23%, reflecting a decline in recurrent episodes and complex OM. The reduction in number of episodes of pneumococcal AOM was 34%, but the reduction in episodes caused by vaccine serotype disease was 57%. Of concern were increases in the number of episodes of AOM caused by nonvaccine organisms in children who received PCV7, a 33% increase in nonvaccine serotype pneumococcal AOM, and an 11% increase in episodes caused by *H. influenzae*. These data suggested that the vaccine was successful in reducing carriage of vaccine serotypes but that pneumococcal carriage was replaced with nonvaccine serotypes, which subsequently spread from the upper respiratory tract to the middle ear to cause AOM. An example of this serotype replacement was the emergence of

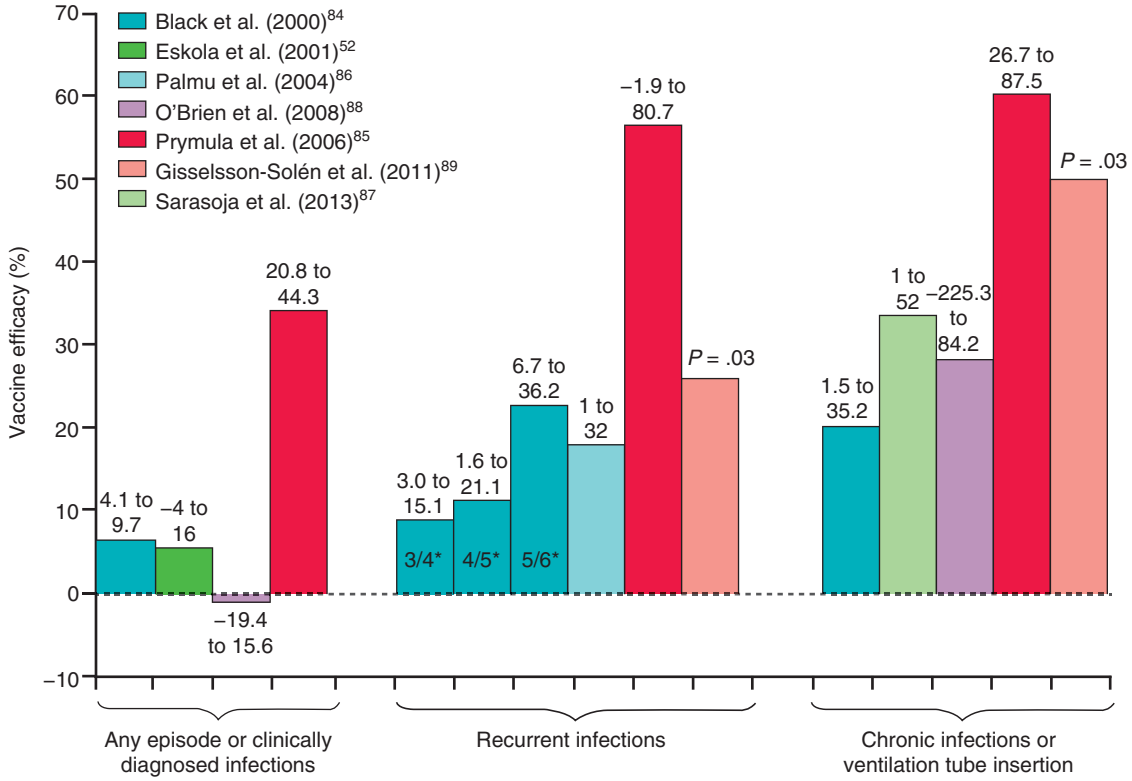


**FIG. 61.2 Impact of pneumococcal conjugate vaccine on acute otitis media, recurrent otitis media, and chronic infection or tympanostomy tube insertions.** *Data are number of episodes in 6 months and 12 months in the Northern California Kaiser Permanente study.[52] †Parents were not blinded to their child's allocation to the vaccine or control group, although they were asked not to reveal this to the study personnel. *(From Dagan, Pelton S, Bakaletz L, et al. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease.* Lancet Infect Dis. *2016;16:480–492.)*

multidrug-resistant serotype 19A, a strain not included in PCV7, as an increasing cause of invasive disease and OM.[74]

PCV13 (Prevnar 13, Wyeth Pharmaceuticals) was introduced in 2010 and replaced PCV7 in the United States. In addition to the serotypes in PCV7, the additional serotypes, including types 1, 3, 5, 6A, 7V, and 19A, were added. Dagan and colleagues[35] reported declines in AOM due to the unique vaccine serotypes in PCV13 with no significant increase in disease due to non-PCV13 serotypes. Marom and colleagues observed an overall downward trend in OM-related health care visits after the introduction of PCV7. They also observed a significant reduction in OM visit rates, tympanostomy tube insertions, and mastoiditis in 2010 and 2011 in children younger than 2 years in concert with the introduction of PCV13.[18] The proposed mechanism for the reduction in complex OM and tympanostomy tube insertion is the prevention of early episodes of pneumococcal OM and a reduction in subsequent episodes.[17] Unfortunately, studies of PCV7 administered to children who had already had two or more episodes of OM in the prior year failed to demonstrate any reduction in otitis.[75] A 10-serotype vaccine with most of the pneumococcal polysaccharides conjugated to protein D from nontypeable *H. influenzae* with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23 was studied and subsequently licensed (Synflorix; GlaxoSmithKline Biologicals). A large clinical trial demonstrated a 16.1% vaccine efficacy against clinically confirmed AOM and 67% against vaccine serotype clinically confirmed AOM. The vaccine has been licensed globally but is not available in the United States.

## Respiratory Virus Vaccines

Because of the importance of respiratory viruses in the pathogenesis of AOM, viral vaccines could be of preventive value. Inactivated parenteral influenza virus vaccines were documented to decrease the incidence of AOM in children in daycare in Finland[76] and North Carolina.[77] A reduction of 30% of episodes of febrile OM was also reported in children after the receipt of live-attenuated intranasal influenza vaccine.[78] High-titer RSV immune globulin and RSV monoclonal antibody (palivizumab) have been studied for prevention of RSV respiratory disease.[79,80] The RSV immune globulin, but not the monoclonal antibody, was effective in reducing the number of episodes of AOM.

## Additional Complications of Acute Otitis Media

Perforation of the TM is the most common complication of AOM and occurs most frequently in younger children. Certain ethnic groups, such as Alaskan Eskimos and Native Americans, have a higher rate of spontaneous perforation with AOM. Differentiation between AOM with perforation and acute otitis externa can be difficult. In general, the history of increasing pain with relief when otorrhea occurs is found with AOM, whereas increasing pain without relief in the face of otorrhea is seen with otitis externa. The natural history of AOM with perforation is usually complete resolution with healing of the TM. Topical otic suspensions, either ofloxacin or ciprofloxacin administered through a tympanostomy tube, are the preferred therapy for uncomplicated episodes of acute otorrhea.

Facial palsy is less frequent with the routine use of antibiotic therapy. Facial weakness and earache are the predominant symptoms. Management with antimicrobial agents and myringotomy (with or without tube insertion) is usually sufficient to achieve complete resolution.

Labyrinthitis develops when AOM spreads (through the round window) into the cochlear space. The process may be suppurative or serous (due to toxins). The onset of labyrinthitis is often sudden, with vertigo and hearing loss being characteristic. Acute surgical intervention (myringotomy with tube insertion) with antimicrobial therapy is the treatment of choice.

Gradenigo syndrome is a rarely seen complication of AOM in which infection spreads to the apex of the petrous temporal bone. A triad of symptoms consisting of unilateral periorbital pain due to trigeminal nerve involvement, diplopia due to sixth nerve palsy, and persistent otorrhea is present. This classic triad has become very uncommon in the antibiotic era.

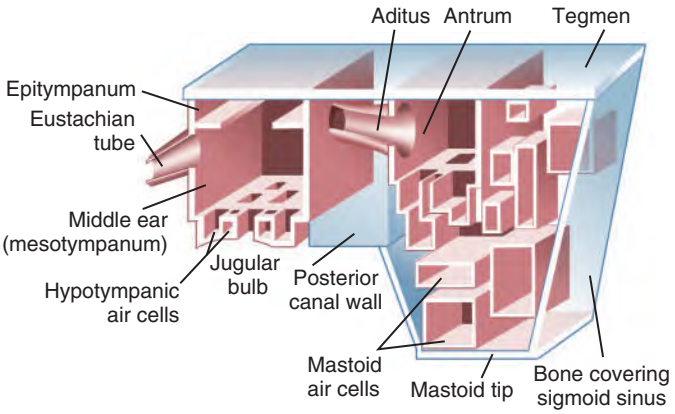


**FIG. 61.3 Diagrammatic representation of the anatomy of the middle and mastoid air cell system showing the narrow connection (aditus and antrum) between the two.**

## MASTOIDITIS

The mastoid is the portion of the petrous temporal bone that lies superior to the middle ear cavity. The mastoid is composed of interconnecting air-filled cells. The mastoid antrum serves as an open passage between the middle ear and mastoid air cells (Fig. 61.3). Thus, most cases of AOM with fluid filling the middle ear space are associated with some degree of inflammation of the mastoid air cells. The incidence of clinically significant mastoiditis, however, declined dramatically once antimicrobial therapy became available for AOM. Nevertheless, acute mastoiditis still occurs and may be responsible for severe illness.

At birth, the mastoid consists of a single cell, the antrum, connected to the middle ear by a small channel. Pneumatization of the mastoid bone takes place soon after birth and is extensive by 2 years of age. The clinical importance of the mastoid is related to contiguous structures, including the posterior cranial fossa, the middle cranial fossa, the sigmoid and lateral sinuses, the canal of the facial nerve, the semicircular canals, and the petrous tip of the temporal bone. The mastoid air cells are lined with modified respiratory mucosa, and all are connected with the antrum. Mastoiditis can occur at any age and may be particularly severe in older adults.[82,83]

Infection in the mastoid follows middle ear infection. Initially, there is hyperemia and edema of the mucosal lining of the air cells followed by serous and then purulent exudate. Necrosis of bone with destruction of the bony septa followed by coalescence of pus results in abscess cavities.

The bacteriology of mastoiditis is the same as that of AOM, including *S. pneumoniae* and *H. influenzae* as the major pathogens. Patients with persistent perforation of the TM may have invasion of organisms from the ear canal, including *Pseudomonas* spp. A pattern similar to the changes in pneumococcal isolates responsible for AOM, the emergence of multidrug-resistant serotype 19A, after the introduction of PCV7 was also observed in children with acute mastoiditis.[83]

### Clinical Manifestations

Acute mastoiditis is usually but not universally accompanied by AOM. During early stages, the signs are those of AOM with otalgia, and fever. Subsequently, swelling, redness, and tenderness are present behind the auricle, over the mastoid bone. The pinna may be displaced outward and downward. A purulent discharge may emerge through a perforation in the TM.

Chronic mastoiditis can develop, usually in association with chronic OM. Infection within the mastoid cells may slowly evolve into an indolent, painless chronic process, with chronic drainage from the external auditory canal through a perforated TM. Decreased hearing is usual and may be accompanied by a cholesteatoma or osteomyelitis of the ossicles. Extension through the tympanum or apex of the middle ear may cause an abscess in the contiguous temporal lobe or may extend posteriorly, causing septic thrombosis of the lateral sinus. Organisms include *S. aureus,* mycobacteria, or molds, usually *Aspergillus.* Mastoidectomy and resection of the cholesteatoma are essential for treatment, which may include tympanoplasty and sometimes resection of the ossicles. Antimicrobial therapy may need to continue for 6 weeks or more in order to prevent relapse.

### Diagnosis

Radiographs of the mastoid area may show a loss of sharpness, demineralization of bony septa, and cloudiness. Computed tomography is helpful in delineating the extent of disease and determining if abscess is present. If the TM is not perforated, tympanocentesis should be performed to obtain material from the middle ear. If otorrhea is present, culture can be performed once the canal has been cleaned and fresh pus obtained as it exudes from the TM.

### Management

The antimicrobial drugs of choice for acute infection are similar to those for AOM: antibiotics with activity against *S. pneumoniae* and *H. influenzae.* Commonly, initial therapy is parenteral ceftriaxone. If the disease in the mastoid has had a prolonged course, coverage for *S. aureus* and gram-negative enteric bacilli may be considered for initial therapy until the results of cultures become available. A mastoidectomy is performed if an abscess has formed in the mastoid bone. The procedure should be performed after initial antimicrobial agents have controlled sepsis.

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*The complete reference list is available online at Expert Consult.*

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# 62 Sinusitis

*Gregory P. DeMuri and Ellen R. Wald*

## SHORT VIEW SUMMARY

**Definition**
- Sinusitis is defined as an inflammatory disorder of the paranasal sinuses.

**Epidemiology**
- Bacterial infection of the sinuses is estimated to occur in 0.5% to 2% of cases of viral upper respiratory infection (URI) in adults and in 6% to 13% of children.

**Microbiology**
- Classic studies of the bacteriology of sinusitis have obtained a specimen of sinus secretions by puncture of the maxillary antrum to reduce the risk of nasal contamination.
- Historically, *Streptococcus pneumoniae* was the most frequently isolated organism, followed by nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis*.
- The frequency of isolation of *S. pneumoniae* has decreased recently, along with an increase in β-lactamase–producing *H. influenzae*.
- *Staphylococcus aureus* is not likely a significant cause of acute sinusitis but does play a role in the complications of sinusitis.

**Diagnosis**
- Imaging studies are not indicated for the routine diagnosis of acute sinusitis but may be useful when complications are suspected.
- The following three clinical presentations will identify patients with acute bacterial sinusitis:
  - Onset with *persistent* symptoms or signs, lasting at least 10 days without evidence of substantial clinical improvement
  - Onset with severe symptoms or signs of high fever (≥39°C) and purulent nasal discharge lasting for 3 to 4 consecutive days
  - Onset with worsening symptoms or signs characterized by the new development of fever, headache, or increase in nasal discharge after a typical viral URI that lasted 5 to 6 days with initial improvement

**Therapy**
- For most adults and children, amoxicillin with or without potassium clavulanate remains an excellent first-line agent for the treatment of sinusitis.
- Second-line agents include fluoroquinolones, cefdinir, cefuroxime, or the combination of cefixime with either clindamycin or linezolid.
- The duration of therapy should be for 7 days after the patient becomes free of signs and symptoms.
- Adjunctive therapies, such as antihistamines, decongestants, nasal steroids, and nasal washes, provide minimal improvement in acute sinusitis.
- Surgical drainage is indicated for the complications of acute bacterial sinusitis.

Sinusitis is defined as an inflammatory disorder of the paranasal sinuses. This condition is one of the most common reasons for a patient to seek care from their primary care physician and is responsible for more than 20 million antibiotic prescriptions per year in the United States.[1] Sinusitis may be classified as acute or chronic. Because most cases of acute bacterial sinusitis are secondary to a viral upper respiratory infection (URI) or allergic inflammation, nasal inflammation is a common finding, and some experts refer to this complex as rhinosinusitis. However, in these instances of bacterial superinfection of the paranasal sinuses, the nose is merely a conduit for the secretions originating in the sinuses. The preferred term is acute community-acquired bacterial sinusitis.[2]

Evidence of maxillary sinusitis has been found in human archeologic specimens discovered in Africa, North America, and Europe.[3] Hippocrates recognized the association between high arched palate, nasal obstruction, headache, and discharging ears—likely rhinosinusitis associated with otitis media. Medieval physicians believed nasal discharge emanated from fluid at the base of the brain. In fact, the pituitary gland is named from the Latin word for slime or mucus as it was believed that the source of yellow discharge from the nose came from the hypophysis. The first accurate description of the paranasal sinuses was by Vesalius in the 16th century, and the first documented cases of suppurative sinusitis were described by Antonio Molinetti in Venice in 1697.[4] The unique and troublesome drainage of the maxillary sinus was recognized by William Cowper in 1707, who eloquently described how "the antra have small openings situated high up in the cavity so that peccant humors could not escape into the nose unless the antrum were full to the top or the head held to one side."[4] Early treatment of sinusitis was mainly surgical, often involving either puncture of the sinus with a trocar or the removal of a molar with drainage through alveolar bone (Fig. 62.1).

## ANATOMY AND PHYSIOLOGY OF THE PARANASAL SINUSES

Infections of the paranasal sinuses are a direct consequence of their unique anatomy and physiology. An appreciation of the anatomic relationships of the sinuses is necessary to understand the pathogenesis and complications of sinusitis. The paranasal sinus cavities consist of the maxillary, ethmoid, frontal, and sphenoid sinuses. The maxillary and ethmoid sinuses develop during the third month of gestation and thus are present, albeit small, at birth.[5] The maxillary sinus originates as a slitlike cavity parallel to the middle turbinate and elongates into a pyramidal shape with a final volume of 15 to 30 mL in the adult. The floor of the maxillary sinus lies over the alveolar ridge of the maxilla, which holds the upper dentition. The walls of the maxillary sinus extend from the lateral wall of the nasal cavity to the zygomatic arch and the roof of the sinus is the floor of the orbit. The proximal location of the paranasal sinuses to structures such as the teeth (maxillary sinus) and eye (ethmoid and frontal sinuses) explain, at least in part, some of the clinical manifestations in the affected patient. The outflow tract of the maxillary sinus is located at the highest part of the medial wall of the sinus where it opens into the nasal cavity. This unfortunate positioning inhibits gravitational drainage of secretions and requires an intact mucociliary apparatus to move secretions and debris from the body of the sinus to the nose, thereby predisposing to infection. The ostium of the sinus empties by the way of the hiatus semilunaris into the nasal cavity via a 7- to 11-mm long passage called the infundibulum, which drains into the middle meatus.[6] The anterior ethmoid and frontal sinuses also empty into this same location, known as the osteomeatal complex (Fig. 62.2). The ethmoid sinuses are a complex group of 5 to 15 tiny air cells separated from one another by very thin bony partitions. The lamina papyracea, named for its paper-like thinness, comprises the

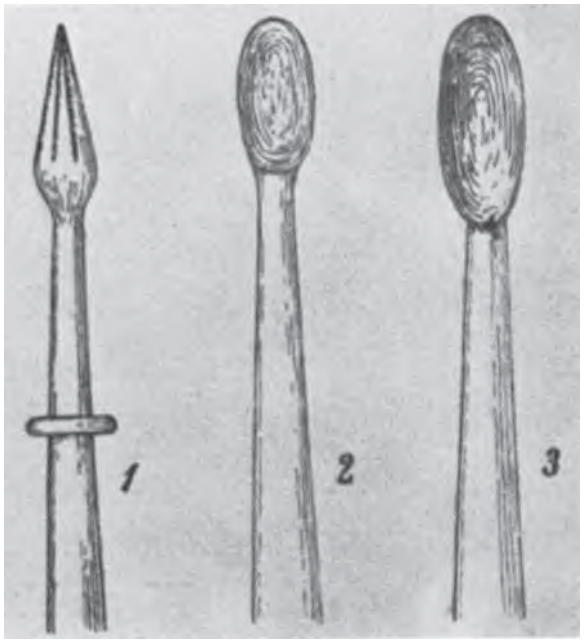


**FIG. 62.1 Trocars used in the early surgical treatment of sinusitis.** *(From Blegvad NR. History of the treatment of maxillary sinusitis.* J Laryngol Otol. *1957;71:806–823.)*

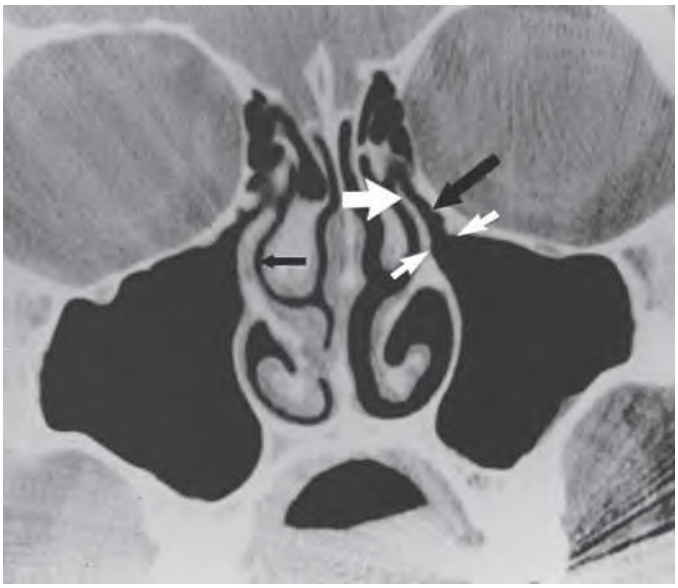

**FIG. 62.2 Selected features of the anatomy of the drainage system of the maxillary sinus shown on computed tomography scan.** The ostium is located between the two small white arrows. The ostium opens into a tubular structure, the infundibulum, shown by the large black arrow. The large white arrow indicates the upper part of the uncinate process, which forms the inferior portion of the infundibulum. The infundibulum empties into the middle meatus. The small black arrow indicates the contralateral middle meatus, which is narrowed as a result of turbinal distention from the normal nasal cycle.

medial wall of the orbit (lateral wall of the ethmoid) and provides a minimal barrier for spread of infection from the sinuses to the orbit. The ethmoid sinuses are divided into anterior and posterior cells. The larger anterior group empties into the middle meatus and the posterior cells into the superior meatus. The frontal sinuses develop from an anterior ethmoid cell and are present above the orbital ridge by the fifth or sixth birthday. Up to 5% of individuals lack one or both frontal sinuses.[7] The posterior wall of the frontal sinus is the anterior wall of the cranial fossa, and the floor of the frontal sinus forms the roof of the orbit. The frontal sinuses drain into the middle meatus via the frontonasal duct.

**TABLE 62.1 Factors That Predispose to Sinus Ostial Obstruction**

| MUCOSAL SWELLING | MECHANICAL OBSTRUCTION |
|---|---|
| **Systemic Factors** | Choanal atresia |
| Viral upper respiratory infection | Deviated septum |
| Allergic inflammation | Nasal polyps |
| Cystic fibrosis | Foreign body |
| Immune disorders | Tumor |
| Ciliary dyskinesia | Ethmoid bullae |
| Tobacco smoke | |
| **Local Insult** | |
| Facial trauma | |
| Swimming, diving | |
| Rhinitis medicamentosa | |
| Nasal intubation | |

The location of the frontal sinuses allows for the easy and rapid spread of infection from the sinus cavity to the central nervous system (CNS) and/or the orbits. The sphenoid sinuses are located just anterior to the pituitary fossa and are surrounded by several vital structures, including the optic nerve, internal carotid arteries, and the cavernous sinuses. The sphenoid sinus drains via a narrow duct into the superior nasal meatus. The sphenoid sinuses are infrequently the only site of infection; rather, they usually accompany a pansinusitis. The sphenoid sinus, similarly to the frontal sinus, is a source for the spread of infection from the sinuses to the CNS.

The paranasal sinuses are lined with a pseudostratified columnar (respiratory) epithelium, which also lines much of the nasal cavity. This epithelial lining contains four types of cells: basal cells, which adhere to the basement membrane; columnar cells, which possess cilia; goblet cells, which produce mucus to protect and lubricate the epithelial surface; and inflammatory cells. These inflammatory cells consist of T and B lymphocytes as well as antigen recognition cells.[6,7]

Mucus and other material produced in the maxillary sinus cavity are transported by ciliary action in a spiral direction up to and through the infundibulum into the middle meatus. These cilia beat at a frequency of 1000 times per minute and move material at a rate of 3 to 25 mm per minute.[8] The mucus blanket in the sinus turns over two to three times per hour and mucus normally does not accumulate in the sinus cavity.[9]

The paranasal sinuses are sterile under normal conditions unlike the nasal passages, which are heavily colonized with bacteria.[10–12] Sterility is maintained in the sinus by mechanisms that are not fully understood but are believed to include mucociliary clearance, the immune response, and possibly antibacterial concentrations of nitric acid in the sinus cavity.[13] Nasal secretions contain the immunoglobulins (Igs) IgA, IgG, IgM, and IgE, enzymes such as lysozymes; and proteins such as lactoferrin and complement, all of which exert an antibacterial effect.[14]

Although the exact function of the paranasal sinuses in humans is unknown, multiple roles have been suggested. These include contributing to the resonance of the voice, warming and humidifying inspired air, and acting as a shock absorber for the brain by absorbing energy during trauma.[6]

## PATHOGENESIS

The pathogenesis of rhinosinusitis involves three key elements: the patency of the sinus ostia, the function of the ciliary apparatus, and the character of sinus secretions. The narrow caliber of the sinus ostia sets the stage for obstruction to occur. Factors that predispose the ostia to obstruction include those that result in mucosal swelling and those that cause direct mechanical obstruction. Table 62.1 lists the most common factors that predispose to ostial obstruction. Of these multiple causes, viral URI and allergic inflammation are the most frequent and most important. During episodes of acute rhinitis, a completely patent ostia is present only 20% of the time.[15]

When obstruction of the sinus ostium occurs, there is a transient increase in pressure within the sinus cavity. As oxygen is depleted in this closed space, the pressure in the sinus becomes negative relative to atmospheric pressure. This negative pressure may allow the

introduction of nasal or nasopharyngeal bacteria into the sinuses during sniffing or nose blowing.[16] When obstruction of the sinus ostia occurs, secretion of mucus by the mucosa continues, resulting in accumulation of fluid in the sinus. A study of adult volunteers investigated the role of nose blowing in introducing nasal fluid, and thus possibly microbes, into the sinus cavities.[17] Serial computed tomography (CT) scans showed that up to 1 mL of viscous fluid was propelled into the sinus when volunteers blew their noses. In accordance, this serves as one potential mechanism for nasal fluid and flora to contaminate the sinuses, particularly during a common cold. It should be noted, however, that young children who do not blow their noses still develop acute bacterial sinusitis. Thus there must be multiple factors that play a role in the development of acute infection.

Dysfunction of the mucociliary apparatus also contributes to the pathogenesis of sinusitis. During viral colds, both the structure and function of the mucociliary apparatus are impaired. In a study of children with viral URI, subjects had nasal mucosal biopsies performed for examination of the ultrastructure of the cilia. Dysmorphic ciliary forms involving microtubular abnormalities were observed during the acute phase (7 days) of illness. Progressive loss of ciliated cells was noted throughout the illness in a patchy pattern.[18] In a study of documented viral URIs in adults, mucociliary clearance was measured using a solution of blue-colored saccharin. Mucociliary clearance times, measured by taste and color, were significantly slower during the acute phase of illness.[19] Presumably, these same changes in the structure and function of the nasal mucosa during viral URI occur in the sinus mucosa. This contributes to the reduced clearance of fluid and material that increases the likelihood of infection of the sinus cavity.

The quality and character of sinus secretions also plays a role in the pathogenesis of sinusitis. Cilia can only beat in a fluid media. The mucus blanket in the respiratory tract consists of two layers. The sol phase is a thin, low-viscosity layer that envelopes the shaft of the cilia and allows the cilia to beat freely. A more viscous layer, the gel phase rides on the sol phase. Alterations in the mucus layer, which occur in patients with cystic fibrosis or allergy, may impair ciliary function. The presence of inflammatory debris, which is found in an infected sinus, may further impair ciliary movement.

Historically, it has been stated that a reduction in airflow through the nasal passages contributes to the development of rhinosinusitis. An extensive review of this hypothesis, however, found no convincing evidence that diminished airflow is a factor in sinus pathology.[20]

Until recently the histologic findings during acute sinusitis had not been well characterized except in experimental models. In a rabbit model of acute sinusitis, histologic changes include epithelial desquamation, edema, and goblet cell hyperplasia. Of note is the distinct loss of ciliated cells from the epithelium.[21,22] Berger[23] examined biopsies of 11 humans who had acute sinusitis. Surprisingly, the epithelial layer of the sinus remained intact. In contrast, the lamina propria showed edema and massive infiltration of neutrophils and mononuclear cells, including lymphocytes and plasma cells. Occasional aggregates of inflammatory cells with microabscesses were also detected. Thrombosed blood vessels and deep necrotic foci were observed in patients with complications of acute sinusitis. Immunohistologic staining showed T lymphocytes scattered throughout the lamina propria with dense aggregates of B lymphocytes.[23]

The role of viral URI preceding episodes of acute bacterial sinusitis should be underscored. Like otitis media, most cases of sinusitis are directly preceded by a viral URI.[24–26] Cytokine production by respiratory epithelial cells is important in viral URI. Interleukin (IL)-1β, IL-8, IL-6, and tumor necrosis factor-α (TNF-α) are markedly elevated in nasal lavage fluid during acute URI compared with baseline.[27] These and other chemokines are responsible for the inflammatory response that predisposes to acute sinusitis. An analysis of cytokine production in sinusitis has shown that IL-8, a potent chemoattractant for neutrophils, is upregulated in the sinus during acute infection.[28] In addition, viral URI has been demonstrated to increase the density and frequency of colonization with known sinus pathogens.[25]

In patients with acute sinusitis, healing of the mucosa occurs over a period of weeks after infection. In a study in which serial magnetic resonance images (MRIs) were performed in patients with acute bacterial sinusitis, clinical symptoms resolved within 3 days of treatment in most patients. Radiographic changes took much longer to show improvement, with only half of the sinuses showing resolution of opacification by 10 days. It took up to 56 days for 80% of the sinuses to be completely aerated.[29]

## MICROBIOLOGY

Knowledge of the microbiology of acute community-acquired sinusitis is essential in choosing appropriate antimicrobial therapy. Studies performed to examine this issue require close attention to the method of specimen collection. The nasal cavity is heavily colonized with respiratory flora, which may easily contaminate material obtained from the paranasal sinuses. Classic studies of the bacteriology of sinusitis have obtained a specimen of sinus secretions by puncture of the maxillary antrum to reduce the risk of nasal contamination. In this method the maxillary sinus is accessed by puncture through a transnasal approach. A trocar is placed beneath the inferior nasal turbinate through the lateral nasal wall. Meticulous efforts to sterilize the mucosal area through which the trocar is placed avoids contaminating the specimen with nasal flora. In a further effort to discriminate true infection from contamination, quantitative methods are used to enumerate the density of microbes. Infection is defined as a colony count of at least $10^4$ colony-forming units per milliliter of aspirated material. [30]

Because of the invasive nature of this procedure, there has been considerable interest in obtaining cultures of sinus material through less invasive means. Cultures obtained via an endoscope have been compared with those obtained by sinus aspiration. In this method the sample is obtained from the middle meatus adjacent to the sinus ostia via swab or aspiration through the endoscope. Because the endoscope is passed through the nonsterile anterior nasal cavity, the potential for contamination is great. Many studies correlating sinus puncture with middle meatal culture attempt to improve the results of cultures obtained endoscopically by analyzing data only for *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis,* while dismissing other bacteria. This may ignore potential pathogens such as β-hemolytic streptococci and anaerobes. Most studies of the performance of endoscopic middle meatal culture in adult patients show a sensitivity of approximately 80%, specificity of 90%, positive predictive value of 80% to 90%, and negative predictive value of 80% to 90%, with maxillary sinus aspiration considered the gold standard.[31–34] (Table 62.2) It should be noted however, that the sensitivity and specificity of cultures obtained by endoscope is much lower in children. This is likely due to the smaller nasal cavity and more difficult technical aspects of the procedure.[33] Furthermore, middle meatal cultures obtained from a group of normal children without respiratory symptoms frequently showed the presence of the sinus pathogens *S. pneumoniae* and *H. influenzae*.[35] In accordance, sinus puncture remains the gold standard in investigating the microbiology of sinusitis in children.

**TABLE 62.2 Comparison of Endoscopic Middle Meatal Culture Versus Sinus Puncture in Acute Sinusitis**

| STUDY | *N* | SENSITIVITY % | SPECIFICITY % | POSITIVE PREDICTIVE VALUE % | NEGATIVE PREDICTIVE VALUE % | POPULATION |
|---|---|---|---|---|---|---|
| Talbot[31] | 46 | 85.7 | 90.6 | 8.0 | 93.5 | Adults |
| Joniau[32] | 24 | 80.0 | 100.0 | 100.0 | 78.6 | Adults |
| Benninger[34] | 126 | 80.9 | 90.5 | 82.6 | 89.4 | Adults |
| Hsin[33] | 41 | 75.0 | 88.9 | 96.0 | 50.0 | Children |

In studies of acute community-acquired bacterial sinusitis in which sinus puncture has been performed with attention to reducing contamination and analyzing results quantitatively, *S. pneumoniae* is the most frequently isolated organism, followed by nontypeable *H. influenzae* and *M. catarrhalis*. Streptococci, *Staphylococcus aureus,* and anaerobes are isolated much less frequently (Table 62.3). In children with acute bacterial sinusitis, *M. catarrhalis* is isolated with a greater frequency than in adults.

The predominance of pneumococci, *Haemophilus,* and *Moraxella* as pathogens in cases of acute sinusitis in children has not changed in more than 50 years.[12,36–42] However, the relative role of *S. pneumoniae* has diminished since the introduction of universal infant immunization with pneumococcal conjugate vaccine, and the serotypes have shifted.[43] This has not been confirmed by direct sinus aspirates, which are rarely performed in children with uncomplicated acute sinusitis. Rather, inferential data may be obtained by performance of tympanocentesis in children with acute otitis media. The similarity in pathogenesis of acute otitis media and acute bacterial sinusitis in children permits this inference to be made. The middle ear is, after all, a paranasal sinus.[44]

Accompanying the decrease in the isolation of *S. pneumoniae* has been an increase in the rate of isolation of nontypeable *H. influenzae* from middle ear isolates. The most recent study from a center performing tympanocentesis in the United States demonstrates a dramatic decrease in the recovery of *S. pneumoniae.* In contrast, *H. influenzae* and *M. catarrhalis* have increased in frequency to account for up to 90% of isolates. The surprising data are that the prevalence of β-lactamase producing organisms is higher than expected, in the range of 70% to 80%.[45] Studies of nasopharyngeal colonization have demonstrated a similar decrease in carriage of pneumococcal serotypes contained in the 13-valent pneumococcal conjugate vaccine and a relative increase in nonvaccine strains.[46] Of importance, the rate of colonization with penicillin- and ceftriaxone-resistant *S. pneumoniae* has decreased recently.[45,47,48] These shifts in microbiology have important implications for the selection of appropriate antimicrobial agents for the treatment of sinusitis.

**TABLE 62.3 Bacterial Etiology of Acute Sinusitis**

| | ADULTS (*n* = 339) | | CHILDREN (*n* = 30) | |
|---|---|---|---|---|
| ORGANISM | NO. OF ISOLATES | % OF ISOLATES | NO. OF ISOLATES | % OF ISOLATES |
| *Streptococcus pneumoniae* | 92 | 41 | 17 | 41 |
| *Haemophilus influenzae* | 79 | 35 | 11 | 27 |
| *Anaerobes* | 16 | 7 | | |
| *Streptococcal species* | 16 | 7 | 3 | 7 |
| *Moraxella catarrhalis* | 8 | 4 | 9 | 22 |
| *Staphylococcus aureus* | 7 | 3 | | |
| Other | 8 | 4 | 1 | 2 |

*Data from references 12 and 30–42.*

The role of *S. aureus* in the etiology of sinusitis has been controversial. Some authors have purported that this organism should be considered a major pathogen of the sinuses. This would have important implications for antimicrobial selection as most guidelines do not recommend agents that are directed at this organism.[34,49,50] However, when examined carefully, the role of *S. aureus* as an etiologic agent of acute bacterial sinusitis is doubtful.[51] In sinus aspiration studies of adults done over a 15-year period, *S. aureus* was detected in only 7 of 226 (3%) positive specimens obtained from 339 patients.[40] In the two studies in which maxillary sinus aspirates were performed in 50 children with acute bacterial sinusitis, no isolates of staphylococci were detected.[37,52] Most studies that argue that *S. aureus* is a pathogen in this setting are based on middle meatal cultures. To critically analyze these studies it is imperative to understand the microbiology of the nose and middle meatus in healthy individuals. The nasal vestibule is a location that is frequently heavily colonized with *S. aureus.* In a study of healthy children in a community setting, *S. aureus* was detected in greater than 65% of cultures obtained from the anterior nares.[53] Any study of the microbiology of the middle meatus will involve passage of the endoscope through this highly colonized region. Even with antiseptic measures, contamination of the specimen is possible. Studies of the middle meatus have also shown similarly high levels of detection of *S. aureus*. Gordts and colleagues[54] performed middle meatal cultures on healthy children undergoing surgery for reasons unrelated to the sinuses. *S. aureus* was found in 20% of children, indicating that this region is also frequently colonized.

Thus caution must be exercised in interpreting studies that highlight the role of *S. aureus* as a major pathogen in acute bacterial sinusitis as there is serious concern that these studies have a high rate of contamination of specimens with normal nasal flora. Nonetheless, although *S. aureus* is a very infrequent cause of acute bacterial sinusitis in children, it is a frequent etiologic agent when complications (intracranial and/or orbital) occur. The reason for this discrepancy is unknown.

Despite their prominent role in the pathogenesis of acute community-acquired bacterial sinusitis, viruses have been isolated from patients with acute sinusitis infrequently. This may relate, at least in part, to the timing of sinus aspiration, which is usually performed when the patient has been symptomatic for at least 7 to 10 days, by which time the viral infection may be waning. Respiratory viruses such as adenovirus, parainfluenza, and rhinovirus have been recovered from approximately 10% of sinus aspirates.[12,37] Approximately 30% to 40% of sinus aspirates in patients with acute sinusitis do not yield bacteria. It is presumed that many of these infections are in fact viral. However, a detailed evaluation of sinus aspirates using modern molecular techniques, such as polymerase chain reaction assay, to establish a viral etiology is lacking.

Fungi have long been recognized as important pathogens in selected patients with either acute or chronic sinusitis. Fungal sinusitis may take one of three forms (Table 62.4). Invasive fungal sinusitis is a fulminant disease, often with dissemination. Most cases occur in patients with serious underlying diseases, such as diabetes mellitus, malignancy, and associated neutropenia, or those using high-dose corticosteroids. Local invasion of the sinus cavity and surrounding structures of the skull occurs and is often accompanied by systemic fungal infection. The second form is mycetoma, or fungus ball, which typically appears in the maxillary or sphenoid sinuses. A dense accumulation of hyphae is

**TABLE 62.4 Types of Fungal Sinus Disease**

| | | NONINVASIVE | |
|---|---|---|---|
| INVASIVE | | MYCETOMA | ALLERGIC FUNGAL SINUSITIS |
| **Underlying Condition** | Immunocompromise<br>Diabetes | None | Atopy, nasal polyps |
| **Histopathology** | Mucosal hyphal invasion | Mycelial mass | Eosinophilic inflammatory infiltrate |
| **Etiological Agents** | *Mucor, Rhizopus, Fusarium, Pseudallescheria boydii, Alternaria, Bipolaris, Cladophialophora, Curvularia* | *Mucor, Rhizopus, Fusarium, Pseudallescheria boydii, Alternaria, Bipolaris, Cladophialophora, Curvularia* | *Aspergillus, Bipolaris, Curvularia, Drechslera* |
| **Therapy** | Surgery<br>Systemic antifungal | Surgery | Antiinflammatories<br>Antihistamines<br>Surgery |

**TABLE 62.5 Microorganisms Associated With Nosocomial Sinusitis Based on Sinus Puncture**

| MICROORGANISM | % OF ISOLATES |
|---|---|
| *Pseudomonas* spp. | 10.7 |
| *Escherichia coli* | 5.9 |
| *Proteus mirabilis* | 5.9 |
| *Klebsiella* spp. | 7.2 |
| *Enterobacter* spp. | 7.2 |
| Other gram negatives | 8.4 |
| *Staphylococcus aureus* | 9.5 |
| Viridans streptococci | 8.3 |
| *Streptococcus pneumoniae* | 2.4 |
| Other gram positives[a] | 22.7 |
| Anaerobic bacteria | 3.6 |
| *Candida* spp. | 8.4 |
| **Total** | **100** |

[a]Organisms of low pathogenicity, such as coagulase-negative *Staphylococci* and *Corynebacterium* spp.
*From George DL, Falk PS, Umberto Meduri G, et al. Nosocomial sinusitis in patients in the medical intensive care unit: a prospective epidemiological study.* Clin Infect Dis. *1998;27:463–470.*

present, and local invasion may occur, but dissemination is rare. Allergic fungal sinusitis occurs in patients who are immunocompetent but atopic and is the third form of fungal infection. An exuberant immune response to fungal spores mediated by IgE results in mucinous material collecting in the sinus. Local invasion is not present, but a mucoid inflammatory infiltrate fills the sinus cavity. The causal agents in invasive fungal sinusitis are the filamentous fungi, including *Aspergillus*, *Mucor*, *Rhizopus*, *Fusarium*, *Pseudallescheria boydii,* and the dematiaceous fungi, such as *Alternaria*, *Bipolaris, Cladophialophora,* and *Curvularia* spp.[55–62] *Aspergillus, Bipolaris, Curvularia,* and *Drechslera* have been associated with allergic fungal sinus disease. Sinus zygomycosis refers to infection with members of the phylum Zygomycota, of which *Mucor* and *Rhizopus* spp. are the most common.

Nosocomial sinusitis is a relatively frequent complication of medical care, usually observed in the critical care setting. The cumulative incidence of sinusitis in critically ill patients has been estimated to be 7.7% to 32%.[63,64] Nasal intubation has long been recognized as a risk factor for this infection. In addition, the use of a nasoenteric tubes increase the risk of sinusitis. A prospective study found an incidence of 15.7 cases of sinusitis per 1000 patient days in patients with nasoenteric tubes versus 1.6 cases per 1000 patient days in patients without such tubes.[64] It is hypothesized that the presence of a tube in the nose irritates the nasal mucosa, resulting in inflammation, edema, and subsequent obstruction of the sinus ostia. Other risk factors include nasal colonization with gram-negative enteric bacilli, sedative use, and a Glasgow Coma Score less than 8. *S. aureus*, gram-negative organisms including *Pseudomonas*, and *S. pneumoniae* are frequently isolated in patients with nosocomial sinusitis (Table 62.5). Ventilator-associated sinusitis has been described in critically ill patients and may be a cause of unexplained fever. Nasotracheal intubation increases the risk for this complication.[65]

## CHRONIC SINUSITIS

Chronic rhinosinusitis, which is often referred to as chronic sinus disease, is defined as symptoms and signs of sinus inflammation that persist for at least 12 weeks. Despite the prevalence of this disorder in the general population, its pathogenesis is incompletely understood. However, many of the same factors that play a role in acute bacterial sinusitis are found in chronic sinus disease, namely obstruction of the sinus ostia, mucociliary impairment, and thickening of secretions. In addition, the risk factors for chronic disease are similar to those of acute sinusitis[66] (see Table 62.1). The histopathology of the sinus in biopsies of patients with chronic sinusitis demonstrates an infiltration of T and B lymphocytes, macrophages, and eosinophils in the mucosa.[67] The microbiology of chronic sinusitis has been studied extensively, but the exact role of microorganisms is unclear. The same bacterial species (*S. pneumoniae* and *H. influenzae*) that are found in acute sinus disease are occasionally found in chronic sinusitis, especially in patients with acute exacerbations of chronic sinusitis. Other bacteria such as *S. aureus*, gram-negative enteric organisms, and anaerobes have been isolated with a greater frequency in sinus puncture studies.[68–72] Despite the isolation of such bacteria, there has been doubt in the medical literature as to their pathogenic role.[40,73] It is possible that in chronic sinusitis mucociliary clearance and host defenses are impaired to the point that the sinus cavity loses its normal sterility and becomes colonized with nasal flora. Thus chronic sinusitis may not truly be an "infectious process" but an aberration of the normal anatomy responsible for drainage with secondary damage to the mucosa of the sinus cavity.[73] The frequent isolation of bacteria of low pathogenicity, such as *Corynebacterium* spp. and coagulase-negative *Staphylococci,* as well as the unsatisfactory response to antimicrobials, support this hypothesis.

Biofilms, in which bacteria form specialized communities of microorganisms encased in complex extracellular polymeric substances, have been found in many patients with chronic rhinosinusitis and may play a role in both chronic inflammation and in exacerbations.[74] Biofilms offer important survival advantages to bacteria. They are more resistant to the effects of antibiotics than free-floating planktonic bacteria. This is accomplished by several mechanisms: (1) greater cell-cell contact to facilitate plasmid exchange for the evolution of resistance, (2) production of β-lactamases, (3) slow bacterial growth resulting in decreased effectiveness of antibiotics that rely on rapid cell growth and turnover for killing, and (4) the presence of "persister" cells that re-form the biofilm when the antibiotic is discontinued.[75] Although biofilms have been demonstrated on the mucosa of patients with chronic sinusitis, their precise role remains to be determined as they are not present in all cases of chronic rhinosinusitis, and limited biofilms are present in some healthy controls.

In addition, it is also important to mention that although most cases of chronic sinusitis are not thought to be an "infectious process," when patients with chronic sinusitis develop CNS complications these are often caused by *S. aureus* and respiratory anaerobes.

Recently, there has been intense interest in the role of fungi in the pathogenesis of chronic sinus disease. One study reported the isolation of multiple species of fungi in 95% of patients with chronic sinusitis. However, similar rates of isolation of fungi were present in control patients.[76] It has been hypothesized that chronic rhinosinusitis is the result of the allergic response to fungi present in the sinus cavity. Immunotherapy in these patients has been disappointing, as have trials of topical or systemic antifungal agents.[77,78]

## EPIDEMIOLOGY

The epidemiology of sinusitis parallels that of the common cold. In the United States the incidence of the common cold is two to three events per person per year in adults and one to eight in children.[26,79] Bacterial infection of the sinuses is estimated to occur in 0.5% to 2% of cases of viral URI in adults and 6% to 13% of children.[80–82] A recent prospective study of URI in children demonstrated that sinusitis complicated URI 8.8% of the time.[26] This makes sinusitis one of the most common infections presenting to the primary care physician. In a national health survey in the United States, 11% of adults reported having been diagnosed with sinusitis by a health care provider in the past year.[83] A study done in 1996, estimating the economic burden of sinusitis, calculated that $5.8 billion in health expenditures was attributable to sinusitis in the United States. It was estimated that sinusitis and its complications are responsible for 23 million visits to health care providers annually and result in more than 20 million prescriptions for antibiotics.[1] Although sinusitis is primarily an outpatient disease, acute sinusitis is associated with more than 8000 inpatient admissions per year in children in the United States.[84] The impact of sinusitis on quality of life is also substantial. In a study of 15 adults with chronic sinusitis, compared with those with other chronic illnesses, scales of bodily pain and social function showed significantly more impairment than in patients with congestive heart failure, angina, chronic obstructive pulmonary disease, and back pain.[85]

Sinusitis is diagnosed more frequently in adult women than men at a ratio of 1.8 : 1. [86]

Risk factors for the development of sinusitis include allergic rhinitis and asthma, swimming, and nasal obstruction due to polyps, foreign body, and tumor. Immunodeficiencies (agammaglobulinemia, human immunodeficiency virus, chronic granulomatous disease), structural defects (polyps, cleft palate), and functional disorders of mucociliary clearance (ciliary dyskinesia, cystic fibrosis) are associated with sinusitis. A weak association between gastroesophageal reflux disease and sinusitis has been documented.[87]

## CLINICAL MANIFESTATIONS

Because the pathogenesis of sinusitis and viral URI are similar, the clinical manifestations of these two diseases overlap greatly and must be compared. The uncomplicated URI will have a typical course of 5 to 10 days, and although the symptoms may not have completely resolved by the 10th day of illness, they have usually peaked in severity on days 3 to 6 and are showing improvement.[88] Nasal symptoms such as congestion and discharge are prominent in viral URI. Nasal discharge has a predictable pattern in its progression, from clear and watery to mucoid and thick and finally colored and opaque before resolving. Mild fever, when present, usually occurs in the first 48 hours of illness and is more common in children presenting with URI than in adults.

The clinical presentation of acute community-acquired bacterial sinusitis falls into one of three predictable patterns.[89] The first is that of persistent symptoms characterized by nasal discharge and/or cough that lasts more than 10 days without improvement. It is expected that the symptoms of a viral URI will have improved by the 10-day mark. Therefore it is the lack of improvement that is a sign of an acute bacterial process. Accompanying symptoms may include periorbital edema, malodorous breath, or low-grade fever. The nasal discharge may vary in character from thin and mucoid to thick and purulent. The second presentation is characterized by the onset of severe symptoms. Fever will accompany purulent nasal discharge that is present over a 3- to 4-day period.[90] These patients are often ill appearing. Worsening symptoms, referred to as "double sickening" in the Scandinavian literature, characterize the third presentation. These patients experience an initial improvement of symptoms of cough, nasal discharge, and congestion, but then worsen again within the first 10 days of illness.[89,91] Worsening may be signaled by new onset of fever, increasing nasal discharge, congestion, or daytime cough.

Patients with chronic rhinosinusitis have symptoms for at least 12 weeks. The presentation of such patients is characterized by anterior or posterior mucopurulent drainage and nasal obstruction. Facial pain or pressure, as well as hyposmia, are frequently present in patients with chronic sinus disease, as are alterations in taste.

The physical examination is of limited usefulness in the diagnosis of acute sinusitis, mainly because of the similarity of findings between patients with a viral URI and those with a bacterial process. Mucopurulent discharge may be found on the nasal mucosa. The mucosa itself is erythematous and mildly edematous. Facial tenderness over the maxillary or frontal area may be present but is an unreliable finding. Periorbital edema and mild discoloration of the skin below the eyelids is an occasional sign. Malodorous breath in the absence of dental disease or exudative pharyngitis may accompany acute sinusitis. Patients with chronic sinusitis may experience facial discomfort and mucopurulent nasal discharge. Polyps may be present in the nasal cavity or the middle meatus.

## DIAGNOSIS OF SINUSITIS

### Clinical Diagnosis

The challenge to the clinician when faced with the patient with upper respiratory symptoms is to identify those patients who have acute bacterial sinusitis and thus would benefit from an antimicrobial agent. The clinician faces a particular challenge in that the symptoms and signs of viral URI (i.e., the common cold) so closely overlap those of a bacterial process. Several studies have attempted to correlate signs and symptoms with the results of radiographic studies or cultures obtained through endoscopy; however, neither of these are reliable in the diagnosis of sinusitis, which brings the validity of these studies into question.

The duration of respiratory symptoms is the single most useful factor in discerning which patients have probable acute bacterial sinusitis. Studies on the microbiology of sinusitis in children showed that if rhinorrhea persisted at least 10 days with no improvement, bacterial burden in the sinuses was high.[37]

Sinusitis is best diagnosed based on the type, duration, and severity of symptoms. Although not entirely specific, the type of symptoms include nasal discharge or congestion reported by the patient or seen on physical examination. In children a persistent cough, especially when present during the daytime, may also be a signal of bacterial infection of the paranasal sinuses.

The following three clinical presentations will identify patients with acute bacterial sinusitis: (1) onset with *persistent* symptoms or signs, lasting at least 10 days without evidence of substantial clinical improvement; (2) onset with severe symptoms of high fever (≥39°C) and purulent nasal discharge lasting for 3 to 4 consecutive days; and (3) onset with worsening symptoms or signs characterized by the new development of fever, headache, or increase in nasal discharge after the initial improvement of a typical viral URI (double sickening).[90,92]

### Imaging

Although imaging (plain film radiography, CT, MRI, and ultrasonography) historically has been used as a confirmatory or diagnostic modality in patients suspected to have acute bacterial sinusitis, it is no longer recommended. The membranes that line the nose are continuous with the membranes (mucosa) that line the sinus cavities, the middle ear, the nasopharynx, and the oropharynx. When an individual experiences a viral URI, there is inflammation of the nasal mucosa and often the mucosa of the middle ear and paranasal sinuses as well. The continuity of the mucosa of the upper respiratory tract is responsible for the controversy regarding the usefulness of images of the paranasal sinuses in contributing to a diagnosis of acute bacterial sinusitis.

As early as the 1940s observations were made regarding the frequency of abnormal sinus radiographs in healthy children without signs or symptoms of current respiratory disease.[93] It was hypothesized that sinus radiographs were frequently abnormal in healthy children because viral URIs are so common in children, and probably the so-called "normal" children either had a cold or were recovering from a URI and had persistent mucosal changes.[94] In the 1970s and 1980s several investigators demonstrated that children with uncomplicated viral URI had frequent abnormalities of the paranasal sinuses on plain radiographs.[94–96] These abnormalities were exactly the same as those usually interpreted as consistent with and emblematic of acute bacterial sinusitis (mucosal thickening of at least 4 mm, complete opacification, or an air-fluid level).

As technology advanced and CT scanning of the CNS and skull was performed, several studies reported on incidental abnormalities of the paranasal sinuses.[95,97,98] Manning and colleagues[99] evaluated children undergoing either CT or MRI of the head for indications other than respiratory complaints or suspected sinusitis. Each patient underwent rhinoscopy and otoscopy before imaging, and each patient's parent was asked to fill out a questionnaire regarding recent symptoms of URI. Sixty-two percent of patients overall had physical findings or history consistent with an upper respiratory inflammatory process, and 55% of the total group showed some abnormalities on sinus imaging; 33% showed pronounced mucosal thickening or an air-fluid level. Finally, Kristo and colleagues,[100,101] performed MRIs in children with uncomplicated viral URI and confirmed the high frequency (68%) of major abnormalities seen in the paranasal sinuses.

Gwaltney and colleagues[102] showed very similar findings in young adults. Previously healthy subjects were recruited within 48 to 96 hours of developing symptoms of an uncomplicated cold. These patients were followed prospectively, and CT scans of the sinuses were performed at the initial presentation of the cold, and a follow-up scan was done 2 weeks later. Almost 90% of the subjects had abnormalities of one or both maxillary sinuses, and 65% had abnormal ethmoid sinuses. The sphenoid and frontal sinuses were abnormal less often. The authors concluded that the common cold is associated with frequent and striking abnormalities of the respiratory mucosa lining the paranasal sinuses, including air-fluid levels.