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Viral Infections

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1. RESPIRATORY VIRUSES

1.1. Influenza

Of the viral infections that cause disease in older adults, influenza is recognized as one of the greatest causes of morbidity and mortality. Pneumonia and influenza together comprise the fifth leading causes of death in persons aged 65 yr and older. Influenza viruses are enveloped ribonucleic acid (RNA) viruses that are classified as A, B, or C, based on stable internal proteins *(1)*. 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 *(2)*.

1.1.1. Epidemiology and Clinical Relevance

Peak influenza activity typically lasts 6–8 wk in a community with attack rates highest in preschool and school-aged children and lowest in older persons. During nonpandemic influenza, attack rates are approx 10% in the elderly *(3)*. Despite lower attack rates, hospitalization rates and complications are highest in this age group *(4)*. Mortality from influenza rises dramatically with age and the presence of underlying medical conditions contribute significantly to influenza-related mortality *(5)*. 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. The devastating impact of influenza is most dramatically seen in long-term care facilities 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% *(6)*. In addition to the suffering caused by influenza, the economic burden is enormous, resulting in more than one billion dollars spent by Medicare in 1989–1990 alone for excess hospitalizations *(7)*.

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Table 1
Respiratory Viral Infections

	Peak season	Incubation (d)	Clinical clues	Antiviral therapy
Influenza A	Winter	1–3	High fever, headache, myalgias	Amantadine Zanamivir, Oseltamivir Rimantadine Zanamivir, Oseltamivir
Influenza B	Winter	1–3	High fever, headache, myalgias	Zanamivir, Oseltamivir
RSV	Winter	3–5	Rhinorrhea, wheezing	Ribavirin
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.

1.1.2. Clinical Manifestations

The classic presentation of influenza is that of the abrupt onset of fever, chills, headache, and myalgias (*see* Table 1). Dry cough, sore throat, and ocular pain are also common *(1)*. Although nasal congestion and discharge occur with influenza, rhinorrhea is usually not as profuse as with other respiratory viruses. 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 influenza symptoms, a substantial number may have more subtle presentations such as fever and confusion or worsening of chronic cardiopulmonary disease. Thus, it is important to consider the possibility of influenza in the ill elderly adult during the winter months.

Lower respiratory tract involvement increases steadily with advancing age with the rates of pneumonia 4–8% in persons aged 5–50 yr and rising to 73% in persons over age 70 *(1)*. Secondary bacterial pneumonia following acute influenza also occurs more frequently in older persons. 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 *(8)*.

1.1.3. Diagnostic Tests

The diagnosis of influenza can be made in a variety of ways including viral culture, rapid antigen testing, and serology. Although many physicians use clinical features to make a diagnosis of "the flu," laboratory confirmation is best if therapeutic decisions are needed, as influenza may be difficult to distinguish from other respiratory viruses. Virus can be detected in nasopharyngeal secretions or sputum. Older persons typically shed less virus than young persons but will have culturable virus for 3–4 d into the illness *(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 offer several hour turnaround times and may be useful for infection control and treatment decisions *(11)*. Influenza infection can also be confirmed retrospectively by demonstrating a greater than fourfold rise in antibody by hemagglutination inhibi-

tion assay or enzyme immunoassay (EIA). A single acute titer is not useful for diagnosis of influenza, as all persons have preexisting antibodies.

1.1.4. Treatment

At the present time, four antiviral agents, amantadine, rimantadine, zanamivir, and oseltamavir are approved for the treatment of influenza A. These agents are 70–90% effective as prophylactic agents and also reduce illness severity, duration of symptoms, and viral shedding when given within 48 h of symptom onset *(12)*. Central nervous symptoms are a problem in older persons given amantadine. Rimantadine is more costly but appears to be better tolerated. Although resistance develops rapidly on therapy with either agent, a net therapeutic benefit is preserved *(13)*. The appropriate dose of amantadine or rimantadine for most elderly persons is 100 mg/day taken orally with further dose adjustments necessary for amantadine based on renal function. Zanamivir and oseltamavir are new agents that inhibit the action of viral neuraminidase and show promise for prophylaxis and treatment of influenza A or B *(14–16)*. Resistance and central nervous system side effects do not appear to be a problem.

1.1.5. Prevention

The cornerstone of infection control in long-term care facilities is yearly vaccination of residents and staff. (*See* also Chapter 23.) In addition, the Centers for Disease Control and Prevention (CDC) recommends that antiviral prophylaxis be given to all residents once influenza A has been documented in the institution *(17)*. Chemoprophylaxis is given regardless of vaccination status and is continued until 1 wk after the onset of the last influenza case. Because some authorities remain concerned about adverse side effects of amantadine, more conservative approaches have been put forward that recommend antivirals to those ill less than 48 h and to their roommates and reserve institutionwide prophylaxis only when more than 10% of residents are ill *(18)*.

Influenza vaccination has been clearly shown to be efficacious and cost effective in older persons and is recommended for all persons aged 65 and older *(17,19)*. Although serologic response is diminished in residents of nursing homes, vaccination reduces the severity of disease and prevents hospitalization and death *(17)*. The current vaccine contains antigens from two type A and one type B viruses. Mild acute local reactions occur in approx one third of vaccinees 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 contraindication to vaccination is anaphylactic hypersensitivity to eggs or other components of the vaccine *(17)*.

1.2. Respiratory Syncytial Virus

1.2.1. Epidemiology and Clinical Relevance

RSV is an enveloped RNA virus that belongs to the paramyxovirus family and consists of two antigenically distinct groups, designated A and B. RSV has long been recognized as the leading cause of lower respiratory tract disease in children; however, recently, it has been increasingly implicated as a cause of serious disease in elderly persons *(20)*. Although the magnitude of the problem of RSV in the elderly has not been completely defined, it appears to rank second to influenza as a major viral respiratory pathogen in this group *(21,22)*.

RSV was initially recognized as a pathogen in older persons when several outbreaks were described in long-term care facilities *(23,24)*. Since 1977, there have been 20 studies published that have identified RSV infections in nursing homes *(25–29)*. Attack rates are variable and may be as high as 90% during outbreaks, but are more commonly range from 1–7% when residents are followed prospectively *(28,30)*. Rates of pneumonia range from 0–53% and death from 0–55% in published reports *(28,31,32)*. The variable severity may be in part due to case selection bias in some studies, but also may reflect differences in strain virulence. In addition to long-term care facilities, RSV has also been found to be a frequent problem in senior daycare centers *(33)*.

Although less data are available, RSV appears to cause serious disease in community-dwelling older persons as well *(21,22)*. Similar to influenza, when peaks of RSV activity occurred among children in the United Kingdom, a peak in excess acute respiratory infection and mortality occurred in persons aged 65 and older *(22)*. In a 3-yr study examining persons aged 65 and older admitted to the hospital with acute cardiopulmonary conditions, RSV accounted for 10% of cases compared with 13% due to influenza A or B *(21)*. The impact of RSV illness was significant; 18% required intensive care, 10% needed ventilatory support, and 10% 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 to 6.2% due to *Streptococcus pneumoniae* and 5.4% due to influenza *(34)*. A recent analysis of the economic burden of RSV in adults concluded that 0.04–0.2% of the population 65 yr of age and older are hospitalized yearly with RSV pneumonia with estimated annual health-care costs of $150–680 million *(35)*.

1.2.2. 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 *(21,34)*. In addition, wheezing is a frequent complaint *(30)*. Fever is present in approx half of the cases but is usually lower than in influenza infection. 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 and wheezing are more frequently associated with RSV infection *(21,27,34)*.

1.2.3. Diagnostic Tests

The diagnosis of RSV infection can be accomplished by viral culture, rapid antigen tests, or serology. Unfortunately, because of the labile nature of the virus and low titers of virus in nasal secretions in adults, diagnosis of acute RSV infection is very difficult. Under ideal circumstances, viral culture is only 50% sensitive when compared with serology using EIA *(30)*. Both commercial rapid antigen tests and indirect immunofluorescence have poor sensitivity in adults *(36)*. New molecular tests, such as polymerase chain reaction (PCR), may offer a significant advantage for the diagnosis of acute RSV in this population and need further development. Infection can also be demonstrated retrospectively by a ≥fourfold rise in RSV-specific IgG, either by complement fixation or EIA. Because RSV in adults always represents reinfection, a single elevated titer is not useful for acute diagnosis. RSV-specific IgM has been detected in 11–81% of older subjects with acute RSV, but its clinical utility has yet to be defined *(26,37)*.

1.2.4. 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 *(38)*. Although inhaled ribavirin is approved in young children with RSV, no controlled data exist in adults. Anecdotal experience suggests it may be beneficial in selected cases; however, general recommendations on its use cannot be made due to lack of data *(39)*. Although relatively nontoxic, the major problems with ribavirin are its high cost and difficulty with administration. The recommended 12–18 h/d of aerosol at 20 mg/mL concentrations may be quite difficult for the elderly adult to tolerate. Recent data indicate that higher concentrations (60 mg/mL) given three times a day may also be effective.

1.2.5. Prevention

Although research is ongoing, an effective RSV vaccine has yet to be developed. Thus, prevention of RSV is limited to good basic infection control policies. RSV is spread primarily by large droplet inoculation and fomites. Therefore, close person-to-person contact or contact with contaminated environmental surfaces is required for transmission to occur. Handwashing is the single most important measure in the control of RSV. Because compliance with hand washing is frequently poor, some authorities advocate the use of gowns and gloves when caring for RSV-infected patients *(40)*.

1.3. Parainfluenza Viruses

1.3.1. 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. Although comprehensive studies are lacking, these common respiratory viruses also affect older adults. The parainfluenza viruses are members of paramyxovirus family with four serotypes and two subgroups 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. Most reinfections in young adults result in mild upper respiratory infections; however, occasional outbreaks of pneumonia have been described *(41)*. Although PIV infections are not commonly documented in older adults, several studies of community-acquired pneumonia implicate PIV as a cause in 2–11% of cases *(42,43)*. The PIV-1 and 3 serotypes account for the majority of isolates in older persons, with PIV-2 being relatively uncommon *(44)*.

1.3.2. Clinical Manifestations

Similar to RSV, outbreaks of PIV infections in nursing homes have been described *(44–46)*. High attack rates and significant morbidity and mortality have 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 20–30%. In a recent institutional outbreak of PIV-3, the attack rates among residents and nursing staff were 31% and 11%, respectively. The epidemic pattern, with a steady number of new cases over a 1-mo period, suggested person-to-person transmission *(46)*.

1.3.3. Diagnostic Tests and Treatment

Diagnosis of PIV infection can be made by viral culture or by demonstrating a rise in serum antibody by EIA or complement fixation. Both PIV-1 and 3 infections result in cross-reactive antibody responses and, thus, cannot be distinguished serologically. At present, a rapid antigen test for PIV is not commercially available and no antiviral agents have been approved for the treatment of PIV infection. Therefore, treatment is supportive

1.4. Rhinoviruses

1.4.1. Epidemiology and Clinical Relevance

Rhinoviruses are the most commonly identified cause of the "common cold," accounting for approx 25–50% of upper respiratory infections *(47)*. These ubiquitous viruses are members of the picornavirus family with over 100 antigenic types. Rhinoviruses circulate at all times of the year, but peak activity tends to be during the spring and fall. Infections with rhinoviruses are common throughout life and, although a major cause of school and work absenteeism, illnesses are generally mild in young persons *(48)*. Pneumonia due to rhinovirus is very uncommon, even in immunocompromised persons and is likely because the virus does not replicate well at the lower airway temperature of 37°C *(49)*.

There are little data on the incidence of rhinovirus infections in independent elderly persons living in the community. However, a recent 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 *(50)*. Rhinoviruses accounted for 121 of 497 (24%) respiratory illnesses that occurred in a cohort of 533 persons over a 2-yr period. Seminested reverse transcriptase (RT)-PCR was used to identify rhinovirus infection and the increased sensitivity of this technique was likely responsible for the high infection rates. Although death and hospitalization rates were low, the mean length of illness was 16 d and 26% were unable to perform their normal household activities. Fifty-six percent had evidence of lower respiratory tract involvement such as productive cough or wheezing. 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 *(50)*.

1.4.2. Clinical Manifestations

Rhinovirus infections are also common in senior daycare settings and long-term care facilities *(30,51,52)*. In frail elderly persons, nasal congestion (79–89%), cough (71–94%), constitutional symptoms (43–91%) and sore throat (21–51%) characterize illnesses. Similar to independent seniors, illnesses were prolonged, lasting approx 2 wk and approx 50% had lower respiratory involvement.

1.4.3. Diagnostic Tests and Treatment

The diagnosis of rhinovirus is usually made by viral culture of nasopharyngeal secretions. Although the use of RT-PCR greatly increases detection rates, this technique is currently only available in research settings *(50)*. Treatment is supportive and care should be exercised when prescribing "cold" medications to elderly persons as many contain combinations of sympathomimetics and antihistamines. At the present time,

specific antiviral therapy of rhinoviruses is not available. Recently, a new compound, tremacamra, which blocks the cellular receptor for rhinovirus, intercellular adhesion molecule 1 (ICAM), shows promise for the treatment of rhinovirus infections *(53)*.

1.5. Coronaviruses

Coronaviruses are RNA viruses of which two major serotypes, 229E and OC43, cause respiratory disease in humans *(54)*. Peak viral activity occurs in the winter and spring *(55)*. 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 *(54)*. Exacerbations of chronic obstructive pulmonary disease have been linked to coronavirus infections in several studies *(56)*.

Coronavirus infections have been evaluated in the community-dwelling elderly in one prospective study from the U.K. and accounted for 9.5% of the respiratory illnesses *(57)*. They were associated with lower respiratory tract symptoms in more than 40% of cases. Coronavirus infections have been documented in long-term care facilities and in frail elderly people attending daycare centers *(52,58)*. The most common symptoms were cough (94%), constitutional symptoms (88%), and nasal congestion (84%). Significantly, 66% had a productive cough, 34% experienced shortness of breath, and 22% developed wheezing. Illnesses lasted approx 2 wk and almost half of the patients required antibiotics. Although many of the subjects were very frail, all recovered without sequelae. Unfortunately, diagnosis of coronavirus infections is not generally available outside of research facilities due to the fastidious nature of the virus and the lack of commercial reagents for serologic diagnosis. No antiviral agents are available and treatment is supportive.

2. VIRAL HEPATITIS

2.1. Hepatitis A

Hepatitis A (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 *(59)*. Recently, a shift in the prevalence of cases from childhood to adulthood has occurred, presumably due to improved living conditions. In the United States and other industrialized nations, the prevalence of anti-HAV antibodies increases with advancing age *(60)*. Seroprevalence in an ambulatory geriatric population (mean age 75) in New York was 94%. In a 1994 serologic study from Colorado, the prevalence of anti-HAV antibodies at ages 60, 70, and 80 was 40%, 60%, and 80%, respectively *(59)*. The steady increase in seroprevalence with age is seen in men and women and in all races and ethnic groups.

The clinical manifestations of acute hepatitis A become more severe and are associated with prolonged cholestasis with advancing age *(61,62)*. In the United States, the overall case fatality rate for HAV infection is 1/1000; however, it rises to 27/1000 in persons 50 yr or older *(61)*. Approx 100 HAV-related deaths occur in the U.S. each year of which 70% are in persons over age 49 *(63)*. The increased death rates in the older population is attributable to higher rates of fulminant hepatitis since chronic infection does not occur *(59)*.

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 Increased mortality	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 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 *(64)*. Similar to young adults, seroconversion rates are 100% in older adults (40–61 yr) *(65)*. 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.

2.2. Hepatitis B

Hepatitis B (HBV) is a complex deoxyribonucleic acid (DNA) virus composed of double-stranded DNA, core antigen (HBcAg), surface antigen (HBSAg), and soluble nucleocapsid antigen (HBeAg). Hepatitis B surface antigen is detectable during acute illness and disappears when antibody to HBSAg develops. Transmission of HBV is by percutaneous and mucous membrane exposure to infectious body fluids. Serum, saliva, and semen have been shown to contain HBSAg. Hepatitis D (HDV), also known as Delta agent, is a small single-stranded, circular RNA particle that is coated with HBSAg. Infection with HDV requires either simultaneous infection with HBV or chronic HBV infection. The co-infection may result in fulminant hepatitis *(60)*.

Infection with HBV accounts for approx 20% of cases of acute viral hepatitis in older adults *(60,66)*. Because the primary risk group in the U.S. and Europe is intravenous drug abusers, a group not highly represented in the elderly population, acute infection is not common in this age group. Transfusion-related HBV infection from contaminated blood in the window period of detection is a now an uncommon event with risk estimated to be 1 in 63,000 transfusions *(67)*. Long-term care facilities were at one time considered a risk area for HBV when several outbreaks occurred during the 1970s–1980s *(60)*. However, recent surveys of geriatric hospitals indicate the prevalence of HBSAg is similar to the general geriatric population (<1%) *(60,68)*.

Acute HBV in older adults is usually mild and many cases are subclinical or present with a cholestatic picture *(66)*. In addition to the typical symptoms of jaundice, anorexia, and fatigue, diarrhea is a common complaint in elderly persons *(66)*. 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 *(60)*. In a multivariant analysis of prognostic factors in 115 patients with HBV, age was an independent predictor of survival. Chronic carriage rates also increase when individuals are infected at older ages. Compared with a 10% carriage rate in young adults, approx 60% of older persons become chronic carriers *(60)*. However, most elderly HBV chronic carriers were infected early in life and have carried the virus for a prolonged period and, although HBSAg is detected, there is little evidence of active viral replication as determined by the presence of HBeAg or viral DNA in the serum *(60)*.

In addition to cirrhosis from chronic active hepatitis, one of the major complications of HBV infection is hepatocellular carcinoma. 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 greatest risk *(69)*. The rate of hepatocellular carcinoma rises from 197/100,000 in 30- to 39-yr olds to 927/100,000 in 60- to 69-yr-old chronic HBV carriers *(62)*.

The treatment of elderly persons with chronic HBV is largely supportive. Although α-interferon shows evidence of suppressing viral replication and may decrease the risk of progression to cirrhosis or cancer, side effects of therapy increase with advancing age *(60)*. Therapy should be reserved for patients in overall good health except for their liver disease and who have evidence of active viral replication. Lamivudine, a nucleoside analogue, holds promise as a new anti-HBV agent.

The currently licensed hepatitis B vaccine is a genetic recombinant vaccine consisting of highly purified HBSAg particles expressed in yeast. The vaccine 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.

2.3. Hepatitis C

Hepatitis C (HCV) is an RNA virus in the flavivirus family and accounts for the majority of cases of acute viral hepatitis in the older adults. The virus is transmitted parenterally and accounts for approx 90% of new cases of posttransfusion hepatitis. Other exposures to contaminated blood, either via occupation or intravenous drug abuse, may also 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 *(61)*. The major risk factor for HCV in older persons is transfusion and most became infected with HCV prior to 1990 when routine screening of the blood supply began *(60)*. The current risk of acquiring HCV from transfusion is approx 1 in 103,000 *(67)*. The seroprevalence of HCV increases with advancing age from 0.6% among 18- to 25-yr olds to 2.5% of persons over age 60. The increased prevalence in older persons is likely due to a greater chance

of transfusion *(60)*. The seroprevalence in long-term care facilities is approx that of the general elderly population. In a Canadian and an Italian chronic care facility, the prevalences of anti-HCV antibodies were 1.4% and 2.2%, respectively, both reflecting rates similar to the community at large *(68,70)*.

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, approx 30–40% had fever, abdominal pain, and jaundice *(60)*. Fulminant hepatitis is rare with HCV, but development of chronic liver disease is very common *(61,66,71)*. Virtually all persons become chronically infected and a significant number develop chronic liver disease. Chronic active hepatitis or cirrhosis develops in 29–76%, on average 20 yr after initial infection *(71)*. In older patients with chronic HCV, the HCV–RNA titer is significantly higher than in younger patients, and there is evidence that disease progression is more rapid *(60)*. 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 (52 vs. 15) *(69)*. In a study of 25 older persons with HCV in the U.K., 36% developed hepatocellular carcinoma *(71)*.

Alpha interferon is administered to patients with chronic HCV infection as an attempt to prevent progression to cirrhosis and possibly liver cancer. Persons with high viral load and viral genotype 1 have a low response rate to α-interferon, and many patients who do have an initial response relapse when therapy is discontinued *(60)*. 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. Of note, the older subjects had higher HCV–RNA titers and more severe fibrosis on liver biopsy compared with young subjects. Response rates in elderly persons correlated with lower HCV–RNA titers *(72)*. Because older persons have more side effects and a lower response rate to interferon, therapy should be reserved for those persons with a low RNA titer, viral genotypes other than 1, and minimal fibrosis on biopsy *(60)*.

2.4. *Hepatitis E*

Hepatitis E virus (HEV) is an enterically transmitted virus found in Africa, Asia, and Mexico. Attack rates of HEV are highest in persons ages 15–40, and mortality is high in pregnant women. Seroprevalence increases with age, reaching 70% in persons over age 60 living in endemic areas *(60)*. No cases of HEV have been reported in the United States.

2.5. *Hepatitis G*

Hepatitis G virus (HGV) is a recently discovered novel agent belonging to the flavivirus family and is distantly related to HCV. The epidemiology and clinical significance of this HGV is still being defined, but it is felt to be a possible cause of the transfusion-associated hepatitis *(73)*. The pattern of HGV seroprevalence is similar to HCV and increases with age, peaking in the sixties *(60)*. In 105 elderly Italian persons with a mean age of 73, anti-HGV antibodies were found in 24%, and 3% were viremic. No subject had clinical evidence of hepatitis *(73)*.

3. GASTROENTERITIS VIRUSES

Recent studies from the CDC have described increased morbidity and mortality associated with gastroenteritis in the elderly. Although deaths related to diarrhea have traditionally been thought to be a problem of young children in developing countries, 51% of the 28,538 diarrhea-related deaths in the United States from 1979–1987 occurred in adults over age 74 compared with 11% in children <5 yr old *(74)*. The odds ratio of dying during a hospitalization involving gastroenteritis was 52.6 for adults over age 70 compared with children less than age 5. Residents of nursing facilities are at particular risk for infectious diarrhea illness because of the outbreaks which can occur in closed populations. The majority of nursing facility outbreaks of gastroenteritis are probably viral in origin since bacterial causes are not usually identified. These include rotavirus, enteric adenoviruses, calicivirus, Norwalk-like agent, Snow Mountain agent, and small round structured viruses (SRSV) *(74–76)*.

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 thus facilitating nosocomial dissemination. Several outbreaks of rotavirus infection in elderly residents of long-term care facilities have been reported *(77–79)*. Attack rates have ranged from 36–66% with mortality rates of 1–10%. The typical illness included voluminous vomiting and watery diarrhea with low-grade fever. Blood in stool was not seen, and diarrhea typically lasts 2–3 d. Death resulted from dehydration progressing to oliguria and acidosis *(77,79)*. Rotavirus serum antibody titers offer some protection against severe disease and tend to diminish with increasing age *(79)*.

In 1998, a live attenuated rotavirus vaccine was approved for use in infants. The vaccine provides 88% protection from severe diarrhea and 75% from dehydration, and produced a 70% reduction in hospital admissions *(80)*. No data on safety or immunogenicity in the elderly exists; however, given the mortality rates in this age group, further study would be reasonable.

4. HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus (HIV) is the cause of a worldwide pandemic with estimates that 50–100 million individuals will be infected by the year 2000. (*See* also Chapter 25.) Although acquired immunodeficiency syndrome (AIDS) is primarily a disease of young persons, elderly persons are also affected and diagnosis is frequently unrecognized *(81–83)*. As of June 1996, 10% of the AIDS cases in the United States were in persons older than age 50 *(81)*. Of these, 28% were over age 60 and 13% were 65 yr and older. Until recently, the primary source of HIV in the elderly was blood transfusion during the period between 1978 and 1985. Currently, the most common risk factor among AIDS patients over age 50 is homosexuality. It is estimated that in the United States, one million homosexuals persons are aged 65 and older *(82)*. Intravenous drug use ranks second and a history of blood transfusion now ranks third as the most common HIV risk factors in older persons *(82)*. In addition, older adults have a greater probability of having no identifiable risk factors that may reflect heterosexual transmission from at-risk partners *(81,82)*. Finally, older at-risk Americans are much

less likely to have adopted AIDS-preventing strategies than persons in their twenties *(84)*. Persons over age 50 are one-sixth as likely to use condoms during sex and one-fifth as likely to have ever been HIV tested.

HIV infection appears to progress more rapidly in older persons. Age over 40 yr is an independent risk factor for poor survival among patients with transfusion-related AIDS *(85)*. Older AIDS patients who develop an AIDS-defining opportunistic infection are also more likely to progress quickly and die. Approx 37% of persons over age 80 die within the same month as they have AIDS diagnosed compared with 12% in young adults *(82)*. The decreased survival time is likely due to a combination of comorbid disease, immunosenescence, and most importantly, delayed diagnosis *(81,83)*. In general, the most frequent illness in older persons with HIV infection is bacterial pneumonia, although opportunistic infections do occur and are similar to those in younger AIDS patients. A significant problem in the elderly is AIDS dementia, as it may be mistaken for Alzheimer's disease or Parkinson's disease. If unrecognized, the opportunity for a trial of antiretroviral medication is lost. Regardless of age, all patients with clinical syndromes compatible with AIDS should be evaluated for HIV infection.

5. HERPES VIRUS INFECTIONS

5.1. 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, which is manifested as chickenpox, and reactivation of latent virus in the dorsal root ganglia, leading to herpes zoster or "shingles." Herpes zoster is a painful, vesicular exanthem which erupts in one to two dermatomes after a prodrome of days to weeks and may take up to a month to heal *(86)*. 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 10–20% with most of the risk concentrated in older age *(87)*. The overall incidence is 215 per 100,000 person-years, but rates rise sharply with increasing age to 1425/100,000 for persons older than 75 yr.

Postherpetic neuralgia (PHN) is the presence of pain more than 1 mo after onset of the eruption *(86)*. PHN afflicts the elderly much more frequently than the young, occurring in 27–68% of persons age 60 and older, compared with 3–10% of persons under age 50 *(88)*. In addition to age, severity of acute pain, rash severity, prodromal symptoms, and the degree of sensory impairment are predictors of PHN *(89)*. Approx 20% of persons with PHN who are over age 60 will have pain for more than 1 yr. The pathological changes seen in PHN include fibrosis and loss of neurons in the dorsal ganglion and axon and myelin loss in the affected side *(86)*. Once PHN develops, treatment of pain is often ineffectual. The great variety of treatments that are available for PHN is an indication that none are very effective. Topical formulations of aspirin and anesthetics, such as lidocaine and prilocaine, may provide some short-term benefit *(86)*. Capsaicin cream, which depletes the neurotransmitter, substance P, is the only drug approved for the treatment of PHN by the Food and Drug Administration. Neuropathic pain is generally not very responsive to narcotics, although some patients derive benefit. The most beneficial systemic agents available for PHN are the tricyclic antide-

Table 3
Therapy for Acute Herpes Zoster Within 72 Hours of Rash

Antiviral	Dose	Duration
Valacyclovir	1 g, three times a day	7 d
Famciclovir	750 mg, three times a day	7 d
Acyclovir	800 mg, five times a day	7–10 d
Consider in persons with no contraindications[a] to corticosteroids: antiviral + prednisone 60 mg/d, tapered over 21 d.		

[a]Contraindications include: diabetes, hypertension, and glaucoma.

pressant drugs. Randomized clinical trials of amitriptyline and desipramine showed that 45–65% of elderly PHN patients achieved some pain relief *(88)*. Anticonvulsants, such as phenytoin, carbamazepine, and gabapentin, may be helpful to reduce the lacinating component of neuropathic pain *(86)*. Other treatments, such as transcutaneous electrical nerve stimulation (TENS), biofeedback, relaxation therapy, and regional neuron blockade have all been used with variable success.

Because PHN is often refractory to treatment, efforts have been directed toward prevention using antivirals and corticosteroids. Five controlled trials have evaluated the use of corticosteroids to prevent PHN. Two studies showed a benefit, but the other two did not *(86)*. The fifth study was done in 208 persons over age 50 with localized zoster of less than 72 h duration. Treatments included acyclovir, 800 mg, five times a day for 21 d, and prednisone, starting at 60 mg/d, with a taper over 21 d. Four treatment arms include acyclovir and prednisone, acyclovir alone, prednisone alone, and placebo. The acyclovir-plus-prednisone group showed accelerated time to cessation of acute pain, time to uninterrupted sleep and time to return to daily activities *(90)*. Of note, no effect on chronic pain at 6 mo was observed. The new antivirals, famciclovir and valacyclovir, also show significant reduction in the duration of zoster pain in placebo-controlled trials *(88,91)*. However, 20% of patients in both studies developed chronic pain despite early treatment with antiviral drugs.

In summary, if begun within 72 h of the rash, acyclovir, famciclovir, and valacyclovir all reduce acute pain in immunocompetent adults with zoster and, thus, are worthwhile, regardless of their effect on PHN. Corticosteroids also do not alter the course of PHN but may improve the quality of life after zoster, and their use, in combination with an antiviral, is reasonable in persons over 50 yr of age with no contraindication to corticosteroids (*see* Table 3) *(86)*.

The optimal way to prevent PHN may be to prevent zoster itself. Trials to evaluate the live OKA-strain varicella vaccine in older adults to prevent herpes zoster are ongoing. Immunization of adults who are immune to varicella-zoster results in increases in humoral and cellular immune responses. However, it will take many years to know if these encouraging results translate into decreased rates of herpes zoster *(86)*.

5.2. Epstein-Barr Virus

The Epstein–Barr Virus (EBV) is a double-stranded DNA virus in the herpes virus family. Infection with EBV 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 *(92)*. Although primary infection is uncommon in old age, the manifestations may be different than in youth, making diagnosis challenging.

Seroepidemiologic studies indicate that 3–10% of older adults are at risk for primary infection as indicated by the absence of EBV antibodies *(92)*. Because primary EBV infection is uncommon in older age, the diagnosis is often not considered. 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 *(93)*. The neurologic manifestations of EBV infection are protean, and acute EBV encephalitis has been documented in an elderly woman *(94)*. To add to the difficulty in 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. Therefore treatment is supportive.

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