Viral Infections

Coley B. Duncan and Ann R. Falsey

Key Points

- Although influenza remains indisputably the most significant viral pathogen in adults, other viruses such as respiratory syncytial virus, parainfluenza viruses, and human metapneumovirus are now recognized as significant pathogens in older populations.
- Oseltamivir and zanamivir are antiviral agents that are effective for the treatment and prophylaxis of influenza A and B. For treatment and for optimal effect, therapy should be initiated within 48 h of symptom onset.
- Infection with hepatitis viruses may be more severe in older adults with more fulminate disease as observed with acute hepatitis A and a more rapid progression to cirrhosis with hepatitis C.
- Outbreaks of viral gastroenteritis are common in long-term care facilities, and infection may lead to death due to dehydration and oliguria.
- The incidence of herpes zoster increases with advancing age and carries with it a significant risk of post herpetic neuralgia. The use of antiviral medications and corticosteroids may reduce the incidence and severity of chronic pain.

Respiratory Viruses

Acute respiratory tract infections (ARI) occur commonly throughout life, accounting for substantial morbidity and mortality in older adults (1). Due to influenza's epidemic nature and its ready growth in cell culture, it was commonly the only viral pathogen identified in many early etiologic studies of ARI in adults. Recent studies employing reverse transcription polymerase chain reaction (RT-PCR) and sensitive serology indicate that a wide variety of viruses including respiratory syncytial virus (RSV),

C.B. Duncan and A.R. Falsey (✉)
Infectious Disease Unit, Rochester General Hospital, 1425 Portland Avenue,
Rochester, NY 14621, USA
e-mail: ann.falsey@viahealth.org

parainfluenza viruses (PIV), human metapneumoviruses (hMPV), coronaviruses (Co-V), and rhinoviruses may cause severe disease in adults and result in hospitalization (2).

Influenza (See Also Chapter "Vaccinations")

Together pneumonia and influenza comprise the fifth leading causes of death in persons aged 65 years and older. Influenza viruses are enveloped ribonucleic acid (RNA) viruses that are classified as A, B, or C, based on stable internal proteins (3). The virus contains two major surface proteins: hemagglutinin (H) and neuraminidase (N), which can undergo minor antigenic changes leading to yearly epidemics or major changes resulting in influenza pandemics. Currently, there are two circulating influenza A viruses, H1N1 and H3N2, in addition to influenza B, present in the United States. H1N1 viruses do not appear to cause serious problems in older persons, possibly due to previous immunity. In 1997, influenza A (H5N1), which was previously seen only in birds, crossed the species barrier and human infection occurred in Southeast Asia (4). This highly pathogenic avian influenza has spread in bird populations throughout Asia and into Europe. To date, human infection has been rare and transmission has occurred primarily by direct contact with infected birds. Unlike seasonal influenza, illness due to avian influenza is more severe in young children as compared to older adults.

Epidemiology and Clinical Relevance

In a community, peak influenza activity typically lasts 6–8 weeks, with attack rates highest in preschool and school-aged children and lowest in older persons (3). Despite lower attack rates, mortality from influenza rises dramatically with age and the presence of underlying medical conditions. The presence of one high-risk medical condition (cardiovascular, pulmonary, renal, metabolic, neurologic, or malignant disease) increases the risk of death from influenza 39-fold. Despite increasing vaccine coverage, current Centers for Disease Control and Prevention (CDC) data indicate increasing influenza-related morbidity and mortality over the past decade (5). In the United States, approximately 226,000 hospitalizations and 34,000 deaths occur each year in persons age 65 years and older (6, 7). The devastating impact of influenza is most dramatically seen in long-term care facilities (LTCFs) where explosive epidemics may occur. During outbreaks, rates of pneumonia and hospitalization are as high as 52% and 29%, respectively, with case fatality rates of 30%.

Clinical Manifestations

The classic presentation of influenza is an abrupt onset of fever, chills, headache, and myalgias (see Table 1). Dry cough, sore throat, and ocular pain are also common (3). Fever remains a common finding in the elderly, although the height of the fever may be lower compared with young persons. Although many elderly adults have classic symptoms, a substantial number may have more nonspecific presentations such as

Table 1 Respiratory viral infections

	Peak season	Incubation (d)	Clinical clues	Antiviral therapies
Influenza A H1N1	Winter	1–3	High fever, headache, myalgias	Zanamivir two 5mg inhalations BID x 5 days or rimantadine 100mg po BID x 5 days*
Influenza A H3N2	Winter	1–3	High fever, headache, myalgias	Oseltamivir 75mg po BID × 5 days** or zanamivir two 5mg inhalations BID × 5 days
Influenza B	Winter	1–3	High fever, headache, myalgias	Oseltamivir 75mg po BID × 5 days** or zanamivir two 5mg inhalations BID × 5 days
RSV	Winter	3–5	Rhinorrhea, wheezing	RibavirinA***
Parainfluenza	Fall-spring	1–2	Pharyngitis, hoarseness	None
Rhinovirus	All	1–2	Rhinorrhea	None
Coronavirus	Winter-spring	1–2	Non-specific	None

RSV, respiratory syncytial virus.
*100 mg daily for severe hepatic dysfunction, renal failure (CrCl 10 mL/min) and for elderly nursing home patients.
**Dosage should be reduced in persons with creatinine clearance of < 30 mL/min
***Ribavirin is not FDA approved for use in adults.
BID twice a day; *po* orally

fever and confusion or worsening of chronic medical conditions. In contrast to young healthy persons, the triad of fever, cough, and acute onset of symptoms has a positive predictive value of only 30% in elderly adults. Given the protean manifestations of influenza in older persons, it is always important to consider influenza in the differential when evaluating an acutely ill elderly adult during the winter.

Influenza lower respiratory tract involvement increases steadily with advancing age with the rates of pneumonia 4–8% in persons aged 5–50 years and rising to 73% in persons over age 70 (8). Secondary bacterial pneumonia following acute influenza also occurs more frequently in older persons. Although the rates of pneumonia rise with age, hospitalization most frequently results from exacerbation of chronic medical conditions. In addition to the immediate complications of influenza, residents of nursing homes who survive influenza experience a significant functional decline in activities of daily living.

Diagnostic Tests

Although many physicians use clinical features to make a diagnosis of "the flu," laboratory confirmation is best, especially if therapeutic decisions are needed because influenza may be difficult to distinguish from other respiratory viruses.

Older persons typically shed the virus for 3–5 days, although shedding up to 14 days has been documented in hospitalized patients (9). Rapid antigen testing may be done directly on nasopharyngeal specimens using an enzyme immunoassay (EIA) (10). Although not as sensitive as viral culture, rapid tests offers quick turnaround times and may be useful for infection control and treatment decisions. Sensitivity of rapid testing in adults is estimated to be 50–60% for influenza A strains and 10–20% for influenza B (11). When available, RT-PCR offers rapidity while retaining excellent sensitivity.

Treatment

As of this writing, zanamivir or rimantadine can be used for the treatment or prophylaxis of influenza A H1N1 strains (*). For influenza A H3N2 or influenza B, oseltamivir or zanamivir can be used. If the strain of influenza is unknown, currently, zanamivir by itself or a combination of oseltamivir and rimantadine is appropriate coverage (3). Resistance to zanamivir remains rare. Zanamivir is not recommended for patients with reactive airway disease, because it may exacerbate bronchospasm. Future influenza treatment and prophylaxis recommendations for influenza will need to be guided by close monitoring of CDC reports on influenza resistance patterns. Treatment should begin < 48 h after onset of symptoms (Table 1). In practice, physicians are often faced with the question of whether to treat patients who present outside the 48-h period. At present, only one observational study addresses this question in hospitalized adults (12). In 327 adults hospitalized with influenza, mortality was significantly lower in those who received antiviral treatment as compared to those who did not receive antiviral treatment. Of the 100 patients who were treated, only 29% had symptoms < 48 h.

Prevention

The cornerstone of reducing the morbidity and mortality of influenza in the elderly is vaccination (see also chapter "Vaccinations"). Although the degree of protective efficacy for current inactivated vaccines in the elderly has recently become a subject of controversy, older adults clearly benefit from vaccination (13). A multi-layered approach for protecting the elderly from influenza is needed and includes vaccinating elderly persons, their close contacts and care givers, and providing oseltamivir if exposure to influenza has been documented (3, 14). When staff was highly vaccinated, several studies have demonstrated a benefit to elderly residents of LTCFs (15). The recommendations of the Advisory Committee on Immunization Practices (ACIP) 2007 relating to the elderly, include vaccination of all persons ≥50 years, vaccination of residents of nursing homes and chronic-care facilities, vaccination of healthcare personnel, and vaccination of healthy household contacts (including children) and caregivers of adults ≥50 years (3).

---

* http://emergency.cdc.gov/coca/ppt/Antivirals_update_010809_Fiore.pps

At the present time, only trivalent inactivated virus (TIV) vaccine, which contains killed H1N1, H3N2 and B strain influenza, is recommended for use in persons 50 years and older (3). Mild acute local reactions occur in approximately one-third of vaccines and systemic reactions such as fever, and myalgias are uncommon in older persons. Influenza vaccine may be safely given simultaneously with pneumococcal vaccine, and the only contraindications to vaccination are anaphylactic hypersensitivity to eggs or other components of the vaccine and a history of Guillian–Barré syndrome. By using adjuvants and higher doses of antigens, active research continues to improve the immunogenicity and efficacy of inactivate influenza vaccine. Live attenuated influenza virus vaccine is not approved for persons over age 49; however, it may be given to healthcare workers and close household contacts of older adults.

Antiviral prophylaxis is recommended for all residents of nursing homes and chronic care facilities and to unvaccinated healthcare providers once influenza A has been documented in the institution (13, 14). Chemoprophylaxis is given regardless of vaccination status and is continued until 1 week after the onset of the last influenza case.

Respiratory Syncytial Virus

Epidemiology and Clinical Relevance

RSV has long been recognized as the leading cause of lower respiratory tract disease in children; however, recently, it has been recognized as a serious adult pathogen (16). It is estimated that RSV results in approximately 178,000 hospitalizations and 14,000 deaths annually in the United States yielding healthcare costs in excess of $1 billion. A number of epidemiologic studies and mathematical models indicate that RSV is second to influenza as a cause of serious viral respiratory disease in adults (7).

RSV was initially recognized as a pathogen in older persons when several outbreaks were described in long-term care facilities (17). Attack rates are variable and may be as high as 90% during outbreaks, but more commonly they range from 1 to 7% when residents are followed prospectively. In published reports, rates of pneumonia range from 0 to 53% and death from 0 to 55%. RSV appears to cause serious disease in community-dwelling older persons as well. In a 2-year prospective study of elderly persons in the United Kingdom (UK) Nicholson et al., identified RSV in 3% of illnesses using serology for diagnosis (18). With the advent of sensitive molecular testing, a more accurate assessment of the true incidence of RSV has emerged. In a 3-year study from the United Kingdom by Zambon et al., RSV was identified by RT-PCR in 10–18% of adults age 65 years and older who were visiting a general practitioner during the winter for a respiratory illness (19). In comparison, during the same period, influenza A was identified in 13–42% of subjects. In a prospective study from Rochester, NY, using a combination of viral culture, RT-PCR and serology for diagnosis, RSV infection was documented in 3–7% of 608 healthy elderly and 4–10% of adults with chronic cardiopulmonary conditions

over four winter seasons (16). Serious disease was more common in high-risk patients: 9% visited the Emergency Room, 16% required hospitalization, and 4% died. Finally, a large study of community-acquired pneumonia in adults found RSV to be the third most commonly identified pathogen at 4.4% compared with 6.2% due to *Streptococcus pneumoniae* and 5.4% due to influenza (20).

Clinical Manifestations

Manifestations of RSV infection can be difficult to distinguish from other viral respiratory infections, particularly influenza. Most individuals with RSV have nasal discharge, cough, sputum production, and constitutional symptoms. Although overlap exists, there are some helpful clues to differentiate RSV from influenza. High fever, sore throat, myalgias, and gastrointestinal complaints are more characteristic of influenza, whereas rhinorrhea, dyspnea, sputum production, and wheezing are more frequently associated with RSV infection.

Diagnostic Tests

Unfortunately, because of the labile nature of the virus and low titers of virus in nasal secretions in adults, diagnosis of acute RSV by standard testing is difficult. Under ideal circumstances, viral culture is only 50% sensitive when compared with serology using EIA. Commercial rapid antigen tests also have poor sensitivity in adults (21). RT-PCR offers the best combination of sensitivity and specificity for the diagnosis of acute RSV in adults but is not widely available to most clinicians.

Treatment

The treatment of RSV infection in adults is largely supportive. Supplemental oxygen and bronchodilators may be useful, and antibiotics should be considered if bacterial super-infection is suspected. Ribavirin is a nucleoside analogue, which has broad antiviral activity, including RSV. Anecdotal experience suggests it may be beneficial in selected cases, particularly in persons with immunosupression. However, due to lack of data in the elderly, general recommendations on its use cannot be made (22). The major problems with ribavirin are its high cost and difficulty with administration. The recommended 12–18 h/day of aerosol at 20 mg/mL concentrations may be quite difficult for the elderly adult to tolerate. Higher concentrations (60 mg/mL) given three times a day may also be effective and more tolerable (23).

Prevention

In healthy elderly patients and in adults with chronic pulmonary disease, low serum neutralizing antibody titers are associated with increased risk of hospitalization with RSV infection suggesting a vaccine may be beneficial. Although research is

ongoing, an effective RSV vaccine has yet to be developed. RSV is spread primarily by large droplet inoculation and fomites, and handwashing is the single most important measure in the control of RSV.

Parainfluenza Viruses

Epidemiology and Clinical Relevance

The parainfluenza viruses (PIV) are most commonly thought of as the etiologic agents of croup, bronchiolitis, and pneumonia in young children (24). Four serotypes and two subgroups of PIV are recognized (1, 2, 3, 4a, and 4b); PIV-3 is endemic throughout the year, whereas PIV-1 and PIV-2 tend to occur during the fall. Although PIV infections are not commonly documented in older adults, several studies of community-acquired pneumonia and chronic obstructive pulmonary disease (COPD) exacerbations implicate PIV as a cause in 2–17% of cases (25, 26). The PIV-1 and 3 serotypes account for the majority of isolates in older persons, with PIV-2 being relatively uncommon (27).

Clinical Manifestations

Similar to RSV, outbreaks of PIV infections in nursing homes have been described (27, 28). Variable morbidity and mortality has been reported. Clinical characteristics of PIV infection are not distinctive and include rhinorrhea, sore throat, hoarseness, and cough with high rates of pneumonia ranging from 20 to 30%. In an institutional outbreak of PIV-3, the attack rates among residents and nursing staff were 31% and 11%, respectively. Antecedent parainfluenza infection in long-term care residents has been linked to outbreaks of pneumococcal pneumonia.

Diagnostic Tests and Treatment

In clinical practice, a diagnosis of PIV infection is usually made by viral culture, although RT-PCR is available in some settings (24). Diagnosis can also be made serologically; however, PIV-1 and 3 infections result in cross-reactive antibody responses and cannot be distinguished. No antiviral agents have been approved for the treatment of PIV infection.

Human Metapneumovirus

In 2001, human metapneumovirus (hMPV) was first identified in the Netherlands from archived respiratory cultures collected from infants and young children in whom other pathogens could not be isolated (29). It is an enveloped RNA virus

closely related to RSV and PIV. Since its discovery, infection has been widely reported each winter in young infants with an illness similar to RSV and characterized by wheezing and bronchiolitis (30). However, as with many pediatric respiratory viral pathogens, hMPV infection induces incomplete immunity and reinfections occur later in life at all ages (31, 32).

Epidemiology and Clinical Relevance

In a 2-year study, hMPV infection was identified in 4.1% of elderly and high-risk adults, using RT-PCR and serology for diagnosis (32). Impact was greatest in subjects with cardiopulmonary diseases, who were ill twice as long as healthy elderly. In a study of adult pneumonia, 4% of subjects were diagnosed by RT-PCR with hMPV (33). Seventy-five percent of those infected were 65 years of age and older. Such hMPV outbreaks can also occur in LTCFs. In a recent outbreak of severe hMPV illness in an LTCF in Quebec, Canada, 17% of those infected had pneumonia and 50% died (31). Autopsy material from an elderly woman with an extensive right middle and lower lobe pneumonia confirmed the presence of virus in the lower airways by immunohistochemical staining. The clinical characteristics of hMPV pneumonia in older adults do not appear to be distinctive from the other wintertime respiratory viruses. Cough is universal and wheezing, dyspnea, and sputum production are common symptoms (32).

Diagnosis and Treatment

In part due to its fastidious growth characteristics, hMPV remained undetected for many years. Although isolation by viral culture is possible, this method of diagnosis is not practical, and RT-PCR is the diagnostic method of choice (30). Rapid tests have been developed for direct antigen detection in respiratory secretions; however, there are little data regarding sensitivity in the elderly. Currently, there is no known effective antimicrobial therapy against this virus. Therapy is primarily symptomatic, supportive, and managing any complications.

Rhinoviruses

Epidemiology and Clinical Relevance

Rhinoviruses are the most commonly identified cause of the "common cold," accounting for 25–50% of upper respiratory infections (34). Rhinoviruses circulate at all times of the year, but peak activity tends to be during the spring and fall. Because the virus does not replicate well at 37°C, infection of the lower airways was previously considered rare. However, recent studies utilizing experimental

challenge and specimens obtained at bronchoscopy clearly demonstrate rhinovirus infection of the lower respiratory epithelium (35).

A prospective study from the United Kingdom indicates that rhinoviruses are an important cause of debility and lower respiratory disease in elderly people in the community (36). Rhinoviruses accounted for 24% of respiratory illnesses in a cohort of 533 persons over a 2-year period. Although death and hospitalization rates were low, the mean length of illness was 16 days, and 26% of people were unable to perform their normal household activities. The presence of chronic medical conditions and smoking increased the likelihood of lower respiratory tract complications. Because of the frequency of rhinovirus infection, the overall burden of disease in the elderly may approach influenza. Rhinovirus has also been identified as the cause of 3.1%–19.6% of COPD exacerbations (37). Lastly, outbreaks of severe respiratory illness due to rhinovirus have been described in nursing homes with attack rates as high as 56% and a mortality as high as 21% of those affected (38, 39).

Clinical Manifestations

In elderly persons, nasal congestion (79–89%), cough (71–94%), constitutional symptoms (43–91%), and sore throat (21–51%) characterize illnesses. Rhinoviruses are now appreciated as a common trigger for asthma exacerbations and, therefore, in persons with preexisting lung disease, the dominant symptom may be wheezing (34).

Diagnostic Tests and Treatment

The diagnosis of rhinovirus is usually made by a viral culture of nasopharyngeal secretions. If available, the use of RT-PCR greatly increases detection rates (34). Treatment is supportive and care should be exercised when prescribing "cold" medications to elderly persons because many of these "cold" medications contain combinations of sympathomimetics and antihistamines.

Coronaviruses

Non-SARS Coronaviruses

Coronaviruses are RNA viruses of which two are major serotypes: human coronavirus 229E (HCo-229E) and HCo-OC43, which, for decades, have been known to cause respiratory disease in humans (34). Two recently discovered coronaviruses (HCo-NL63 and HCo-HKU1) cause lower and upper respiratory tract infections with similar frequency (40–42). In temperate climates, peak viral activity occurs in

the winter. Reinfections with coronaviruses are common throughout life, and, similar to rhinoviruses, illnesses are generally mild upper respiratory infections in healthy adults; symptoms include malaise, headache, sore throat, and nasal congestion. Exacerbations of chronic obstructive pulmonary disease have been linked to coronavirus infections in several studies.

Coronavirus infections have been evaluated in the community-dwelling elderly and have, in one prospective study from the United Kingdom, accounted for 9.5% of the respiratory illnesses (18). Coronavirus's were associated with lower respiratory tract symptoms in more than 40% of cases; infections have also been documented in LTCFs and in frail elderly people attending daycare centers (43). Coronaviruses have also been implicated in severe respiratory infections requiring hospitalization in older adults (44). RT-PCR is now available for diagnosis of coronavirus infection but frequently a specific viral diagnosis is not made (34). No antiviral agents are available, and treatment is supportive.

Hepatitis Viruses

Hepatitis A

Hepatitis A virus (HAV) is an RNA virus in the picornavirus family (see Table 2). The virus is easily transmitted by the fecal–oral route. In countries where the virus is endemic and sanitation is poor, most people become infected in early childhood when the disease is mild and life-long immunity results (45). Recently, a shift in the prevalence of cases from childhood to adulthood has occurred, presumably due to improved living conditions. The incidence of hepatitis A in the United States has fallen 88% from a peak in 1996 to an all-time low of presently 1.2 cases per 100,000 persons (46). The prevalence of anti-HAV antibodies increases with advancing age (47). In a 1994 study from Colorado, the prevalence of anti-HAV antibodies at ages 60, 70, and 80 was 40%, 60%, and 80%, respectively (45).

Table 2 Viral hepatitis

Virus	Transmission	Incubation range in days (average)	Clinical characteristics in older persons	Chronic infection
A	Fecal–oral	14–50 (28)	Prolonged cholestasis	No
B	Parenteral, sexual	45–160 (120)	Milder acute infection, but chronic infection more common. Sequelae: cancer and cirrhosis	Yes
C	Parenteral, other?	15–150 (42)	Same as hepatitis B virus (HBV)	Yes
D	Parenteral, sexual	45–130	May worsen existing cirrhosis from HBV	Yes
E	Fecal–oral	14–60	No data	No
G	Parenteral	Limited data	Clinical significance unknown	Yes

An acute hepatitis A, advancing age correlates with more severe clinical manifestations, higher bilirubin levels and increased hospitalization rates (48). Liver failure and death are also more common with increased age (49). In the United States, the overall case fatality rate for HAV infection is 0.3%; however, it rises to 1.5% in persons 60 years or older (46).

An inactivated hepatitis A vaccine has been available since 1993, and clinical studies have shown the vaccine to be safe, very well tolerated, and highly immunogenic in all age groups. Immunization of toddlers in Israel resulted in a >95% reduction of hepatitis A in the general population (50). Although the benefit was least for ages ≥65 years, a 77.3% reduction in cases was observed in this age group. Immunogenicity in frail elderly persons such as residents of long-term care has not been reported. Although disease may be more severe in older adults, current vaccination policies do not specifically target the elderly. However, vaccination is recommended for older travelers who plan to visit countries endemic for HAV.

Hepatitis B

Hepatitis B virus (HBV) is a complex deoxyribonucleic acid (DNA) virus transmitted by percutaneous and mucous membrane exposure to infectious body fluids. Serum, saliva, and semen have been shown to contain hepatitis B surface antigen (HBSAg). Since 1990, the incidence of acute hepatitis B has declined in all age groups with the largest decline (98%) being in children <15 years (46). Because the primary risk group in the United States and Europe is intravenous drug abusers, acute infection is not common in the elderly. Transfusion-related HBV infection is now an uncommon event with risk estimated to be 1 in 205,000 transfusions (51). When several outbreaks occurred during the 1970s–1980s, LTCF's were thought to be a risk area for HBV (47). However, recent surveys of geriatric hospitals indicate the prevalence of HBSAg is similar to the general geriatric population (<1%) (47).

Acute HBV in older adults is usually mild, and many cases are subclinical or presents with manifestations of cholestasis. In addition to the typical symptoms of jaundice, anorexia, and fatigue, diarrhea is a common complaint in elderly persons. Complaints reflecting immune complex disease such as myalgias and arthalgias are rare in older adults. Although acute HBV is generally not a severe disease in older adults, the mortality from fulminant HBV increases with age (47). In a multivariate analysis of prognostic factors in 115 patients with HBV, age was an independent predictor of survival (46). Mortality for persons over age 60 years was 3.1% compared with 1.2% for persons ages 40–59. When individuals are infected at older ages, chronic carriage rates also increase. Compared with a 10% carriage rate in young adults, approximately 60% of older persons become chronic carriers (47).

In addition to cirrhosis from chronic active hepatitis, one of the major complications of HBV infection is hepatocellular carcinoma (HCC). The length of time infected is an important factor in the development of cancer, and, thus, elderly persons who have been infected for many years are at the greatest risk. The rate of

HCC rises from 197 per 100,000 in 30- to 39-year olds to 927 per 100,000 in 60- to 69-year-old chronic HBV carriers (52).

Most cases of acute hepatitis B clear spontaneously and do not require treatment. In young patients with compensated disease, alpha-interferon is primarily used in the treatment of chronic hepatitis B. Those who respond favorably may see suppression of viral replication and a decrease in the risk of progression to cirrhosis or to cancer. Side effects of therapy are frequent and increase with advancing age (47). Therapy should be reserved for patients in overall good health, except for their liver disease, and who have evidence of active viral replication. Five nucleotide/nucleoside analogs (lamivudine, adefovir, entecavir, tenofovir, and telbuvidine) are currently approved by the Food and Drug Administration to treat chronic hepatitis B (53). These drugs are usually better tolerated than interferon, although they have not been studied specifically in the elderly. Patients with chronic hepatitis B should be tested for immunity to hepatitis A and, if seronegative, should be vaccinated against hepatitis A to prevent acute decompensation that could occur with hepatitis A superinfection. In addition, patients should be counseled to abstain from alcohol, to maintain a healthy body weight, and to use condoms to protect their sexual partners from infection.

The currently licensed hepatitis B vaccine is a genetic recombinant vaccine; it is very well tolerated and highly immunogenic with excellent protective efficacy in children and young adults. However, response rates to HBV vaccine diminish significantly with increased age. Ninety percent of persons under age 40 achieve an adequate seroresponse compared with only 50% in persons over age 60.

Hepatitis C

Hepatitis C virus (HCV) is an RNA virus in the flavivirus family. Exposures to contaminated blood, either through occupation or through intravenous drug abuse, may transmit HCV. Although 40–50% of community-acquired HCV cases do not report a parenteral exposure, nonparenteral transmission of HCV is not well understood. Sexual transmission, if it occurs, is not efficient. The major risk factor for HCV in older persons is transfusion, and most became infected prior to routine screening of the blood supply in 1990 (47). For southern Europe and Japan, the peak era of transfusion-associated HCV was between 1940 and 1960 whereas in the United States and northern Europe, the peak transmission was between 1960 and 1980. The current risk of acquiring HCV from transfusion in the United States is approximately 1 in 1,935,000 (51). In southern Europe, numerous population-based studies have shown that the prevalence of HCV is 16–42% in persons over 60 years and 33–50% in those over 80 years; infection is extremely rare in subjects <40 years (54).

The seroprevalence of 1.4–2.2% in LTCF residents is approximately that of the general elderly population (55). The clinical manifestations of acute HCV are generally mild and nonspecific. In a series of 20 older people with acute non-A

non-B hepatitis, approximately 30–40% had fever, abdominal pain, and jaundice (47). Fulminant hepatitis is rare with HCV, but development of chronic liver disease is very common (56). Virtually all persons become chronically infected, and a significant number develop chronic liver disease. On average, 20 years after initial infection, chronic active hepatitis or cirrhosis develops in 29–76% of persons.

Age affects the rate of progression to cirrhosis in two important ways: The younger a patient is when HCV is acquired, the slower the rate of progression to cirrhosis; however, the longer one is infected, the greater the risk of development of cirrhosis and HCC (54). Hepatocellular carcinoma is clearly associated with chronic HCV infection, and the relative risk of cancer from HCV may be even greater than that from HBV. In a study of 25 older persons with HCV in the United Kingdom, 36% developed HCC (56).

Chronic HCV infection is currently treated with pegylated interferon alpha and oral ribavirin. Goals of therapy include clearance of viremia and prevention of decompensated cirrhosis and HCC. Persons with high viral load and viral genotype 1 have a low response rate to α-interferon, and, many patients who initially respond, relapse when therapy is discontinued (47). Most studies of interferon treatment of HCV have not included older participants. In one study from Japan, interferon was administered to 19 patients aged 65 and older with HCV, and the response rate was 26% compared with 33% in younger persons (57). Of note, the older subjects had higher HCV–RNA titers and more severe fibrosis on their liver biopsy as compared to their younger subjects. Response rates in elderly persons correlated with lower HCV–RNA titers. Because older persons have more side effects and a lower response rate to interferon, treatment should be carefully considered on an individual basis; it should be proposed only in patients up to 75 years who have a significant risk of progression of liver disease, no serious co-morbidities, and an otherwise good life expectancy (54).

Patients with chronic hepatitis C should be tested for immunity to hepatitis A and B and, if seronegative to either, they should be vaccinated to prevent acute decompensations that could occur with hepatitis A or B superinfection. They should be counseled to abstain from alcohol, to maintain a healthy body weight, and to use condoms to protect their sexual partners from infection.

Gastroenteritis Viruses

Although deaths related to diarrhea have traditionally been thought to be a problem of young children in developing countries, in the United States from 1979 to 1987, 51% of the 28,538 diarrhea-related deaths occurred in adults over the age of 74 as compared to 11% in children <5 year old (58). The odds ratio of dying during a hospitalization involving gastroenteritis was 52.6 for adults over the age of 70 as compared with children less than 5 years of age. Residents of nursing facilities are at particular risk for infectious diarrhea illness because of the outbreaks that can occur in closed populations. The majority of nursing facility outbreaks of gastroenteritis are probably viral and

include rotavirus, enteric adenoviruses, norovirus, Snow Mountain agent, and small round structured viruses (SRSV) (58, 59).

Rotaviruses are small RNA viruses in the retrovirus family and are the most important cause of gastroenteritis in infants and young children worldwide. The mode of transmission is assumed to be fecal-oral, and the virus is relatively resistant to common disinfectants and facilitating nosocomial dissemination. Several outbreaks of rotavirus infection in elderly residents of LTCFs have been reported with attack rates ranging from 36 to 66% and mortality rates of 1–10% (60, 61). A typical illness lasts 2–3 days and includes voluminous vomiting and watery diarrhea with low-grade fever. Death may result from dehydration progressing to oliguria and acidosis (60, 61). In an analysis of specimens from gastroenteritis outbreaks in aged care facilities in Australia, rotavirus was detected by electron microscopy in 18 of 29 individuals in 7 out of 53 outbreaks (62). Although rotavirus infections are most common in winter, outbreaks can occur at other times of the year (63).

Rotavirus serum antibody titers offer some protection against severe disease and tend to diminish with increasing age (61). Two rotavirus vaccines were released in 2006 for use in children, a pentavalent human-bovine reassortant rotavirus vaccine called RotaTeq® and a live-attenuated human rotavirus vaccine called Rotarix®. No data on safety or immunogenicity in the elderly exists; however, given the mortality rates in this age group, further study would be reasonable.

Norovirus (formerly called Norwalk-like virus) is also a frequent cause of diarrhea in adults including the elderly (see also chapter "Infectious Diarrhea"). In a study of 20 gastroenteritis outbreaks in Maryland, 52% of stool samples were positive for Norwalk-like virus (NLV) (64). The median duration of symptoms with NLV gastroenteritis is 2–3 days (65).

Herpes Virus Infections

Varicella Zoster

Varicella-zoster virus (VZV) is a DNA virus and a member of the herpes virus family. It causes two distinct clinical syndromes: primary disseminated infection (chickenpox) and reactivation of latent virus in the dorsal root ganglia, leading to herpes zoster or "shingles" (66). Herpes zoster is a painful, vesicular exanthem that erupts in one to two dermatomes after a prodrome of days to weeks and may take up to a month to heal. Most patients report a deep aching or burning sensation, altered sensation to touch with paresthesias, dysesthesia, or hyperesthesia. Herpes zoster is a common condition with a cumulative lifetime incidence of 20–30% with most of the risk concentrated in older age. The overall incidence is 1.2–3.4 per 1,000 person-years, but rates rise sharply with increasing age to 11.8 per 1,00,0 for persons age 65 years and older (67). Chapter "Herpes Zoster" is devoted to the topic of herpes zoster, and the reader is referred to this section for further details.

Epstein–Barr Virus

The Epstein–Barr Virus (EBV) is a herpes virus that establishes lifelong infection. Primary infection may occur in childhood when infection is asymptomatic or during adolescence when the symptoms of classic mononucleosis are most often observed (66). Although primary infection is uncommon in old age, the manifestations may be different than those in youth, which makes diagnosis challenging. Seroepidemiologic studies indicate that 3–10% of older adults are at risk for primary infection (66). Diagnosis is also often delayed because symptoms may be misleading. Lymphadenopathy, pharyngitis, and splenomegaly are significantly less common and jaundice is more common in older persons as compared with the young persons (67). Fever is more common and often lasts more than 2 weeks (68, 69). The neurologic manifestations of EBV infection are protean, and acute EBV encephalitis has been described (70). Adding to the difficulty of making a correct diagnosis, development of atypical lymphocytosis may be absent or delayed in the elderly. Diagnosis of primary EBV is made by the presence of heterophile antibodies or EBV-specific IgM. Although acyclovir has in vitro activity against EBV, no benefit has been demonstrated in the treatment of acute EBV infection.

References

1. Fry, A.M., Shay, D.K., Holman, R.C., Curns, A.T., Anderson, L.J. (2005). Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *Journal of the American Medical Association*, 294, 2712–2719.
2. Templeton, K.E., Scheltinga, S.A., van den Eeden, W.C., Graffelman, A.W., van den Broek, P.J., Claas, E.C. (2005). Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clinical Infectious Diseases*, 41, 345–351.
3. Fiore, A.E., Shay, D.K., Haber, P., et al. (2007). *Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices* (ACIP), 2007. (Mort Morb Wkly Rep, 56, 1–54).
4. World Health Prganization. (2005). Current Concepts: Avian influenza A (H5N1) infection in humans. *New England Journal of Medicine,* 353, 1374–1385.
5. Simonsen, L., Reichert, T.A., Viboud, C., Blackwelder, W.C., Taylor, R.J., Miller, M.A. (2005). Impact of influenza vaccination on seasonal mortality in the US elderly population. *Archives of Internal Medicine*, 165, 265–272.
6. Thompson, W.W., Shay, D.K., Weintraub, E., et al. (2004). Influenza-associated hospitalizations in the United States. *Journal of the American Medical Association*, 292, 1333–1340.
7. Thompson, W.W., Shay, D.K., Weintraub, E., et al. (2003). Mortality associated with Influenza and respiratory syncytial virus in the United States. *Journal of the American Medical Association*, 289, 179–186.
8. Fry, J. (1951). Lung involvement in influenza. *British Medical Journal*, 2, 1374–1377.
9. Leekha, S., Zitterkopf, N.L., Espy, M.J., Smith, T.F., Thompson, R.L., Sampathkumar, P. (2007). Duration of influenza A virus shedding in hospitalized patients and implications for infection control. *Infection Control and Hospital Epidemiology*, 28, 1071–1016.
10. Storch, G.A. (2003). Rapid tests for influenza. *Current Opinions in Pediatrics*, 15, 77–84.
11. Hurt, A.C., Alexander, R., Hibbert, J., Deed, N., Barr, I.G. (2007). Performance of six influenza rapid tests in detecting human influenza in clinical specimens. *Journal of Clinical Virology*, 39, 132–135.

12. McGeer, A., Green, K.A., Plevneshi, A., et al. (2007). Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clinical Infectious Diseases*, 45, 1568–1575.

13. Nichol, K.L., Nordin, J.D., Nelson, D.B., Mullooly, J.P., Hak, E. (2007). Effectiveness of influenza vaccine in the community-dwelling elderly. *New England Journal of Medicine*, 357, 1373–1381.

14. Hota, S., McGeer, A. (2007). Antivirals and the control of influenza outbreaks. *Clinical Infectious Diseases*, 45:1362–1368.

15. Carman, W.F., Elder, A.G., Wallace, L.A. et al. (2000). Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet*, 355:93–97.

16. Falsey, A.R., Hennessey, P.A., Formica, M.A., Cox, C., Walsh, E.E. (2005). Respiratory syncytial virus infection in elderly and high-risk adults. *New England Journal of Medicine*, 352, 1749–1759.

17. Falsey, A.R., Walsh, E.E. (2000). Respiratory syncytial virus infection in adults. *Clinical Microbiology Review*, 13, 371–384.

18. Nicholson, K.G., Kent, J., Hammersley, V., Cancio, E. (1997). Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *British Medical Journal*, 315, 1060–1640.

19. Zambon, M.C., Stockton, J.D., Clewley, J.P., Fleming, D.M. (2001). Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet*, 358, 1410–1416.

20. Dowell, S.F., Anderson, L.J., Gary, H.E. Jr., et al. (1996). Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. *Journal of Infectious Diseases*, 174, 456–462.

21. Casiano-Colon, A.E., Hulbert, B.B., Mayer, T.K., Walsh, E.E., Falsey, A.R. (2003). Lack of sensitivity of rapid antigen tests for the diagnosis of respiratory syncytial virus infection in adults. *Journal of Clinical Virology*, 28, 169–174.

22. Aylward, B.R., Burdge, D.R. (1991). Ribavirin therapy of adult respiratory syncytial virus pneumonitis. *Archives of Internal Medicine*, 2303–2304.

23. Englund, J.A., Piedra, P.A., Ahn, Y., Gilbert, B.E., Hiatt, P.W. (1994). High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *Journal of Pediatrics*, 125, 635–641.

24. Henrickson, K.J. (2003). Parainfluenza viruses. *Clinical Microbiology Review*, 16, 242–264.

25. Glezen, P.W., Greenberg, S.B., Atmar, R.L., Piedra, P.A., Couch, R.B. (2000). Impact of respiratory virus infections on persons with chronic underlying conditions. *Journal of the American Medical Association*, 283, 499–505.

26. Marx, A., Gary, H.E., Martston, B.J., et al. (1999). Parainfluenza virus infection among adults hospitalized for lower respiratory tract infection. *Clinical Infectious Diseases*, 29, 134–140.

27. Public Health Laboratory Service Communicable Disease Surveillance Centre. (1983). Parainfluenza infections in the elderly 1976–82. *British Medical Journal*, 287, 1619.

28. Hui, D.S., Woo, J., Hui, E., et al. (2008). Influenza-like illness in residential care homes: A study of the incidence, aetiological agents, natural history, and health resource utilization. *Thorax*, 63, 690–697.

29. van den Hoogen, B.G., de Jong, J.C., Groen, J., et al. (2001). A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nature Medicine*, 7, 719–724.

30. Deffrasnes, C., Hamelin, M.E., Boivin, G. (2007). Human metapneumovirus. *Seminar Respiratory Critical Care Medicine*, 28, 213–221.

31. Boivin, G., De Serres, G., Hamelin, M.E., et al. (2007). An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. *Clinical Infectious Diseases*, 44, 1152–1158.

32. Falsey, A.R., Erdman, D., Anderson, L.J., Walsh, E.E. (2003). Human metapneumovirus infections in young and elderly adults. *Journal of Infectious Diseases*, 187, 785–790.

33. Johnstone, J., Majumdar, S.R., Fox, J.D., Marrie, T.J. (2008). Human metapneumovirus pneumonia in adults: results of a prospective study. *Clinical Infectious Diseases*, 46, 571–574.
34. Greenberg, S.B. (2007). Rhinovirus and coronavirus infections. *Seminar Respiratory Critical Care Medicine*, 28, 182–192.
35. Mosser, A.G., Vrtis, R., Burchell, L., et al. (2005). Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. *American Journal of Respiratory Critical Care Medicine*, 171, 645–651.
36. Nicholson, K.G., Kent, J., Hammersley, V., Cancio, E. (1996). Risk factors for lower respiratory complications of rhinovirus infections in elderly people living in the community: prospective cohort study. *British Medical Journal*, 313, 1119–1123.
37. Wilkinson, T.M., Hurst, J.R., Perera, W.R., Wilks, M., Donaldson, G.C., Wedzicha, J.A. (2006). Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. *Chest*, 129, 317–324.
38. Louie, J.K., Yagi, S., Nelson, F.A., et al. (2005). Rhinovirus outbreak in a long term care facility for elderly persons associated with unusually high mortality. *Clinical Infectious Diseases*, 41, 262–265.
39. Hicks, L.A., Shepard, C.W., Britz, P.H., et al. (2006). Two outbreaks of severe respiratory disease in nursing homes associated with rhinovirus. *Journal of the American Geriatrics Society*, 54, 284–289.
40. van der Hoek, L. (2007). Human coronaviruses: what do they cause?. *Antiviral Therapy*, 12, 651–58.
41. Garbino, J., Crespo, S., Aubert, J.D., et al. (2006). A prospective hospital-based study of the clinical impact of non-severe acute respiratory syndrome (Non-SARS)-related human coronavirus infection. *Clinical Infectious Diseases*, 43, 1009–1015.
42. Pyrc, K., Berkhout, B., van der Hoek, L. (2007). The novel human coronaviruses NL63 and HKU1. *Journal of Virology*, 81, 3051–3057.
43. Birch, C.J., Clothier, H.J., Seccull, A., et al. (2005). Human coronavirus OC43 causes influenza-like illness in residents and staff of aged-care facilities in Melbourne, Australia. *Epidemiology of Infection*, 133, 273–277.
44. El-Sahly, H.M., Atmar, R.L., Glezen, W.P., Greenberg, S.B. (2000). Spectrum of clinical illness in hospitalized patients with "common cold" virus infections. *Clinical Infectious Diseases*, 31, 96–100.
45. Melnick, J.L. (1995). History and epidemology of hepatitis A virus. *Journal of Infectious Diseases*, 171, S2–S8.
46. Wasley, A., Grytdal, S., Gallagher, K., and Centers for Disease Control and Prevention (CDC). (2006). *Surveillance for acute viral hepatitis – United States, 2006*. (Mort Morb Wkly Rep, 57, 1–24).
47. Marcus, E., Tur-Kaspa, R. (1997). Viral hepatitis in older adults. *Journal of American Geriatrics Society*, 45, 755–763.
48. Brown, G.R., Persley, K. (2002). Hepatitis A epidemic in the elderly. *Southern Medical Journal*, 95, 826–833.
49. Kyrlagkitsis, I., Cramp, M.E., Smith, H., Portmann, B., O'Grady, J. (2002). Acute hepatitis A virus infection: a review of prognostic factors from 25 years experience in a tertiary referral center. *Hepatogastroenterology*, 49, 524–528.
50. Dagan, R., Leventhal, A., Anis, E., Slater, P., Ashur, Y., Shouval, D. (2005). Incidence of hepatitis A in Israel following universal immunization of toddlers. *Journal of the American Medical Association*, 294, 202–210.
51. Dodd, R.Y., Notari, E.P., IV, Stramer, S.L. (2002). Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*, 42, 975–979.
52. MacMahon, M., James, O.F.W. (1994). Liver disease in the elderly. *Journal of Clinical Gastroenterology*, 18, 330–334.
53. Palumbo, E. (2008). New drugs for chronic hepatitis B: a review. *American Journal of Therapeutics*, 15, 167–172.

54. Cainelli, F. (2008). Hepatitis C virus infection in the elderly: epidemiology, natural history and management. *Drugs Aging*, 25, 9–18.

55. Simor, A.E., Gordon, M., Bishai, F.R. (1992). Prevalence of hepatitis B surface antigen, hepatitis C antibody, and HIV-1 antibody among residents of a long-term care facility. *Journal of American Geriatrics Society*, 40, 218–220.

56. Brind, A.M., Watson, J.P., James, O.F.W., Bassendine, M.F. (1996). Hepatitis C virus infection in the elderly. *The Quarterly Journal of Medicine*, 89, 291–296.

57. Horiike, N., Masumoto, T., Nakanishi, K., et al. (1995). Interferon therapy for patients more than 60 years of age with chronic hepatitis C. *Journal of Gastroenterology and Hepatology*, 10, 246–249.

58. Bennett, R., Greenough, W. (1993). Approach to acute diarrhea in the elderly. *Gastroenterology Clinics of North America*, 517–533.

59. Jiang, X., Turf, E., Hu, J., et al. (1996). Outbreaks of gastroenteritis in elderly nursing homes and retirement facilities associated with human calciviruses. *Journal of Medical Virology*, 50, 335–341.

60. Marrie, T., Lee, S., Faulkner, R., Ethier, J., Young, C. (1982). Rotavirus infection in a geriatric population. *Archives of Internal Medicine*, 142, 313–316.

61. Halvorsrud, J., Orstavik, I. (1980). An epidemic of rotavirus-associated gastroenteritis in a nursing home for the elderly. *Scandinavian Journal of Infectious Disease*, 12, 161–164.

62. Marshall, J., Botes, J., Gorrie, G., et al. (2003). Rotavirus detection and characterisation in outbreaks of gastroenteritis in aged-care facilities. *Journal of Clinical Virology*, 28, 331–340.

63. Edmonson, L.M., Ebbert, J.O., Evans, J.M. (2000). Report of a rotavirus outbreak in an adult nursing home population. *Journal of the American Medical Directors Association*, 1, 175–179.

64. Green, K.Y., Belliot, G., Taylor, J.L., et al. (2002). A predominant role for Norwalk-like viruses as agents of epidemic gastroenteritis in Maryland nursing homes for the elderly. *Journal Infectious Diseases*, 185, 133–146.

65. Lopman, B.A., Reacher, M.H., Vipond, I.B., Sarangi, J., Brown, D.W. (2004). Clinical manifestation of norovirus gastroenteritis in health care settings. *Clinical Infectious Diseases*, 39, 318–324.

66. Schmader, K., van der Horst, C.M., Klotman, M.E. (1989). Epstein–Barr virus and the elderly host. *Reviews of Infectious Diseases*, 11, 64–73.

67. Horwitz, C.A., Henle, W., Henle, G., et al. (1976). Clinical and laboratory evaluation of elderly patients with heterophil-antibody positive infectious monoculeosis. *American Journal of Medicine*, 61, 333–339.

68. Auwaerter, P.G. (1999). Infectious mononucleosis in middle age. *Journal of the American Medical Association*, 281, 454–459.

69. Horwitz, C.A., Henle, W., Henle, G., Schapiro, R., Borken, S., Bundtzen, R. (1983). Infectious mononucleosis in patients aged 40 to 72 years: report of 27 cases, including 3 without heterophil-antibody responses. *Medicine*, 62, 256–262.

70. Edelstein, H., Knight, R.T. (1989). Epstein–Barr virus causing encephalitis in an elderly woman. *Southern Medical Journal*, 82, 1192–1193.

Suggested Reading

Cainelli, F. (2008). Hepatitis C virus infection in the elderly: epidemiology, natural history and management. *Drugs Aging*, 25, 9–18.

Dworkin, R.H., Johnson, R.W., Breuer, J., et al. (2007). Recommendations for the management of herpes zoster. *Clinical Infectious Diseases*, 44 (Supp.1) S1–S26.

McGeer, A., Green, K.A., Plevneshi, A., et al. (2007). Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clinical Infectious Diseases*, 45, 1568–1575.