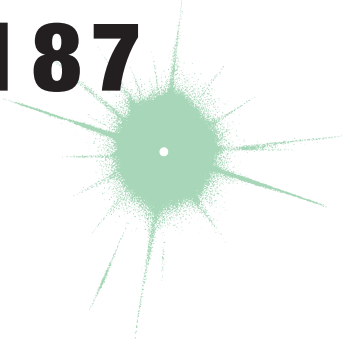


CHAPTER 187

Influenza

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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 year. Such outbreaks result in significant morbidity rates 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/California/07/2009 (H1N1). Influenza A has 16 distinct H subtypes and 9 distinct N subtypes, of which only H1, H2, H3, N1, and N2 have been associated with epidemics 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. Type A and type B viruses are morphologically similar. The virions are irregularly shaped spherical particles, measure 80–120 nm in diameter, and have a lipid envelope from the surface of which the H and N glycoproteins project (Fig. 187-1). The hemagglutinin is the site by which the virus binds to sialic acid cell receptors, whereas the neuraminidase degrades the receptor and plays a role in the release of the 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

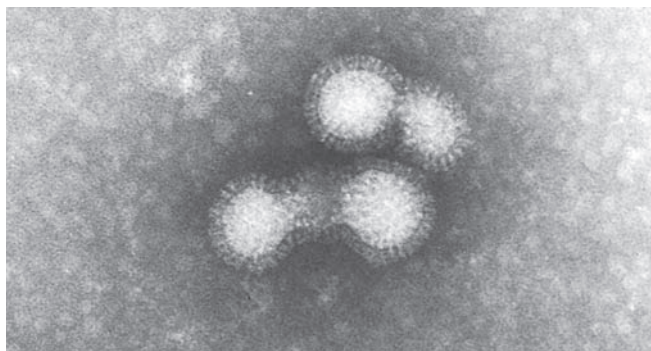


Figure 187-1 An electron micrograph of influenza A virus ($\times 40,000$).

mediates fusion of the endosomal membrane with the virus envelope, and viral nucleocapsids are subsequently released into the cytoplasm. Immune responses to the H antigen are the major determinants of protection against infection with influenza virus, while those to the N antigen limit viral spread and contribute to reduction of the infection. The lipid envelope of influenza A virus also 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-strand 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.

EPIDEMIOLOGY



Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals, usually every 1–3 years. Global pandemics have occurred at variable intervals, but much less frequently than interpandemic outbreaks (Table 187-1). The most recent pandemic emerged in March of 2009 and was caused by an influenza A/H1N1 virus that rapidly spread worldwide over the next several months.

Influenza A virus

Antigenic variation and influenza outbreaks and pandemics The most extensive and severe outbreaks of influenza 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*, are seen only

TABLE 187-1 Emergence of Antigenic Subtypes of Influenza A Virus Associated With Pandemic or Epidemic Disease

Years	Subtype	Extent of Outbreak
1889–1890	H2N8 ^a	Severe pandemic
1900–1903	H3N8 ^a	?Moderate epidemic
1918–1919	H1N1 ^b (formerly HswN1)	Severe pandemic
1933–1935	H1N1 ^b (formerly HON1)	Mild epidemic
1946–1947	H1N1	Mild epidemic
1957–1958	H2N2	Severe pandemic
1968–1969	H3N2	Moderate pandemic
1977–1978 ^c	H1N1	Mild pandemic
2009–2010 ^d	H1N1	Pandemic

^aAs determined by retrospective serologic survey of individuals alive during those years (“seroarchaeology”).

^bHemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1.

^cFrom this time until 2008–2009, viruses of the H1N1 and H3N2 subtypes circulated either in alternating years or concurrently.

^dNovel influenza A/H1N1 emerged to cause this pandemic.

with influenza A viruses and may be associated with pandemics. Minor variations are called *antigenic drifts*. 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 187-1, 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. The pandemic of 2009–2010 was caused by an A/H1N1 virus against which little immunity was present in the general population, although approximately one-third of individuals born before 1950 had some apparent immunity to related H1N1 strains.

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. In 2009–2010, the pandemic A/H1N1 virus appeared to circulate nearly exclusively.



Avian influenza A viruses In 1997, human cases of influenza caused by avian influenza viruses (A/H5N1) were detected in Hong Kong during an extensive outbreak of influenza in poultry. Between that time and February 2010, 478 cases of avian influenza in humans were reported in Asia and the Middle East. Nearly all of these cases were associated with contact with infected poultry. Efficient person-to-person transmission has not been observed to date. Mortality rates have been high (60%), and clinical manifestations have differed somewhat from those associated with “typical” outbreaks of influenza (see below). Transmission of avian influenza A/H7N7 viruses from infected poultry to humans has been observed, including outbreaks in the Netherlands, which resulted predominantly in cases of conjunctivitis and some respiratory illnesses. Infection with avian A/H9N2 viruses along with mild respiratory illness has been reported in children in Hong Kong. Because of the absence of widespread immunity to the H5, H7, and H9 viruses, concern persists that avian-to-human transmission might also contribute to the emergence of pandemic strains.

The origin of actual pandemic influenza A virus strains has been partially elucidated with molecular virologic techniques. It appears that the pandemic strains of 1957 and 1968 resulted from a genetic reassortment between human viruses and avian viruses with novel surface glycoproteins (H2N2, H3). The pandemic A/H1N1 virus of 2009–2010 was a quadruple reassortant among swine influenza viruses that circulated in North America and Eurasia, an avian virus, and a human influenza virus. The influenza A/H1N1 virus responsible for the most severe pandemic of modern times (1918–1919) appears to have represented an adaptation of an avian virus to efficient infection of humans.

Features of pandemic and interpandemic influenza A Pandemics provide the most dramatic evidence of the impact of influenza A. However, illnesses occurring between pandemics (interpandemic disease) also account for extensive mortality and morbidity rates, albeit over a longer period. In the United States, influenza was associated with at least 19,000 excess deaths per season in 1976–1990 and with 36,000 excess deaths per season in 1990–1999. On average, there were 226,000 influenza-associated hospitalizations per year in this country in 1979–2001.

Influenza A viruses that circulate between pandemics demonstrate antigenic drifts in the H antigen. These antigenic drifts result from point mutations involving the RNA segment that codes for the hemagglutinin, which occur 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.

Interpandemic influenza A outbreaks usually begin abruptly, peak over a 2- to 3-week period, generally last for 2–3 months, and often subside almost as rapidly as they began. In contrast, pandemic influenza may begin with rapid transmission at multiple locations, have high attack rates, and extend beyond the usual seasonality, with multiple waves of attack before or after the main outbreak. In interpandemic outbreaks, the first indication of influenza activity 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 in interpandemic influenza but most commonly are in the range of 10–20% of the general population.

While pandemic influenza may occur throughout the year, interpandemic influenza occurs 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 rises in serum antibody titer 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 viruses persist between outbreaks in temperate zones is unknown. It is possible that the 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 A 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 immunity is present in a community, extensive outbreaks may occur. When the absence of immunity 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. It has been suggested that certain influenza A viruses 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 and C viruses

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.

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 widespread prevalence of serum antibody to this virus indicates that asymptomatic infection may be common.

Influenza-associated morbidity and mortality rates

The morbidity and mortality rates 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 (Table 187-2). Excess annual hospitalizations for groups of adults and children with high-risk medical conditions ranged from 40 to 1900 per 100,000 during outbreaks of influenza in 1973–2004. The most prominent high-risk conditions are chronic cardiac and pulmonary diseases and old age. Mortality rates among individuals with chronic metabolic or renal diseases or certain immunosuppressive diseases have also been elevated, albeit lower than those among patients with chronic cardiopulmonary diseases. In the pandemic of 2009–2010, increased risk for severe disease was noted in children from birth to 4 years of age and in pregnant women. The morbidity rate attributable to influenza in the general population is considerable. It is estimated that inter-pandemic outbreaks of influenza currently incur annual economic

costs of more than \$87 billion in the United States. For pandemics, it is estimated that annual economic costs would range from \$89.7 to \$209.4 billion for attack rates of 15–35%.

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, the virus is transmitted 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 μm) 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 4–6 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 , interleukin 6, and interleukin 8, 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 to the hemagglutinin appear to be the most important mediators of immunity; in several studies, HI titers of ≥ 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 ≥ 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+ human leukocyte antigen class I-restricted cytotoxic T lymphocytes (CTLs) are directed at conserved regions of internal proteins (NP, M, and P) as well as at 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 2–5 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,

TABLE 187-2 Persons at Higher Risk for Complications of Influenza

Children from birth to 4 years old
Pregnant women
Persons ≥ 65 years old
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
Adults and children who have chronic disorders of the pulmonary or cardiovascular system, including asthma
Adults and children who have chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by HIV)
Adults and children who have any condition that can compromise respiratory function or compromise the handling of respiratory secretions or can increase the risk of aspiration
Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions

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 this regard.

■ CLINICAL MANIFESTATIONS

Influenza has most frequently been described as an illness characterized by the abrupt onset of systemic symptoms, such as headache, feverishness, chills, myalgia, and malaise, as well as 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°–41°C (100.4°–105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days, although, on occasion, fever may last as long as 1 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 symptoms often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for ≥1 week 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 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 common than is appreciated.

In uncomplicated influenza, the acute illness generally resolves over 2–5 days, and most patients have largely recovered in 1 week, although cough may persist 1–2 weeks longer. In a significant minority (particularly the elderly), however, symptoms of weakness or lassitude (postinfluenza 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 (Table 187-2) occur most frequently in patients >65 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 predisposes to complications with influenza. Children <5 years old (especially infants) are also at high risk for complications.

Pulmonary complications

Pneumonia 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 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 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 pandemics 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, which were also noted in the pandemic of 2009–2010.

Secondary bacterial pneumonia Secondary bacterial pneumonia follows acute influenza. Improvement of the patient's condition over 2–3 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.

Mixed viral and bacterial pneumonia 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 antibacterial drugs. Mixed viral and bacterial pneumonia occurs primarily in patients with chronic cardiovascular and pulmonary diseases.

Other pulmonary complications 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.

Extrapulmonary complications

In addition to the pulmonary complications of influenza, a number of extrapulmonary complications may occur. These include *Reye's syndrome*, 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 boggy muscles. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient develops 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. 135 and 136).

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 deaths contribute to the overall excess mortality rate associated with influenza A outbreaks.

Complications of avian influenza

Cases of influenza caused by avian A/H5N1 virus are reportedly associated with high rates of pneumonia (>50%) and extrapulmonary manifestations such as diarrhea and CNS involvement. Deaths have been associated with multisystem dysfunction, including cardiac and renal failure.

LABORATORY FINDINGS AND DIAGNOSIS

During acute influenza, virus may be detected in throat swabs, nasopharyngeal swabs or washes, or sputum. The virus can be isolated by use of tissue culture—or, less commonly, chick embryos—within 48–72 h after inoculation. Most commonly, the

laboratory diagnosis is established with rapid tests that detect viral antigens by means of immunologic or enzymatic techniques. The tests are relatively specific but are of variable sensitivity depending on the technique and the virus to be detected. Some rapid tests can distinguish between influenza A and B viruses, but detection of differences in hemagglutinin subtypes requires additional subtype-specific immunologic techniques. The most sensitive and specific in vitro test for influenza virus is reverse-transcriptase polymerase chain reaction; this test proved particularly important in detecting the 2009–2010 pandemic A/H1N1 viruses, for which some rapid antigen detection tests were poorly sensitive. Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10–14 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. Other laboratory tests generally are not helpful in the 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, 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 INFLUENZA

Specific antiviral therapy is available for influenza (Table 187-3): the neuraminidase inhibitors zanamivir, oseltamivir, and peramivir for both influenza A and influenza B and the adamantane agents amantadine and rimantadine for influenza A (Chap. 178). A 5-day course of oseltamivir or zanamivir reduces the duration of signs and symptoms of uncomplicated influenza by 1–1.5 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 administration of the drug with food. Oseltamivir has also been associated with neuropsychiatric side effects in children. Peramivir, an investigational neuraminidase inhibitor that can be administered intravenously, is being evaluated in clinical trials, as is an intravenous form of zanamivir. Access to these medications can be sought through the FDA's Emergency Investigational New Drug (E-IND) application procedures.

Amantadine or rimantadine treatment of illness caused by sensitive strains of influenza A virus similarly reduces the duration of symptoms of uncomplicated influenza by ~50% if begun within 48 h of onset of illness. Five to 10% of amantadine recipients experience mild CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty concentrating. These side effects

TABLE 187-3 Antiviral Medications for Treatment and Prophylaxis of Influenza

Antiviral Drug	Age Group (Years)		
	Children (≤ 12)	13–64	≥ 65
Oseltamivir			
Treatment, influenza A and B	Age 1–12, dose varies by weight ^a	75 mg PO bid	75 mg PO bid
Prophylaxis, influenza A and B	Age 1–12, dose varies by weight ^b	75 PO qd	75 mg PO qd
Zanamivir			
Treatment, influenza A and B	Age 7–12, 10 mg bid by inhalation	10 mg bid by inhalation	10 mg bid by inhalation
Prophylaxis, influenza A and B	Age 5–12, 10 mg qd by inhalation	10 mg qd by inhalation	10 mg qd by inhalation
Amantadine^c			
Treatment, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥ 10 , 100 mg PO bid	≤ 100 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥ 10 , 100 mg PO bid	≤ 100 mg/d
Rimantadine^c			
Treatment, influenza A	Not approved	100 mg PO bid	100–200 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥ 10 , 100 mg PO bid	100–200 mg/d

^a<15 kg: 30 mg bid; >15–23 kg: 45 mg bid; >23–40 kg: 60 mg bid; >40 kg: 75 mg bid. For children <1 year of age, see www.cdc.gov/h1n1flu/recommendations.htm.

^b<15 kg: 30 mg qd; >15–23 kg: 45 mg qd; >23–40 kg: 60 mg qd; >40 kg: 75 mg qd. For children <1 year of age, see www.cdc.gov/h1n1flu/recommendations.htm.

^cAmantadine and rimantadine are not currently recommended (2009–2010) because of widespread resistance in influenza A viruses. Their use may be reconsidered if viral susceptibility is reestablished.

disappear promptly upon cessation of therapy. 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 3–7 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.

The epidemiologic patterns of resistance to the influenza antiviral drugs are crucial elements in agent selection. Since 2005–2006, the vast majority of A/H3N2 viruses, including >90% of U.S. isolates, have been resistant to the adamantanes but have remained sensitive to neuraminidase inhibitors. In contrast, the seasonal A/H1N1 viruses that circulated in 2008–2009 remained sensitive to the adamantanes but were resistant to oseltamivir (although still sensitive to zanamivir). The pandemic A/H1N1 viruses that circulated in 2009–2010 were resistant to the adamantanes but sensitive to zanamivir and usually to oseltamivir; a few oseltamivir-resistant isolates were identified. Up-to-date information on patterns of resistance to influenza antiviral drugs is available through www.cdc.gov/flu.

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 has not been established.

The therapeutic efficacy of antiviral compounds in influenza has been demonstrated primarily in studies of young adults with uncomplicated disease. The effectiveness of these drugs in the treatment or prevention of complications of influenza is unclear. Pooled analyses of observational investigations and some efficacy studies have suggested that treatment with oseltamivir may

reduce the frequency of lower respiratory complications and hospitalization. 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.

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. 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. 134, 135, and 145**).

For uncomplicated influenza in individuals at low risk for complications, symptom-based rather than antiviral therapy may be considered. Acetaminophen or nonsteroidal anti-inflammatory agents can be used for relief of headache, myalgia, and fever, but salicylates should be avoided in children <18 years of age because of the possible association with Reye's syndrome. Since cough is ordinarily self-limited, treatment with cough suppressants generally is not indicated; 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.

■ PROPHYLAXIS

The major public health measure for prevention of influenza is vaccination. Both inactivated (killed) and live attenuated vaccines are

available and are generated from influenza A and B virus isolates that circulated in the previous influenza seasons and are anticipated to circulate in the upcoming season. For inactivated vaccines, 50–80% protection against influenza is expected if the vaccine virus and the currently circulating viruses are closely related. 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 8–24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Since the vaccine used in the United States and many other countries 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 1 case per million vaccine recipients. However, the overall health risk following influenza outweighs the potential risk associated with vaccination.

A live attenuated influenza vaccine administered by intranasal spray is available. The vaccine is generated by reassortment between currently circulating strains of influenza A and B virus and a cold-adapted, attenuated master strain. The cold-adapted vaccine is well tolerated and highly efficacious (>90% protective) in young children; in one study, it provided protection against a circulating influenza virus that had drifted antigenically away from the vaccine strain. Live attenuated vaccine is approved for use in healthy non-pregnant persons 2–49 years of age.

Historically, the U.S. Public Health Service has recommended influenza vaccination for certain groups at high risk for complications of influenza on the basis of age or underlying disease or for their close contacts (Table 187-2). While such individuals will continue to be the focus of vaccination programs, the recommendations have been progressively expanded. In 2009–2010, immunization of all children 6 months to 18 years of age was recommended; for 2010–2011, recommendations are for immunization of the entire population above the age of 6 months, including adults. This expanded recommendation reflects increased recognition of previously unappreciated risk factors, including obesity, postpartum conditions, and racial or ethnic influences, as well as an appreciation that more widespread use of vaccine is required for influenza control. Inactivated vaccines 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.

Although antiviral drugs provide chemoprophylaxis against influenza, their use for that purpose has been limited because of concern about current patterns and further development of resistance. Chemoprophylaxis with oseltamivir or zanamivir has been 84–89% efficacious against influenza A and B (Table 187-3).

Chemoprophylaxis with amantadine or rimantadine is no longer recommended because of widespread resistance to these drugs. In earlier studies with sensitive viruses, prophylaxis with amantadine or rimantadine (100–200 mg/d) was 70–100% effective against illness associated with influenza A.

Chemoprophylaxis for healthy persons after community exposure generally is not recommended but may be considered for individuals at high risk of complications who have had close contact with an acutely ill person with influenza. 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. However, concurrent administration of chemoprophylaxis and live attenuated vaccine may interfere with the immune response to the latter. Antiviral drugs should not be administered until at least 2 weeks after administration of live vaccine, and administration of live vaccine should not begin until at least 48 h after antiviral drug administration has been stopped. Chemoprophylaxis may also be considered to control nosocomial outbreaks of influenza. For that purpose, prophylaxis should be instituted promptly when influenza activity is detected and must be continued daily for the duration of the outbreak.

FURTHER READINGS

- BEIGEL JH et al: Avian influenza A (H5N1) infection in humans. *N Engl J Med* 353:1374, 2005
- BELSHE RB et al: The efficacy of live attenuated, cold adapted trivalent, intranasal influenza vaccine in children. *N Engl J Med* 38:1405, 1998
- DAWOOD FS et al: Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 360:2605, 2009
- DOLIN R: Interpandemic as well as pandemic disease. *N Engl J Med* 353:2535, 2005
- FIORE AE et al: Prevention and control of influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Rec Rap* 59:1, 2010
- GARTEN RJ et al: Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. *Science* 325:197, 2009
- JEFFERSON T et al: Neuraminidase inhibitors for preventing and treating influenza in healthy adults: Systematic review and meta-analyses. *Br Med J* 339:b5106, 2009
- MELTZER MI et al: The economic impact of pandemic influenza in the United States: Priorities for intervention. *Emerg Infect Dis* 5:659, 1999
- MIST [MANAGEMENT OF INFLUENZA IN THE SOUTHERN HEMISPHERE TRIALISTS] STUDY GROUP: Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B infections. *Lancet* 352:1871, 1998
- TREANOR JJ: Influenza virus, in *Principles and Practice of Infectious Diseases*, 7th ed, GL Mandell et al (eds). Philadelphia, Elsevier, 2010, pp 2265–2288