170 COMMON VIRAL RESPIRATORY INFECTIONS AND SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

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GENERAL CONSIDERATIONS Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses. The incidence of acute respiratory disease in the United States is from 3 to 5.6 cases per person per year. The rates are highest among children <1 year old (6.1 to 8.3 cases per year) and remain high until age 6, when a progressive decrease begins. Adults have 3 to 4 cases per person per year. Morbidity from acute respiratory illnesses accounts for 30 to 50% of time lost from work by adults and for 60 to 80% of time lost from school by children. The use of antibacterial agents to treat viral respiratory infections represents a major source of abuse of that category of drugs.

It has been estimated that two-thirds to three-fourths of cases of acute respiratory illnesses are caused by viruses. More than 200 antigenically distinct viruses from 9 different genera have been reported to cause acute respiratory illness, and it is likely that additional agents will be described in the future. The vast majority of these viral infections involve the upper respiratory tract, but lower respiratory tract disease can also develop, particularly in younger age groups and in certain epidemiologic settings.

The illnesses caused by respiratory viruses traditionally have been divided into multiple distinct syndromes, such as the "common cold," pharyngitis, croup (laryngotracheobronchitis), tracheitis, bronchiolitis, bronchitis, and pneumonia. Each of these general categories of illness has a certain epidemiologic and clinical profile; for example, croup occurs exclusively in very young children and has a characteristic clinical course. Some types of respiratory illness are more likely to be associated with certain viruses (e.g., the common cold with rhinoviruses), while others occupy characteristic epidemiologic niches (e.g., adenovirus infections in military recruits). The syndromes most commonly associated with infections with the major respiratory virus groups are summarized in Table 170-1. Most respiratory viruses clearly have the potential to cause more than one type of respiratory illness, and frequently features of several types of illness are found in the same patient. Moreover, the clinical illnesses induced by these viruses are rarely sufficiently distinctive to permit an etiologic diagnosis on clinical grounds alone, although the epidemiologic setting increases the likelihood that one group of viruses rather than another is involved. In general, laboratory methods must be relied on to establish a specific viral diagnosis.

This chapter reviews viral infections caused by six of the major groups of respiratory viruses: rhinoviruses, coronaviruses, respiratory syncytial viruses, metapneumoviruses, parainfluenza viruses, and adenoviruses. The recent extraordinary outbreaks of lower respiratory tract disease associated with coronaviruses (severe acute respiratory syndrome, or SARS) are also discussed. Influenza viruses, which are a major cause of mortality as well as morbidity, are reviewed in Chap. 171. Herpesviruses, which occasionally cause pharyngitis and which also cause lower respiratory tract disease in immunosuppressed patients, are reviewed in Chap. 163. Enteroviruses, which account for occasional respiratory illnesses during the summer months, are reviewed in Chap. 175.

RHINOVIRUS INFECTIONS

ETIOLOGIC AGENT Rhinoviruses are members of the Picornaviridae family, small (15 to 30 nm) nonenveloped viruses that contain a single-stranded RNA genome. In contrast to other members of the picornavirus family, such as enteroviruses, rhinoviruses are acid-labile and are almost completely inactivated at pH ≤ 3. Rhinoviruses grow preferentially at 33° to 34°C—the temperature of the human nasal passages—rather than at the higher temperature (37°C) of the lower respiratory tract. A total of 102 distinct serotypes of rhinovirus are recognized. Of these serotypes, 91 use intercellular adhesion molecule 1 (ICAM-1) as a cellular receptor and comprise the "major" receptor

TABLE 170-1 Illnesses Associated with Respiratory Viruses

Virus	Frequency of Respiratory Syndromes		
	Most Frequent	*Occasional*	*Infrequent*
Rhinoviruses	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia in children
Coronaviruses[a]	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia and bronchiolitis
Respiratory syncytial virus	Pneumonia and bronchiolitis in young children	Common cold in adults	Pneumonia in elderly and immunosuppressed patients
Parainfluenza viruses	Croup and lower respiratory tract disease in young children	Pharyngitis and common cold	Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed patients
Adenoviruses	Common cold and pharyngitis in children	Outbreaks of acute respiratory disease in military recruits[b]	Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed patients
Influenza A viruses	Influenza[c]	Pneumonia and excess mortality in high-risk patients	Pneumonia in healthy individuals
Influenza B viruses	Influenza[c]	Rhinitis and pharyngitis alone	Pneumonia
Enteroviruses	Acute undifferentiated febrile illnesses[d]	Rhinitis and pharyngitis	Pneumonia
Herpes simplex viruses	Gingivostomatitis in children; pharyngotonsillitis in adults	Tracheitis and pneumonia in immunocompromised patients	Disseminated infection in immunocompromised patients
Human metapneumoviruses[e]	—	—	—

[a] SARS-associated coronavirus (SARS-CoV) caused epidemics of pneumonia from November 2002 to July 2003 (see text).
[b] Serotypes 4 and 7.
[c] Fever, cough, myalgia, malaise.
[d] May or may not have a respiratory component.
[e] Newly recognized human metapneumoviruses that cause upper and lower respiratory tract illnesses; their relative frequency has not yet been established.

group, 10 use the low-density lipoprotein receptor and comprise the "minor" receptor group, and 1 uses a sialoprotein cellular receptor.

EPIDEMIOLOGY Rhinoviruses are a major cause of the common cold and have been isolated from 15 to 40% of adults with common cold–like illnesses. Overall rates of infection with rhinoviruses are higher among infants and young children and decrease with increasing age. Rhinovirus infections occur throughout the year, with seasonal peaks in early fall and spring in temperate climates. These infections are most often introduced into families by preschool or grade-school children <6 years old. Between 25 and 70% of initial illnesses in family settings are followed by secondary cases, with the highest attack rates among the youngest siblings at home. Attack rates also increase with family size.

Rhinoviruses appear to spread through direct contact with infected secretions, usually respiratory droplets. In some studies of volunteers, transmission was most efficient by hand-to-hand contact, with subsequent self-inoculation of the conjunctival or nasal mucosa. In other studies, transmission by large- or small-particle aerosol was demonstrated. Virus can also be recovered from plastic surfaces inoculated 1 to 3 h previously; this observation suggests that environmental surfaces contribute to transmission. In studies of married couples in which neither partner had detectable serum antibody, transmission was associated with prolonged contact (≥122 h) during a 7-day period. Transmission was infrequent unless virus was recoverable from the donor's hands and nasal mucosa, at least 1000 $TCID_{50}$ of virus was present in nasal washes from the donor, and the donor was at least moderately symptomatic with the "cold." Despite anecdotal observations, exposure to cold temperatures, fatigue, or sleep deprivation has not been associated with increased rates of rhinovirus-induced illness in volunteers, although some studies have suggested that psychologically defined "stress" may contribute to development of symptoms.

Infection with rhinoviruses is worldwide in distribution. By the time they reach adulthood, nearly all individuals have neutralizing antibodies to multiple serotypes, although the prevalence of antibody to any one serotype varies widely. Multiple serotypes circulate simultaneously, and generally no single serotype or group of serotypes has been more prevalent than the others.

PATHOGENESIS Rhinoviruses infect cells through attachment to specific cellular receptors; as mentioned above, most serotypes attach to ICAM-1, while a few use the low-density lipoprotein receptor. Relatively limited information is available on the histopathology and pathogenesis of acute rhinovirus infections in humans. Examination of biopsy specimens obtained during experimentally induced and naturally occurring illness indicates that the nasal mucosa is edematous, is often hyperemic, and—during acute illness—is covered by a mucoid discharge. There is a mild infiltrate with inflammatory cells, including neutrophils, lymphocytes, plasma cells, and eosinophils. Mucus-secreting glands in the submucosa appear hyperactive; the nasal turbinates are engorged, a condition that may lead to obstruction of nearby openings of sinus cavities. Several mediators, such as bradykinin, lysylbradykinin, prostaglandins, histamine, and interleukins 1, 6, and 8, have been linked to the development of signs and symptoms in rhinovirus-induced colds.

The incubation period for rhinovirus illness is short, generally 1 or 2 days. Virus shedding coincides with the onset of illness or may begin shortly before symptoms develop. The mechanisms of immunity to rhinovirus are not well worked out. In some studies, the presence of homotypic antibody has been associated with significantly reduced rates of subsequent infection and illness, but data conflict regarding the relative importance of serum and local antibody in protection from rhinovirus infection.

CLINICAL MANIFESTATIONS The most common clinical manifestations of rhinovirus infections are those of the common cold. Illness usually begins with rhinorrhea and sneezing accompanied by nasal congestion. The throat is frequently sore, and in some cases sore throat is the initial complaint. Systemic signs and symptoms, such as malaise and headache, are mild or absent, and fever is unusual. Illness generally lasts for 4 to 9 days and resolves spontaneously without sequelae. In children, bronchitis, bronchiolitis, and bronchopneumonia have been reported; nevertheless, it appears that rhinoviruses are not major causes of lower respiratory tract disease in children. Rhinoviruses may cause exacerbations of asthma and chronic pulmonary disease in adults. The vast majority of rhinovirus infections resolve without sequelae, but complications related to obstruction of the eustachian tubes or sinus ostia, including otitis media or acute sinusitis, can develop. In immunosuppressed patients, particularly bone marrow transplant recipients, severe and even fatal pneumonias have been associated with rhinovirus infections.

DIAGNOSIS Although rhinoviruses are the most frequently recognized cause of the common cold, similar illnesses are caused by a variety of other viruses, and the etiologic diagnosis cannot be made on clinical grounds alone. Rather, rhinovirus infection is diagnosed by isolation of the virus from nasal washes or nasal secretions in tissue culture. In practice, this procedure is rarely undertaken because of the benign, self-limited nature of the illness. In most settings, detection of rhinovirus RNA by polymerase chain reaction (PCR) is more sensitive than that by tissue culture; however, this PCR is largely a research procedure. Given the many serotypes of rhinovirus, diagnosis by serum antibody tests is currently impractical. Likewise, common laboratory tests, such as white cell count and sedimentation rate, are not helpful.

℞ TREATMENT

Rhinovirus infections are generally mild and self-limited, so treatment is not usually necessary. Therapy in the form of first-generation antihistamines and nonsteroidal anti-inflammatory drugs may be beneficial in patients with particularly pronounced symptoms, and an oral decongestant may be added if nasal obstruction is particularly troublesome. Reduction of activity is prudent in instances of significant discomfort or fatigability. Antibacterial agents should be used only if bacterial complications such as otitis media or sinusitis develop. Specific antiviral therapy is not available.

PREVENTION Application of interferon sprays intranasally has been effective in the prophylaxis of rhinovirus infections but is also associated with local irritation of the nasal mucosa. Studies of the prevention of rhinovirus infection by administration of antibodies to ICAM-1 or by the soluble purified receptors themselves have yielded disappointing results. Experimental vaccines to certain rhinovirus serotypes have been generated, but their usefulness is questionable because of the myriad serotypes and the uncertainty about mechanisms of immunity. Thorough hand washing, environmental decontamination, and protection against autoinoculation may help to reduce rates of transmission of infection.

CORONAVIRUS INFECTIONS, INCLUDING SARS

ETIOLOGIC AGENT Coronaviruses are pleomorphic, single-strand RNA viruses that measure 100 to 150 nm in diameter. The name derives from the crownlike appearance produced by the club-shaped projections that stud the viral envelope. Coronaviruses infect a wide variety of animal species and have been divided into three antigenic groups. Previously recognized coronaviruses that infect humans fell into two of these groups (I and II), which are represented by prototype isolates HCoV-229E and HCoV-OC43, respectively. The coronavirus associated with SARS (SARS-CoV) appears to be of a novel and distinct group (Fig. 170-1). To date, the SARS-CoV strains that have been fully sequenced have shown only minimal variation.

In general, human coronaviruses have been difficult to cultivate in vitro, and some strains grow only in human tracheal organ cultures rather than in tissue culture. SARS-CoV is an exception whose ready growth in African green monkey kidney (Vero E6) cells greatly facilitates its study.

EPIDEMIOLOGY Generally, human coronavirus infections are present throughout the world. Seroprevalence studies of strains HCoV-229E and HCoV-OC43 have demonstrated that serum antibodies are acquired early in life and increase in prevalence with advancing age, so that >80% of adult populations have antibodies as measured by enzyme-linked immunosorbent assay (ELISA). Overall, coronaviruses account for 10 to 35% of common colds, depending on the season. Coronavirus infections appear to be particularly prevalent in late fall, winter, and early spring—times when rhinovirus infections are less common.

The epidemic of the coronavirus-associated illness known as SARS apparently began in Guangdong Province of China in November 2002 and possibly originated from contact with semidomesticated animals such as the palm civet or the dog raccoon. These animals are prized as edible delicacies in the area and harbor infections with coronaviruses related to SARS-CoV. Between November 16, 2002, and February 28, 2003, 792 cases of apparent SARS were noted in Guangdong, and it was recognized that health care workers and their contacts accounted for many of the cases. A physician from Guangdong who traveled to Hong Kong to visit his family 5 days after the onset of his illness may represent the index case that introduced SARS into Hong Kong. In March 2003, a large number of cases of severe respiratory disease were reported to the World Health Organization (WHO) from Hong Kong. Many of the patients had had contact with the putative index case, had stayed at the hotel where he resided, or had had contact with secondary cases. At nearly the same time, similar cases were noted in Singapore, Thailand, Vietnam, Taiwan, and Toronto (Canada), initially in travelers from Hong Kong or Guangdong. Ultimately, 8422 cases were identified by WHO in 28 countries of Asia, Europe, and North America, although ~90% of cases occurred in China and Hong Kong. Case-fatality rates varied among the outbreaks, with an overall figure of ~11%. The disease appeared to be somewhat milder in cases in the United States and was clearly less severe among children (see below).

The mechanisms of transmission of SARS are incompletely understood. Clusters of cases suggest that spread may occur by both large and small aerosols and perhaps by the fecal-oral route as well. The outbreak of illness in a large apartment complex in Hong Kong suggested that environmental sources, such as sewage or water, may also play a role in transmission. Some ill individuals appeared to be hyperinfectious ("super-spreaders") and were capable of transmitting infection to 10 to 40 contacts, although most infections resulted in spread either to no one or to up to three individuals.

PATHOGENESIS Coronaviruses that cause the common cold (e.g., strains HCoV-229E and HCoV-OC43) infect ciliated epithelial cells in the nasopharynx. Viral replication leads to damage of ciliated cells and induction of chemokines and interleukins, which result in common-cold symptoms similar to those induced by rhinoviruses.

The pathogenesis of SARS is that of a systemic illness in which virus likely enters and infects cells of the respiratory tract but is also found in the bloodstream, in the urine, and (for up to 2 months) in the stool. Virus persists in the respiratory tract for 2 to 3 weeks, and titers peak ~10 days after the onset of systemic illness. Pulmonary pathology consists of hyaline membrane formation, desquamation of pneumocytes in alveolar spaces, and an interstitial infiltrate consisting of lymphocytes and mononuclear cells. Giant cells are frequently seen, and coronavirus particles have been detected in type II pneumocytes.

CLINICAL MANIFESTATIONS After an incubation period that generally lasts 2 to 7 days (range, 1 to 10 days), SARS usually begins as a systemic illness marked by the onset of fever, which is often accompanied by malaise, headache, and myalgias and is followed in 1 to 2 days by a nonproductive cough and dyspnea. Approximately 25% of patients have diarrhea. Chest x-rays can show a variety of infiltrates, including patchy areas of consolidation—most frequently in peripheral and lower lung fields—or interstitial infiltrates, which can progress to diffuse involvement (Fig. 170-2).

FIGURE 170-1 Electron micrograph of SARS-associated coronavirus (SARS-CoV) isolated in fetal rhesus kidney tissue culture from a lung biopsy sample from a patient with SARS. Viral particles are 55 to 90 mm in diameter. [*Reprinted with permission from Elsevier (JSM Peiris et al., Lancet 361:1319, 2003).*]

In severe cases, respiratory function may worsen during the second week of illness and progress to frank adult respiratory distress syndrome (ARDS) accompanied by multiorgan dysfunction. Risk factors for severity of disease include an age of >50 and comorbidities such as cardiovascular disease, diabetes, or hepatitis. Illness in pregnant women may be particularly severe, but SARS-CoV infection appears to be milder in children than in adults.

The clinical features of common colds caused by human coronaviruses are similar to those of illness caused by rhinoviruses. In studies of volunteers, the mean incubation period of colds induced by coronaviruses (3 days) is somewhat longer than that of illness caused by rhinoviruses, and the duration of illness is somewhat shorter (mean, 6 to 7 days). In some studies, the amount of nasal discharge was somewhat greater in colds induced by coronaviruses than in those induced by rhinoviruses. Coronaviruses other than SARS-CoV have been recovered occasionally from infants with pneumonia and from military recruits with lower respiratory tract disease and have been associated with worsening of chronic bronchitis.

LABORATORY FINDINGS AND DIAGNOSIS Laboratory abnormalities in SARS include lymphopenia, which is present in ~50% of cases and which mostly affects CD4+ T cells but also involves CD8+ T cells and NK cells. Total white blood cell counts are normal or slightly low, and thrombocytopenia may develop as the illness progresses. Elevated serum levels of aminotransferases, creatine kinase, and lactate dehydrogenase have been reported.

The WHO and the Centers for Disease Control and Prevention have developed case definitions for diagnosis of SARS. These definitions include clinical, epidemiologic, and laboratory features, which are being refined as additional information on SARS is gathered. SARS-CoV can be grown from respiratory tract samples by inoculation into Vero E6 tissue culture cells, in which a cytopathic effect can be seen within days. A rapid diagnosis can be made by reverse-transcriptase PCR (RT-PCR) of respiratory tract samples and plasma early in illness and of urine and stool later on. RT-PCR appears to be more sensitive than tissue culture, but only around one-third of cases are positive by PCR at initial presentation. Serum antibodies can be detected by ELISA or immunofluorescence, and nearly all patients develop detectable serum antibodies within 28 days after the onset of illness.

Laboratory diagnosis of coronavirus-induced colds is rarely required. Coronaviruses that cause those illnesses are frequently difficult to cultivate in vitro but can be detected in clinical samples by ELISA or immunofluorescence assays or by RT-PCR for viral RNA. These research procedures can be used to detect coronaviruses in unusual clinical settings.

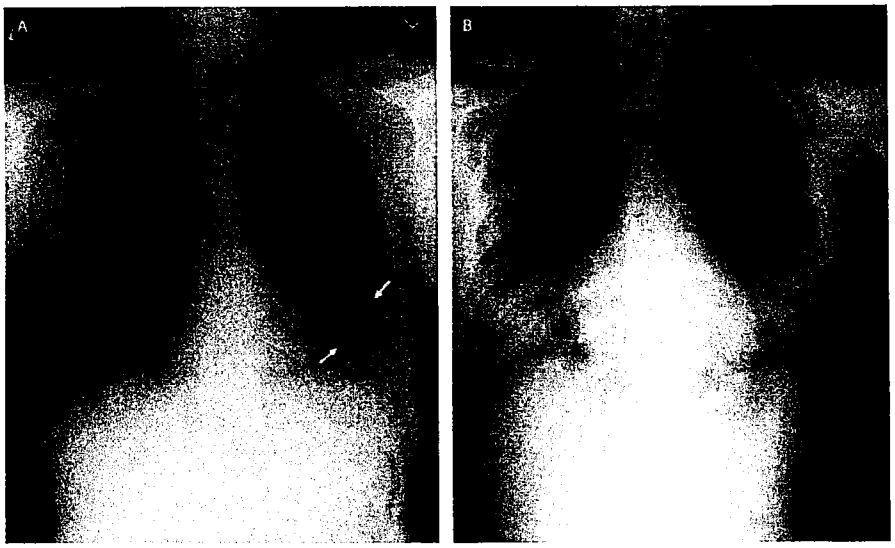

FIGURE 170-2 Chest x-rays of a 46-year-old man with SARS. The left lower lung infiltrate seen initially (*A*) progressed to multiple bilateral opacities (*B*). (*Reprinted with permission from L Lee et al. © 2003 Massachusetts Medical Society.*)

℞ TREATMENT

There is no specific therapy of established efficacy for SARS. Although ribavirin has frequently been used, it has little if any activity against SARS-CoV in vitro, and no beneficial effect on the course of illness has been demonstrated. Because of suggestions that immunopathology may contribute to the disease, glucocorticoids have also been widely used, but their benefit, if any, is likewise unestablished. Supportive care to maintain pulmonary and other organ system functions remains the mainstay of therapy.

The approach to the treatment of common colds caused by coronaviruses is similar to that discussed above for rhinovirus-induced illnesses.

PREVENTION The recognition of SARS led to a worldwide mobilization of public health resources to apply infection control practices and thus to contain the disease. Case definitions were established, travel advisories were proposed, and quarantines were imposed in certain locales. In line with criteria based on the absence of new cases for 30 days (three times the estimated incubation period of 10 days for the disease), all travel advisories have been lifted as of this writing (February 2004). It remains unknown whether the disappearance of cases is a result of the above control measures, whether it is part of a seasonal or otherwise unexplained epidemiologic pattern of SARS, and when or whether SARS might reemerge. The frequent transmission of the disease to health care workers makes it mandatory that strict infection control practices be employed by health care facilities to prevent airborne, droplet, and contact transmission from any suspected cases of SARS in the fruture.

Vaccines have been developed against several animal coronaviruses but not against known human coronaviruses. The emergence of SARS-CoV has emphasized the importance of the development of vaccines against such agents.

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

ETIOLOGIC AGENT Respiratory syncytial virus (RSV) is a member of the Paramyxoviridae family (genus *Pneumovirus*). RSV, an enveloped virus ~150 to 300 nm in diameter, is so named because its replication in vitro leads to the fusion of neighboring cells into large multinucleated syncytia. The single-stranded RNA genome codes for 11 virus-specific proteins. Viral RNA is contained in a helical nucleocapsid surrounded by a lipid envelope bearing two glycoproteins: the G protein, by which the virus attaches to cells, and the F (fusion) protein, which facilitates entry of the virus into the cell by fusing host and viral membranes. RSV was once considered to be of a single antigenic type, but two distinct groups (A and B) and multiple subtypes within each group have now been described. Antigenic diversity is reflected by differences in the G protein, while the F protein is highly conserved. Both antigenic groups can circulate simultaneously in outbreaks, although the relative proportions of each vary. Infections with group B viruses may be somewhat milder than those with group A viruses.

EPIDEMIOLOGY RSV is the major respiratory pathogen of young children and the foremost cause of lower respiratory disease in infants. Infection with RSV is seen throughout the world in annual epidemics that occur in late fall, winter, or spring and last up to 5 months. The virus is rarely encountered during the summer. Rates of illness are highest among infants 1 to 6 months of age, peaking between 2 and 3 months of age. The attack rates among susceptible infants and children are extraordinarily high, approaching 100% in settings such as day-care centers where large numbers of susceptible infants are present. By age 2, virtually all children will have been infected with RSV. RSV accounts for 20 to 25% of hospital admissions of young infants and children for pneumonia and for up to 75% of cases of bronchiolitis in this age group. It has been estimated that more than half of infants who are at risk will become infected during an RSV epidemic.

In older children and adults, reinfection with RSV is frequent but disease is milder than in infancy. A common cold–like syndrome is the illness most commonly associated with RSV infection in adults. Severe lower respiratory tract disease with pneumonitis can occur in elderly (often institutionalized) adults and in patients with immunocompromising disorders or treatment, including recipients of bone-marrow and solid-organ transplants. RSV is also an important nosocomial pathogen; during an outbreak, it can infect pediatric patients and up to 25 to 50% of the staff on pediatric wards. The spread of virus among families is efficient: up to 40% of siblings may become infected when RSV is introduced into the family setting.

RSV is transmitted primarily by close contact with contaminated fingers or fomites and by self-inoculation of the conjunctiva or anterior nares. Virus may also be spread by coarse aerosols produced by coughing or sneezing, but it is inefficiently spread by fine-particle aerosols. The incubation period is ~4 to 6 days, and virus shedding may last for ≥2 weeks in children and for shorter periods in adults. In immunosuppressed patients, shedding can be prolonged for multiple weeks.

PATHOGENESIS Little is known about the histopathology of minor RSV infection. Severe bronchiolitis or pneumonia is characterized by necrosis of the bronchiolar epithelium and a peribronchiolar infiltrate of lymphocytes and mononuclear cells. Interalveolar thickening and filling of alveolar spaces with fluid can also be found. The correlates of protective immunity to RSV are incompletely understood. Because reinfection occurs frequently and is often associated with illness, the immunity that develops after single episodes of infection clearly is not complete or long-lasting. However, the cumulative effect of multiple reinfections is to temper subsequent disease and to provide some temporary measure of protection against infection. Studies of experimentally induced disease in healthy volunteers indicate that the presence of nasal IgA neutralizing antibody correlates more closely with protection than does the presence of serum antibody. Studies in infants, however, suggest that maternally acquired antibody provides some protection from lower respiratory tract disease, although illness can be severe even in infants who have moderate levels of maternally derived

serum antibody. The relatively severe disease observed in immunosuppressed patients and experimental animal models indicates that cell-mediated immunity is an important mechanism of host defense against RSV. Evidence suggests that class I MHC-restricted cytotoxic T cells may be particularly important in this regard.

CLINICAL MANIFESTATIONS RSV infection leads to a wide spectrum of respiratory illnesses. In infants, 25 to 40% of infections result in lower respiratory tract involvement, including pneumonia, bronchiolitis, and tracheobronchitis. In this age group, illness begins most frequently with rhinorrhea, low-grade fever, and mild systemic symptoms, often accompanied by cough and wheezing. Most patients recover gradually over 1 to 2 weeks. In more severe illness, tachypnea and dyspnea develop, and eventually frank hypoxia, cyanosis, and apnea can ensue. Physical examination may reveal diffuse wheezing, rhonchi, and rales. Chest radiography shows hyperexpansion, peribronchial thickening, and variable infiltrates ranging from diffuse interstitial infiltrates to segmental or lobar consolidation. Illness may be particularly severe in children born prematurely and in those with congenital cardiac disease, bronchopulmonary dysplasia, nephrotic syndrome, or immunosuppression. One study documented a 37% mortality rate for infants with RSV pneumonia and congenital cardiac disease.

In adults, the most common symptoms of RSV infection are those of the common cold, with rhinorrhea, sore throat, and cough. Illness is occasionally associated with moderate systemic symptoms such as malaise, headache, and fever. RSV has also been reported to cause lower respiratory tract disease with fever in adults, including severe pneumonia in the elderly—particularly in nursing-home residents, among whom its impact can rival that of influenza. RSV pneumonia can be a significant cause of morbidity and mortality in patients undergoing bone-marrow and solid-organ transplantation, where case-fatality rates of 20 to 80% have been reported. Sinusitis, otitis media, and worsening of chronic obstructive and reactive airway disease have also been associated with RSV infection.

LABORATORY FINDINGS AND DIAGNOSIS The diagnosis of RSV infection can be suspected on the basis of a suggestive epidemiologic setting—that is, severe illness among infants during an outbreak of RSV in the community. Infections in older children and adults cannot be differentiated with certainty from those caused by other respiratory viruses. The specific diagnosis is established by isolation of RSV from respiratory secretions, such as sputum, throat swabs, or nasopharyngeal washes. Virus is isolated in tissue culture and is identified specifically by immunofluorescence, ELISA, or other immunologic techniques. Rapid viral diagnosis is available by immunofluorescence techniques or ELISA of nasopharyngeal washes, aspirates, and (less satisfactorily) nasopharyngeal swabs. In children, these techniques have sensitivities and specificities of 80 to 95%; they are somewhat less sensitive in specimens from adults. Serologic diagnosis may be made by comparison of acute- and convalescent-phase serum specimens by ELISA, neutralization, or complement-fixation tests. These tests may be useful in older children and adults but are less sensitive in children <4 months of age.

℞ TREATMENT

Treatment of upper respiratory tract RSV infection is aimed primarily at the alleviation of symptoms and is similar to that for other viral infections of the upper respiratory tract. For lower respiratory tract infections, respiratory therapy, including hydration, suctioning of secretions, and administration of humidified oxygen and antibronchospastic agents, is given as needed. In severe hypoxia, intubation and ventilatory assistance may be required. Studies of infants with RSV infection who were given aerosolized ribavirin, a nucleoside analogue active in vitro against RSV, have demonstrated a beneficial effect on the resolution of lower respiratory tract illness, including alleviation of blood-gas abnormalities. Treatment with aerosolized ribavirin is recommended for infants who are severely ill or who are at high risk for complications of RSV infection; included are premature infants and those with bronchopulmonary dysplasia, congenital heart disease, or immunosuppression. The efficacy of ribavirin in older children and adults with RSV pneumonia, including those with immunosuppression, has not been established. Administration of standard immunoglobulin, immunoglobulin with high antibody titers to RSV (RSVIg), or chimeric mouse-human monoclonal IgG against RSV (palivizumab) has not been found to be beneficial in the treatment of RSV pneumonia. Combined therapy with aerosolized ribavirin and palivizumab is being evaluated in the treatment of immunosuppressed patients with RSV pneumonia.

PREVENTION Monthly administration of RSVIg or palivizumab has been approved as prophylaxis against RSV for children <2 years of age who have bronchopulmonary dysplasia or were born prematurely. Considerable interest exists in the development of vaccines against RSV. Inactivated whole-virus vaccines have been ineffective; in one study, they actually potentiated the disease in infants. Other approaches include immunization with purified F and G surface glycoproteins of RSV or generation of stable, live attenuated virus vaccines. In settings such as pediatric wards where rates of transmission are high, barrier methods for the protection of hands and conjunctivae may be useful in reducing the spread of virus.

METAPNEUMOVIRUS INFECTIONS

Human metapneumovirus (HMPV) is a newly described viral respiratory pathogen that has been assigned to the Paramyxoviridae family (genus *Metapneumovirus*). Its morphology and genomic organization are similar to those of avian metapneumoviruses, which are recognized respiratory pathogens of turkeys. HMPV particles may be spherical, filamentous, or pleomorphic in shape and measure 60 to 280 nm in diameter. Particles contain 15-nm projections from the surface that are similar in appearance to those of other Paramyxoviridae. Studies of the RNA genome indicate that there are at least two genetic subgroups or genotypes of HMPV.

HMPV was initially detected in nasal aspirates from 28 children hospitalized with lower respiratory tract illnesses over a 20-year period (1981–2001) in the Netherlands. HMPV infections have since been reported in a wide variety of age groups, including elderly adults, and in both immunocompetent and immunosuppressed hosts. Initial seroepidemiologic studies suggest that HMPV infections are worldwide in distribution, are most frequent during the winter, and occur early in life, so that serum antibodies to the virus are present in nearly all children by the age of 5. The spectrum of clinical illnesses associated with HMPV is similar to that associated with RSV and includes both upper and lower respiratory tract illnesses, such as bronchiolitis, croup, and pneumonia.

HMPV can be detected in nasal aspirates and respiratory secretions by PCR or by growth in rhesus monkey kidney (LLC-MK2) tissue cultures. Serologic diagnosis can be made by ELISA, which utilizes HMPV-infected tissue culture lysates as sources of antigens.

Preliminary studies indicate that HMPV infections account for 4% of respiratory tract illnesses requiring hospitalization of children and for 2 to 4% of acute respiratory illnesses in ambulatory adults and elderly patients. HMPV has been detected in a few cases of SARS, but its role (if any) in these illnesses has not been established. Assessment of the overall significance of HMPV infections awaits the conduct of large-scale epidemiologic studies.

PARAINFLUENZA VIRUS INFECTIONS

ETIOLOGIC AGENT Parainfluenza viruses belong to the Paramyxoviridae family (genera *Respirovirus* and *Rubulavirus*). They are 150 to 200 nm in diameter, are enveloped, and contain a single-stranded RNA genome. The envelope is studded with two glycoproteins: one possesses both hemagglutinin and neuraminidase activity and the other

contains fusion activity. The viral RNA genome is enclosed in a helical nucleocapsid and codes for six structural and several accessory proteins. All four distinct serotypes of parainfluenza viruses share certain antigens with other members of the Paramyxoviridae family, including mumps and Newcastle disease viruses.

EPIDEMIOLOGY Parainfluenza viruses are distributed throughout the world; infection with type 4 (subtypes 4A and 4B) has been reported less widely, probably because type 4 is more difficult to grow in tissue culture. Infection is acquired in early childhood, so that by 5 years of age most children have antibodies to serotypes 1, 2, and 3. Types 1 and 2 cause epidemics during the fall, often occurring in an alternate-year pattern. Type 3 infection has been detected during all seasons of the year, but epidemics have occurred annually in the spring.

The contribution of parainfluenza infections to respiratory disease varies with both the location and the year. In studies conducted in the United States, parainfluenza virus infections have accounted for 4.3 to 22% of respiratory illnesses in children. In adults, parainfluenza infections are generally mild and account for <10% of respiratory illnesses. The major importance of parainfluenza viruses is as a cause of respiratory illness in young children, in whom they rank second only to RSV as causes of lower respiratory tract illness. Parainfluenza virus type 1 is the most frequent cause of croup (laryngotracheobronchitis) in children, while serotype 2 causes similar, although generally less severe, disease. Type 3 is an important cause of bronchiolitis and pneumonia in infants, while illnesses associated with type 4 have generally been mild. Unlike types 1 and 2, type 3 frequently causes illness during the first month of life, when passively acquired maternal antibody is still present. Parainfluenza viruses are spread through infected respiratory secretions, primarily by person-to-person contact and/or by large droplets. The incubation period has varied from 3 to 6 days in experimental infections but may be somewhat shorter for naturally occurring disease in children.

PATHOGENESIS Immunity to parainfluenza viruses is incompletely understood, but evidence suggests that immunity to infections with serotypes 1 and 2 is mediated by local IgA antibodies in the respiratory tract. Passively acquired serum neutralizing antibodies also confer some protection against infection with types 1, 2, and—to a lesser degree—3. Studies in experimental animal models and in immunosuppressed patients suggest that T cell–mediated immunity may also be important in parainfluenza virus infections.

CLINICAL MANIFESTATIONS Parainfluenza virus infections occur most frequently among children, in whom initial infection with serotype 1, 2, or 3 is associated with an acute febrile illness 50 to 80% of the time. Children may present with coryza, sore throat, hoarseness, and cough that may or may not be croupy. In severe croup, fever persists, with worsening coryza and sore throat. A brassy or barking cough may progress to frank stridor. Most children recover over the next 1 or 2 days, although progressive airway obstruction and hypoxia ensue occasionally. If bronchiolitis or pneumonia develops, progressive cough accompanied by wheezing, tachypnea, and intercostal retractions may occur. In this setting, sputum production increases modestly. Physical examination shows nasopharyngeal discharge and oropharyngeal injection, along with rhonchi, wheezes, or coarse breath sounds. Chest x-rays can show air trapping and occasionally interstitial infiltrates.

In older children and adults, parainfluenza infections tend to be milder, presenting most frequently as a common cold or as hoarseness, with or without cough. Lower respiratory tract involvement in older children and adults is uncommon, but tracheobronchitis in adults has been reported. Severe, prolonged, and even fatal parainfluenza infection has been reported in children and adults with severe immunosuppression, including bone-marrow and solid-organ transplant recipients.

LABORATORY FINDINGS AND DIAGNOSIS The clinical syndromes caused by parainfluenza viruses (with the possible exception of croup in young children) are not sufficiently distinctive to be diagnosed on clinical grounds alone. A specific diagnosis is established by detection of virus in respiratory tract secretions, throat swabs, or nasopharyngeal washings. Viral growth in tissue culture is detected either by hemagglutination or by a cytopathic effect. Rapid viral diagnosis may be made by identification of parainfluenza antigens in exfoliated cells from the respiratory tract with immunofluorescence or ELISA, although these techniques appear to be less sensitive than tissue culture. Highly specific and sensitive PCR assays have also been described. Serologic diagnosis can be established by hemagglutination inhibition, complement-fixation, or neutralization tests of acute- and convalescent-phase specimens. However, as frequent heterotypic responses occur among the parainfluenza serotypes, the serotype causing illness often cannot be identified by serologic techniques alone.

Acute epiglottitis caused by *Haemophilus influenzae* type b must be differentiated from viral croup. Influenza A virus is also a common cause of croup during epidemic periods.

℞ TREATMENT

For upper respiratory tract illness, symptoms can be treated as discussed for other viral respiratory tract illnesses. If complications such as sinusitis, otitis, or superimposed bacterial bronchitis develop, appropriate antibiotics should be administered. Mild cases of croup should be treated with bed rest and moist air generated by vaporizers. More severe cases require hospitalization and close observation for the development of respiratory distress. If acute respiratory distress develops, humidified oxygen and intermittent racemic epinephrine are usually administered. Aerosolized or systemically administered glucocorticoids are beneficial; the latter have a more profound effect. No specific antiviral therapy is available, although ribavirin is active against parainfluenza viruses in vitro and anecdotal reports describe its use clinically, particularly in immunosuppressed patients. Effective vaccines against parainfluenza viruses have not been developed.

ADENOVIRUS INFECTIONS

ETIOLOGIC AGENT Adenoviruses are complex DNA viruses that measure 70 to 80 nm in diameter. Human adenoviruses belong to the genus *Mastadenovirus*, which includes 51 serotypes. Adenoviruses have a characteristic morphology consisting of an icosahedral shell composed of 20 equilateral triangular faces and 12 vertices. The protein coat (capsid) consists of hexon subunits with group-specific and type-specific antigenic determinants and penton subunits at each vertex primarily containing group-specific antigens. A fiber with a knob at the end projects from each penton; this fiber contains type-specific and some group-specific antigens. Human adenoviruses have been divided into six subgenera (A through F) on the basis of the homology of DNA genomes and other properties. The adenovirus genome is a linear double-stranded DNA that codes for structural and nonstructural polypeptides. The replicative cycle of adenovirus may result either in lytic infection of cells or in the establishment of a latent infection (primarily involving lymphoid cells). Some adenovirus types can induce oncogenic transformation, and tumor formation has been observed in rodents; however, despite intensive investigation, adenoviruses have not been associated with tumors in humans.

EPIDEMIOLOGY Adenovirus infections most frequently affect infants and children. Infections occur throughout the year but are most common from fall to spring. Adenoviruses account for ~10% of acute respiratory infections in children but for <2% of respiratory illnesses in civilian adults. Nearly 100% of adults have serum antibody to multiple serotypes—a finding indicating that infection is common in childhood. Types 1, 2, 3, and 5 are the most frequent isolates from children. Certain adenovirus serotypes—particularly 4 and 7 but also 3, 14, and 21—are associated with outbreaks of acute respiratory disease in military recruits in winter and spring. Adenovirus infection can

be transmitted by inhalation of aerosolized virus, by inoculation of virus into conjunctival sacs, and probably by the fecal-oral route as well. Type-specific antibody generally develops after infection and is associated with protection, albeit incomplete, against infection with the same serotype.

CLINICAL MANIFESTATIONS In children, adenoviruses cause a variety of clinical syndromes. The most common is an acute upper respiratory tract infection, with prominent rhinitis. On occasion, lower respiratory tract disease, including bronchiolitis and pneumonia, also develops. Adenoviruses, particularly types 3 and 7, cause pharyngoconjunctival fever, a characteristic acute febrile illness of children that occurs in outbreaks, most often in summer camps. The syndrome is marked by bilateral conjunctivitis in which the bulbar and palpebral conjunctivae have a granular appearance. Low-grade fever is frequently present for the first 3 to 5 days, and rhinitis, sore throat, and cervical adenopathy develop. The illness generally lasts for 1 to 2 weeks and resolves spontaneously. Febrile pharyngitis without conjunctivitis has also been associated with adenovirus infection. Adenoviruses have been isolated from cases of whooping cough with or without *Bordetella pertussis*; the significance of adenovirus in that disease is unknown.

In adults, the most frequently reported illness has been acute respiratory disease caused by adenovirus types 4 and 7 in military recruits. This illness is marked by a prominent sore throat and the gradual onset of fever, which often reaches 39°C (102.2°F) on the second or third day of illness. Cough is almost always present, and coryza and regional lymphadenopathy are frequently seen. Physical examination may show pharyngeal edema, injection, and tonsillar enlargement with little or no exudate. If pneumonia has developed, auscultation and x-ray of the chest may indicate areas of patchy infiltration.

Adenoviruses have been associated with a number of non–respiratory tract diseases, including acute diarrheal illness caused by types 40 and 41 in young children and hemorrhagic cystitis caused by types 11 and 21. Epidemic keratoconjunctivitis, caused most frequently by types 8, 19, and 37, has been associated with contaminated common sources such as ophthalmic solutions and roller towels. Adenoviruses have also been implicated in disseminated disease and pneumonia in immunosuppressed patients, including recipients of solid-organ or bone-marrow transplants. In bone-marrow transplant recipients, adenovirus infections have manifested as pneumonia, hepatitis, nephritis, colitis, encephalitis, and hemorrhagic cystitis. In solid-organ transplant recipients, adenovirus infection may involve the organ transplanted (e.g., hepatitis in liver transplants, nephritis in renal transplants) but can disseminate to other organs as well. In patients with AIDS, high-numbered and intermediate adenovirus serotypes have been isolated, usually in the setting of low CD4+ cell counts, but their isolation frequently has not been clearly linked to disease manifestations. Adenovirus nucleic acids have been detected in myocardial cells from patients with "idiopathic" myocardiopathies, and adenoviruses have been suggested as causative agents in some cases.

LABORATORY FINDINGS AND DIAGNOSIS Adenovirus infection should be suspected in the epidemiologic setting of acute respiratory disease in military recruits and in certain of the clinical syndromes (such as pharyngoconjunctival fever or epidemic keratoconjunctivitis) in which outbreaks of characteristic illnesses occur. In most cases, however, illnesses caused by adenovirus infection cannot be differentiated from those caused by a number of other viral respiratory agents and *Mycoplasma pneumoniae*. A definitive diagnosis of adenovirus infection is established by detection of the virus in tissue culture (as evidenced by cytopathic changes) and by specific identification with immunofluorescence or other immunologic techniques. Rapid viral diagnosis can be established by immunofluorescence or ELISA of nasopharyngeal aspirates, conjunctival or respiratory secretions, urine, or stool. Highly sensitive and specific PCR assays or nucleic acid hybridization is also available. Adenovirus types 40 and 41, which have been associated with diarrheal disease in children, require special tissue-culture cells for isolation, and these serotypes are most commonly detected by direct ELISA of stool. Serum antibody rises can be demonstrated by complement-fixation or neutralization tests, ELISA, radioimmunoassay, or (for those adenoviruses that hemagglutinate red cells) hemagglutination inhibition tests.

℞ TREATMENT

Only symptom-based treatment and supportive therapy are available for adenovirus infections, and no clinically useful antiviral compounds have been identified. Ribavirin and cidofovir have activity in vitro against adenoviruses, and anecdotes of their use in disseminated infection have been reported.

PREVENTION Live vaccines have been developed against adenovirus types 4 and 7 and have been used to control illness in military recruits. These vaccines consist of live, unattenuated virus administered in enteric-coated capsules. Infection of the gastrointestinal tract with types 4 and 7 does not cause disease but stimulates local and systemic antibodies that are protective against subsequent acute respiratory disease due to those serotypes. This vaccine has not been produced since 1999, and outbreaks of acute respiratory illness caused by adenovirus types 4 and 7 have emerged again among military recruits. Vaccines prepared from purified subunits of adenovirus are being investigated. Adenoviruses are also being studied as live-virus vectors for the delivery of vaccine antigens and for gene therapy.

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171 INFLUENZA

Raphael Dolin

DEFINITION Influenza is an acute respiratory illness caused by infection with influenza viruses. The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness. Outbreaks of illness of variable extent and severity occur nearly every winter. Such outbreaks result in significant morbidity in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.

ETIOLOGIC AGENT Influenza viruses are members of the Orthomyxoviridae family, of which influenza A, B, and C viruses constitute three separate genera. The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens. Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (H) and neuraminidase (N) antigens (see below); individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype—for example, influenza A/Moscow/10/99 (H3N2). Influenza A has 15 distinct H and 9 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with extensive outbreaks of disease in humans. Influenza B and C viruses are similarly designated, but H and N antigens from these viruses do not receive subtype designations, since intratypic variations in influenza B antigens are less extensive than those in influenza A viruses and may not occur with influenza C virus.

Influenza A and B viruses are major human pathogens and the most extensively studied of the Orthomyxoviridae. The type A and type B viruses are morphologically similar. The virions are irregularly shaped spherical particles, 80 to 120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (Fig. 171-1). The hemagglutinin is the site by which virus binds to cell receptors, whereas the neuraminidase degrades the receptor and plays a role in the release of virus from infected cells after replication has taken place. Influenza viruses enter cells by receptor-mediated endocytosis, forming a virus-containing endosome. The viral hemagglutinin mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Antibodies to the H antigen are the major determinants of immunity to influenza virus, while those to the N antigen limit viral spread and contribute to reduction of the infection. The inner surface of the lipid envelope contains the M proteins M1 and M2, which are involved in stabilization of the lipid envelope and in virus assembly. The virion also contains the NP antigen, which is associated with the viral genome, as well as three polymerase (P) proteins that are essential for transcription and synthesis of viral RNA. Two nonstructural proteins function as an interferon antagonist and posttranscriptional regulator (NS1) and a nuclear export factor (NS2 or NEP).

The genomes of influenza A and B viruses consist of eight single-stranded RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for gene reassortment during infection is high; reassortment often occurs during infection of cells with more than one influenza A virus.

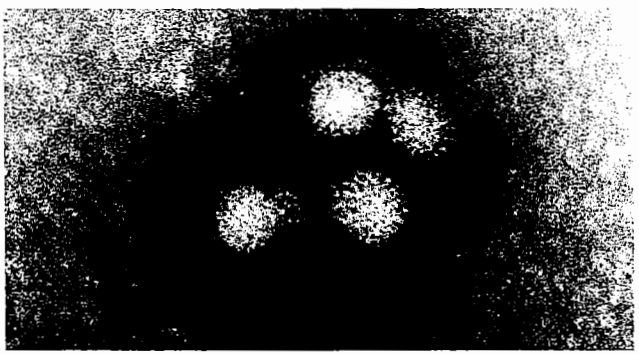

FIGURE 171-1 An electron micrograph of influenza A virus (×140,000).

EPIDEMIOLOGY Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1 to 3 years. Except in the past 25 years, global epidemics or pandemics have occurred approximately every 10 to 15 years since the 1918–1919 pandemic (Table 171-1).

The most extensive and severe outbreaks are caused by influenza A viruses, in part because of the remarkable propensity of the H and N antigens of these viruses to undergo periodic antigenic variation. Major antigenic variations, called *antigenic shifts*, may be associated with pandemics and are restricted to influenza A viruses. Minor variations are called *antigenic drifts*. These types of antigenic variation may involve the hemagglutinin alone or both the hemagglutinin and the neuraminidase. An example of an antigenic shift involving both the hemagglutinin and the neuraminidase is that of 1957, when the predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, with an estimated 70,000 excess deaths (i.e., deaths in excess of the number expected without an influenza epidemic) in the United States alone. In 1968, an antigenic shift involving only the hemagglutinin occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that of 1957. In 1977, an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals (i.e., those born after 1957). As can be seen in Table 171-1, H1N1 viruses circulated from 1918 to 1956; thus, individuals born prior to 1957 would be expected to have some degree of immunity to H1N1 viruses. During most outbreaks of influenza A, a single subtype has circulated at a time. However, since 1977, H1N1 and H3N2 viruses have circulated simultaneously, resulting in outbreaks of varying severity. In some outbreaks, influenza B viruses have also circulated simultaneously with influenza A viruses.

The origin of pandemic strains is unknown. Given the marked differences between the primary structures of the hemagglutinins of different subtypes of influenza A viruses (H1, H2, and H3), it seems unlikely that antigenic shifts result from spontaneous mutations in the hemagglutinin gene. Because the segmented genome of influenza viruses may result in high rates of reassortment, it has been suggested that pandemic strains may emerge by reassortment of genes between human and animal influenza A viruses that are known to have a broad host range of infection. There was concern that such reassortment might have occurred in 1997 in Hong Kong, where cases of infection caused by influenza virus A/H5N1 were detected in humans during an extensive outbreak of avian influenza A/H5N1 in poultry. However, only a few cases of A/H5N1 influenza in humans were documented, and the infection did not spread into the community. Recently, H9N2 viruses, which circulate in poultry and swine, have also been associated with limited infections in humans. Influenza B viruses have a much more restricted host range and do not undergo antigenic shifts, although they do undergo antigenic drift.

TABLE 171-1 Emergence of Antigenic Subtypes of Influenza A Virus Associated with Pandemic or Epidemic Disease

Years	Subtype	Extent of Outbreak
1889–90	H2N8[a]	Severe pandemic
1900–03	H3N8[a]	?Moderate epidemic
1918–19	H1N1[b] (formerly HswN1)	Severe pandemic
1933–35	H1N1[b] (formerly H0N1)	Mild epidemic
1946–47	H1N1	Mild epidemic
1957–58	H2N2	Severe pandemic
1968–69	H3N2	Moderate pandemic
1977–78[c]	H1N1	Mild pandemic

[a] As determined by retrospective serologic survey of individuals alive during those years ("seroarcheology").

[b] Hemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1.

[c] From this time until the present (2002–2003), viruses of the H1N1 and H3N2 subtypes have circulated either in alternating years or concurrently.

Pandemics provide the most dramatic evidence of the impact of influenza. However, illnesses that occur between pandemics account for greater total mortality and morbidity, albeit over a longer period. From 1972 through the present, influenza has been associated with at least 20,000 excess deaths during more than half of the interpandemic epidemics in the United States; >40,000 influenza-associated deaths occurred in each of six of these epidemics. Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts apparently result from point mutations involving the RNA segment that codes for the hemagglutinin, which occurs most frequently in five hypervariable regions. Epidemiologically significant strains—that is, those with the potential to cause widespread outbreaks—exhibit changes in amino acids in at least two of the major antigenic sites in the hemagglutinin molecule. Since two point mutations are unlikely to occur simultaneously, it is believed that antigenic drifts result from point mutations occurring sequentially during the spread of virus from person to person. Antigenic drifts have been reported nearly annually since 1977 for H1N1 viruses and since 1968 for H3N2 viruses.

Influenza A epidemics begin abruptly, peak over a 2- to 3-week period, generally last for 2 to 3 months, and often subside almost as rapidly as they began. The first indication of influenza activity in a community is an increase in the number of children with febrile respiratory illnesses who present for medical attention. This increase is followed by increases in rates of influenza-like illnesses among adults and eventually by an increase in hospital admissions for patients with pneumonia, worsening of congestive heart failure, and exacerbations of chronic pulmonary disease. Rates of absence from work and school also rise at this time. An increase in the number of deaths caused by pneumonia and influenza is generally a late observation in an outbreak. Attack rates have been highly variable from outbreak to outbreak but most commonly are in the range of 10 to 20% of the general population. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50% in urban populations and that an additional 25% or more of individuals in these populations may have been subclinically infected with influenza A virus. Among institutionalized populations and in semiclosed settings with many susceptible individuals, even higher attack rates have been reported.

Epidemics of influenza occur almost exclusively during the winter months in the temperate zones of the northern and southern hemispheres. In those locations, it is highly unusual to detect influenza A virus at other times, although serologic rises or even outbreaks have been noted rarely during warm-weather months. In contrast, influenza virus infections occur throughout the year in the tropics. Where or how influenza A virus persists between outbreaks in temperate zones is unknown. It is possible that influenza A viruses are maintained in the human population on a worldwide basis by person-to-person transmission and that large population clusters support a low level of interepidemic transmission. Alternatively, human strains may persist in animal reservoirs. Convincing evidence to support either explanation is not available. In the modern era, rapid transportation may contribute to the transmission of viruses among widespread geographic locales.

The factors that result in the inception and termination of outbreaks of influenza are incompletely understood. A major determinant of the extent and severity of an outbreak is the level of immunity in the population at risk. With the emergence of an antigenically novel influenza virus to which little or no antibody is present in a community, extensive outbreaks may occur. When the absence of antibody is worldwide, epidemic disease may spread around the globe, resulting in a pandemic. Such pandemic waves can continue for several years, until immunity in the population reaches a high level. In the years following pandemic influenza, antigenic drifts among influenza viruses result in outbreaks of variable severity in populations with high levels of immunity to the pandemic strain that circulated earlier. This situation persists until another antigenically novel pandemic strain emerges. On the other hand, outbreaks sometimes end despite the persistence of a large pool of susceptible individuals in the population.

Occasionally, the emergence of a significantly different antigenic variant will result only in a localized outbreak. The swine influenza outbreak of 1976 in the United States, caused by an A/H1N1 virus antigenically similar to the virus that circulated in 1918–1919, may be an example, although this outbreak may have represented simply the introduction of a swine influenza virus into a crowded human population without spread beyond that setting. The cluster of human infections with influenza A/H5N1 in Hong Kong in 1997 may also be an example of this phenomenon. It has been suggested that certain viruses, such as recently circulating A/H1N1 strains, may be intrinsically less virulent and cause less severe disease than other variants, even in immunologically virgin subjects. If so, then other (undefined) factors besides the level of preexisting immunity must play a role in the epidemiology of influenza.

Influenza B virus causes outbreaks that are generally less extensive and are associated with less severe disease than those caused by influenza A virus. The hemagglutinin and neuraminidase of influenza B virus undergo less frequent and less extensive variation than those of influenza A viruses; this characteristic may account, in part, for the lesser extent of disease. Influenza B outbreaks are seen most frequently in schools and military camps, although outbreaks in institutions in which elderly individuals reside have also been noted on occasion. The most serious complication of influenza B virus infection is Reye's syndrome (Chap. 290). In contrast to influenza A and B viruses, influenza C virus appears to be a relatively minor cause of disease in humans. It has been associated with common cold–like symptoms and occasionally with lower respiratory tract illness. The wide prevalence of serum antibody to this virus indicates that asymptomatic infection may be common.

The morbidity and mortality caused by influenza outbreaks continue to be substantial. Most individuals who die in this setting have underlying diseases that place them at high risk for complications of influenza. Excess hospitalizations for adults and children with high-risk medical conditions have ranged from 56 to 1900 per 100,000 during recent outbreaks of influenza. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases and old age. Mortality among individuals with chronic metabolic, renal, and certain immunosuppressive diseases has also been elevated, although lower than that among patients with chronic cardiopulmonary diseases. The morbidity attributable to influenza in the general population is considerable. It is estimated that interpandemic outbreaks of influenza currently incur annual costs of $12 billion in the United States. If a pandemic were to occur, it is estimated that annual costs would range from $71 to $167 billion for attack rates of 15 to 35%.

PATHOGENESIS AND IMMUNITY The initial event in influenza is infection of the respiratory epithelium with influenza virus acquired from respiratory secretions of acutely infected individuals. In all likelihood, transmission occurs via aerosols generated by coughs and sneezes, although hand-to-hand contact, other personal contact, and even fomite transmission may take place. Experimental evidence suggests that infection by a small-particle aerosol (particle diameter $<10\ \mu m$) is more efficient than that by larger droplets. Initially, viral infection involves the ciliated columnar epithelial cells, but it may also involve other respiratory tract cells, including alveolar cells, mucous gland cells, and macrophages. In infected cells, virus replicates within 4 to 6 h, after which infectious virus is released to infect adjacent or nearby cells. In this way, infection spreads from a few foci to a large number of respiratory cells over several hours. In experimentally induced infection, the incubation period of illness has ranged from 18 to 72 h, depending on the size of the viral inoculum. Histopathologic study reveals degenerative changes, including granulation, vacuolization, swelling, and pyknotic nuclei, in infected ciliated cells. The cells eventually become necrotic and desquamate; in some areas, previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. The severity of illness is correlated with the quantity of virus shed in secretions; thus, the degree of viral replication itself may be an important

factor in pathogenesis. Despite the frequent development of systemic signs and symptoms such as fever, headache, and myalgias, influenza virus has only rarely been detected in extrapulmonary sites (including the bloodstream). Evidence suggests that the pathogenesis of systemic symptoms in influenza may be related to the induction of certain cytokines, particularly tumor necrosis factor α, interferon α, and interleukin 6, in respiratory secretions and in the bloodstream.

The host response to influenza infections involves a complex interplay of humoral antibody, local antibody, cell-mediated immunity, interferon, and other host defenses. Serum antibody responses, which can be detected by the second week after primary infection, are measured by a variety of techniques: hemagglutination inhibition (HI), complement fixation (CF), neutralization, enzyme-linked immunosorbent assay (ELISA), and antineuraminidase antibody assay. Antibodies directed against the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of $\geq$40 have been associated with protection from infection. Secretory antibodies produced in the respiratory tract are predominantly of the IgA class and also play a major role in protection against infection. Secretory antibody neutralization titers of $\geq$4 have also been associated with protection. A variety of cell-mediated immune responses, both antigen-specific and antigen-nonspecific, can be detected early after infection and depend on the prior immune status of the host. These responses include T-cell proliferative, T-cell cytotoxic, and natural killer cell activity. In humans, CD8+, HLA class I–restricted cytotoxic T cells (CTLs) are directed at conserved regions of internal proteins (NP, M, and polymerases) as well as against the surface proteins (H and N). Interferons can be detected in respiratory secretions shortly after the shedding of virus has begun, and rises in interferon titers coincide with decreases in virus shedding.

The host defense factors responsible for cessation of virus shedding and resolution of illness have not been defined specifically. Virus shedding generally stops within 2 to 5 days after symptoms first appear, at a time when serum and local antibody responses often are not detectable by conventional techniques (although antibody rises may be detected earlier by use of highly sensitive techniques, particularly in individuals with previous immunity to the virus). It has been suggested that interferon, cell-mediated immune responses, and/or nonspecific inflammatory responses all contribute to the resolution of illness. CTL responses may be particularly important in that regard.

MANIFESTATIONS Influenza has most frequently been described as an illness characterized by the abrupt onset of systemic symptoms, such as headache, feverishness, chills, myalgia, or malaise, and accompanying respiratory tract signs, particularly cough and sore throat. In many cases, the onset is so abrupt that patients can recall the precise time they became ill. However, the spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either a gradual or an abrupt onset) to severe prostration with relatively few respiratory signs and symptoms. In most of the cases that come to a physician's attention, the patient has a fever, with temperatures of 38° to 41°C (100.4° to 105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by a gradual defervescence over a 2- to 3-day period, although, on occasion, fever may last for as long as a week. Patients report a feverish feeling and chilliness, but true rigors are rare. Headache, either generalized or frontal, is often particularly troublesome. Myalgias may involve any part of the body but are most common in the legs and lumbosacral area. Arthralgias may also develop.

Respiratory complaints often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for a week or more and which is often accompanied by substernal discomfort. Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eyes.

Physical findings are usually minimal in cases of uncomplicated influenza. Early in the illness, the patient appears flushed and the skin is hot and dry, although diaphoresis and mottled extremities are sometimes evident, particularly in older patients. Examination of the pharynx may yield surprisingly unremarkable results despite a severe sore throat, but injection of the mucous membranes and postnasal discharge are apparent in some cases. Mild cervical lymphadenopathy may be noted, especially in younger individuals. The results of chest examination are largely negative in uncomplicated influenza, although rhonchi, wheezes, and scattered rales have been reported with variable frequency in different outbreaks. Frank dyspnea, hyperpnea, cyanosis, diffuse rales, and signs of consolidation are indicative of pulmonary complications. Patients with apparently uncomplicated influenza have been reported to have a variety of mild ventilatory defects and increased alveolar-capillary diffusion gradients; thus, subclinical pulmonary involvement may be more frequent than is appreciated.

In uncomplicated influenza, the acute illness generally resolves over a 2- to 5-day period, and most patients have largely recovered in 1 week, although cough may persist for 1 to 2 weeks longer. In a significant minority (particularly the elderly), however, symptoms of weakness or lassitude (postinfluenzal asthenia) may persist for several weeks and may prove troublesome for persons who wish to resume their full level of activity promptly. The pathogenetic basis for this asthenia is unknown, although pulmonary function abnormalities may persist for several weeks after uncomplicated influenza.

COMPLICATIONS Complications of influenza occur most frequently in patients >64 years old and in those with certain chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnancy in the second or third trimester also predisposes to complications with influenza. The most significant complication of influenza is pneumonia: "primary" influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Primary influenza viral pneumonia is the least common but most severe of the pneumonic complications. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest x-ray findings consistent with diffuse interstitial infiltrates and/or acute respiratory distress syndrome may be present. In such cases, arterial blood-gas determinations show marked hypoxia. Viral cultures of respiratory secretions and lung parenchyma, especially if samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils. Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Eosinophilic hyaline membranes can be found lining alveoli and alveolar ducts.

Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but has also been reported in otherwise-healthy young adults as well as in older individuals with chronic pulmonary disorders. In some epidemics of influenza (notably those of 1918 and 1957), pregnancy increased the risk of primary influenza pneumonia. Subsequent epidemics of influenza have been associated with increased rates of hospitalization among pregnant women.

Secondary bacterial pneumonia follows acute influenza. Improvement of the patient's condition over 2 to 3 days is followed by a reappearance of fever along with clinical signs and symptoms of bacterial pneumonia, including cough, production of purulent sputum, and physical and x-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*—organisms that can colonize the nasopharynx and that cause infection in the wake of changes in bronchopulmonary defenses. The etiology can often be determined by Gram's staining and culture of an appropriately obtained sputum specimen. Secondary bacterial pneumonia occurs most frequently in

high-risk individuals with chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Perhaps the most common pneumonic complications during outbreaks of influenza have mixed features of viral and bacterial pneumonia. Patients may experience a gradual progression of their acute illness or may show transient improvement followed by clinical exacerbation, with eventual manifestation of the clinical features of bacterial pneumonia. Sputum cultures may contain both influenza A virus and one of the bacterial pathogens described above. Patchy infiltrates or areas of consolidation may be detected by physical examination and chest x-ray. Patients with mixed viral and bacterial pneumonia generally have less widespread involvement of the lung than those with primary viral pneumonia, and their bacterial infections may respond to appropriate antibiotics. Mixed viral and bacterial pneumonia occurs primarily in patients with chronic cardiovascular and pulmonary diseases.

Other pulmonary complications associated with influenza include worsening of chronic obstructive pulmonary disease and exacerbation of chronic bronchitis and asthma. In children, influenza infection may present as croup. Sinusitis as well as otitis media (the latter occurring particularly often in children) may also be associated with influenza.

In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include *Reye's syndrome* (Chap. 290), a serious complication in children that is associated with influenza B and to a lesser extent with influenza A virus infection as well as with varicella-zoster virus infection. An epidemiologic association between Reye's syndrome and aspirin therapy for the antecedent viral infection has been noted, and the syndrome's incidence has decreased markedly with widespread warnings regarding aspirin use by children with acute viral respiratory infections.

Myositis, rhabdomyolysis, and myoglobinuria are occasional complications of influenza infection. Although myalgias are exceedingly common in influenza, true myositis is rare. Patients with acute myositis have exquisite tenderness of the affected muscles, most commonly in the legs, and may not be able to tolerate even the slightest pressure, such as the touch of bedsheets. In the most severe cases, there is frank swelling and bogginess of muscles. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient has developed renal failure from myoglobinuria. The pathogenesis of influenza-associated myositis is also unclear, although the presence of influenza virus in affected muscles has been reported.

Myocarditis and pericarditis were reported in association with influenza virus infection during the 1918–1919 pandemic; these reports were based largely on histopathologic findings, and these complications have been reported only infrequently since that time. Electrocardiographic changes during acute influenza are common among patients who have cardiac disease but have been ascribed most often to exacerbations of the underlying cardiac disease rather than to direct involvement of the myocardium with influenza virus.

Central nervous system (CNS) diseases, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza. The etiologic relationship of influenza virus to such CNS illnesses remains uncertain. Toxic shock syndrome associated with *S. aureus* or group A streptococcal infection following acute influenza infection has also been reported (Chaps. 120 and 121).

In addition to complications involving the specific organ systems described above, influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function—changes that occasionally are irreversible and lead to death. These fatalities contribute to the overall excess mortality associated with influenza A outbreaks.

LABORATORY FINDINGS AND DIAGNOSIS Influenza virus may be isolated during acute influenza from throat swabs, nasopharyngeal washes, or sputum. Virus is usually detected by use of tissue culture or, less commonly, chick embryos within 48 to 72 h after inoculation. Most commonly, the diagnosis is established by the use of rapid viral tests that detect viral nucleoprotein or neuraminidase with high sensitivity and a specificity of 60 to 90% compared with that of tissue culture. Viral nucleic acids can be detected in clinical samples by reverse transcriptase polymerase chain reaction. The type of influenza virus (A or B) may be determined by either immunofluorescence or HI techniques, and the hemagglutinin subtype of influenza A virus (H1, H2, or H3) may be identified by HI with use of subtype-specific antisera. Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10 to 14 days after the onset of illness and are useful primarily in retrospect. Fourfold or greater titer rises as detected by HI or CF or significant rises as measured by ELISA are diagnostic of acute infection. CF tests are generally less sensitive than other serologic techniques, but, as they detect type-specific antigens, they may be particularly useful when subtype-specific reagents are not available.

Other laboratory tests are generally not helpful in making a specific diagnosis of influenza virus infection. Leukocyte counts are variable, frequently being low early in illness and normal or slightly elevated later. Severe leukopenia has been described in overwhelming viral or bacterial infection, while leukocytosis with >15,000 cells/μL raises the suspicion of secondary bacterial infection.

DIFFERENTIAL DIAGNOSIS During a community-wide outbreak of influenza, a clinical diagnosis of influenza can be made with a high degree of certainty in patients who present to a physician's office with the typical febrile respiratory illness described above. In the absence of an outbreak (i.e., in sporadic or isolated cases), influenza may be difficult to differentiate on clinical grounds alone from an acute respiratory illness caused by any of a variety of respiratory viruses or by *Mycoplasma pneumoniae*. Severe streptococcal pharyngitis or early bacterial pneumonia may mimic acute influenza, although bacterial pneumonias generally do not run a self-limited course. Purulent sputum in which a bacterial pathogen can be detected by Gram's staining is an important diagnostic feature in bacterial pneumonia.

℞ TREATMENT

In uncomplicated cases of influenza, symptom-based therapy with acetaminophen for the relief of headache, myalgia, and fever may be considered, but the use of salicylates should be avoided in children <18 years of age because of the possible association of salicylates with Reye's syndrome. Since cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated, although codeine-containing compounds may be employed if the cough is particularly troublesome. Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved, especially if it has been severe.

Specific antiviral therapy is available for influenza: amantadine and rimantadine for influenza A and the neuraminidase inhibitors zanamivir and oseltamivir for both influenza A and influenza B. If begun within 48 h of the onset of illness, treatment with amantadine or rimantadine has reduced the duration of systemic and respiratory symptoms of influenza by ~50%. From 5 to 10% of individuals who receive amantadine experience mild CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty in concentrating. These side effects disappear promptly upon cessation of the drug. Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine. In adults, the usual dose of amantadine or rimantadine is 200 mg/d for 3 to 7 days. Since both drugs are excreted via the kidney, the dose should be reduced to ≤100 mg/d in elderly patients and in patients with renal insufficiency. Zanamivir, inhaled orally at a dose of 10 mg twice a day for 5 days, or oseltamivir, ingested orally at a dose of 75 mg twice a day for 5 days, has reduced the duration of signs and symptoms of influenza by 1 to 1.5 days if treatment is started within 2 days of the onset of illness. Zanamivir may exacerbate bronchospasm in asthmatic patients, and oseltamivir

has been associated with nausea and vomiting, whose frequency can be reduced by drug administration with food. Resistant viruses emerge frequently during treatment with amantadine or rimantadine and can be transmitted among family members. The development of resistance appears to be infrequent with zanamivir or oseltamivir. Treatment of children is approved for amantadine and oseltamivir (≥1 year of age) and for zanamivir (≥7 years of age). Ribavirin is a nucleoside analogue with activity against influenza A and B viruses in vitro. It has been reported to be variably effective against influenza when administered as an aerosol but ineffective when administered orally. Its efficacy in the treatment of influenza A or B is unestablished.

Studies demonstrating the therapeutic efficacy of antiviral compounds in influenza have primarily involved young adults with uncomplicated disease; it is not known whether such compounds are effective in the treatment of influenza pneumonia or of other complications of influenza. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed. Bypass membrane oxygenators have been employed in this setting with variable results. When an acute respiratory distress syndrome develops, fluids must be administered cautiously, with close monitoring of blood gases and hemodynamic function.

Antibacterial drugs should be reserved for the treatment of bacterial complications of acute influenza, such as secondary bacterial pneumonia. The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum or transtracheal aspirates. If the etiology of a case of bacterial pneumonia is unclear from an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (*S. pneumoniae*, *S. aureus*, and *H. influenzae*) should be selected (Chaps. 119, 120, and 130).

PROPHYLAXIS The major public health measure for prevention of influenza has been the use of inactivated influenza vaccines derived from influenza A and B viruses that circulated during the previous influenza season. If the vaccine virus and the currently circulating viruses are closely related, 50 to 80% protection against influenza would be expected. Presently available inactivated vaccines have been highly purified and are associated with few reactions. Up to 5% of individuals experience low-grade fever and mild systemic symptoms 8 to 24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Since the vaccine is produced in eggs, individuals with true hypersensitivity to egg products either should be desensitized or should not be vaccinated. Although the 1976 swine influenza vaccine appears to have been associated with an increased frequency of Guillain-Barré syndrome, influenza vaccines administered since 1976 generally have not been. Possible exceptions were noted during the 1992–1993 and 1993–1994 influenza seasons, when there may have been an excess risk of Guillain-Barré syndrome of slightly more than one case per million among vaccine recipients. However, the overall health risk following influenza outweighs the potential risk associated with vaccination.

The U.S. Public Health Service recommends influenza vaccination for any individual >6 months of age who is at an increased risk for complications of influenza, as noted earlier (Table 171-2). Since commercially available vaccines are inactivated ("killed"), they may be administered safely to immunocompromised patients. Influenza vaccination is not associated with exacerbations of chronic nervous-system diseases such as multiple sclerosis. Vaccine should be administered early in the autumn before influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains.

Recently, an advisory committee of the U.S. Food and Drug Administration recommended approval of a live attenuated influenza vaccine that is administered by intranasal spray. The vaccine is generated by reassortment of currently circulating strains of influenza A and B virus with a cold-adapted, attenuated master strain. The cold-adapted vaccine is well tolerated and highly efficacious (92% protective) in young children; in one study, it provided protection against a circulating influenza virus that had drifted antigenically away from the vaccine strain. The committee recommended approval of the cold-adapted vaccine for use in healthy children and adults from 5 to 49 years of age.

TABLE 171-2 Recommendations for Influenza Vaccination[a]

Persons at increased risk for complications
Persons ≥65 years of age
Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
Adults and children (≥6 months) who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
Adults and children (≥6 months) who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by HIV)
Children and adolescents (6 months to 18 years old) who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye's syndrome after influenza infection
Women who will be in the second or third trimester of pregnancy during the influenza season
Persons 50 to 64 years of age
Included because of increased prevalence of high-risk conditions
Persons who can transmit influenza to those at high risk
Physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g., paramedics and emergency medical technicians)
Employees of nursing homes and chronic-care facilities who have contact with patients or residents
Employees of assisted-living and other residences for persons in groups at high risk
Persons who provide home care to individuals in groups at high risk
Household members (including children) of persons in groups at high risk

[a] Vaccination of healthy children 6 to 23 months of age is encouraged.
Source: Centers for Disease Control and Prevention.

Chemoprophylaxis with amantadine or rimantadine, at dosages of 100 to 200 mg/d, has efficacy rates of 70 to 100% against illness associated with influenza A infection. Chemoprophylaxis with oseltamivir (75 mg/d by mouth) or zanamivir (10 mg/d inhaled) has resulted in efficacy rates of 84 to 89% against influenza A and B. Chemoprophylaxis is most likely to be used for high-risk individuals who have not received influenza vaccine or in a situation where the vaccines previously administered are relatively ineffective because of antigenic changes in the circulating virus. During an outbreak, antiviral chemoprophylaxis can be administered simultaneously with inactivated vaccine, since the drugs do not interfere with an immune response to the vaccine. In fact, there is evidence that the protective effects of chemoprophylaxis and vaccine may be additive. However, concurrent administration of chemoprophylaxis and the live attenuated vaccine may interfere with the immune response to the latter. Chemoprophylaxis may also be employed to control nosocomial outbreaks of influenza. For prophylaxis, administration should be instituted promptly when influenza activity is detected and must be continued daily for the duration of the outbreak. Amantadine and rimantadine are approved for prophylaxis in adults and in children ≥1 year old; oseltamivir is approved for prophylaxis in adults and in children ≥13 years old.

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Section 14 Infections Due to Human Immunodeficiency Virus and Other Human Retroviruses

172 THE HUMAN RETROVIRUSES

Dan L. Longo, Anthony S. Fauci

The retroviruses, which make up a large family (Retroviridae), infect mainly vertebrates. They have a unique replication cycle whereby their genetic information is encoded by RNA rather than DNA. Retroviruses contain an RNA-dependent DNA polymerase (a reverse transcriptase) that directs the synthesis of a DNA form of the viral genome after infection of a host cell. The designation *retrovirus* denotes that information in the form of RNA is transcribed into DNA in the host cell—a sequence that overturned a central dogma of molecular biology: that information passes unidirectionally from DNA to RNA to protein. The observation that RNA was the source of genetic information in the causative agents of certain animal tumors led to a number of paradigm-shifting biologic insights regarding not only the direction of genetic-information passage but also the viral etiology of certain cancers and the concept of oncogenes as normal host genes scavenged and altered by a viral vector.

The family Retroviridae includes three subfamilies (Table 172-1): Oncovirinae, of which human T-cell lymphotropic virus (HTLV) type I is the most important in humans; Lentivirinae, of which HIV is the most important in humans; and Spumavirinae, the "foamy" viruses, named for the pathologic appearance of infected cells. A number of spumaviruses have been isolated from humans; however, they are not associated with any known disease and therefore are not discussed further in this chapter.

The wide variety of interactions of a retrovirus with its host range from completely benign events (e.g., silent carriage of endogenous retroviral sequences in the germ-line genome of many animal species) to rapidly fatal infections (e.g., exogenous infection with an oncogenic virus such as Rous sarcoma virus in chickens). The ability of retroviruses to acquire and alter the structure and function of host cell sequences has revolutionized our understanding of molecular carcinogenesis. The viruses can insert into the germ-line genome of the host cell and behave as a transposable or movable genetic element. They can activate or inactivate genes near the site of integration into the genome. They can rapidly alter their own genome by recombination and mutation under selective environmental stimuli.

Most human viral diseases occur as a consequence of either tissue destruction by the virus itself or the host's response to the virus. Although these mechanisms are operative in retroviral infections, retroviruses have additional mechanisms of inducing disease, including the malignant transformation of an infected cell and the induction of an immunodeficiency state that leads to opportunistic diseases (infections and neoplasms; Chap. 173).

STRUCTURE AND LIFE CYCLE Despite the wide range of biologic consequences of retroviral infection, all retroviruses are similar in structure, genome organization, and mode of replication. Retroviruses are 70 to 130 nm in diameter and have a lipid-containing envelope surrounding an icosahedral capsid with a dense inner core. The core contains two identical copies of the single-strand RNA genome. The RNA molecules are 8 to 10 kb long and are complexed with reverse transcriptase and tRNA. Other viral proteins, such as integrase, are also components of the virion particle. The RNA has features usually found in mRNA: a cap site at the 5′ end of the molecule, which is important in the initiation of mRNA translation, and a polyadenylation site at the 3′ end, which influences mRNA turnover (i.e., messages with shorter polyA tails turn over faster than messages with longer polyA tails). However, the retroviral RNA is not translated; instead it is transcribed into DNA. The DNA form of the retroviral genome is called a *provirus*.

The replication cycle of retroviruses proceeds in two phases (Fig. 172-1). In the first phase, the virus enters the cytoplasm after binding to a specific cell-surface receptor (with HIV, a cell-surface co-receptor is also utilized for binding and entry); the viral RNA and reverse transcriptase synthesize a double-strand DNA version of the RNA template; and the provirus moves into the nucleus and integrates into the host cell genome. This proviral integration is permanent. Although some animal retroviruses integrate into a single specific site of the host

TABLE 172-1 Classification of Retroviruses: the Family Retroviridae

Subfamily, Group[a]	Example	Feature
Oncovirinae (oncogenic viruses)		
Avian leukosis	Rous sarcoma virus	Contains *src* oncogene
Mammalian C-type	Abelson leukemia virus	Contains *abl* oncogene
B-type	Murine mammary tumor virus	Can be endogenous or exogenous
D-type	Mason-Pfizer monkey virus	—
HTLV-BLV	HTLV-I	Causes T-cell lymphoma and neurologic disease
Lentivirinae (slow viruses)	HIV-1, HIV-2	Causes AIDS
	Visna virus	Causes lung and brain diseases in sheep
	Feline immunodeficiency virus	Causes immunodeficiency in cats
Spumavirinae (foamy viruses)	Simian foamy virus, human foamy virus	Causes no known disease

[a] The Oncovirinae were originally grouped into types A–D on the basis of morphologic features (size, core location, budding) under electron microscopy; however, this system has been replaced by groupings based on relationships of genome structure and sequence.

Note: HTLV, human T-lymphotropic virus; BLV, bovine leukemia virus.

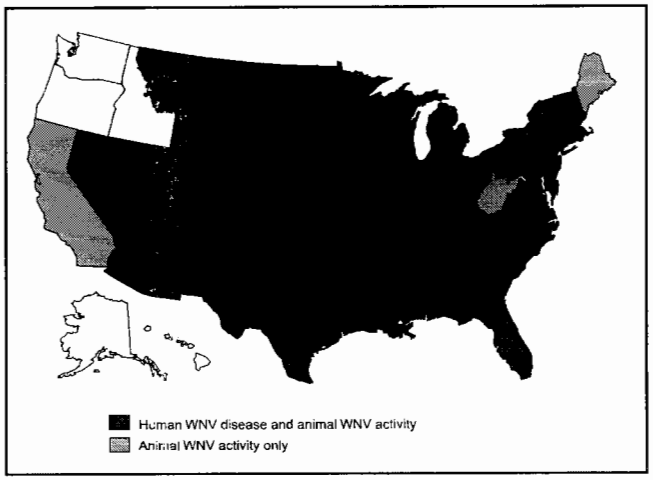
West Nile Virus Activity — United States, September 25–October 1, 2003

This report summarizes West Nile virus (WNV) surveillance data reported to CDC through ArboNET as of 3 a.m., Mountain Daylight Time, October 1, 2003.

During the reporting week of September 25–October 1, a total of 1,034 human cases of WNV infection were reported from 27 states (Colorado, Connecticut, Georgia, Illinois, Iowa, Kansas, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, South Dakota, Tennessee, Texas, Vermont, Virginia, and Wyoming), including 22 fatal cases from 10 states (Colorado, Georgia, Maryland, Michigan, Montana, Nebraska, New York, Pennsylvania, Texas, and Wyoming). During the same period, WNV infections were reported in 692 mosquito pools, 549 dead birds, 306 horses, four squirrels, two unidentified animal species, and one dog.

During 2003, a total of 5,861 human cases of WNV infection have been reported from Colorado (n = 1,991), Nebraska (n = 999), South Dakota (n = 840), Texas (n = 335), Wyoming (n = 313), Montana (n = 207), New Mexico (n = 174), North Dakota (n = 148), Iowa (n = 98), Minnesota (n = 96), Pennsylvania (n = 91), Louisiana (n = 67), Ohio (n = 57), Mississippi (n = 51), New York (n = 45), Oklahoma (n = 40), Kansas (n = 40), Missouri (n = 38), Florida (n = 32), Alabama (n = 26), Illinois (n = 22), Maryland (n = 20), North Carolina (n = 19), New Jersey (n = 17), Georgia (n = 13), Arkansas (n = 11), Massachusetts (n = 10), Wisconsin (n = 10), Connecticut (n = nine), Tennessee (n = eight), Virginia (n = seven), Indiana (n = six), Kentucky (n = six), Delaware (n = four), Rhode Island (n = three), New Hampshire (n = two), Arizona (n = one), Michigan (n = one), Nevada (n = one), South Carolina (n = one), Utah (n = one), and Vermont (n = one) (Figure). Of 5,787 (99%) cases for which demographic data were available, 3,028 (52%) occurred among males; the median age was 47 years (range: 1 month–99 years), and the dates of illness onset ranged from March 28 to September 26. Of the 5,787 cases, 115 fatal cases were reported from Colorado (n = 36), Nebraska (n = 15), Texas (n = 11), South Dakota (n = eight), Wyoming (n = eight), New York (n = six), New Mexico (n = four), Alabama (n = three), Iowa (n = three), Minnesota (n = three), Ohio (n = three), Georgia (n = two), Maryland (n = two), Missouri (n = two), Montana (n = two), Kansas (n = one), Louisiana (n = one), Michigan (n = one), Mississippi (n = one), New Jersey (n = one), North Dakota (n = one), and Pennsylvania (n = one). A total of 617 presumptive West Nile viremic blood donors have been reported to ArboNET. Of these, 558 (90%) were reported from the following nine western and midwestern states: Colorado, Kansas, Nebraska, New Mexico, North Dakota, Oklahoma, South Dakota, Texas, and Wyoming. Of the 489 donors for whom data was completely reported, four subsequently had meningoencephalitis, and 66 subsequently had West Nile fever. In addition, 8,955 dead birds with WNV infection were reported from 42 states, the District of Columbia, and New York City; 2,449 WNV infections in horses have been reported from 36 states, 19 infections in unidentified animal species, 13 infections in dogs, and nine infections in squirrels. During 2003, WNV seroconversions have been reported in 612 sentinel chicken flocks from 13 states. Of the eight seropositive sentinel horses reported, Minnesota reported four; South Dakota, three; and West Virginia, one. A total of 5,633 WNV-positive mosquito pools have been reported from 39 states and New York City.

FIGURE. Areas reporting West Nile virus (WNV) activity — United States, 2003*



* As of 3 a.m., Mountain Daylight Time, October 1, 2003.

Additional information about WNV activity is available from CDC at http://www.cdc.gov/ncidod/dvbid/westnile/index.htm and http://www.westnilemaps.usgs.gov.

Notice to Readers

SARS, Influenza, and Use of Influenza Vaccine

CDC supports and emphasizes the use of influenza vaccination for reducing influenza infections and their associated complications. CDC does not recommend influenza vaccination for the primary purpose of reducing the number of persons who might be evaluated for severe acute respiratory syndrome (SARS).

Influenza vaccine is effective only against influenza virus infection and is the best option for preventing influenza and its complications. These complications occur most often in children aged <24 months, persons aged ≥65 years, and those of any age who have certain medical conditions placing them at high-risk for having complications from influenza infection.* Annual vaccination is recommended for persons at high risk aged ≥6 months and for persons in other target groups, including family members and other close contacts of high-risk persons, those aged 50–64 years, and health-care workers. Vaccination is encouraged, when feasible, for children aged 6–23 months and for their household contacts and out-of-home caregivers. Influenza vaccination of health-care workers is especially important for reducing transmission of influenza viruses to patients with high-risk conditions in hospital and other health-care settings and for protecting the health-care workforce during the influenza season. Additional information about prevention and control of influenza is available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5208a1.htm.

On a population level, widespread use of the influenza vaccine will reduce the number of influenza cases and might decrease the number of persons with a febrile respiratory illness who are evaluated for SARS. However, such secondary benefits cannot be reliably anticipated. For example, the overall decrease in febrile respiratory illnesses would be minimal if circulating levels of influenza viruses are low or if other respiratory pathogens are actively circulating in a community.

Persons vaccinated against influenza can still have a febrile respiratory illness because influenza vaccine will not prevent infection by noninfluenza agents and the effectiveness of influenza vaccine is <100%. Therefore, receipt of influenza vaccination in a person who subsequently experiences a febrile respiratory illness does not eliminate influenza as a possible cause nor necessarily increase the likelihood that the illness is SARS.

*Persons at high risk include residents of chronic care facilities, persons with chronic pulmonary or cardiovascular disorders (e.g., asthma, chronic metabolic diseases, renal dysfunction, hemoglobinopathies, or immunosuppression), children receiving long-term aspirin therapy, and women who will be in the second or third trimester of pregnancy during the influenza season.

Notice to Readers

Domestic Violence Awareness Month, October 2003

October is Domestic Violence Awareness Month (DVAM). Approximately 1.5 million U.S. women and 835,000 U.S. men are raped or physically assaulted by a current or former spouse, cohabitating partner, or date each year (*1*). The annual health-related costs of intimate partner violence in the United States is approximately $5.8 billion (*2*). During October, state and territorial domestic violence coalitions, corporations, health-care providers, faith-based groups, and CDC will highlight activities that increase awareness about intimate partner violence.

A packet of materials designed to help plan events, initiate outreach in communities, and generate public awareness about domestic violence during October and throughout the year is available from the National Resource Center on Domestic Violence, Domestic Violence Awareness Month Project, 6400 Flank Drive, Suite 1300, Harrisburg, PA 17112-2778, telephone 800-537-2238, and at http://dvam.vawnet.org. Additional information about DVAM is available from CDC at http://www.cdc.gov/injury.

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Erratum: Vol. 52, No. SS-9

In the Surveillance Summary, "Assisted Reproductive Technology Surveillance—United States, 2000," dated August 29, 2003, an error occurred on page 6, in the third paragraph of the Discussion section. The text should read, "This divergence is not surprising because Massachusetts had a statewide mandate for insurance coverage for ART procedures in 2000." Although a similar mandate was introduced in New Jersey in early 2000, it was not approved until August 2001 and did not take effect until January 1, 2002.

Erratum: Vol. 52, No. 38

In the article, "Update: Detection of West Nile Virus in Blood Donations United States, 2003," an error occurred on page 918 in the second sentence of the third full paragraph discussing Case 2. The sentence should read, "These 20 samples were tested by NAT at three different laboratories; one sample tested equivocal at one laboratory (Lab A), reactive in a second, and nonreactive in a third." This sample subsequently tested positive for West Nile virus RNA at a fourth laboratory and was reactive when retested at Lab A by using a larger extraction volume (estimated virus titer: 0.1 plaque-forming units/mL).

Antibiotic Use in Acute Upper Respiratory Tract Infections

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Upper respiratory tract infections account for millions of visits to family physicians each year in the United States. Although warranted in some cases, antibiotics are greatly overused. This article outlines the guidelines and indications for appropriate antibiotic use for common upper respiratory infections. Early antibiotic treatment may be indicated in patients with acute otitis media, group A beta-hemolytic streptococcal pharyngitis, epiglottitis, or bronchitis caused by pertussis. Persistent cases of rhinosinusitis may necessitate the use of antibiotics if symptoms persist beyond a period of observation. Antibiotics should not be considered in patients with the common cold or laryngitis. Judicious, evidence-based use of antibiotics will help contain costs and prevent adverse effects and drug resistance. (*Am Fam Physician.* 2012;86(9):817-822. Copyright © 2012 American Academy of Family Physicians.)

ILLUSTRATION BY JOHN KARAPELOU

▶ **Patient information:** A handout on antibiotic use is available online at http://familydoctor.org/familydoctor/en/drugs-procedures-devices/prescription-medicines/antibiotics-when-they-can-and-cant-help.html.

▶ **See related editorial on page 810.**

Upper respiratory tract infections (URIs) are commonly treated in family physicians' practices. Uncomplicated URIs account for 25 million visits to family physicians and about 20 to 22 million days of absence from work or school each year in the United States.[1] Despite the majority of these infections being viral, a high percentage are treated with antibiotics[2] (*Table 1*[3-18]). A study from a large, outpatient ambulatory network of more than 52,000 cases of URI showed that antibiotics were prescribed in 65 percent of patients.[19] Overuse of antibiotics may lead to resistance, increased cost, and increased incidence of adverse effects, including anaphylaxis.[20]

Common Cold

The common cold is a mild, self-limited URI with symptoms of runny nose, sore throat, cough, sneezing, and nasal congestion. It is a heterogeneous group of viral diseases, and therefore does not respond to antibiotics.[1,21] Between 1991 and 1999, the rate of overall antibiotic use for URIs decreased in the United States. However, the use of broad-spectrum antibiotics increased.[22] One study reviewed randomized controlled trials (RCTs) from 1966 to 2009 that compared antibiotic therapy with placebo in persons who had symptoms of acute URI of less than seven days' duration, or acute purulent rhinitis of less than 10 days' duration.[11] The authors found insufficient evidence to recommend antibiotics for the treatment of purulent or clear rhinitis in children or adults.

Influenza

Influenza is an acute URI caused by influenza virus A or B. It affects patients of all ages, but the highest incidence is in children. Adults older than 65 years and children younger than two years have the highest mortality rates from influenza.[23,24] Vaccination is the mainstay of prevention. Supportive care is the foundation of treatment, but antiviral therapy, such as the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), may decrease the duration of the illness by one day if started within 48 hours of symptom onset.[16,17] The Centers for Disease Control and Prevention no longer recommends the use of amantadine for influenza therapy.[24]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Amoxicillin is the preferred treatment in patients with acute bacterial rhinosinusitis.	C	10
Short-course antibiotic therapy (median of five days' duration) is as effective as longer-course treatment (median of 10 days' duration) in patients with acute, uncomplicated bacterial rhinosinusitis.	B	31
Antibiotic therapy should be considered for children six to 35 months of age with acute otitis media.	B	37, 38
Antibiotics should not be used in patients who have otitis media with effusion.	C	43
Penicillin should be used in patients with streptococcal pharyngitis to decrease the risk of rheumatic fever, alleviate symptoms, and decrease communicability.	B	45, 46, 49, 52
Antibiotics should not be prescribed for acute laryngitis.	A	18, 54

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Table 1. Diagnostic Findings and Appropriate Treatments for Upper Respiratory Tract Infections

Condition	Key diagnostic findings	Treatment
Acute bronchitis and tracheitis	Cough, possible phlegm production	Symptomatic treatment; antibiotics are not recommended[3-6]
Acute otitis media	Acute onset of symptoms, presence of middle ear effusion, signs of middle ear inflammation	Amoxicillin, 80 to 90 mg per kg per day, in two divided doses (first-line treatment)[7-9]
Acute rhinosinusitis	Nasal obstruction, anterior or posterior purulent nasal discharge, facial pain, cough, decreased sense of smell	Watchful waiting in mild cases; amoxicillin for severe or complicated bacterial rhinosinusitis[10]
Common cold	Runny nose, cough, sore throat, sneezing, nasal congestion	Symptomatic treatment; antibiotics are not recommended[11]
Epiglottitis	Dysphagia, voice change, tachycardia (heart rate > 100 beats per minute), drooling, fever, subjective shortness of breath, tachypnea (respiratory rate > 24 breaths per minute), stridor, respiratory distress, leaning forward	Intravenous combination of a third-generation cephalosporin and an antistaphylococcal agent active against methicillin-resistant *Staphylococcus aureus*[12] or intravenous monotherapy with ceftriaxone (Rocephin), cefotaxime (Claforan), or ampicillin/sulbactam (Unasyn)[13-15]
Influenza	Abrupt onset of fever, headache, myalgia, malaise	Influenza vaccination for prevention; supportive care; initiation of antiviral therapy within 48 hours of symptom onset may decrease illness duration by one day[16,17]
Laryngitis	Loss or muffling of voice, sore throat, cough, fever, runny nose, headache	Symptomatic treatment; antibiotics are unnecessary[18]
Pharyngitis and tonsillitis	Sore throat, fever, absence of cough	Treatment based on modified Centor score (Table 2)

Information from references 3 through 18.

Patients with severe illness, those older than 65 years or younger than two years, pregnant women, and those with chronic illnesses should be treated with antivirals.[24] Empiric antibiotic therapy should not be continued after influenza is diagnosed unless there is concern about a secondary bacterial process. Gram stain and cultures of body fluids can be useful in determining whether antibiotics should be added to an antiviral regimen.

Rhinosinusitis

Acute rhinosinusitis is a common diagnosis in the outpatient setting, with an annual incidence of approximately 13 percent in adults.[25] It is defined as inflammation of the nasal mucosa and sinuses. Symptoms include nasal obstruction, anterior or posterior purulent nasal discharge, facial pain, decrease in sense of smell, and cough.[26] Rhinosinusitis is classified as acute when symptoms

are present for less than four weeks, subacute for four to 12 weeks, and chronic for more than 12 weeks.[26]

Differentiating between viral and bacterial rhinosinusitis is important because treatment of all cases would result in the overprescribing of antibiotics.[26] The diagnosis of acute bacterial rhinosinusitis should not be made until symptoms have persisted for at least 10 days or after initial improvement followed by worsening of symptoms.[10] Four symptoms are more predictive of bacterial rather than viral rhinosinusitis: purulent nasal discharge, maxillary tooth or facial pain, unilateral maxillary sinus tenderness, and worsening symptoms after initial improvement.[27,28]

Mild cases of acute bacterial rhinosinusitis can be managed with watchful waiting if appropriate follow-up can be ensured.[10] Worsening symptoms within seven days warrant the initiation of antibiotics in these patients. Antibiotic treatment is acceptable in patients with severe or complicated acute bacterial rhinosinusitis.[28] A Cochrane review of five studies in the primary care setting (n = 631 patients) found that antibiotic therapy for acute maxillary sinusitis has a slight statistical advantage over placebo.[29] However, the clinical significance was equivocal because the clinical cure rate was high in both groups (90 percent in the treatment group compared with 80 percent in the placebo group). The antibiotic chosen should provide coverage for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*,[30] with amoxicillin as the first choice or trimethoprim/sulfamethoxazole (Bactrim, Septra) for patients allergic to penicillin.[10] A different antibiotic is justified if symptoms worsen within seven days.[10] A meta-analysis of 12 RCTs (10 double-blinded, n = 4,430 patients) found no statistically significant difference between long- and short-course antibiotics for cure or improvement of symptoms.[31] Short-course antibiotic therapy (median of five days' duration) was as effective as longer-course treatment (median of 10 days' duration) in patients with acute, uncomplicated bacterial rhinosinusitis.

Otitis Media

The diagnosis of acute otitis media (AOM) requires an acute onset of symptoms, the presence of middle ear effusion, and signs and symptoms of middle ear inflammation.[7] The most common pathogens are nontypeable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.[32] Viruses have been found in the respiratory secretions of patients with AOM and may account for many cases of antibiotic failure.[33-35] Group B streptococcus, gram-negative enteric bacteria, and *Chlamydia trachomatis* are common middle ear pathogens in infants up to eight weeks of age.[8]

Cohort studies and RCTs have shown that AOM typically resolves without antibiotic therapy in children.[36] In 2004, the American Academy of Pediatrics and the American Academy of Family Physicians developed guidelines for the treatment of AOM.[7] These guidelines list observation as an option for children older than six months; observation involves deferring antibiotic treatment for 48 to 72 hours and initiating therapy only if symptoms persist or worsen. However, two RCTs conducted in 2011 found that immediate antibiotic use in children six to 35 months of age was more effective than observation.[37,38] These studies used strict criteria, tympanometry, or otoscopy for diagnosis and follow-up. Febrile infants (up to eight weeks of age) with AOM should have a full sepsis workup. These infants should undergo an otolaryngology consultation, if available, for tympanocentesis.[8] Immediate initiation of antibiotics is recommended in children younger than two years with bilateral AOM and in those with AOM and otorrhea.[39,40] Amoxicillin (80 to 90 mg per kg per day, in two divided doses) is recommended as first-line treatment for AOM.[7-9]

Amoxicillin is the first-line antibiotic for treatment of acute otitis media.

If there is no response to initial antibiotic therapy within 48 to 72 hours, the patient should be reexamined to confirm the diagnosis, and amoxicillin/clavulanate (Augmentin) should be initiated.[7,8] Ceftriaxone (Rocephin) can be used as a second-line agent or in children with vomiting.[7] Trimethoprim/sulfamethoxazole and erythromycin/sulfisoxazole are not effective for the treatment of AOM.[7,8] Longer courses of antibiotics (more than seven days) have lower failure rates than shorter courses.[41]

Children with AOM should be reevaluated in three months to document clearance of middle ear effusion.[8] Long-term antibiotic therapy has been shown to reduce the number of recurrent AOM episodes,[42] but is not recommended because of the risk of antibiotic resistance.[8] Antibiotics are not recommended for the treatment of otitis media with effusion because they have only a modest short-term benefit.[43]

Pharyngitis and Tonsillitis

Approximately 90 percent of adults and 70 percent of children with pharyngitis have viral infections.[44-46] In those with bacterial cases of pharyngitis, the leading

pathogen is group A beta-hemolytic streptococcus. Appropriate antibiotic treatment in these cases has been shown to decrease the risk of rheumatic fever, alleviate symptoms, and decrease communicability.[20,45,47] Antibiotic treatment does not prevent glomerulonephritis and has inconsistent results in the prevention of peritonsillar abscess.[20,44]

The Infectious Diseases Society of America recommends diagnostic testing to confirm group A beta-hemolytic streptococcal infection before initiating antibiotics to avoid overuse.[45] However, the American Academy of Family Physicians and the American College of Physicians recommend using the modified Centor criteria, which are based on age and the presence or absence of fever, tonsillar erythema or exudates, anterior cervical lymphadenopathy, and cough[48-51] *(Table 2[47-50])*. In patients with a score of 1 or less, no further diagnostic testing or treatment is indicated because the likelihood of streptococcal infection is low. However, in patients with a score of 1, other factors should be considered, such as contact with a person who has documented streptococcal infection; rapid antigen detection testing should be performed in these patients. In those with a score of 2 or 3, streptococcal rapid antigen detection testing should also be performed. If test results are positive, antibiotic treatment is indicated. Antibiotic therapy is recommended for patients with a score of 4 or 5.[49]

Approximately 90 percent of adults and 70 percent of children with pharyngitis have viral infections.

The recommended first-line treatment is a 10-day course of penicillin.[45,49,52] Erythromycin can be used in patients who are allergic to penicillin.[49,53] Amoxicillin, azithromycin (Zithromax), and first-generation cephalosporins are appropriate alternatives.[45,49]

Laryngitis

Acute laryngitis is inflammation of the vocal cords and larynx lasting less than three weeks.[54] Symptoms include loss or muffling of the voice, sore throat, and other classic URI symptoms such as cough, fever, runny nose, and headache. A Cochrane review of antibiotic therapy in patients with laryngitis found two studies (n = 206 patients) showing that antibiotic use does not reduce the duration of symptoms or lead to voice improvement.[54] Although these studies are older, there are no recent studies to indicate that these conclusions have changed. Laryngitis is a self-limited, viral disease that does not respond to antibiotic therapy.[18]

Epiglottitis

Epiglottitis is an inflammatory condition of the epiglottis and adjacent supraglottic structures that can rapidly progress to airway compromise and, potentially, death.[55,56] The incidence of epiglottitis in children has decreased with the use of *H. influenzae* type b (Hib) conjugate vaccines in early infancy.[13,57] A combination of an intravenous antistaphylococcal agent that is active against methicillin-resistant *Staphylococcus aureus* and a third-generation cephalosporin may be effective.[12] Intravenous monotherapy with ceftriaxone, cefotaxime (Claforan), or ampicillin/sulbactam (Unasyn) is also recommended.[13-15]

Bronchitis and Tracheitis

Acute bronchitis is a self-limited inflammation of the large airways (including the trachea) that presents with cough and possibly phlegm production. The predominant etiology of acute bronchitis is viral; therefore, antibiotics are not indicated in most patients.[3-5,58] Many studies have evaluated the use of antibiotics in the treatment of acute bronchitis and found no significant benefit from their use. Guidelines from the National Institute for Health and Clinical Excellence and the Centers for Disease Control and Prevention do not recommend antibiotics for the treatment of adults with acute bronchitis.[4,5] A 2004 Cochrane review found a small decrease in cough and days of feeling ill in patients who received antibiotics;

Table 2. Modified Centor Criteria for Pharyngitis and Tonsillitis

Clinical finding	*Points*
Absence of cough	1
Age	
3 to 14 years	1
15 to 45 years	0
Older than 45 years	–1
Anterior cervical lymphadenopathy	1
Fever	1
Tonsillar erythema or exudates	1

NOTE: *Patients with a score of 1 or less do not require further testing or treatment, although contact with a person who has documented streptococcal infection should be considered in patients with a score of 1, and testing should be performed in these cases; those with a score of 2 or 3 should have rapid antigen detection testing and, if results are positive, should receive antibiotics; and those with a score of 4 or 5 should receive antibiotics.*

Information from references 47 through 50.

however, the authors do not recommend their use because of adverse reactions, antibiotic resistance, and cost.[3] Individualized care focusing on symptom relief, as well as explaining to patients why antibiotics are not indicated, is appropriate in managing acute bronchitis in the outpatient setting.

It is important to differentiate pneumonia and influenza from bronchitis because antibiotics are recommended for patients with pneumonia, and antivirals may be indicated for those with influenza. Few cases of acute bronchitis are caused by *Bordetella pertussis* or atypical bacteria, such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. However, these infections are self-limited and do not warrant antibiotic use except in rare cases in which pneumonia develops or the patient is immunocompromised.[5] The British Thoracic Society does not recommend using antibiotics to treat cough or head colds in children except when pertussis is suspected, and then macrolides should be administered early in the course of the disease.[6] In patients with suspected pertussis, antibiotics are prescribed to curb the spread of disease rather than to change patient outcomes.[4]

Data Sources: A PubMed search was completed in Clinical Queries using the key terms upper respiratory tract infections, URI, antibiotics, and treatment. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were the Agency for Healthcare Research and Quality evidence reports, Clinical Evidence, the Cochrane database, Essential Evidence Plus, the National Guideline Clearinghouse database, and DynaMed. Search date: September 29, 2011.

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