77

INFLUENZA AND VIRAL RESPIRATORY INFECTIONS

Joseph P. Lynch, III

Community-acquired respiratory viruses (CARVs) are a diverse group of viruses belonging to several families, including the Orthomyxoviridae (influenza A and B), Paramyxoviridae (respiratory syncytial virus, parainfluenza virus, human metapneumovirus), Coronaviridae (coronavirus), Picornaviridae (rhinovirus), and Adenoviridae (adenovirus). CARVs are generally transmitted directly from person to person, through fomites in respiratory secretions or via direct contact with infected secretions.[1] Most infections arise in the community, but nosocomial transmission can occur.[1] Infection control measures are critical to contain the spread of these viruses.[1] In the sections that follow, each of these viruses is discussed in depth.

INFLUENZA

Influenza A and B viruses infect on average 10% to 15% of the population annually (all age groups are affected).[2,3] Influenza causes seasonal outbreaks globally, and (rarely) pandemics.[4] Seasonal influenza epidemics from 1976 through 2001 were responsible for more than 200,000 annual hospitalizations and more than 30,000 influenza-associated deaths (IADs) (all causes) in the United States[5] (Fig. 77-1). The toll is considerably higher during pandemics.[4]

Virology

Influenza virus belongs to the virus family Orthomyxoviridae, which includes *Influenzavirus* A, B, and C.[6] Influenza A and B cause most human infections.[6] Most seasonal epidemics and all recognized pandemics in humans are due to influenza A. Influenza A viruses are characterized by their antigenicity, according to hemagglutinin (H) and neuraminidase (N) proteins; there are 16 H and 9 N subtypes.[6] All antigen subtypes circulate among avian species.[6] Globally, the most common circulating influenza A viruses from 1994 to 2005 included H3N2 (90.6%), H1N1 (8%), and H1N2 (1.1%).[7] There is significant variability among seasons, with H3N2-dominant years being worse than H1N1 years.[2,8]

Influenza viruses have evolved mechanisms that promote antigenic variability. Point mutations in the H gene give rise to new influenza strains of the same H type (termed *antigenic drift;* Fig. 77-2).[3] In this context, existing antibodies may fail to cover the new variant. Antigenic drift mandates modification of influenza vaccines annually.[3] A second mechanism, known as *antigenic shift,* is more dramatic and allows one influenza strain (such as H3N2) to acquire a completely new H or N gene (such as H1 or N1), resulting in a new virus (such as H3N1 or H1N2) (Fig. 77-3).

Pandemic influenza results when the antigenic mutations are dramatically different from previously circulating strains; this could occur by *antigenic shift* or by cross-species transmission of novel H- or N-type viruses.[3] The recent emergence of the highly pathogenic avian viruses (H5N1)[4] is discussed later.

Epidemiology

Influenza is one of the most common and important respiratory illnesses, affecting all ages. In temperate climates, influenza exhibits a

A

B
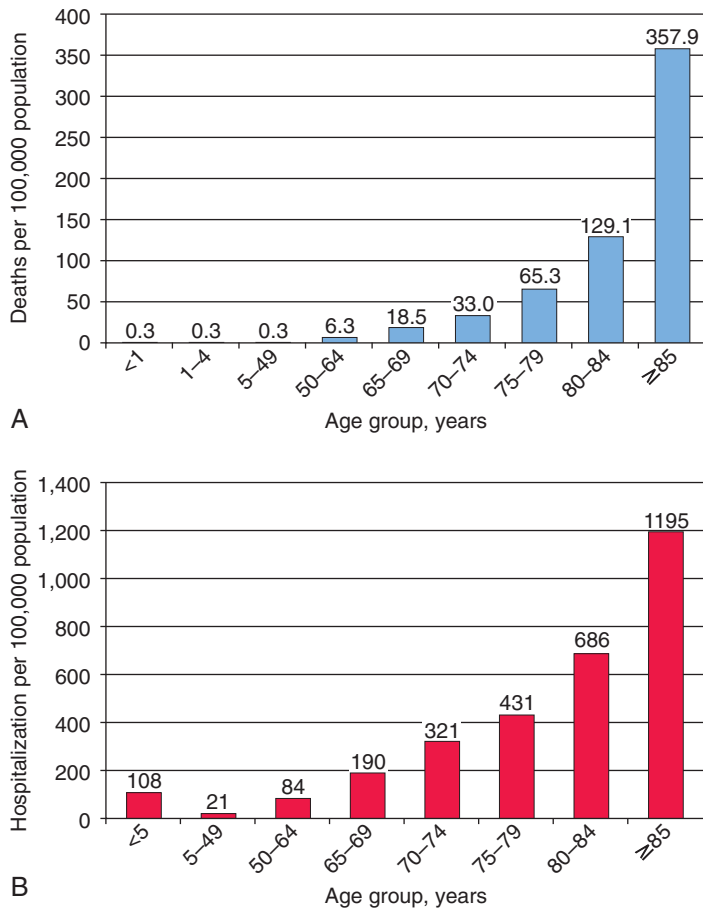
FIGURE 77-1 • A, Influenza-associated mortality rates, by age group, during 1976-2000. **B,** Influenza-associated hospitalization rates, by age group, during 1979-2001. (Data from Thompson et al.[5])
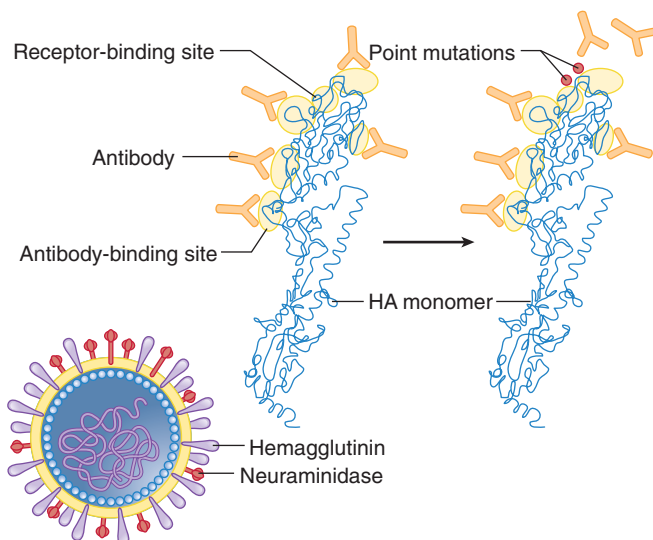
FIGURE 77-2 • Antigenic drift. Structure of a hemagglutinin monomer and location of the five known antibody-binding sites in the HA1 subunit. (Adapted from Treanor J: Influenza virus—outmaneuvering antigenic drift and shift. N Engl J Med 2004;350:218.)
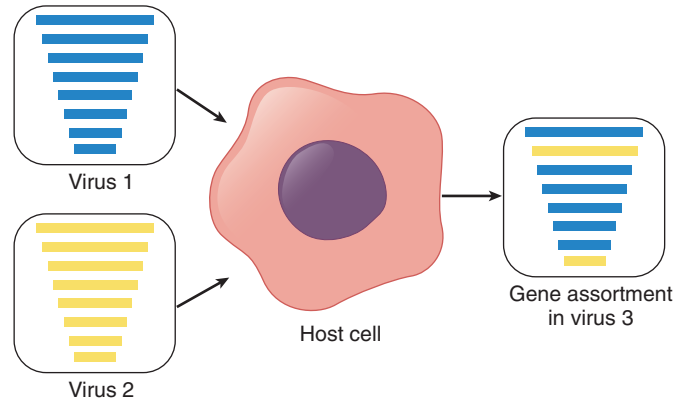
FIGURE 77-3 • Antigenic shift.

seasonal pattern, with peak activity during the winter months (December through March).[2] Local outbreaks abate after 6 to 8 weeks.[2] Influenza A predominates in most seasons, but epidemics of influenza B occur.[9]

The virus is present in high titer in respiratory secretions and is transmitted as a small-particle aerosol generated by coughing and sneezing.[2] Person-to-person spread by direct contact with respiratory secretions may also occur. Children are important as vectors for transmission to adult populations.[10] Spread throughout the general population often includes nosocomial outbreaks in nursing homes and other closed communities.[1]

The severity of influenza epidemics varies among seasons, depending upon the virulence and antigenicity of the predominant circulating strain and immune status of the population at risk. The 1984-1985 influenza season was severe, with an estimated 51,000 IADs in the United States compared to fewer than 8000 IADs during the 1978-1979 season.[8] Approximately 90% of deaths occur among the elderly, in contrast to approximately 150 annual deaths in the United States in children under age 5 years.[8] Influenza and serious complications of influenza are more common in the elderly (age >65 years), children under age 2 years, adults or children with concurrent illness (e.g., pulmonary, cardiac, metabolic), residents of chronic care facilities, and pregnant women.[2,11]

Pandemics occur infrequently but can be devastating.[12] The most recent global pandemics included 1918-1919 (Spanish flu, H1N1; responsible for up to 50 to 100 million deaths worldwide); 1957-1958 (Asian flu, H2N2; >1 million deaths); and 1968-1970 (Hong Kong flu, H3N2; >700,000 deaths).[4] Given the considerable growth of the population worldwide and exponential growth in foreign travel over the past 50 years, another pandemic could be catastrophic (Fig. 77-4).

Clinical Features

Following an incubation period of 2 to 5 days, symptom onset is generally abrupt, distinguishing influenza from other viral respiratory infections. Fever is present in more than 90% of cases; other symptoms include a dry, nonproductive cough, nasal congestion or rhinorrhea, headache, sore throat, and constitutional complaints (e.g., myalgias, malaise, fatigue, prostration).[10,13] Influenza is an important cause of respiratory illness in children.[10] Most influenza infections in children are self-limited, but influenza may be severe in young children (age <2 years) or those with chronic medical conditions.[2] Influenza is associated with increased hospitalizations,[14] outpatient visits,[15] and health care costs[15] in children.

In previously healthy individuals (children or adults), symptoms resolve spontaneously within 5 to 8 days. The course may be protracted, and complications more frequent, in high-risk or immunocompromised patients.[2,16,17] Primary influenza pneumonia, characterized by diffuse interstitial infiltrates and severe hypoxemia, is unusual except during pandemics or in individuals with specific risk factors.[2] Secondary bacterial pneumonia may complicate influenza, usually 7 to

Two mechanisms whereby pandemic influenza originates
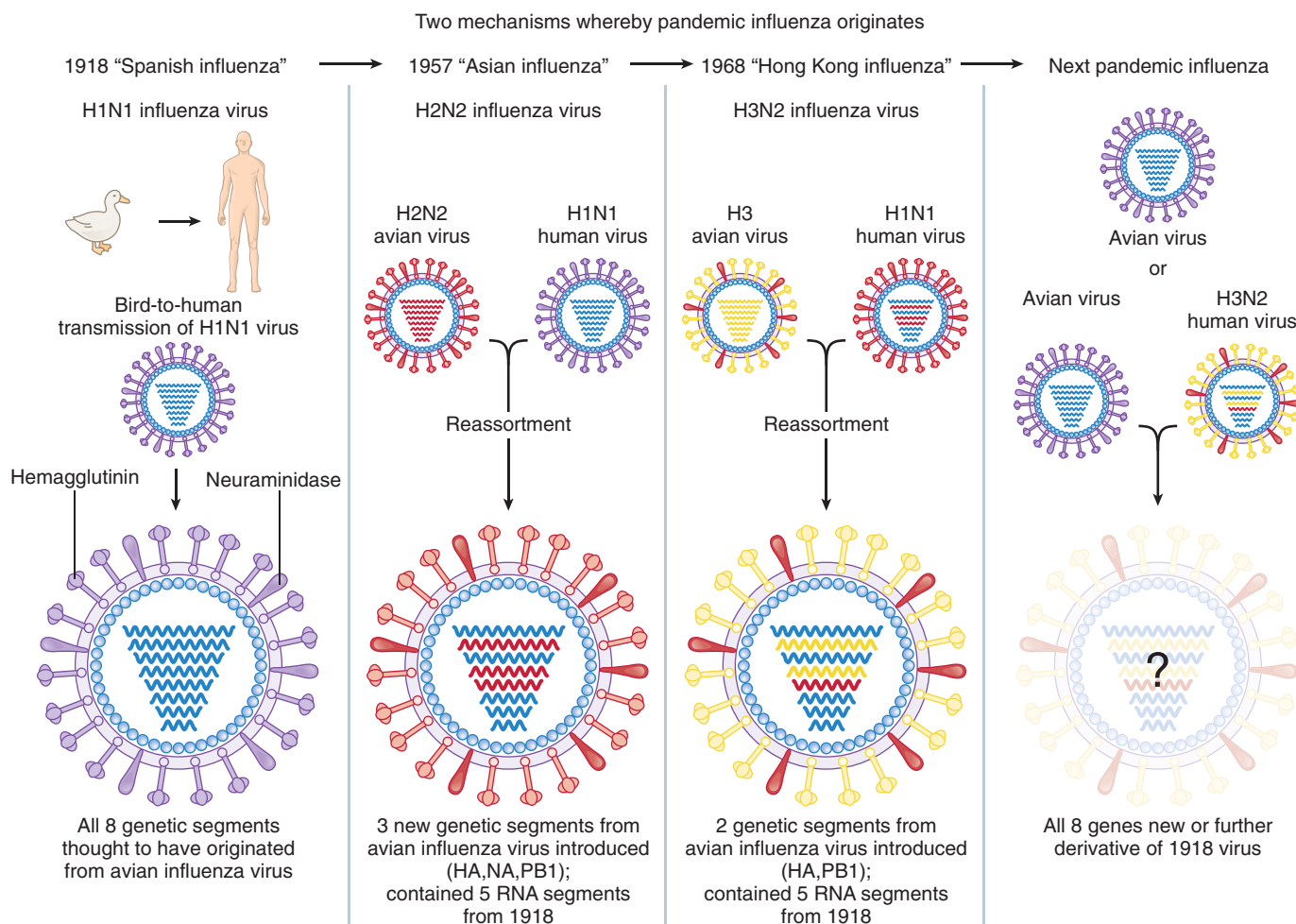
FIGURE 77-4 • The two mechanisms whereby pandemic influenza originates. In 1918, an H1N1 virus closely related to avian viruses adapted to replicate efficiently in humans. In 1957 and in 1968, reassortment events led to new viruses that resulted in pandemic influenza. The 1957 influenza virus (Asian influenza, an H2N2 virus) acquired three genetic segments from an avian species (a hemagglutinin, a neuraminidase, and a polymerase gene, PB1), and the 1968 influenza virus (Hong Kong influenza, an H3N2 virus) acquired two genetic segments from an avian species (hemagglutinin and PB1). Future pandemic strains could arise through either mechanism. (Adapted from Belshe RB. The origins of pandemic influenza—lessons from the 1918 virus. N Engl J Med 2005;353:2209-2211.)

21 days following resolution of the initial illness.[2] Acute respiratory distress syndrome may occur with some influenza strains, likely mediated by a virus-induced cytokine storm.[18]

Serious nonrespiratory complications of influenza are rare, but include encephalopathy, pericarditis, rhabdomyolysis, and renal failure.[2,19] Central nervous system complications are more common in children than adults.[19] Reye's syndrome, a severe neurologic complication of influenza in children, has largely disappeared since the link between aspirin use and Reye's syndrome was discovered.[20]

Diagnosis

Clinical features of influenza are nonspecific.[21] Laboratory confirmation of influenza is necessary if infection control measures and treatment are to be optimized. Culture of respiratory secretions is the gold standard, but can take 3 to 5 days and is expensive and often not available in an outpatient setting. Virus titers are high early in the illness, but fall rapidly in adults. In one study, only 48% of hospitalized elderly persons with confirmed influenza had a positive culture.[21] Commercialized kits allow rapid detection of influenza antigens in less than 1 hour with a sensitivity of 40% to 80%.[6,21] Reverse transcriptase–polymerase chain reaction (RT-PCR) is more sensitive than viral cultures or antigen detection tests, but is less readily available.[10] Rapid diagnostic tests may be invaluable during epidemics in emergency departments and outpatient and inpatient settings.

Treatment

Currently, four drugs are licensed in the United States for the treatment or prophylaxis of influenza.[22] These include the adamantanes (i.e., amantadine and rimantadine) and the neuraminidase inhibitors (NAIs) (e.g., oseltamivir and zanamivir).[23] Currently, NAIs are the therapeutic agents of choice for *treatment or prevention* of influenza infections. Treatment should be considered for patients with influenza-like illness (ILI) in communities where influenza has been documented, especially those with underlying high-risk conditions.[22] Further, patients hospitalized with acute respiratory illness during an epidemic period may be candidates for treatment. Prophylaxis with NAIs is appropriate during influenza seasons for household contacts or asymptomatic high-risk patients such as nursing home residents or staff during an outbreak, or for unvaccinated persons at high risk (e.g., with chronic lung disease, immunosuppressed, etc.).[23,24]

Adamantanes (M2 Inhibitors)

The adamantanes block the influenza A virus M2 ion channel protein, thereby preventing replication within infected cells; these agents have no activity against influenza B[2,22] (Fig. 77-5).

In early studies, both amantadine (Symmetrel; licensed in 1966) and rimantadine (Flumadine; licensed in 1993) were shown to be effective to treat[22,25] or prevent[22] uncomplicated infections due to sensitive influenza A. Amantadine or rimantadine are equally effective, provided that
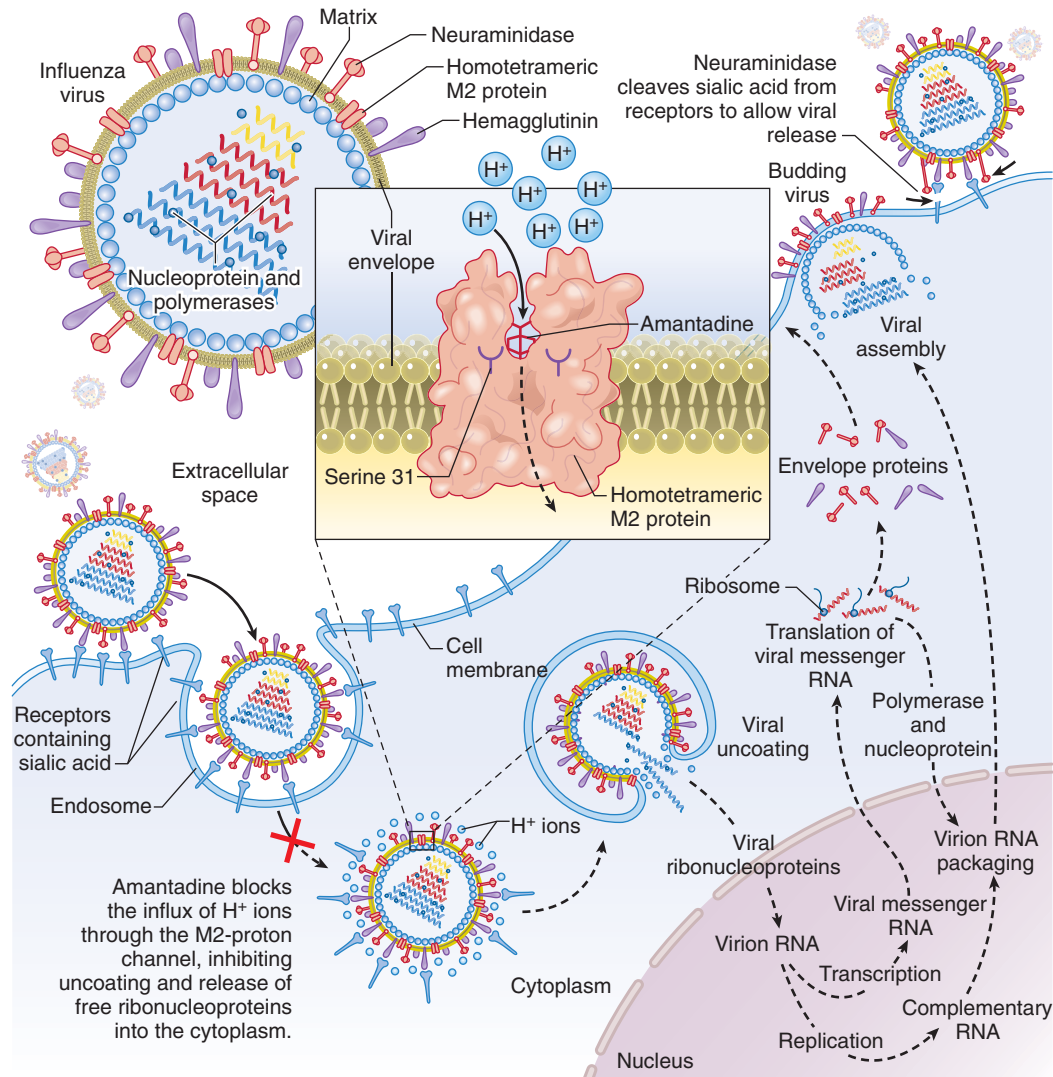
FIGURE 77-5 • Mechanism of action of and development of resistance to M2 inhibitors. In the absence of amantadine, the proton channel mediates an influx of H^+ ions into the infecting virion early in the viral replication cycle, which facilitates the dissociation of the ribonucleoproteins from the virion interior and allows them to be released into the cytoplasm and transported into the cell nucleus. In highly pathogenic avian viruses (H5 and H7), the matrix protein 2 (M2) proton channel protects the hemagglutinin from acid-induced inactivation in the trans-Golgi network during transport to the cell surface. In the presence of amantadine, the channel is blocked and replication is inhibited. The serine at position 31 lies partially in the protein-protein interface and partially in the channel (*inset*). Replacement of serine by a larger asparagine leads to the loss of amantadine binding and the restoration of channel function. Depending on the particular amino acid, other mutations at position 26, 27, 30, or 34 may inhibit amantadine binding or allow binding without the loss of ion channel function. (Adapted from Hayden FG. Antiviral resistance in influenza viruses—implications for management and pandemic response. N Engl J Med 2006;354:785-788.)

the drug is administered within 48 hours of onset of symptoms.[22,25] Importantly, resistance to adamantanes may emerge rapidly.[7,26,27] Resistance to adamantanes is due to single amino acid substitutions within the viral M2 protein[7] that confer cross-resistance to both agents.[22,26] Although resistance to adamantanes among *untreated* individuals has remained low (<1%) through the 1990s,[7] resistance rates to influenza A viruses (H3N2, H1N1, or H1N2) have skyrocketed within the past few years.[7,26] The increase in resistance was weighted heavily by isolates from Asia.[7,28] By 2004-2005, rates of adamantane resistance in selected Asian locales included 96% (China), 72% (Hong Kong), 42% (Singapore), and 36% (South Korea).[27]

Resistance to adamantanes has also escalated dramatically in North America.[7] By the 2005-2006 influenza season in the United States, greater than 90% of isolates of influenza A (H3N2) from the United States or Canada submitted to the Centers for Disease Control and Prevention (CDC) were resistant to adamantanes.[27] In view of these extraordinarily high rates of resistance, adamantanes should not be used for the treatment or prophylaxis of influenza A in the United

States.[29] Currently, adamantanes have little role to treat or prevent influenza**.**

Neuraminidase Inhibitors

NAIs are analogues of *N*-acetylneuraminic acid (the cell surface receptor for influenza viruses) and inhibit the enzyme neuraminidase, reducing viral replication[22,23] (Fig. 77-6). Inhibition of neuraminidase reduces viral replication.[22] NAIs are active against both influenza A and B, but activity against influenza B is less.[9,23] Currently available NAIs include oseltamivir and zanamivir.

Oseltamivir. Oral oseltamivir (Tamiflu) is approved to *treat* infections due to influenza A or B and for *prophylaxis* of influenza among persons greater than 1 year old. Oseltamivir is not approved for infants less than 1 year of age since studies are lacking in this age group.[23] For treating acute influenza, the dose in adults or children greater than 12 years old is 75 mg twice daily for 5 days; the dose is lower in children 1 to 12 years old (adjusted for weight).[22,30] For prophylaxis, the dose is 75 mg daily for 10 days.[22,30]

Mechanism of action of neuraminidase inhibitors
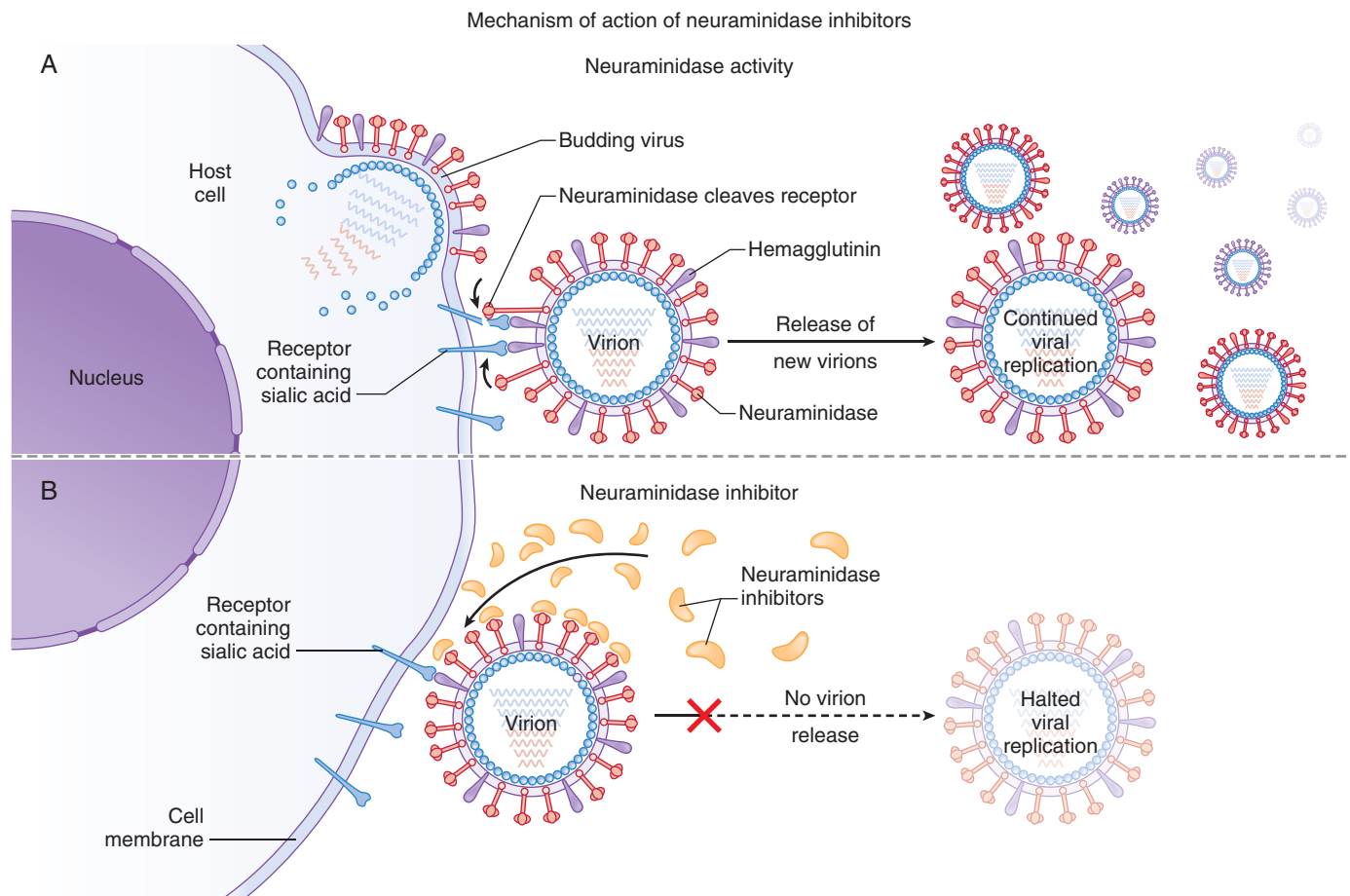
FIGURE 77-6 • Mechanism of action of neuroaminidase inhibitors. A, Action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors **(B),** which prevent virions from being released from the surface of infected cells. (From Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363-1373.)

Early treatment with oral oseltamivir in patients with acute influenza (A or B) shortens the course and reduces complications in previously healthy children or adults and high-risk patients.[9,25,31] NAIs are efficacious only if administered within 48 hours of onset of symptoms.[23,25] Duration of symptoms is shortened by 1 to 2 days in patients receiving NAIs (compared to placebo).[23] Large studies in North America found that patients with ILI treated with oseltamivir during the influenza seasons from 1999 to 2004 had lower rates of pneumonia, hospitalizations, or deaths (within 30 days) compared to untreated patients.[31,32]

In controlled, randomized trials, administration of oseltamivir as prophylaxis reduced the risk of influenza in unvaccinated healthy adults, household contacts, nursing home residents, and the elderly.[30,33] Oseltamivir prophylaxis was efficacious in a cohort of 45 hematopoietic stem cell transplant recipients at high risk.[24] The use of oseltamivir during influenza outbreaks in nursing homes was associated with reductions in hospitalizations, deaths, and antibiotic use compared to patients receiving either amantadine or no therapy.[34]

Zanamivir. Zanamivir (Relenza) is approved to *treat* infections due to influenza A or B and for *prophylaxis* of influenza in children greater than 5 years of age.[22,23] Zanamivir is administered by a dry powder inhaler (Diskhaler) delivered directly to the respiratory tract.[23] For treating acute influenza, the dose is 10 mg twice daily for 5 days (children or adults).[22] For prophylaxis (e.g., contacts of index cases), the dose is 10 mg once daily for 10 days.[22] Zanamivir achieves high concentrations in the respiratory tract (1000 times the 50% inhibitory concentration for neuraminidase).[23] The inhibitory effect starts within 10 seconds.[23] These properties reduce the chance for emergence of resistant viruses. The major drawback to zanamivir is the inability of

young children or adults with neurologic or muscular deficits to use the Diskhaler.

Zanamivir (10 mg twice daily for 5 days) is effective therapy for influenza A or B in adults and children (age >5 years) and has minimal toxicity.[22] The duration of symptoms was shorted by 1 to 2.5 days, and complications were reduced, provided zanamivir was initiated within 30 hours of the onset of symptoms.[22] Inhaled zanamivir (10 mg once daily for 10 days) was effective (55% to 80%) as chemoprophylaxis of influenza in healthy adults and healthy household contacts (children >5 years old or adults).[2,35]

Adverse Effects with NAIs. Adverse effects with NAIs are uncommon.[22,23,29] Resistance to NAIs is rare[36-38] but can arise by single amino acid substitutions at N or H residues.[39] Mutations at N residues are more clinically relevant.[39] Mutations in N that prevent oseltamivir from binding to the N active do *not* affect zanamivir.[37] Resistance to oseltamivir was noted in 4% to 8% of children and less than 1% of adults after treatment with oseltamivir.[2,40] Higher rates of oseltamivir-resistant mutants were detected in Japan (18%) in children treated with oseltamivir (possibly reflecting subtherapeutic doses).[41] The recent epidemic of avian influenza A (H5N1) infection in Asia[42] raises the possibility that NAI-resistant mutants could emerge as a result of increasing exposure to oseltamivir.[43] Importantly, most oseltamivir-resistant isolates remain susceptible to zanamivir.[37]

Prevention

Vaccines are the cornerstone for control of influenza.[22,44,45] Influenza vaccines are developed annually, with input from the World Health Organization (WHO) and national authorities.[46] Viruses must be
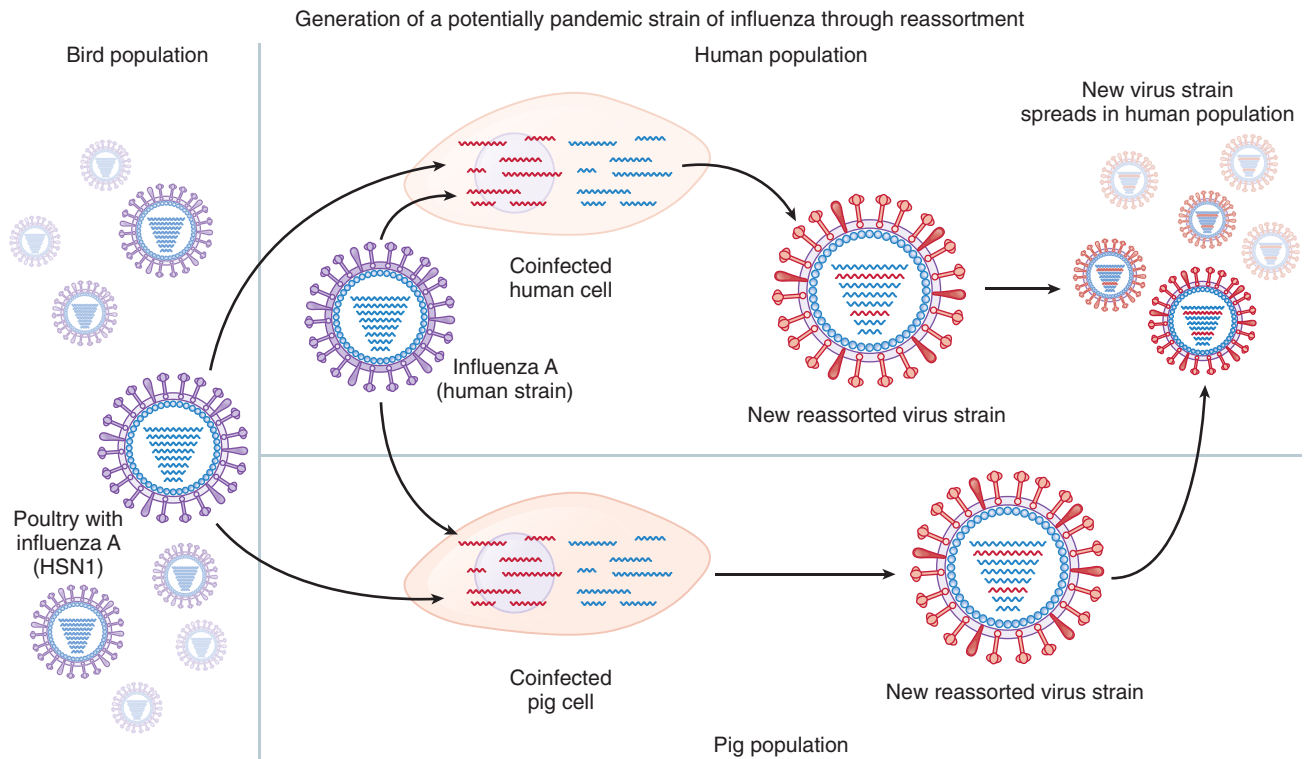
FIGURE 77-7 • Generation of a potentially pandemic strain of influenza through reassortment. (From Hien T, de Jong M, Farrar J. Avian influenza—a challenge to global health care structures. N Engl J Med 2004;351:2363-2365.)

reformulated annually, since genetic mutations arise continuously in influenza viruses in a process termed *antigenic drift.*[46] Given the potential for pandemic influenza (e.g., with the antigen shift or the avian H5N1 strain) (Fig. 77-7),[12] the WHO has developed an action plan to increase vaccine supply.[46] However, current technologies for developing vaccines (i.e., egg-based manufacturing process) are slow, and existing supplies of vaccines would be inadequate in the face of a global pandemic.[12]

Currently available influenza vaccines include the trivalent inactivated vaccines (TIVs) and live, attenuated influenza vaccine (LAIV).[47] Both vaccines contain the predicted antigenic variants of influenza A (H3N2, H1N1) and influenza B viruses.[3] The inactivated vaccine is administered intramuscularly; LAIV is given as an intranasal spray (FluMist; MedImmune).[3] TIV evokes a higher systemic response (i.e., serum immunoglobulin G antibody response) whereas LAIV elicits a better immunoglobulin A mucosal response at the site where viruses enter the body.[3] In the United States, TIV is approved for individuals greater than 6 months of age; LAIV is approved for healthy persons 5 to 49 years of age.[48] No vaccines are approved for infants under the age of 6 months.

Provided the strains encompassed by the vaccine match the circulating epidemic strain, inactivated vaccines provided 70% to 100% protection among healthy adults and 30% to 60% protection among the elderly or young children.[22,47] Serum antibody responses to influenza vaccination may be blunted in the elderly, immunocompromised individuals, and preschool children.[22] In adults, LAIV may be less effective than TIV, which may reflect reduced activity against influenza B viruses.[47]

Influenza vaccination is beneficial in adults greater than 65 years old living in the community[45,49] or nursing homes.[13] Benefits of vaccination include lower mortality (all causes), hospitalizations, and pneumonias.[2,45,49] Further, influenza vaccination reduced mortality, hospitalizations, and outpatient visits for patients less than 65 years of age with concurrent medical conditions.[50] Additionally, vaccination of health care workers is highly effective in protecting high-risk patients.[44,51,52]

Influenza vaccination (either TIV or LAIV) in healthy children reduces the incidence of laboratory-confirmed cases of influenza and acute otitis media (AOM).[53-55] Vaccination of children in day care centers or schools reduced the incidence of ILI among family contacts or in the community at large.[2,55] Indirect benefits of vaccinating children include fewer parental days lost from work and less impaired work productivity.[3]

Recommendations for annual influenza vaccination are published annually by the CDC. In 2007, the CDC recommended annual influenza vaccination for the following populations: children or adults at high risk for complications of influenza, close contacts of high-risk persons, all children ages 6 to 59 months, and all adults greater than 50 years old (regardless of health status)[29] (Box 77-1). Indications for vaccination continue to evolve. Many experts favor expanding influenza vaccination, potentially toward universal vaccination.[44]

Adverse effects from influenza vaccination are minimal.[22] With the inactivated vaccine, mild soreness of the arm at the site of vaccination may persist for 1 to 2 days.[22] Serious adverse effects are rare. The vaccine is contraindicated in patients who are allergic to eggs, but even in this context serious hypersensitivity reactions to the vaccine are rare. LAIV is well tolerated[3,47,56] but should *not* be administered to immunocompromised individuals.

AVIAN INFLUENZA

Avian influenza is a highly virulent H5N1 subtype of influenza.[4] The ongoing global epidemic of epizootic avian influenza infection has been responsible for the death or destruction of greater than 140 million birds.[4] Infections due to avian influenza viruses are rare in humans, but the antigenic novelty of H5N1 suggests the potential for pandemic spread.[4]

Virology

Infections in humans due to H7 and H9 avian influenza viruses are typically mild. By contrast, the H5N1 avian virus causes serious respi-

BOX 77-1 ANNUAL VACCINATION AGAINST INFLUENZA

Annual vaccination against influenza is recommended for
- All persons, including school-aged children, who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others;
- All children aged 6-59 months (i.e., 6 months-4 years);
- All persons aged 50 years and older;
- Children and adolescents (aged 6 months-18 years) receiving long-term aspirin therapy who therefore might be at risk for experiencing Reye's syndrome after influenza virus infection;
- Women who will be pregnant during the influenza season;
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
- Adults and children who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus);
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- Residents of nursing homes and other chronic-care facilities;
- Health-care personnel;
- Healthy household contacts (including children) and caregivers of children aged <5 years and adults aged 50 years and older, with particular emphasis on vaccinating contacts of children aged <6 months; and
- Healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

From Prevention and control of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56(RR06):1-54.

ratory infections, with case fatality rates of greater than 50%.[4] Sequence analysis suggests that the current H5N1 virus originated by reassortment between multiple co-circulating avian influenza strains prevalent in Hong Kong in 1997.[57] Certain unique structural features in the H5N1 virus are present among highly pathogenic viruses infecting chickens but are not common among the avian viruses circulating among wild birds.[4] This suggests that transmission to humans originated from poultry rather than wild birds. The avian viruses exhibit preferential binding to sialic acid α2-3 linkages, which are sparse in the human upper respiratory tract.[58] This may explain the absence of human-to-human transmission.

Epidemiology

Outbreaks of severe influenza in humans with highly virulent H5N1 strains derived from infected poultry were reported in China and Southeast Asia in 2003.[59] The first known transmission of H5N1 viruses from birds to humans took place in 1997, shortly following an outbreak of sick geese on a farm in Guangdong Province of China.[60] A fatal infection in May 1997 in Hong Kong was followed by 17 cases (5 died) in November-December 1997.[4] The outbreak ceased after Hong Kong culled 1.5 million poultry in 3 days and banned the import of poultry from mainland China.[57] No further human cases were recognized until February 2003, when at least two confirmed cases were identified in Hong Kong.[61] Subsequent cases in China, Vietnam, Thailand, Cambodia, and other Southeast Asian countries were followed by human cases in Europe, Russia, the Middle East, and Africa[4,59] (Fig. 77-8). The virus has spread along the flyways of migratory birds to more than 30 countries worldwide.[4] By August 2006, 238 cases had

been cited in humans, with 139 deaths (58%).[4,59] Large-scale culling operations and intensified surveillance led to eradication of H5N1 infection in poultry in some countries. However, in many countries, H5N1 infection is endemic in wild birds and poultry.[4] In countries where human contact with poultry is common, the likelihood of further adaptation of the virus to humans and transmission between humans is high.

Clinical Features

H7 and H9 avian influenza viruses are highly lethal in poultry, but typically cause mild symptoms in humans (e.g., conjunctivitis with subtype H7[62,63] or mild ILI with H9N2).[59,64] In sharp contrast, human cases of H5N1 have been characterized by severe pneumonia with high fatality rates (58%).[59] Ninety percent of cases occurred in individuals less than 40 years old.[59] Most cases had close contact with poultry in the week preceding the illness.[42] Human-to-human transmission has been rare.[65]

The most common symptoms among documented cases of H5N1 include fever (98%), cough (88%), dyspnea (62%), rhinorrhea (55%), sore throat (52%), diarrhea (39%), myalgias (29%), headache (28%), and abdominal pain (23%).[42] Diarrhea may precede the onset of respiratory symptoms. Pulmonary infiltrates on chest radiographs were noted in 88% of cases[42]; this likely overestimates the true incidence since asymptomatic or mild cases may have been missed. Elevated liver enzymes, lymphopenia, and thrombocytopenia were noted in 50% to 67% of cases.[4,42] Pathology revealed diffuse alveolar damage, reactive hemophagocytosis in the bone marrow, and lymphoid depletion in the spleen and lymph nodes.[4]

Diagnosis

Cultures of pharyngeal or nasal swabs or respiratory secretions may confirm the diagnosis,[42] but should be performed only in laboratories meeting biosafety level III or higher requirements.[4] Rapid antigen tests are insensitive.[4] RT-PCR methods are more sensitive and specific, and do not require handling of live virus.[4]

Treatment

Because of the high risk of nosocomial spread, patients with suspected H5N1 should be isolated and placed in negative pressure rooms (if available).[4] Strict infection control measures among health care workers and all contacts are mandatory. Antiviral treatment should be initiated as early as possible, and should be continued if active viral replication continues.[42] Controlled trials evaluating adamantanes to treat H5N1 infections in humans are lacking. However, resistance to adamantanes is considerable in some regions. Point mutations in the M2 region (conferring resistant to adamantanes) were detected in greater than 95% of H5N1 isolates from Vietnam and Thailand but fewer than 10% of isolates from Indonesia and China.[66] Because of the potential for rapid emergence of resistance, adamantanes should not be used irrespective of in vitro susceptibility.[4]

NAIs display in vitro activity against H5N1, but controlled trials assessing these agents in humans are lacking. Currently, the WHO recommends oseltamivir as the first-line drug to treat suspected H5N1 infections.[4] Because humans lack immunity against H5N1, a higher dose (150 mg twice daily) and longer duration (7 to 10 days) should be considered.[4] Resistance to oseltamivir has been detected in some treated patients.[4] Some oseltamivir-resistant isolates displaying the H274Y mutation remain susceptible to zanamivir.[37]

Prevention

Chemoprophylaxis with oseltamivir or zanamivir should be considered for patients at high risk for transmission (e.g., household or close contact, exposure to infected poultry or environmental source, health care workers or laboratory personnel without appropriate protec-
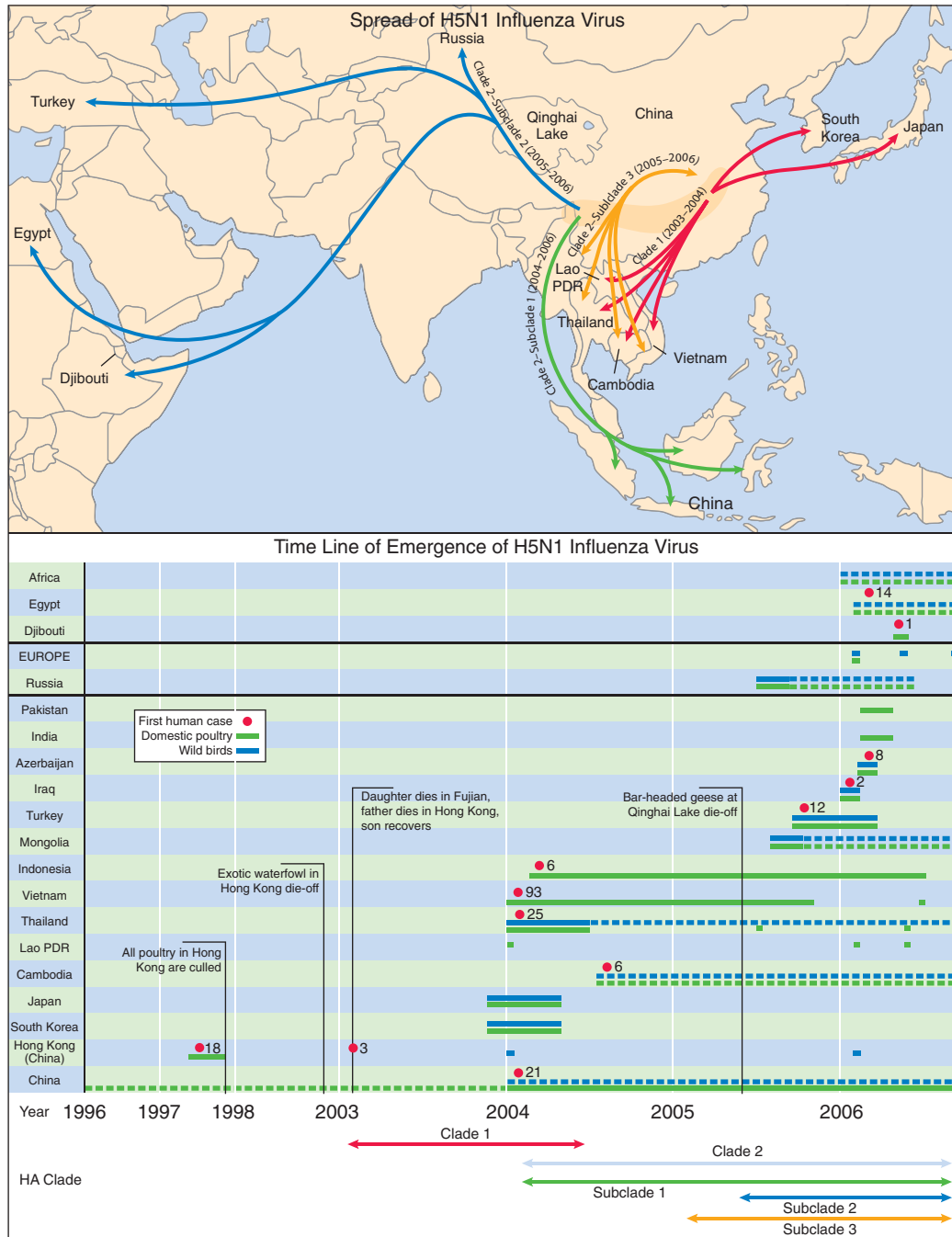
FIGURE 77-8 • **The spread of H5N1 influenza virus and time line showing its emergence.** The *shaded area* across southern China is the hypothetical epicenter for the emergence of H5N1 clades and subclades. The H5N1 viruses are being perpetuated in the domestic birds of the region, despite the use of universal vaccination of all domestic poultry. The *red dot* in the time line denotes the occurrence of the first human case, followed by the number of confirmed human cases in that country. The *green and blue solid bars* represent documented H5N1 infection in domestic poultry and wild birds, and *dashed bars* indicate that H5N1 in the avian population is suspected. These limited surveillance data are adapted from the World Health Organization and the U.N. Food and Agriculture Organization (*http://www.fao.org*). HA, hemagglutinin. (Adapted from Webster RG, Govorkova EA. H5N1 influenza—continuing evolution and spread. N Engl J Med 2006;355:2174-2177.)

tion).[4] Vaccines against H5N1 are not currently available, but research and development in this area are ongoing.[67]

important pathogen in adults,[70] particularly in the elderly[71] or patients with comorbidities.[68,70,72]

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is a common respiratory virus affecting persons of all ages.[68,69] The spectrum of RSV disease ranges from a mild "cold" to severe respiratory failure.[68,69] RSV is the leading cause of lower respiratory tract infection in young children but is also an

Virology

RSV is an enveloped RNA virus within the family Paramyxoviridae and the genus *Pneumovirus*.[68] Human RSV isolates are classified into two major groups (A and B) based primarily upon antigenic differences in the G protein.[68] Both A and B strains circulate concurrently, with A

Hemagglutin neuraminidase (PIV only) or attachment protein (RSV only)

Fusion protein

Lipid bilayer

Small hydrophobic protein (RSV only)

Matrix proteins

Large polymerase complex

Nucleus protein

Phosphoprotein
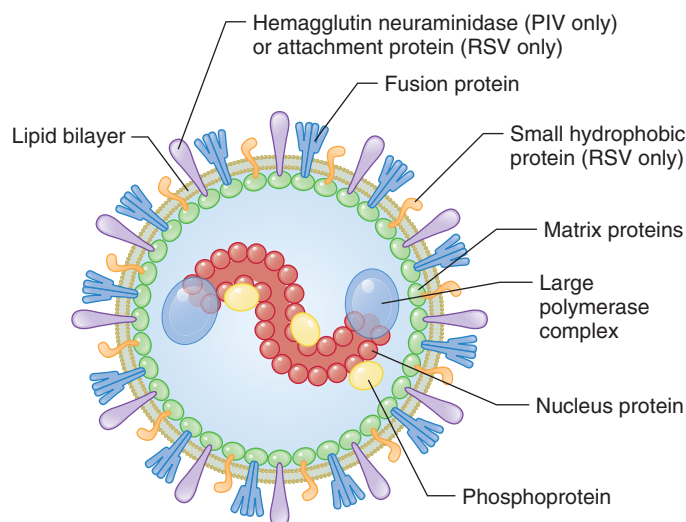
FIGURE 77-9 • Structure of respiratory syncytial virus (RSV) and parainfluenza virus (PIV).

strains usually predominating.[69] Several distinct genotypes exist; annual changes in the dominant strains may evade immune defenses, leading to frequent reinfections[69] (Fig. 77-9).

Epidemiology

RSV is the chief cause of hospitalization for respiratory tract infections (RTIs) in children,[69] and is second to influenza as a cause of serious viral RTIs in adults.[68,71,73,74] Primary RSV infection is nearly universal by age 2; due to incomplete immunity, reinfections are common throughout life.[68,69] In adults, RSV infections are more common in those with comorbidities (e.g., pulmonary or cardiac disorders), impaired immunity, or advanced age.[68,71] However, RSV may infect previously healthy adults.[75] Epidemiologic studies implicated RSV in 3% to 5% of cases of community-acquired pneumonia in adults and in 6% to 22% of acute exacerbations of chronic obstructive pulmonary disease (COPD).[68,73] Outbreaks of RSV infections have been described in closed populations (e.g., nursing homes, senior day care centers, health care workers,[68] and military recruits in training[75]).

Clinical Features

The spectrum of RSV (in both children and adults) ranges from a trivial cold to severe (sometimes fatal) respiratory failure.[68] In infants, RSV typically presents as bronchiolitis, with low-grade fever, rhinorrhea, cough, wheezing, and poor feeding.[68,69] Physical examination reveals crackles and expiratory wheezing. In severe cases, intercostal retraction, hypoxemia, and respiratory failure may ensue. The disease usually resolves spontaneously, but cough or bronchial hyperreactivity may persist for days or even weeks. In young adults, RSV typically gives rise to mild upper respiratory tract (URT) symptoms (e.g., nasal congestion, rhinorrhea, sore throat) that resolve over 4 to 10 days.[68] However, cough, wheezing, dyspnea, and a protracted course may occur.[68,69] Symptoms of RSV and influenza overlap, but nasal symptoms, cough, wheezing, and sputum are more common with RSV, whereas myalgias are more common with influenza.[76] Even in previously healthy adults, RSV may cause missed work days and incurs economic costs.[68,69] Severe RSV pneumonia is uncommon, but can occur in elderly patients or those with comorbidities[71,76] or (rarely) in previously normal adults.[68,70]

Chest radiographs in RSV pneumonia are variable, and range from faint interstitial opacities (mimicking heart failure) to lobar consolidation.[68,76] Concomitant infection with bacterial pathogens has been noted in 15% to 30% of patients with RSV pneumonia.[68,76] RSV may be a cause of exacerbations of asthma[68,71] or COPD[77,78] in adults (par-

ticularly during the winter months) and was linked to a more rapid decline in lung function in a cohort of COPD patients.[79]

Diagnosis

Laboratory diagnosis of RSV can be established via four methods: viral culture, antigen detection by immunofluorescence assay (IFA) or enzyme immune assay (EIA), RNA detection by RT-PCR, and serologies.[68] Sensitivity of cultures or antigen detection ranges from 9% to 45%; sensitivity of RT-PCR is higher (60% to 90%).[68] RT-PCR is sensitive (>70%) and specific (99%),[68] and is the preferred method to detect RSV. RT-PCR may be obtained from nasal swabs, nasal washes, sputum, or bronchoalveolar lavage fluid (BALF).[68] In adults, sputum or BALF are more sensitive than nasal specimens.[68] Unfortunately, RT-PCR is complex, expensive, and not available in many hospitals. Serologies are useful in epidemiologic surveys, but are of limited practical value in individual patients.[68] Given the limitations of diagnostic methods, and limited therapeutic options (discussed later), an aggressive diagnostic evaluation for RSV is rarely performed in clinical practice. However, nasal or BALF cultures and antigen detection assays should be considered for patients with severe disease or immunocompromised status.[68] RT-PCR is reserved for research or commercial laboratories in selected high-risk patients.

Treatment

Treatment is supportive. Bronchodilators may be useful in patients with wheezing or a history of asthma or COPD.[71] Aerosolized ribavirin is approved for RSV infections in infants, but not all studies cited benefit.[68] Ribavirin is difficult to administer, requiring continuous inhalation by face mask or tent for 18 hr/day.[68] Alternatively, high-dose ribavirin (i.e., 2 g aerosolized for 2 hr three times daily) may be considered.[80] One multicenter trial randomized 14 hematopoietic stem cell transplant (HSCT) recipients with RSV URT infections to aerosolized ribavirin (2 gm t.i.d.) or standard care.[80] Progression to pneumonia was noted in one of nine patients receiving ribavirin compared to two of five patients receiving supportive care ($P = 0.51$). At 10 days, viral loads were lower in ribavirin recipients ($P = 0.07$). These data are insufficient to judge efficacy. Currently the role of ribavirin (either aerosolized or intravenous) in adults remains controversial. In a nonrandomized trial, RSV-IVIG (a human polyclonal immunoglobulin with high neutralizing antibody titers), combined with inhaled ribavirin, decreased viral shedding and was associated with lower mortality in HSCT recipients with RSV pneumonia.[81]

Palivizumab (Synagis) (a humanized monoclonal antibody directed against the fusion protein of RSV) is approved for prophylaxis against RSV (once monthly for 5 months during winter season) in high-risk infants.[68] However, in a randomized trial of 43 immunocompetent children with RSV infection, palivizumab ($n = 22$) was no better than placebo ($n = 21$).[82] Further, a retrospective study of 40 allogeneic HSCT recipients (mostly adolescents) with symptomatic RSV infection found that palivizumab (administered to 19 patients) had no effect on survival or clinical end points.[83]

Prevention

No RSV vaccine is currently available, but several candidate vaccines are under development.[67,68] Data regarding passive immunization with intravenous immune globulin (IVIG) or palivizumab in adults are lacking. Since RSV is transmitted by fomites and large droplets, infection control (particularly handwashing) is important to limit the spread of nosocomial RSV.[68] Masks are not required because RSV is not transmitted via aerosol.[68]

PARAINFLUENZA VIRUS

Parainfluenza viruses (PIVs) cause a spectrum of respiratory illnesses similar to those caused by RSV, but are usually milder.[69] Infection is limited to the URT in 40% to 60% of cases, and croup (laryngotra-

cheobronchitis) is a cardinal symptom, noted in 10% to 44%; lower respiratory tract infections (LRTI) are infrequent (<10%) in immunocompetent patients.[69,84] PIV typically infects children less than 3 years of age, but reinfections may occur in adults, particularly the elderly or those with pulmonary disease[77,78] or immunosuppression.[16,69]

Virology

PIV types 1, 2, 3, and 4 are enveloped RNA virus within the family Paramyxoviridae[69] (see Fig. 77-9).

Epidemiology

Most children are infected with PIV within the first 2 years of life. While URT symptoms predominate, parainfluenza is second only to RSV (and possibly human metapneumovirus [hMPV]) as a cause of viral bronchiolitis and pneumonia in children.[67,69] Most children are infected with PIV type 3 by age 2 years and by types 1 and 2 by age 5 years.[69] PIV type 4 is rare.[16,69] Pneumonia or bronchitis from type 3 PIV occurs primarily in infants less than 6 months old.[69]

PIV infections exhibit distinct seasonal patterns.[69] Type 1 PIV causes the largest outbreaks, with sharp rises in autumn of odd-numbered years.[69] PIV type 2 infections are less predictable but usually follow type 1 outbreaks. Type 3 PIV infections occur annually, usually in the spring and summer. A seasonal pattern has not been noted for PIV type 4.

PIV replicates in the nasopharyngeal epithelium and spreads to the lower respiratory tract 1 to 3 days later.[69] Transmission occurs by close or direct contact with large droplets or fomites.[69] The duration of viral shedding in healthy people is approximately 1 week, but PIV shedding for greater than 4 weeks has been noted in immunocompromised patients.[16,85]

Infections with PIV are less common than RSV in children and adults, and are typically milder. PIV can infect COPD patients during peak seasons[77,78] and can infect the elderly or healthy adults. In a cohort of senior day care attendees, PIV was implicated in 2.7% of acute respiratory infections; RSV accounted for 21%.[86] In a study of respiratory infections in 256 military recruits, PIV was isolated by culture in 3%; adenovirus (AdV) was detected in 48% and influenza in 11%.[75] PIV infections were cited in 2% to 7% of adult and pediatric HSCT recipients.[16,85,87,88] Data on solid organ transplant (SOT) recipients are limited.

Clinical Features

PIVs cause a spectrum of respiratory illnesses similar to those caused by RSV, but are milder.[69] Most are upper respiratory tract infections (URTIs); 30% to 50% are complicated by AOM.[69] Croup is the cardinal symptom of PIV infections (noted in 10% to 44%), and is the main cause of hospitalization from PIV infections in children 2 to 6 years of age.[69] The lower respiratory tract is involved in only 15% of cases; 2.8 of 1000 children with such infections require hospitalization.[69] Similar to RSV, PIV may precipitate exacerbations of asthma in children and adults.[69] Reinfections may occur in adults, particularly the elderly.[69] PIV may cause bronchitis or pneumonia in organ transplant recipients[87] and human immunodeficiency virus–infected or immunocompromised[16] patients. However, even among HSCT recipients, PIV infections are often confined to the URT. In a series of 198 HSCT patients with PIV-3 infection, 87% presented with URTI symptoms only; 6% had simultaneous URTI and LRTI symptoms.[88] The disease progressed from URTI to LRTI in 25 patients (13%). Progression was more likely among patients receiving corticosteroids.[88] PIV is a risk factor for airflow decline in HSCT recipients and a cause of long-term pulmonary complications.[89]

Diagnosis

As with other viruses, laboratory diagnosis of PIV can be established by viral culture, antigen detection (by IFA or EIA), RT-PCR, or serologies.[69] Given the low prevalence of PIV in adults, and the lack of effective therapy, diagnostic assays are rarely performed in clinical practice.

Treatment

No licensed or proven therapy for PIV is available. Ribavirin has in vitro activity against PIV, and aerosolized or intravenous ribavirin has been used to treat or prevent PIV infections in immunocompromised hosts,[87,88,90] but efficacy remains uncertain.[16,69]

Prevention

Currently there is no vaccine for PIV,[16] but several vaccines are being developed.[67]

HUMAN METAPNEUMOVIRUS

hMPV, a paramyxovirus discovered in 2001 in the Netherlands,[91] causes upper and lower RTIs in all age groups, but predominantly affects young children[92,93] and immunocompromised or frail, elderly patients.[94] The spectrum of hMPV is similar to RSV, ranging from mild URTIs to severe bronchiolitis and pneumonia.[91,92,95,96]

Virology

hMPV is a member of the Paramyxoviridae family, Pneumovirinae subfamily, and *Metapneumovirus* genus[94] (Fig. 77-10). Two major genotypes (A and B) and four subgroups (A1, A2, B1, and B2) are recognized.[93,97] One research group suggested that genotype A may be more virulent than genotype B,[97] but others found no difference between genotypes.[93] The predominant genotype (A or B) may vary between seasons.[93,94]

Epidemiology

hMPV has a global distribution.[93,94,98] It was first identified in 2001,[91] but has been circulating (based on serologic studies) for 50 years in the Netherlands[98] and at least 15 to 20 years in North America.[99] hMPV accounts for 5% to 12% of acute RTIs in children (next to RSV and influenza).[93,97,98,100] Serologic studies suggest that virtually all children are infected by the age of 5 to 10 years.[91,94] More than three quarters of hMPV infections are in children less than 2 years old,[101] but all ages may be affected.[95,98] Infections due to hMPV (both children and adults) are more common in immunosuppressed individuals.[102-104] In adults, hMPV accounts for 2% to 7% of acute RTIs[101,105] or ILIs and may be implicated in 5% to 10% of acute exacerbations of asthma,[92] COPD,[106] or congestive heart failure.[106]
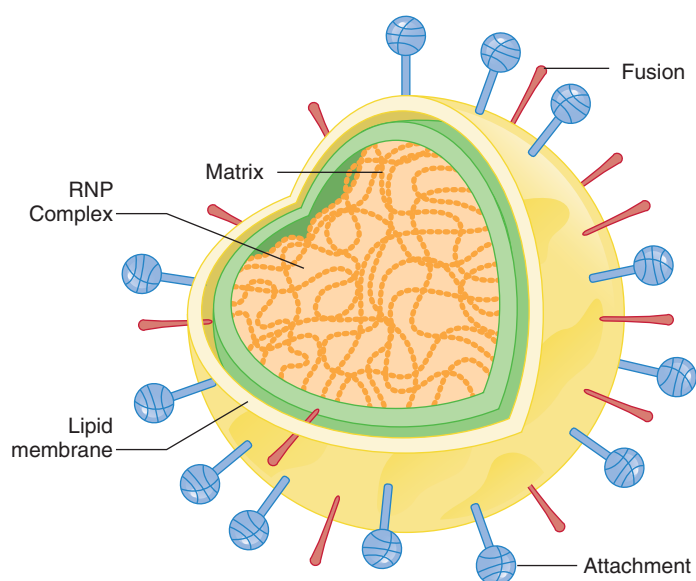

FIGURE 77-10 • Human metapneumovirus.

Transmission of hMPV is similar to RSV (i.e., via respiratory droplets and hand-to-mouth or hand-to-eye contact with contaminated surfaces).[94] Outbreaks of hMPV respiratory infections have been described in long-term care facilities[95,107] and health care workers (i.e., case contacts).[107] Like other respiratory viruses, hMPV predominates in winter and spring in temperate climates.[97,98,101] However, outbreaks may occur in the late spring[93] or summer.[107]

Clinical Features

Clinical symptoms of hMPV infections in infants and young children are indistinguishable from RSV.[92,97,98,100,101,108] In previously healthy children, the most common features of hMPV were bronchiolitis (59%), croup (18%), exacerbation of asthma (14%), and pneumonia (8%).[101] Vomiting was less common in hMPV infections (10%) compared to RSV (31%) or influenza (28%).[101] Hospitalization is rarely required in previously healthy children,[101] but severe pneumonia can occur in children with comorbidities or immunosuppression.[97,98] Co-infection with RSV and hMPV occurs in 4% to 6% of cases.[101,109] Like other respiratory viruses, hMPV may evoke exacerbations of asthma in children.[94] In young children, AOM occurs in one third to one half of cases.[92,94,101] Conjunctivitis was noted in 4% of children with hMPV versus 22% of children with influenza infections.[101] In adults, hMPV may cause exacerbations of asthma[92] or COPD.[110]

Infections due to hMPV are usually self-limited (in children and adults),[94,101] but fatal pneumonia may occur.[94,95] Among fatal cases, diffuse alveolar hyaline membrane damage and peribronchiolitis have been observed.[94,95] Because of the presence of multiple viral genotypes and waning immunity,[95] reinfections may occur throughout life.[94] Reinfections are typically milder than primary infections.[94]

Diagnosis

hMPV exhibits fastidious growth requirements in culture and may require 14 to 21 days to grow.[93,94] A rapid antigen test is not available. RT-PCR is the preferred means to diagnose hMPV.[93,95,98] No sensitive anti-hMPV antibody tests are currently available.[93]

Treatment

No antiviral or antibody preparation is approved for the treatment of hMPV. Intravenous ribavirin has shown promise in vitro and in animal models.[111,112] Inhaled ribavirin was ineffective in one HSCT recipient[104]; however, in a lung transplant recipient, intravenous ribavirin was associated with a favorable response.[103] Intravenous polyclonal antibodies inhibit hMPV, and have a plausible (albeit untested) role in treating serious cases.[112]

Prevention

Live, attenuated vaccines have shown efficacy in animals, but vaccines are not yet available in humans.[67]

RHINOVIRUS AND CORONAVIRUS INFECTIONS

Rhinovirus and coronavirus infections account for more than 50% of common colds.[113,114] Symptoms include rhinitis, pharyngitis, sneezing, hoarseness, sinusitis, and cough; bronchopneumonia is rare.[113,115] These viral infections usually are self-limited,[113] but complications may arise in immunosuppressed individuals[16,116] or patients with cardiac or pulmonary disease.[113,117]

Virology

Both are single-stranded RNA viruses (Fig. 77-11). Rhinoviruses are members of the Picornaviridae family; more than 100 serotypes exist.[113] Variations in surface proteins account for antigenic diversity.[113] Coro-
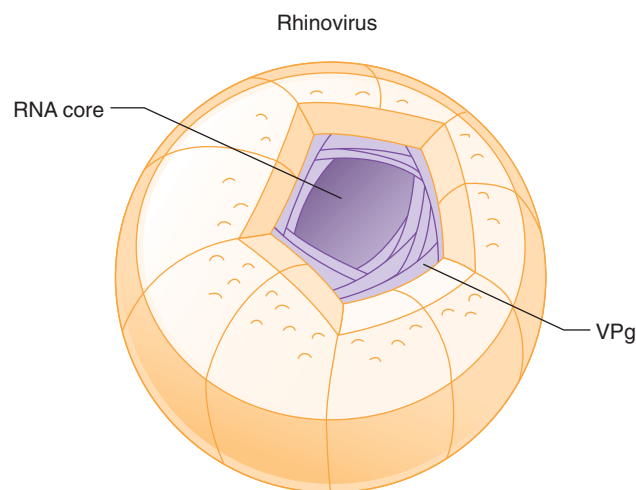

Rhinovirus

RNA core

VPg

FIGURE 77-11 • **Rhinovirus and coronavirus.**

naviruses are divided into three genera and can infect humans, animals, and birds.[113]

Epidemiology

Both rhinoviruses and coronaviruses cause respiratory infections (predominantly URTIs) in all age groups.[113,115] In temperate climates, rhinoviral illnesses peak in the early fall and spring[115]; coronaviruses peak in the late fall, winter, and early spring.[113] Schools, day care centers, family members, and businesses are sources of transmission.[113]

Clinical Features

Rhinoviruses account for approximately 50% of common colds; coronaviruses, 15%.[113,114] Rhinoviruses or coronaviruses may also cause exacerbations of asthma[115] or COPD.[117] In children, these viruses may serve as cofactors for AOM.[118,119] These viral infections usually are self-limited,[113,115] but complications (including fatal pneumonias) may arise in immunosuppressed individuals.[16,116]

Diagnosis

Conventional virus culture methods are sensitive for rhinoviruses, but insensitive for coronaviruses.[113,120] RT-PCR is more sensitive than cultures for rhinovirus and coronavirus.[120] Serologies are not helpful in clinical practice and are not available in most centers.[113] Given the mild and self-limited course observed with these viruses, cultures or RT-PCT are rarely performed, except in epidemiologic or research studies.

Treatment and Prevention

No proven therapy for rhinoviruses or coronaviruses is available. Vaccines are not available.[113]

SEVERE ACUTE RESPIRATORY SYNDROME–RELATED CORONAVIRUS

Severe acute respiratory syndrome (SARS) emerged in the Guangdong Province of southern China in 2002[121] and was followed by a pandemic. In less than one year, more than 8000 cases were identified in 26 countries, with a case fatality rate of 9.6%.[122] The epidemic was over by July 2003, and human-to-human transmission of the SARS virus globally has not been reported since.[122]

Virology

The etiologic agent of SARS is a novel human coronavirus (SARS-CoV) that is *not* closely related to other human or animal coronavi-
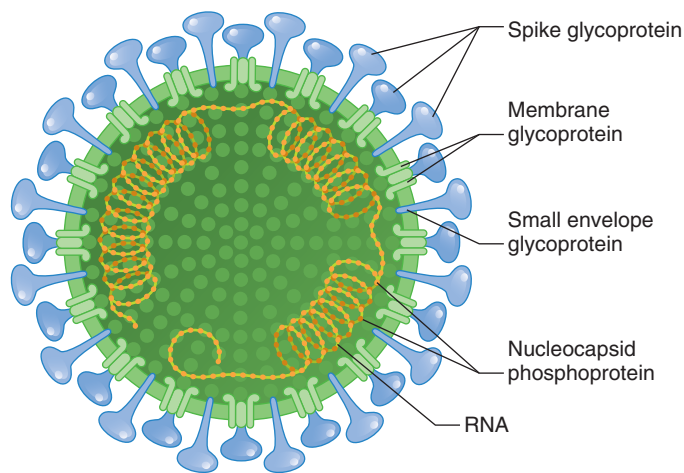
FIGURE 77-12 • **SARS-related coronavirus.** (Adapted from Drazen JM. SARS—looking back over the first 100 days. N Engl J Med 2003;349:319-320.)

ruses[122] (Fig. 77-12). SARS-CoV exhibits 99.8% homology between SARS-like coronaviruses found in animal markets.[122,123]

Epidemiology

SARS is a zoonotic disease that can be transmitted by droplet or contact routes.[122,124,125] The virus was transmitted from exotic animals to food handlers or workers in the food markets in Guangdong Province and other Asian countries.[122]

The incubation period of SARS ranges from 2 to 14 days (mean 5 days).[122,126] Maximal infectivity occurs in the second week of illness, at the time of rapid clinical deterioration, which correlates with the peak viral load.[126] It is important to emphasize that a single case of SARS could trigger a global pandemic. Vigilant surveillance and *strict* infection control measures among suspected cases and contacts are critical to minimize spread.[122]

Clinical Features

Presenting symptoms include chills, myalgias, malaise, and headache.[127,128] Fever is present in greater than 95% of cases.[122,127,128] Rhinorrhea and sore throat are uncommon in SARS.[128] Diarrhea occurs in up to 70% of patients.[126,127] Lymphopenia, thrombocytopenia, and elevations in creatine kinase (CK) and lactate dehydrogenase (LDH) are early findings.[127,128] During the first few days of the illness, respiratory symptoms are absent and chest radiographs may be normal. By 7 to 10 days, respiratory symptoms develop or worsen.[126] Pulmonary infiltrates, ground-glass opacities, and multifocal consolidation are usually evident on chest computed tomography scans.[126] Most patients recover spontaneously by the second or third week of illness.[122] However, 20% to 30% develop progressive respiratory failure requiring mechanical ventilation (similar to acute respiratory distress syndrome [ARDS]).[122,129] The median time from disease onset to mechanical ventilation among patients who developed respiratory failure was 9 days (range 7 to 13 days).[122] Mortality in this subset is approximately 50%.[122] SARS is uncommon in children, and has a milder course.[122] Atypical presentations of SARS (e.g., fever and diarrhea without respiratory manifestations[130,131] or lack of symptoms) may result in delayed diagnosis.

Diagnosis

Given the potential for pandemic spread of SARS, rapid diagnostic confirmation is essential for suspected cases. SARS should be considered in patients with pneumonia and ARDS of unknown etiology and one of the following risk factors: travel to mainland China or Asia (within 10 days) or employment in occupations at high risk (e.g., exposure to wildlife or other animals that may be reservoirs; health care workers or laboratory workers with close contact to SARS-CoV).[122] Even a single case mandates immediate efforts to identify the source and potential contacts.[122] When a case of SARS is suspected, public health authorities should be contacted *immediately* and can guide appropriate diagnostic workup and infection control measures.

Samples of nasopharyngeal aspirates, respiratory secretions, and stool should be sent for cultures and RT-PCR.[122] However, virus isolation using cell culture is relatively insensitive, requires several days, and must be performed in a laboratory with biosafety level III capability.[132] Detection of viral RNA by RT-PCR provides rapid results, with sensitivity rates greater than 80% at days 9 to 12 of the illness, but less than 50% at earlier or later time points.[122] Serologic detection of an antibody response to SARS-CoV is the gold standard.[122] Acute and convalescent (3 to 4 weeks) sera should be obtained.[122] Seroconversion occurs in 50% of patients by day 10 and greater than 90% by day 28.[122] Serologies are useful for epidemiologic investigations, but are less valuable in individual patients because of the time lag between infection and seroconversion. Personal protective equipment, handwashing, and infection control measures are essential when collecting, transporting, and handling specimens.[122]

Treatment

Because of the potential for rapid epidemic spread, patients with SARS should be admitted to the hospital, and rigorous infection control measures are essential.[122] Droplet and Contact Precautions are mandatory.[122] Hypoxemic patients require careful monitoring, and in severe cases, mechanical ventilation.[122] Procedures that involve airway manipulation (e.g., intubation, bronchoscopy, suctioning, nebulized therapy) should be performed only when essential, and under tightly controlled conditions.[122]

No treatment has been shown to influence mortality or clinical outcomes in SARS.[122] Intravenous ribavirin was ineffective and had significant toxicity.[133] Corticosteroids were used in uncontrolled studies, but were of unproven benefit.[122] Other strategies employed include interferon alfa, lopinavir/ritonavir, and Chinese herbal medications[122]; none is of proven efficacy.

Prevention

Vaccines are not yet available in humans.[67]

HANTAVIRUS

Hantavirus is an RNA virus that causes the hantavirus pulmonary syndrome (HPS) or hantavirus cardiopulmonary syndrome (HCPS) in the Americas[134-136] and hemorrhagic fever renal syndrome (HFRS) in Asia and Europe.[136]

Virology

Hantavirus is a genus of RNA viruses in the Bunyaviridae family and is the only group in this family that is not a naturally arthropod-borne virus[136] (Fig. 77-13). More than 25 viruses have been identified within the genus *Hantavirus*.[36] Hantaviruses are hosted in nature by rodents (the source of transmission to humans).[135,136]

Epidemiology

Three distinct groups of hantaviruses have been recognized, and result in distinct clinical presentations. The Hantaan virus (HTN), first isolated in Korea in 1978, is a cause of HFRS in Asia and Europe.[136] The second group of viruses, primarily found in the Americas, is associated with a severe pulmonary capillary leak syndrome and high mortality.[137] The first cases of HPS, due to the Sin Nombre (SN) virus, were described in the Four Corners region of New Mexico in 1993.[137] In North America, the SN virus is by far the most common, but other types have been described (e.g., Bayou virus, Black Creek Canal virus, New York virus, Monongahela virus).[135,136] The first cases of HPS in
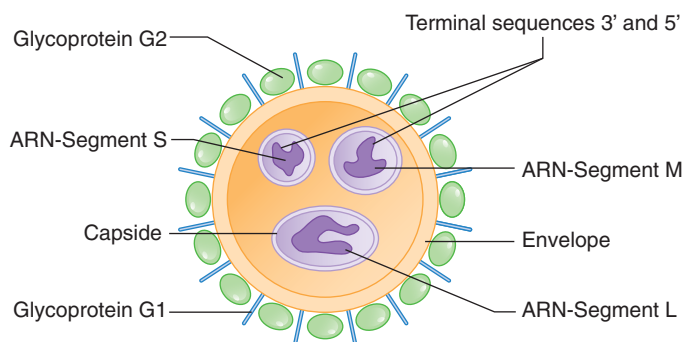
Glycoprotein G2 — Terminal sequences 3' and 5'

ARN-Segment S — ARN-Segment M

Capside — Envelope

Glycoprotein G1 — ARN-Segment L

FIGURE 77-13 • Hantavirus.

South America were described in 1997.[138] By 2002, HPS had been confirmed in at least six countries in South America (Argentina, Bolivia, Brazil, Chile, Uruguay, and Paraguay).[135] The first case of human hantavirus infection in Central America was described in Panama in February 2000.[135] Several types of hantavirus were described in those outbreaks. The Andes virus was the predominant species in Chile and Argentina, whereas other subtypes were identified in other countries (e.g., Laguna Negra virus in Paraguay; Choclo virus in Panama; Juquitiba virus in Brazil).[135,136] A third group of hantaviruses, associated with the subfamily Arvicolinae, has been detected in North America and Europe, and may result in less severe forms of HFRS.[139]

In this chapter, we restrict our discussion to respiratory infections due to hantaviruses in North America (principally the SN virus). Hantaviral infections in North America remain exceedingly rare, with a seroprevalence of less than 0.1%.[136] Since the initial report of HCPS in New Mexico in 1993, fewer than 500 cases have been reported in North America.[136] Inhalation of aerosolized virus particles present in urine, feces, or saliva of rodents is the most important route of human infection.[136] Following excretion by rodents, hantaviruses may remain infectious for several days.[136] Outbreaks of hantavirus infections in humans are related to variations in rodent density (e.g., due to climate and food supply) and rodents invading peridomestic environments.[135,136,139] Person-to-person transmission has not been described in North America, Europe, or Asia,[136] but was described in several cases in Argentina and Chile.[138,140] Incubation period ranges from 7 to 39 days.[136,141]

Clinical Features

In the most severe cases, hantavirus elicits a pulmonary capillary leak syndrome, producing ARDS and cardiogenic shock.[136] Typically, HCPS is characterized by three phases: prodromal, cardiopulmonary, and recovery.[136] In the prodromal phase (1 to 5 days), nonspecific symptoms of fever, headache, malaise, and myalgia are present.[136] Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain) may be present.[136] Importantly, rhinorrhea or nasal congestion (often the presenting features of other respiratory viral syndromes) are absent in this early phase.[136] During the next (cardiopulmonary) phase, dyspnea, cough, and pulmonary infiltrates develop.[136] Thrombocytopenia occurs in 80% to 95% of patients with HCPS, and is usually present even in the early (prodromal phase).[136] Other laboratory aberrations may include hypoalbuminemia and elevations in transaminases, creatinine, CK, and LDH.[136] With the onset of the cardiopulmonary phase, dyspnea, hypoxemia, hypotension, or cardiovascular collapse may develop.[136] During this phase, hematocrit and leukocyte counts rise.[136] Rapid progression to fulminant pulmonary and/or cardiac failure may occur over the next 8 to 24 hours, with mortality rates exceeding 30% to 50%.[136] Pulmonary hemorrhage is rare with SN virus, but may complicate severe HCPS due to Andes virus.[136] Pulmonary edema may reflect capillary leak as well as severe myocardial depression.[136] As myocardial function worsens, pulmonary capillary wedge pressure rises and cardiac index is low and resistant to

fluid resuscitation.[136] In addition, arrhythmias and cardiogenic shock may develop. Interestingly, at least one third of patients with SN infection do well, with modest or no pulmonary edema.[136]

No clinical or laboratory features during the prodromal or early cardiopulmonary phases predict the ultimate severity of the disease.[136] Further, serologic epidemiologic studies cited serum antibodies to hantavirus in up to 13% of local community residents with no clinical evidence for illness,[135] suggesting that mild or asymptomatic hantavirus infections occur in humans.

Diagnosis

A careful history is critical. Hantavirus exposure should be considered in individuals who reside in or visit rural locations, even if an overt history of rodent exposure is lacking. Laboratory criteria suggestive of HCPS include thrombocytopenia ($<150 \times 10^3/\mu L$), hemoconcentration (hematocrit >50% in men or >48% in women), lack of toxic granulations in neutrophils, left shift of myeloid series, and greater than 10% immunoblasts.[136] A definitive diagnosis is made by serologies; serum antibodies are usually present on the first day of symptoms.[136] Viral antigen detection in fixed tissue by immunohistochemistry is sensitive and specific.[136] Viral RNA can be detected from serum or tissues by RT-PCR.[136]

Treatment

No specific antiviral therapy for HCPS exists.[136] Treatment is supportive and directed toward treating shock and acute respiratory, cardiac, or renal failure.[136] Because HCPS is associated with severe myocardial depression, aggressive fluid resuscitation is *discouraged*.[136] Early use of vasopressors should be initiated. Extracorporeal membrane oxygenation may be efficacious in extreme, fulminant cases of HPS.[136] Hyperimmune serum from convalescent patients is promising.[136] High levels of neutralizing antibodies correlated with improved survival and persist for years in survivors.[136]

ADENOVIRUS

Adenoviruses typically cause mild, self-limited infections involving the URT, gastrointestinal tract, or conjunctivae.[142] Adenovirus infections are more common in children, owing to lack of humoral immunity.[16,142] The disease is more severe and dissemination is more likely in immunocompromised hosts.[16,142-144] Pneumonia develops in fewer than 1% of immunocompetent patients with AdV infections,[145,146] but in up to 10% of immunocompromised patients.[16,142] Fatality rates for severe AdV pneumonia range from 10% to 70%.[16,142]

Virology

Human AdV is a family of double-stranded nonenveloped DNA viruses[147] (Fig. 77-14). Fifty-one serotypes and six species (A through F) are recognized; one third of serotypes are associated with human disease.[147] Manifestations of AdV are related to specific species and strains.[142,144] In immunocompetent children, species B and C predominate (>95%), typically AdV strains 1 to 7.[144,148] Most infections among military recruits are due to AdV strains 4 and 7.[145,146] Gastroenteritis is associated with enteric AdV strains 40 and 41, and hemorrhagic gastritis with AdV 11, 33, 34, and 35.[16] Among HSCT recipients, most infections are due to AdV species B and C,[142,149] but significant diversity[144] and even multiple serotypes in individual patients[144,150] have been noted.

Epidemiology

Adenovirus is a common pathogen among children and adults, and accounts for at least 5% to 10% of pediatric and 1% to 7% of adults RTIs.[142] Infections occur throughout the year, with no seasonal variation.[142] Transmission of AdV can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, fecal-oral spread, or exposure
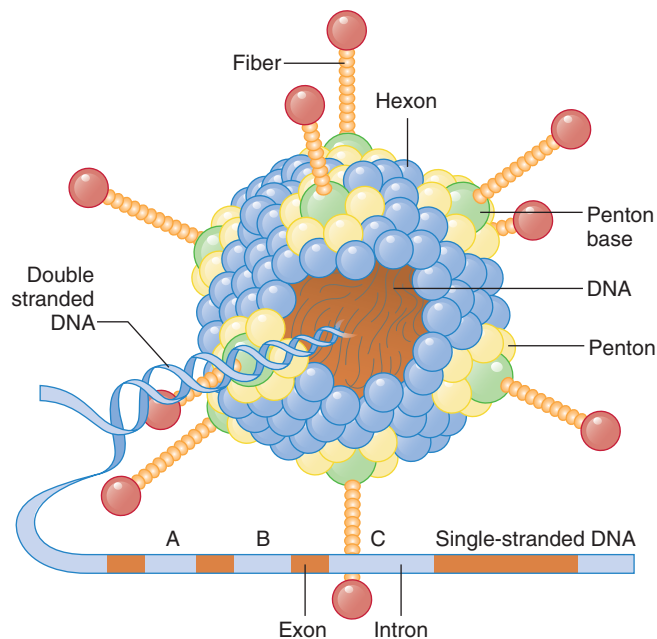
FIGURE 77-14 • **Adenovirus.**

to infected tissue or blood.[142] The incubation period ranges from 2 to 14 days, and depends upon viral serotype and mechanism of transmission.[142] Infection can be by reactivation or new acquisition from exogenous sources.[142,144] Rates of AdV infection are higher among children (due to lack of immunity) and immunosuppressed patients.[16,142,151] The incidence of AdV infections is 5% to 22% among SOT recipients[142,152,153] and 3% to 47% among HSCT recipients.[16,142-144,148,150,153-155] Risk factors for AdV infections among HSCT recipients include pediatric age group, allogeneic HSCT, severe T-cell depletion, and graft-versus-host disease.[142,143,153-155] Severe lymphopenia is associated with disseminated and often fatal disease.[142] Among SOT recipients, risk factors include pediatric age group, receipt of antilymphocyte antibodies, and donor-positive/recipient-negative AdV status.[142]

Epidemic AdV infections may spread rapidly in closed environments such as military recruit barracks,[145,156] civilian job training facilities,[151] long-term care facilities,[151] and psychiatric care facilities,[157] as well as among hospitalized or institutionalized civilians.[158] Adenovirus accounts for greater than 50% of febrile respiratory illnesses among healthy military recruits.[145,146,156] Surveillance of U.S. recruits in training from 1999 to 2004 cited greater than 73,000 AdV infections, with peak illness rates in weeks 3 to 5 of training.[156] Serotype 4 accounted for greater than 95% of infections.[156] Importantly, the annual rate of AdV infections rose more than threefold after vaccine usage ceased.[156] High baseline immunity against AdV (titer of >1:32) confers substantial protection.[146]

Clinical Features

Adenoviral infections typically cause self-limited respiratory, gastrointestinal, or conjunctival disease.[142] Less common manifestations of AdV infections include hepatitis, hemorrhagic cystitis, nephritis, encephalitis, pancreatitis, and disseminated disease.[159,160] Respiratory symptoms range from mild coldlike symptoms to severe (sometimes lethal) pneumonia and ARDS.[142,157] Pneumonia due to AdV is rare in immunocompetent adults, but life-threatening cases have been described.[146] Gastrointestinal symptoms range from mild diarrhea to hemorrhagic colitis.[142] Hepatitis is often associated with subgroup C viruses (types 1, 2, and 5), and hemorrhagic cystitis with AdV types 11, 34, and 35.[142] The presence of AdV in urine is usually associated with hemorrhagic cystitis.[142] Severe AdV infections are rare among

immunocompetent hosts, but dissemination occurs in 10% to 30% of HSCT recipients.[16,142-144,150,154,155] Adenovirus infections in SOT recipients may lead to graft loss or death.[161] Among HSCT recipients with *symptomatic* AdV disease, fatality rates range from 19% to 65%.[16,142,143,153,154] Case fatality rates for untreated AdV pneumonia may exceed 50%.[16,142]

Diagnosis

Viral cultures are difficult and may take up to 21 days to isolate AdV.[16,142] The commercially available AdV EIA test for stool specimens detects only serotypes 40 and 41.[16] Adenovirus nuclear inclusions may be observed in tissue.[142] RT-PCT of AdV DNA in plasma or infected sites is the preferred technique[142] and is highly sensitive for disseminated disease.[160,162] Persistently high titers correlate with clinical disease.[160] Serial RT-PCR assays of blood and stool weekly may detect AdV disease prior to the onset of symptoms, and facilitate early "preemptive" therapy.[144,152,154,163] However, the role of routine surveillance is controversial.[142]

Treatment

No antiviral drug has been approved to treat adenovirus. Prospective randomized controlled trials are lacking. Cidofovir, a cytosine nucleotide analogue that inhibits DNA polymerase, has the greatest in vitro activity; most, but not all, species are resistant to ribavirin.[164,165] Ganciclovir displays in vitro activity against AdV, but has no role to treat AdV infections.[142] While not all AdV infections require treatment, cidofovir (available only intravenously) is the preferred therapeutic agent.[142] Numerous studies of HSCT and SOT recipients have documented favorable responses to cidofovir.[143,144,154,163,166,167] Major dosing regimens include intravenous cidofovir 5 mg/kg once weekly or 1 mg/kg thrice weekly for 4 to 6 weeks.[163] Cidofovir is generally well tolerated,[154,163] but may cause nephrotoxicity.[142] Hydration and probenacid may minimize nephrotoxicity.[142,154,167,168] Newer lipid formulations of cidofovir exhibit increased activity against AdV and are less toxic, but not yet available.[169]

Reduction of immunosuppression[154] or immune reconstitution of HSCT recipients[143] may have adjunctive roles. IVIG has been used (together with cidofovir), but data are insufficient to assess efficacy.[143] Not all patients with AdV infections require treatment.[142] Interestingly, in a cohort of SOT recipients, all 19 with AdV infection recovered spontaneously.[152] Similarly, in one study of pediatric HSCT recipients, AdV viremia was detected in 42% and cleared without therapy in 64%.[170]

Prevention

Oral vaccines against AdV types 4 and 7 were developed for the U.S. military, and routine vaccination began at U.S. recruit training camps in 1971.[156] These vaccines were safe and highly efficacious,[145] but production ceased in 1996, and available stores were depleted by 1999.[156] Restoration of an effective AdV vaccine is anticipated in 2008.[156]

REFERENCES

1. Hall CB. The spread of influenza and other respiratory viruses: complexities and conjectures. Clin Infect Dis 2007;45:353-359.
2. Lynch JP 3rd, Walsh EE. Influenza: evolving strategies in treatment and prevention. Semin Respir Crit Care Med 2007;28:144-158.
3. Nichol KL, Treanor JJ. Vaccines for seasonal and pandemic influenza. J Infect Dis 2006;194(Suppl 2):S111-S118.
4. Rajagopal S, Treanor J. Pandemic (avian) influenza. Semin Respir Crit Care Med 2007;28:159-170.
5. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis 2006;194(Suppl 2):S82-S91.
6. Petric M, Comanor L, Petti CA. Role of the laboratory in diagnosis of influenza during seasonal epidemics and potential pandemics. J Infect Dis 2006;194(Suppl 2): S98-S110.
7. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175-1181.

8. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179-186.

9. Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. Clin Infect Dis 2007;44:197-202.

10. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006;355:31-40.

11. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39:1300-1306.

12. Osterholm MT. Preparing for the next pandemic. N Engl J Med 2005;352:1839-1842.

13. Whitley RJ, Monto AS. Prevention and treatment of influenza in high-risk groups: children, pregnant women, immunocompromised hosts, and nursing home residents. J Infect Dis 2006;194(Suppl 2):S133-S138.

14. Grijalva CG, Craig AS, Dupont WD, et al. Estimating influenza hospitalizations among children. Emerg Infect Dis 2006;12:103-109.

15. O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. Pediatrics 2004;113(3 Pt 1):585-593.

16. Kim Y-J, Boeckh M, Englund J. Community respiratory virus infections in immunocompromised patients: hematopoietic stem cell and solid organ transplant recipients, and individuals with human immunodeficiency virus infection. Semin Respir Crit Care Med 2007;28:222-242.

17. Ison MG, Gubareva LV, Atmar RL, et al. Recovery of drug-resistant influenza virus from immunocompromised patients: a case series. J Infect Dis 2006;193:760-764.

18. Kobasa D, Takada A, Shinya K, et al. Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus. Nature 2004;431:703-707.

19. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. Clin Infect Dis 2003;36:299-305.

20. Starko KM, Ray CG, Dominguez LB, et al. Reye's syndrome and salicylate use. Pediatrics 1980;66:859-864.

21. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. J Am Geriatr Soc 2002;50:1498-1503.

22. Couch RB. Prevention and treatment of influenza. N Engl J Med 2000;343:1778-1787.

23. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363-1373.

24. Vu D, Peck AJ, Nichols WG, et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 2007;45:187-193.

25. Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. Clin Infect Dis 2005;40:1309-1316.

26. Weinstock DM, Zuccotti G. Adamantane resistance in influenza A. JAMA 2006;295:934-936.

27. Bright RA, Shay DK, Shu B, et al. Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States. JAMA 2006;295:891-894.

28. Ilyushina NA, Govorkova EA, Webster RG. Detection of amantadine-resistant variants among avian influenza viruses isolated in North America and Asia. Virology 2005;341:102-106.

29. Smith NM, Bresee JS, Shay DK, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55(RR-10):1-42.

30. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004;189:440-449.

31. Hayden FG, Pavia AT. Antiviral management of seasonal and pandemic influenza. J Infect Dis 2006;194(Suppl 2):S119-S126.

32. Nordstrom BL, Sung I, Suter P, Szneke P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. Curr Med Res Opin 2005;21:761-768.

33. Monto AS, Rotthoff J, Teich E, et al. Detection and control of influenza outbreaks in well-vaccinated nursing home populations. Clin Infect Dis 2004;39:459-464.

34. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. J Am Geriatr Soc 2002;50:608-616.

35. Cooper NJ, Sutton AJ, Abrams KR, et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ 2003;326:1235.

36. Moscona A. Oseltamivir-resistant influenza? Lancet 2004;364:733-734.

37. Moscona A. Oseltamivir resistance—disabling our influenza defenses. N Engl J Med 2005;353:2633-2636.

38. Brett AS, Zuger A. The run on Tamiflu—should physicians prescribe on demand? N Engl J Med 2005;353:2636-2637.

39. Yen HL, Herlocher LM, Hoffmann E, et al. Neuraminidase inhibitor-resistant influenza viruses may differ substantially in fitness and transmissibility. Antimicrob Agents Chemother 2005;49:4075-4084.

40. McKimm-Breschkin J, Trivedi T, Hampson A, et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. Antimicrob Agents Chemother 2003;47:2264-2272.

41. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004;364:759-765.

42. Beigel JH, Farrar J, Han AM, et al. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005;353:1374-1385.

43. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353:2667-2672.

44. Schwartz B, Hinman A, Abramson J, et al. Universal influenza vaccination in the United States: are we ready? Report of a meeting. J Infect Dis 2006;194(Suppl 2):S147-S154.

45. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med 2007;357:1373-1381.

46. Fukuda K, Kieny MP. Different approaches to influenza vaccination. N Engl J Med 2006;355:2586-2587.

47. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med 2006;355:2513-2522.

48. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2005;54(RR-8):1-40.

49. Jefferson T, Rivetti D, Rivetti A, et al. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005;366:1165-1174.

50. Hak E, Buskens E, van Essen GA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. Arch Intern Med 2005;165:274-280.

51. Pearson ML, Bridges CB, Harper SA. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55(RR-2):1-16.

52. Burls A, Jordan R, Barton P, et al. Vaccinating healthcare workers against influenza to protect the vulnerable—is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation. Vaccine 2006;24:4212-4221.

53. Jefferson T, Smith S, Demicheli V, et al. Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. Lancet 2005;365:773-780.

54. Negri E, Colombo C, Giordano L, et al. Influenza vaccine in healthy children: a meta-analysis. Vaccine 2005;23:2851-2861.

55. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. Vaccine 2005;23:1540-1548.

56. King JC Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. N Engl J Med 2006;355:2523-2532.

57. Chan PK. Outbreak of avian influenza A (H5N1) virus infection in Hong Kong in 1997. Clin Infect Dis 2002;34(Suppl 2):S58-S64.

58. Matrosovich MN, Matrosovich TY, Gray T, et al. Human and avian influenza viruses target different cell types in cultures of human airway epithelium. Proc Natl Acad Sci U S A 2004;101:4620-4624.

59. Epidemiology of WHO-confirmed human cases of avian influenza A (H5N1) infection. Wkly Epidemiol Rec 2006;81:249-257.

60. Shortridge KF, Zhou NN, Guan Y, et al. Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. Virology 1998;252:331-342.

61. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004;363:617-619.

62. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet 2004;363:587-593.

63. Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis 2004;10:2196-2199.

64. Butt KM, Smith GJ, Chen H, et al. Human infection with an avian H9N2 influenza A virus in Hong Kong in 2003. J Clin Microbiol 2005;43:5760-5767.

65. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005;352:333-340.

66. Cheung CL, Rayner JM, Smith GJ, et al. Distribution of amantadine-resistant H5N1 avian influenza variants in Asia. J Infect Dis 2006;193:1626-1629.

67. Schmidt A. Progress in respiratory virus vaccine development. Semin Respir Crit Care Med 2007;28:243-252.

68. Falsey AR. Respiratory syncytial virus infection in adults. Semin Respir Crit Care Med 2007;28:171-181.

69. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001;344:1917-1928.

70. Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. Clin Infect Dis 2001;33:792-796.

71. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749-1759.

72. Beckham JD, Cadena A, Lin J, et al. Respiratory viral infections in patients with chronic, obstructive pulmonary disease. J Infect 2005;50:322-330.

73. Falsey AR, Formica MA, Hennessey PA, et al. Detection of respiratory syncytial virus in adults with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;173:639-643.

74. Mullooly JP, Bridges CB, Thompson WW, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine 2007;25:846-855.

75. O'Shea MK, Ryan MA, Hawksworth AW, et al. Symptomatic respiratory syncytial virus infection in previously healthy young adults living in a crowded military environment. Clin Infect Dis 2005;41:311-317.

76. Walsh EE, Peterson DR, Falsey AR. Is clinical recognition of respiratory syncytial virus infection in hospitalized elderly and high-risk adults possible? J Infect Dis 2007;195:1046-1051.

77. Johnston NW. The similarities and differences of epidemic cycles of chronic obstructive pulmonary disease and asthma exacerbations. Proc Am Thorac Soc 2007;4:591-596.

78. Martinez FJ. Pathogen-directed therapy in acute exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2007;4:647-658.

79. Wilkinson TM, Donaldson GC, Johnston SL, et al. Respiratory syncytial virus, airway inflammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;173:871-876.

80. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. Clin Infect Dis 2007;44:245-249.

81. DeVincenzo JP, Hirsch RL, Fuentes RJ, Top FH Jr. Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation—a compassionate use experience. Bone Marrow Transplant 2000;25:161-165.

82. Saez-Llorens X, Moreno MT, Ramilo O, et al. Safety and pharmacokinetics of palivizumab therapy in children hospitalized with respiratory syncytial virus infection. Pediatr Infect Dis J 2004;23:707-712.

83. de Fontbrune FS, Robin M, Porcher R, et al. Palivizumab treatment of respiratory syncytial virus infection after allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2007;45:1019-1024.

84. Reed G, Jewett PH, Thompson J, et al. Epidemiology and clinical impact of parainfluenza virus infections in otherwise healthy infants and young children <5 years old. J Infect Dis 1997;175:807-813.

85. Nichols WG, Erdman DD, Han A, et al. Prolonged outbreak of human parainfluenza virus 3 infection in a stem cell transplant outpatient department: insights from molecular epidemiologic analysis. Biol Blood Marrow Transplant 2004;10:58-64.

86. Falsey AR, McCann RM, Hall WJ, et al. Acute respiratory tract infection in daycare centers for older persons. J Am Geriatr Soc 1995;43:30-36.

87. Dignan F, Alvares C, Riley U, et al. Parainfluenza type 3 infection post stem cell transplant: high prevalence but low mortality. J Hosp Infect 2006;63:452-458.

88. Nichols WG, Corey L, Gooley T, et al. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. Blood 2001;98:573-578.

89. Erard V, Chien JW, Kim HW, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the role of community respiratory viruses. J Infect Dis 2006;193:1619-1625.

90. Wright JJ, O'Driscoll G. Treatment of parainfluenza virus 3 pneumonia in a cardiac transplant recipient with intravenous ribavirin and methylprednisolone. J Heart Lung Transplant 2005;24:343-346.

91. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719-724.

92. Williams JV, Crowe JE Jr, Enriquez R, et al. Human metapneumovirus infection plays an etiologic role in acute asthma exacerbations requiring hospitalization in adults. J Infect Dis 2005;192:1149-1153.

93. Agapov E, Sumino KC, Gaudreault-Keener M, et al. Genetic variability of human metapneumovirus infection: evidence of a shift in viral genotype without a change in illness. J Infect Dis 2006;193:396-403.

94. Deffrasnes C, Hamelin ME, Boivin G. Human metapneumovirus. Semin Respir Crit Care Med 2007;28:213-221.

95. Boivin G, De Serres G, Hamelin ME, et al. An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. Clin Infect Dis 2007;44:1152-1158.

96. Sumino KC, Agapov E, Pierce RA, et al. Detection of severe human metapneumovirus infection by real-time polymerase chain reaction and histopathological assessment. J Infect Dis 2005;192:1052-1060.

97. Vicente D, Montes M, Cilla G, et al. Differences in clinical severity between genotype A and genotype B human metapneumovirus infection in children. Clin Infect Dis 2006;42:e111-e113.

98. van den Hoogen BG, van Doornum GJ, Fockens JC, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 2003;188:1571-1577.

99. Boivin G, Abed Y, Pelletier G, et al. Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. J Infect Dis 2002;186:1330-1334.

100. Williams JV, Wang CK, Yang CF, et al. The role of human metapneumovirus in upper respiratory tract infections in children: a 20-year experience. J Infect Dis 2006;193:387-395.

101. Williams JV, Harris PA, Tollefson SJ, et al. Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 2004;350:443-450.

102. Larcher C, Geltner C, Fischer H, et al. Human metapneumovirus infection in lung transplant recipients: clinical presentation and epidemiology. J Heart Lung Transplant 2005;24:1891-1901.

103. Raza K, Ismailjee SB, Crespo M, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. J Heart Lung Transplant 2007;26:862-864.

104. Englund JA, Boeckh M, Kuypers J, et al. Brief communication: fatal human metapneumovirus infection in stem-cell transplant recipients. Ann Intern Med 2006;144:344-349.

105. Falsey AR, Erdman D, Anderson LJ, Walsh EE. Human metapneumovirus infections in young and elderly adults. J Infect Dis 2003;187:785-790.

106. Hamelin ME, Cote S, Laforge J, et al. Human metapneumovirus infection in adults with community-acquired pneumonia and exacerbation of chronic obstructive pulmonary disease. Clin Infect Dis 2005;41:498-502.

107. Louie JK, Schnurr DP, Pan CY, et al. A summer outbreak of human metapneumovirus infection in a long-term-care facility. J Infect Dis 2007;196:705-708.

108. Boivin G, De Serres G, Cote S, et al. Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 2003;9:634-640.

109. Semple MG, Cowell A, Dove W, et al. Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. J Infect Dis 2005;191:382-386.

110. Martinello RA, Esper F, Weibel C, et al. Human metapneumovirus and exacerbations of chronic obstructive pulmonary disease. J Infect 2006;53:248-254.

111. Hamelin ME, Prince GA, Boivin G. Effect of ribavirin and glucocorticoid treatment in a mouse model of human metapneumovirus infection. Antimicrob Agents Chemother 2006;50:774-777.

112. Wyde PR, Chetty SN, Jewell AM, et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 2003;60:51-59.

113. Greenberg SB. Rhinovirus and coronavirus infections. Semin Respir Crit Care Med 2007;28:182-192.

114. Wat D. The common cold: a review of the literature. Eur J Intern Med 2004;15:79-88.

115. Hayden FG. Rhinovirus and the lower respiratory tract. Rev Med Virol 2004;14:17-31.

116. Ison MG, Hayden FG, Kaiser L, et al. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis 2003;36:1139-1143.

117. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2004;1:115-120.

118. Bulut Y, Guven M, Otlu B, et al. Acute otitis media and respiratory viruses. Eur J Pediatr 2007;166:223-228.

119. Chantzi FM, Papadopoulos NG, Bairamis T, et al. Human rhinoviruses in otitis media with effusion. Pediatr Allergy Immunol 2006;17:514-518.

120. Loens K, Goossens H, de Laat C, et al. Detection of rhinoviruses by tissue culture and two independent amplification techniques, nucleic acid sequence-based amplification and reverse transcription-PCR, in children with acute respiratory infections during a winter season. J Clin Microbiol 2006;44:166-171.

121. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003;362:1353-1358.

122. Muller MP, McGeer A. Severe acute respiratory syndrome (SARS) coronavirus. Semin Respir Crit Care Med 2007;28:201-212.

123. Song HD, Tu CC, Zhang GW, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proc Natl Acad Sci U S A 2005; 102:2430-2435.

124. Kan B, Wang M, Jing H, et al. Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in palm civets at an animal market and on farms. J Virol 2005;79:11892-11900.

125. Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310:676-679.

126. Peiris JS, Yuen KY, Osterhaus AD, Stohr K. The severe acute respiratory syndrome. N Engl J Med 2003;349:2431-2441.

127. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767-1772.

128. Muller MP, Richardson SE, McGeer A, et al. Early diagnosis of SARS: lessons from the Toronto SARS outbreak. Eur J Clin Microbiol Infect Dis 2006;25:230-237.

129. Yu IT, Wong TW, Chiu YL, et al. Temporal-spatial analysis of severe acute respiratory syndrome among hospital inpatients. Clin Infect Dis 2005;40:1237-1243.

130. Ho KY, Singh KS, Habib AG, et al. Mild illness associated with severe acute respiratory syndrome coronavirus infection: lessons from a prospective seroepidemiologic study of health-care workers in a teaching hospital in Singapore. J Infect Dis 2004;189:642-647.

131. Christian MD, Poutanen SM, Loutfy MR, et al. Severe acute respiratory syndrome. Clin Infect Dis 2004;38:1420-1427.

132. Chan KH, Poon LL, Cheng VC, et al. Detection of SARS coronavirus in patients with suspected SARS. Emerg Infect Dis 2004;10:294-299.

133. Chiou HE, Liu CL, Buttrey MJ, et al. Adverse effects of ribavirin and outcome in severe acute respiratory syndrome: experience in two medical centers. Chest 2005;128:263-272.

134. Mertz GJ, Hjelle B, Crowley M, et al. Diagnosis and treatment of New World hantavirus infections. Curr Opin Infect Dis 2006;19:437-442.

135. Bayard V, Kitsutani PT, Barria EO, et al. Outbreak of hantavirus pulmonary syndrome, Los Santos, Panama, 1999-2000. Emerg Infect Dis 2004;10:1635-1642.

136. Chang B, Crowley M, Campen M, Koster F. Hantavirus cardiopulmonary syndrome. Semin Respir Crit Care Med 2007;28:193-200.

137. Nichol ST, Spiropoulou CF, Morzunov S, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:914-917.

138. Toro J, Vega JD, Khan AS, et al. An outbreak of hantavirus pulmonary syndrome, Chile, 1997. Emerg Infect Dis 1998;4:687-694.

139. Rosa ES, Mills JN, Padula PJ, et al. Newly recognized hantaviruses associated with hantavirus pulmonary syndrome in northern Brazil: partial genetic characterization of viruses and serologic implication of likely reservoirs. Vector Borne Zoonotic Dis 2005;5:11-19.

140. Martinez VP, Bellomo C, San Juan J, et al. Person-to-person transmission of Andes virus. Emerg Infect Dis 2005;11:1848-1853.

141. Vial PA, Valdivieso F, Mertz G, et al. Incubation period of hantavirus cardiopulmonary syndrome. Emerg Infect Dis 2006;12:1271-1273.

142. Ison MG. Adenovirus infections in transplant recipients. Clin Infect Dis 2006;43:331-339.

143. Neofytos D, Ojha A, Mookerjee B, et al. Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. Biol Blood Marrow Transplant 2007;13:74-81.

144. Zheng X, Lu X, Erdman DD, et al. Identification of adenoviruses from high risk pediatric stem cell transplant recipients and controls. J Clin Microbiol 2008;46:317-320.

145. Sanchez JL, Binn LN, Innis BL, et al. Epidemic of adenovirus-induced respiratory illness among US military recruits: epidemiologic and immunologic risk factors in healthy, young adults. J Med Virol 2001;65:710-718.

146. Kolavic-Gray SA, Binn LN, Sanchez JL, et al. Large epidemic of adenovirus type 4 infection among military trainees: epidemiological, clinical, and laboratory studies. Clin Infect Dis 2002;35:808-818.

147. Lu X, Erdman DD. Molecular typing of human adenoviruses by PCR and sequencing of a partial region of the hexon gene. Arch Virol 2006;151:1587-1602.

148. Ebner K, Rauch M, Preuner S, Lion T. Typing of human adenoviruses in specimens from immunosuppressed patients by PCR-fragment length analysis and real-time quantitative PCR. J Clin Microbiol 2006;44:2808-2815.

149. Suparno C, Milligan DW, Moss PA, Mautner V. Adenovirus infections in stem cell transplant recipients: recent developments in understanding of pathogenesis, diagnosis and management. Leuk Lymphoma 2004;45:873-885.

150. Kroes AC, de Klerk EP, Lankester AC, et al. Sequential emergence of multiple adenovirus serotypes after pediatric stem cell transplantation. J Clin Virol 2007;38:341-347.

151. James L, Vernon MO, Jones RC, et al. Outbreak of human adenovirus type 3 infection in a pediatric long-term care facility—Illinois, 2005. Clin Infect Dis 2007;45:416-420.

152. Humar A, Kumar D, Mazzulli T, et al. A surveillance study of adenovirus infection in adult solid organ transplant recipients. Am J Transplant 2005;5:2555-2559.

153. de Mezerville MH, Tellier R, Richardson S, et al. Adenoviral infections in pediatric transplant recipients: a hospital-based study. Pediatr Infect Dis J 2006;25:815-818.

154. Sivaprakasam P, Carr TF, Coussons M, et al. Improved outcome from invasive adenovirus infection in pediatric patients after hemopoietic stem cell transplantation using intensive clinical surveillance and early intervention. J Pediatr Hematol Oncol 2007;29:81-85.

155. Robin M, Marque-Juillet S, Scieux C, et al. Disseminated adenovirus infections after allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcome. Haematologica 2007;92:1254-1257.

156. Russell KL, Hawksworth AW, Ryan MA, et al. Vaccine-preventable adenoviral respiratory illness in US military recruits, 1999-2004. Vaccine 2006;24:2835-2842.

157. Klinger JR, Sanchez MP, Curtin LA, et al. Multiple cases of life-threatening adenovirus pneumonia in a mental health care center. Am J Respir Crit Care Med 1998;157:645-649.

158. Singh-Naz N, Brown M, Ganeshananthan M. Nosocomial adenovirus infection: molecular epidemiology of an outbreak. Pediatr Infect Dis J 1993;12:922-925.

159. Bateman CM, Kesson AM, Shaw PJ. Pancreatitis and adenoviral infection in children after blood and marrow transplantation. Bone Marrow Transplant 2006;38:807-811.

160. Erard V, Huang ML, Ferrenberg J, et al. Quantitative real-time polymerase chain reaction for detection of adenovirus after T cell-replete hematopoietic cell transplantation: viral load as a marker for invasive disease. Clin Infect Dis 2007;45:958-965.

161. Bridges ND, Spray TL, Collins MH, et al. Adenovirus infection in the lung results in graft failure after lung transplantation. J Thorac Cardiovasc Surg 1998;116:617-623.

162. Lankester AC, Heemskerk B, Claas EC, et al. Effect of ribavirin on the plasma viral DNA load in patients with disseminating adenovirus infection. Clin Infect Dis 2004;38:1521-1525.

163. Yusuf U, Hale GA, Carr J, et al. Cidofovir for the treatment of adenoviral infection in pediatric hematopoietic stem cell transplant patients. Transplantation 2006;81:1398-1404.

164. Naesens L, Lenaerts L, Andrei G, et al. Antiadenovirus activities of several classes of nucleoside and nucleotide analogues. Antimicrob Agents Chemother 2005;49:1010-1016.

165. Morfin F, Dupuis-Girod S, Mundweiler S, et al. In vitro susceptibility of adenovirus to antiviral drugs is species-dependent. Antivir Ther 2005;10:225-229.

166. Wallot MA, Dohna-Schwake C, Auth M, et al. Disseminated adenovirus infection with respiratory failure in pediatric liver transplant recipients: impact of intravenous cidofovir and inhaled nitric oxide. Pediatr Transplant 2006;10:121-127.

167. Doan ML, Mallory GB, Kaplan SL, et al. Treatment of adenovirus pneumonia with cidofovir in pediatric lung transplant recipients. J Heart Lung Transplant 2007;26:883-889.

168. Keswani M, Moudgil A. Adenovirus-associated hemorrhagic cystitis in a pediatric renal transplant recipient. Pediatr Transplant 2007;11:568-571.

169. Hartline CB, Gustin KM, Wan WB, et al. Ether lipid-ester prodrugs of acyclic nucleoside phosphonates: activity against adenovirus replication in vitro. J Infect Dis 2005;191:396-399.

170. Walls T, Hawrami K, Ushiro-Lumb I, et al. Adenovirus infection after pediatric bone marrow transplantation: is treatment always necessary? Clin Infect Dis 2005;40:1244-1249.